(large)

Proceedings of the Conference

OF

Army Physicians

Central Mediterranean Forces

Held at the

INSTITUTE SUPERIORE DI SANITA

VIALE REGINA MARGUERITA, ROME

29th January to 3rd February 1945

CONFERENCE
OF ARMY PHYSICIANS

Central Mediterranean Forces, Rome, 1945

ROME 1945

Foreword

We have done our best to give a faithful record of the proceedings at the Conference but we realise there are probably many mistakes and if we have put into anyone's mouth things they have not said, we apologise, as we do if we have omitted contributions to the discussions through faults of reporting.

E. R. Boland,
Brigadier

J. H. L. Easton,
Lt. Col., RAMC

J. D. Wade,
Sgt., RAMC

Conference of Army Physicians

The Conference was opened by Major-General M. C. Stayer, Surgeon, MTOUSA, on Monday, 29th January, 1945.

"Gentlemen,

General Hartgill is sorry he cannot be here; he is in conference in Cairo, but he hopes to be here before the session ends.

It is a distinct privilege for me to be here to hear the various papers I see on this programme. It is amazing to me having been in wars since 1898 to see the great advances our profession has made over that period of time, one man's lifetime, and those of you who were in the last war can well imagine what might have happened to us in this war; the major disasters that befell us in the last war do not now amount to anything as far as we are concerned. For instance, Meningitis. Some of my troops landed in Liverpool during the last war; there had been Meningitis on one of the transports and a number of them had died. On the train, no one was allowed to leave; at stations the windows were kept closed. We got to Southampton and entrained for Le Havre. We were all very much disturbed at the number of deaths we had had from epidemic Meningitis. Today we are not very scared of it at all, the mortality is very low, and the incidence is very low. As a result of our Sulpha drugs and Penicillin we have been able to keep our days in hospital to a minimum. But there are diseases which we still have to face which appear in this programme. After the period of war that this theatre has had, more than any other theatre, you people have solved problems in medicine as well as in surgery that will go down as a lasting example of the courage, skill and ability of our officers, nurses and enlisted men. But there are some which we have not solved, but I believe we are well on the way to bringing to the countries all through the world interesting knowledge which will do much to solve mysteries which still exist.

The programme is very interesting and I am sure that all of us will benefit by being here and by having been in contact with each other, and I hope there will be further discussions on these subjects of intense interest. I wish to thank Brigadier Boland for arranging this meeting. My only sorrow is that I cannot shake the hand of each one of you, and hope that you get home at an early date."

Programme

Monday, 29th January 1945

MORNING SESSION

Opening of Conference by Major-General M. C. Stayer, Surgeon, Mediterranean Theatre of Operations, United States Army.

Subject: MALARIA

Speakers:

Discussion

AFTERNOON SESSION

Subject: SHORT PAPERS

Speakers:

Discussion

Discussion

Tuesday, 30th January 1945

MORNING

PAGE

Visit to Vatican Museum, Sistine Chapel and Special Audience with the Pope.

AFTERNOON SESSION

Subject: INFECTIVE HEPATITIS

Speakers:

Discussion

Wednesday, 31st January 1945

MORNING SESSION

Subject: PENETRATING WOUNDS OF THE CHEST

Speakers:

Discussion

AFTERNOON SESSION

No Meeting

Thursday, 1st February 1945

MORNING SESSION

Subject: AMOEBIASIS

Speakers:

Discussion

Subject: FOOT CONDITIONS DUE TO COLD AND WET

Friday, 2nd February 1945

MORNING SESSION

Subject: DIPHTHERIA

AFTERNOON SESSION

Subject: NEUROPSYCHIATRIC PROBLEMS IN ITALY
(The Problem of the Inadequate Personality)

Subject: MEDICAL USES OF PENICILLIN

Closing address by Major-General M. C. Stayer, Surgeon,
Mediterranean Theatre of Operations, United States Army.

Monday, 29th January, 1945

MORNING SESSION

Subject: MALARIA

Presiding:

Major-General M. C. Stayer, Surgeon

Mediterranean Theatre of Operations, United States Army.

MALARIA

by

Lt.-Col. A. WILLCOX, RAMC

Introduction

There is no need to stress the importance of malaria in this theatre. It impressed itself upon us in a forcible manner in the summer of 1943, and yet I suppose the incidence was small compared with that in some other theatres. To quote my own experience, in the twelve months from July, 1943, to June 1944, 8 months of which were spent in North Africa and 4 in Italy, 5,184 cases of malaria were treated in the Medical Division, comprising 38% of all admissions. Two-thirds of the patients had B.T. infections and the remaining third had M.T. and Clinical Malaria in approximately equal proportions. Quartan Malaria was diagnosed in 14 patients. 4,080 patients were admitted with Primary attacks and 1,104 with Relapses.

Bulmer in the Middle East had 735 cases of malaria out of 13,542 admissions (5%), and Leishman and Kelsall, in India, had 2,819 out of 11,645 admissions (24%).

Diagnosis

I have nothing original to say about diagnosis, which ultimately depends on finding the parasite.

The typical periodic temperature has proved rare. In a recent examination of over a thousand case records of patients with malaria I found only twenty "text-book" B.T. temperature charts.

It is a truism to state that malaria can simulate any disease, but even so I have had many surprises and I have often been grateful for the rule that in any case of pyrexia, however obvious the cause, a blood smear will be taken. While on the subject of blood smears I am told that venous blood will often produce a positive result when smears taken in the ordinary way are negative. I should be grateful for information on this point. Personally I have not found sternal puncture more successful than ordinary smears, neither have I found the determination of the blood sedimentation rate helpful.

There is no time to deal at length with the differential diagnosis of malaria, but I would like to mention the conditions which gave me the most difficulty.

In July and August, 1943, in the Robertville area of North Africa, the dysenteric form of M.T. malaria frequently occurred. The text books say that in this condition the stools contain blood and mucus but little pus. However, our cases produced blood and pus, but with no significant growth or culture. Failure to respond to sulphaguanidine and a positive blood smear led to the correct diagnosis, and response to quinine was usually rapid.

In the autumn of 1943 cases of infective hepatitis in the pyrexial preicteric phase proved most difficult, particularly when the spleen was enlarged. Many were provisionally called and treated as clinical malaria until jaundice developed. Even so some of these may have had malarial jaundice and not infective hepatitis.

In the first three months of 1944 primary atypical pneumonia and relapses of B.T. malaria occurred simultaneously, and produced very similar pictures. I think many patients had the two conditions, but unfortunately it was not possible to X-ray as many as we could have wished. Some of the patients with atypical pneumonia were admitted in a stuporose condition very like cerebral malaria, and a few had enlarged spleens. The white blood count was useless diagnostically. However, there was no response to quinine given orally or intravenously, unlike those with malaria, and eventually physical and radiological signs developed in the lungs.

In cerebral malaria I think a lumbar puncture is advisable. It may do good therapeutically and it can certainly prevent unfortunate mistakes. In August, 1943, I confidently diagnosed cerebral malaria in a patient whose cerebrospinal fluid on puncture was found to be loaded with meningococci.

Malaria should be remembered in cases of intractable anaemia. I have seen two patients with a megalocytic anaemia which was resistant to liver therapy and which eventually proved to be due to B.T. malaria. There was an immediate reticulocyte response to quinine therapy.

Persistent headaches, limb pains and malaise without pyrexia may not infrequently occur in latent infections, as we found in the chronically relapsing cases collected at 96 General Hospital.

Clinical Malaria

It was the tendency in the early days to call all cases of pyrexia malaria and to treat them as such, regardless of the blood film results. I think that at that time, when we were inexperienced, this was a wise procedure and saved lives. However, it led to many faulty diagnoses, and to much unnecessary and wasteful hospitalization. Unfortunately, like all bad habits, it proved difficult to break. Clinical malaria was a convenient diagnosis. It was a relief in those days to be able to forget the patient for ten days or so whilst he pursued his way through the routine treatment. With experience this became inexcusable, and it was possible to reduce the diagnosis of clinical malaria to 5%—10% of patients. I am convinced that under service conditions clinical malaria must be accepted as a diagnosis in a small number of patients. Its use should be strictly controlled and should be confined to those with a suggestive clinical picture, repeatedly negative films and a response to anti-malarial treatment. Even so mistakes are likely to occur. For instance, every one of the ten cases of Kala Azar which I have seen has at one time been diagnosed as clinical malaria.

Treatment

Most authorities seem agreed that short courses of combined drugs give the best results both in terminating the acute attack and in preventing relapses.

The 4th General Report of the Malaria Commission of the League of Nations advises short courses with moderate doses both for primary attacks and for relapses. It also states that prolonged administration of drugs when the disease is latent does no good and may be harmful. The National Research Council of the U.S. and the Medical Department of Tanganyika express the same views.

Regarding the comparative merits of quinine and mepacrine the U.S. Board for the Co-ordination of Malarial Studies and the Drug Prophylaxis and Therapy Committees of the M.R.C. Committee on Malaria both agree that:—

"In the therapy of the acute attack.—Experience in the past two years has demonstrated conclusively that mepacrine (atebrin), when properly administered, is fully as effective as quinine in the termination of the acute attack and is safer than quinine. The intramuscular injection of mepacrine is highly effective in securing a rapid therapeutic response. Evidence is not at hand to decide on the relative merits of mepacrine administered intramuscularly as compared with quinine administered intravenously in patients with fulminating cerebral malaria.

In the therapy of vivax malaria.—Neither mepacrine nor quinine can be relied on to prevent relapses in vivax malaria following the discontinuation of therapy, although the interval between attacks is significantly longer following mepacrine than following quinine in the dosage schedules currently used by the armed forces.

In the therapy of falciparum malaria.—There is convincing evidence that mepacrine not only suppresses the clinical symptoms of falciparum malaria, but also cures this malignant form. The evidence of a similar curative effect of quinine is not conclusive."

A short course of quinine, mepacrine and in B.T. infections pamaquin is the rule in this theatre for primary attacks and relapses. The dosage is as follows:—

Quinine—90 grains in 3 days,
Mepacrine—2.5 grams in 5 days,

and for B.T. infections pamaquin 0.09 gram in 3 days. Patients with M.T. infections continue to take mepacrine 0.1 gram daily for six weeks after the completion of the course.

Manson Bahr, in a recent letter to the B.M.J., states that he considers this course inadequate for the prevention of B.T. relapses. He considers it necessary to continue with quinine 10 to 15 grains daily and pamaquin 0.04 gram daily for three weeks or longer. I have not been impressed with the results of combined quinine and pamaquin treatment for reasons I will mention later. Neither do I think it would be safe or practicable to give pamaquin in this dosage and for this period to men on full duty. Nor would it be possible to retain all patients with B.T. infections in medical units for the five or more weeks that this course would cover.

In the present state of our knowledge I think the official course is the best that can be devised. It controls the fever almost invariably, it is easy to give and, with the malarial treatment card, it stands up well to the trials of evacuation, and it keeps the patients in hospital for an adequate but not excessive period.

In the Spring of 1944, on Brigadier Boland's suggestion, we carried out some experiments to test the effect of giving quinine and mepacrine simultaneously. Quinine 30 grains in three 10-grain doses and mepacrine 0.8 gram were given daily for two days. In one series of patients the mepacrine was given in four doses of 0.2 gram and in a second series it was given in a single dose of 0.8 gram. No changes were found in the White Blood Count, in the urine or in the nervous system, but vomiting occurred in 12% of the first series and 56% of the second. It was obvious that this scheme was impracticable. Brigadier Boland has some personal experiences of the experiment which I hope he will describe.

Intravenous Quinine

In addition to those cases obviously needing intravenous quinine, such as patients with cerebral malaria, repeated vomiting, etc., I gave last summer an initial dose of quinine 10 grains intravenously to all M.T. infections. I met with no reactions and I believe I saved myself many worries. I prefer to give the quinine by intravenous drip in glucose saline. This takes no longer to set up than it does to give the quinine slowly by needle and syringe, unpleasant side effects seem less common, and in hot weather the extra fluid is beneficial.

Intramuscular Quinine

Manson Bahr says there seems to be a prejudice against this method of giving quinine. I admit that until recently I shared it myself, and I think it was inculcated by the lectures I attended in the United Kingdom in which we were impressed by story and picture with the risks of quinine abscesses.

However, I found at 96 General Hospital that Lt-Col Hunt had given many intramuscular injections without ill effect, and I continued to give some, particularly to some patients with chronically relapsing malaria. I still think, though, that in serious cases quinine should if possible be given by the intravenous route. In other cases intramuscular mepacrine is probably as effective and, I believe, less painful.

Intramuscular Mepacrine

I have used this successfully in three cases of blackwater fever and in some cases where absorption of mepacrine by mouth appeared to be defective.

I have no experience of its use in cerebral malaria.

Chronically Relapsing Malaria

In January, 1944, the following treatments were instituted for relapse cases of Malaria:—

Treatment A. For M.T. relapses.
Mepacrine 0.2 gram every 6 hours for 48 hours, followed by mepacrine 0.1 gram three times a day for 10 days, and finally mepacrine 0.1 gram daily for 6 weeks.

Treatment B. For B.T. relapses.
Quinine 30 grains with pamaquin 0.03 gram a day for 10 days.

We were warned to beware of toxic manifestations with Treatment B, but in 122 patients carefully observed they were very infrequent. Three patients developed cyanosis, one patient complained of colic, one patient developed severe nerve deafness and one patient produced urticaria.

From the start Treatment B appeared disappointing, as many patients relapsed a week or two after the course.

However, I was able to acquire more experience of the chronically relapsing cases at 96 General hospital, where for a time they were collected from throughout the theatre. The scheme of investigation was started by Lt-Col T. C. Hunt and Major Keall and was continued by Major Keall and myself.

Arbitrarily the cases were confined to those who had had four or more attacks of malaria. We received 107 patients of this category, 37 with M.T. infections, 40 with B.T. infections and 30 with mixed M.T. and B.T. infections. 35 patients referred to 96 General Hospital were excluded as there was insufficient evidence that their so-called relapses were in fact true atacks of malaria.

Although some of these patients had had twelve attacks of malaria in as many months, their general condition was surprisingly good. Only ten (10%) had to be repatriated to the United Kingdom, and in all of these there was some complication such as chronic bronchitis or anxiety states. A significant anaemia (Hb less than 80%) occurred in five (5%) and a persistent splenomegaly in six (6%).

The relapse rate for M.T. infections after Treatment A was 20%. Five patients with chronically relapsing M.T. malaria ran a prolonged low-grade pyrexia whilst on mepacrine 0.1 gram daily. Repeated blood smears and sternal puncture failed to show malarial parasites. The urinary mepacrine test, however, was negative and in each case the pyrexia subsided with a course of intramuscular mepacrine.

The relapse rate for B.T. infections after Treatment B was 50%. Some patients who relapsed had received as many as five courses of quinine and pamaquin. Three are of interest. In these three patients the fever failed to respond to quinine by mouth. We found in each case that Tancret's test was negative, and in each case the fever subsided with a course of intramuscular quinine.

As the results of the combined quinine and pamaquin course were so disappointing we gave 21 patients with B.T. infections a course of Treatment A (mepacrine). The relapse rate was 33% and on the whole the time interval between relapses was increased.

The patients with mixed M.T. and B.T. infections showed a relapse rate of 50% after Treatment A and 75% after Treatment B.

We gave N.A.B. to 15 patients, three with M.T., ten with B.T. and two with mixed M.T. and B.T. infections, and ten relapsed.

T.A.B. injections and a high calorie diet were also tried. The first appeared to be valueless. The second improved the patient's general condition but had no effect on the relapse rate.

We concluded from these results that the mepacrine treatment was the more effective in both M.T. and B.T. infections.

Summary

1. Malaria accounted for 38% of the admissions to the Medical Division during 12 months' work in North Africa and Italy. B.T. 66%. M.T. 17%. Clinical 17%. Quartan occurred in 14 patients.

2. Clinical malaria is an acceptable diagnosis in 5 to 10% of cases.

3. The following conditions proved difficult in the the differential diagnosis:—
Dysentery, Infective Hepatitis, Atypical Pneumonia, Anaemia, Chronic Malaise with headaches and limb pains.

4. Lumbar puncture is advisable in cerebral malaria.

5. The official course of treatment with combined drugs is the most satisfactory that can be devised with our present knowledge.

6. Treatment with quinine and mepacrine given simultaneously is found to be impracticable.

7. Intravenous quinine is best given by intravenous drip in glucose saline.

8. Of 107 patients with chronically relapsing malaria:—

(a) 37 had M.T. infections, 40 B.T. and 30 mixed M.T. and B.T.

(b) 10% were repatriated to the United Kingdom.

(c) Relapse rate for M.T. infections after Treatment A was 20%.

(d) Relapse rate for B.T. infections after Treatment A was 33%.
Relapse rate for B.T. infections after Treatment B was 50%.

(e) Relapse rate for mixed infections after Treatment A was 50%.
Relapse rate for mixed infections after Treatment B was 75%.

(f) N.A.B. injections, T.A.B. injections and high calorie diet appeared to have no influence on the relapse rate.

(g) Treatment A was considered the most effective for both M.T. and B.T. infections.

STUDIES OF RELAPSE IN MALARIA

by

Lt.-Col. JAMES B. McLESTER, MC

1. (a) To confirm clinical impressions concerning probability of recurrence in malaria in relation to sedimentation rate, serum bilirubin and hemoglobin, follow-up of patients with malaria was attempted. Answers to questionnaires have been slightly incomplete and the length of follow-up has been relatively short. It is felt, however, that there is sufficient data to justify correlation and that more complete follow-up would not materially change the conclusions.

(b) The 527 cases followed had all been patients in the 17th General Hospital. Data concerning the original 17th General Hospital admission was gathered by officers of the Medical Service of the 17th General Hospital. As the clinical records of these patients were not filed at the hospital, available data has consisted entirely in recorded notes not forwarded with the patient. It has been, at times, quite meagre.

(c) Patients relapsing in this hospital or entering the hospital more than once were considered separately for each attack, with follow-up of the first admission ending with the onset of recurrence. There were sixteen (16) such patients, bringing the total number of cases studied to 543.

2. (a) These cases were of various types of malaria, followed for varying lengths of time, and relapsed as is shown in Table I.

TABLE I

Months followed	Vivax			Falciparum			Unclassified and Mixed		
	Number of cases	Number relapsing	Relapse rate	Number of cases	Number relapsing	Relapse rate	Number of cases	Number relapsing	Relapse rate
			%			%			%
0	21	0	0.0	2	0	0.0	1	0	0.0
1	46	7	15.7	2	0		2	0	
2	55	15	27.3	3	0		0	0	
3	54	17	31.5	0	0		0	0	
4	20	7	35.0	1	0		0	0	
5	21	3	14.3	0	0		1	1	
6	31	10	32.2	1	0		2	1	
7	59	23	34.0	5	2	40.0	3	1	
8	44	18	40.9	17	3	17.7	1	0	
9 or more	19	7	36.9	26	11	42.3	0	0	
Total followed	349	107	30.7	55	16	29.1	9	3	33.3
Total cases	370			57			10		

TABLE I *(continued)*

Months followed	All Proven Cases			Clinical			Total		
	Number of cases	Number relapsing	Relapse rate	Number of cases	Number relapsing	Relapse rate	Number of cases	Number relapsing	Relapse rate
			%			%			%
0	24	0	0.0	0	0		24	0	0.0
1	50	7	14.0	2	0		52	7	13.5
2	58	15	25.8	3	1		61	16	26.2
3	54	17	31.5	6	0		60	17	28 3
4	21	7	33.3	4	0		25	7	28.0
5	22	5	22.7	6	2	33.3	28	7	25.0
6	34	11	32.4	9	3	33.3	43	14	32.6
7	67	25	37.3	10	1	10.0	77	26	32.4
8	62	21	33.8	27	9	33.3	89	30	33.7
9 or more	45	18	40.0	39	5	12.8	84	23	27.4
Total followed	413	126	30.5	106	21	19.8	519	147	28.3
Total cases	437			106			543		

"Number relapsing" indicates the number of cases relapsing one or more times during the period of follow-up. Relapses after the first following discharge from the hospital are not considered.

"Relapse rate" is calculated on a simple percentage basis: Number relapsing/number of cases × 100. This is more properly called "reported relapse rate during the period followed".

(b) Cases of "clinical malaria" were included in this study to determine the accuracy of diagnosis. The 19.8% relapse rate in "clinical malaria" compared with 30.5% relapse in proven cases suggests that the diagnosis of "clinical malaria", as made, was accurate in only about two thirds of the cases. The inability to determine which non-relapsing "clinical malaria" was accurately diagnosed has necessitated limiting all studies reported below to proven cases.

(c) The accuracy of the species identification is also questionable. One Vivax case was reported with a Falciparum relapse and one with Malariae; all others were Vivax, unclassified, or clinical. In the Falciparum cases, about half of the reported relapses were Vivax.

For this reason, most studies reported below are not differentiated by type of malaria. Where such differentiation is made, the possibility of error in species diagnosis is realized.

(d) To show that these short follows-ups are adequate for the study of relapse, Table II has been constructed for proven cases. It will be observed from the "cumulative relapse rate" column of Table II that an appreciable number of relapses occurred within one month after discharge from the hospital, that over half occurred within the first two months, and that three quarters occurred before the end of the fourth month. After the fourth month, the number of additional first relapses is at a very low, probably progressively lower, figure. Although it is realized that malaria may relapse after several years, it is felt that these figures indicate that the significant number occur within a very few months.

TABLE II

Number of months	Cases followed for this period or longer	First relapse during this month	Relapse rate this month	Cumulative relapse rate
			%	%
0	437	0	0.0	0.0
1	413	41	9.92	9.92
2	363	49	13.50	23.42
3	305	16	5.20	28.62
4	251	7	2.79	31.41
5	230	2	0.86	32.27
6	208	4	1.90	34.17
7	173	2	1.15	35.32
8	106	2	1.85	37.17
9 or more	45	3	6.67	43.84

"Relapse rate this month" indicates the proportion of cases followed for at least the time in question who had their first relapse during the month in question. Subsequent relapses are disregarded.

The "cumulative relapse rate" is the total of the rates for this and shorter periods.

3. (a) These cases were about half primary malaria and about half recurrent when first seen by us. An attempt was made to determine if this was a factor in the probability of relapse.

(b) Among the cases of proven malaria, there were 366 with a definite record of the number of previous attacks. These cases relapsed as follows:

Number of previous attacks	Number of cases followed	Cases relapsing	Relapse rate
			%
0	167	44	26.3
1	97	31	32.0
2	34	12	35.3
3	27	13	48.1
4 or more	41	10	24.4
0	167	44	26.3
1 or more	199	66	33.1

(c) The same question was approached differently: Of 540 cases of proven malaria (including a number not in the follow-up series) who gave a definite history of the number of previous attacks, the distribution was as given in Table III. The figure for "relapse rate", was calculated by assuming that those with one previous attack represented recurrence in those cases listed as having primary malaria, that those with two previous attacks represented a second recurrence in those here listed as having a first relapse, etc. This reasoning is falacious: These cases were only in rare instances the same individuals; those cases with more frequent relapse were progressively more apt to be admitted to a General hospital; and because of the increasing time and the increasing number of men in the theatre over this period, the groups of cases are drawn from populations of different size and cannot be compared. It is felt, however, that these factors, if corrected, would tend to increase the proportion of cases with more previous attacks and, therefore, increase still further the apparent relapse rate after recurrent malaria.

TABLE III

Number of previous attacks	Number of cases	Number with one more previous attack	"Relapse rate"
			%
0	254	121	47.6
1	121	53	43.8
2	53	35	66.0
3	35	27	77.2
4	27	17	63.0
5	17	14	82.4
6	14	10	71.5
7	10	5	50.0
8	5	1	
9	1	1	
10	1	0	
11	0	2	
12	2	—	
	Total 540		

See par 3c for explanations of this table.

(d) It is felt that the data discussed in paragraphs 3b and c indicates an increasing probability of further relapse as the number of previous attacks increases. This difference is not sufficiently great to materially affect data obtained from cases without respect to the number of previous attacks.

4. No accurate relapse rate can be determined from the figures shown in Tables I, II and III. These data suggest that about 50% within the first year is the correct relapse rate for primary malaria but that it becomes progressively higher as the number of previous attacks increases. If this is correct, the relapses actually reported in the follow-up studies represent about half of the number that these patients will have had. It is felt that this is a sufficiently large fraction to justify use of reported relapses as a criterion in the study of factors involved in relapse.

5. Erythrocyte sedimentation rate in malaria:

(a) It was observed that the erythrocyte sedimentation rate was elevated in many cases of acute malaria. Very high values were obtained in some cases. The general distribution in the lower ranges as found on admission to the hospital was as follows:

Sedimentation rate mm hr (Westergren)	Number of cases	Per cent of total
0-5	26	9.1
6-10	38	13.2
11-15	40	14.0
16-20	49	17.1
over 20	134	46.6

All values were determined by the Westergren method and were not corrected for volume of packed cells. In examining the notes on these patients, the impression is gained that sedimentation rate rises while there is parasitemia and relatively slowly approaches normal at other times. There were insufficient cases with persistent parasitemia seen early in the attack to confirm this. The determination of time of onset of the disease was too inexact to allow correlation with that figure.

(b) It was thought that the level of the sedimentation rate after treatment might have value in predicting relapse. The following values were determined after treatment in proven cases:

Sedimentation rate mm/hr (Westergren)	Number of cases	Cases relapsing	Relapse rate
			%
0-5	32	9	28.5
6-10	64	17	26.6
11-15	20	6	30.0
16-20	16	7	43.7
over-20	24	11	45.8
below 11	96	26	27.1
over 10	60	24	40.0

There is some apparent correlation. It will be shown (in par 6(d), below) that this correlation is probably due to other factors and that the sedimentation rate, in itself, is unassociated with relapse rate.

6. Serum bilirubin in malaria.

(a) It has been observed that the serum bilirubin (quantitative indirect van den Bergh) was elevated in malaria. The following distribution of values on admission to the hospital was found in cases of proven Vivax malaria not known to be associated with infectious hepatitis:

Serum Bilirubin mgm per cent	Number of cases	Serum Bilirubin mgm per cent	Number of cases
0-0.5	105	1.1	8
0.6	18	1.2	4
0.7	42	1.3	3
0.8	18	1.4	4
0.9	22	1.5	12
1.0	15	over 1.5	19

The relation of this observation to malaria might be questioned in view of the coincident presence of infectious hepatitis in the theatre. The existence of abnormal serum bilirubin values (over 0.5%) in 61.1% of the above series of cases and the gradual decrease in number of cases up to bilirubin levels of 1.3 mgm% with increase thereafter suggests that levels above 1.2 to 1.4 are likely due to unrecognized hepatitis but that lower levels are not. The distribution of cases also suggests the validity of the use of 0.5 mgm% as the upper limit of normal.

(b) Whether the increased serum bilirubin values are due to blood destruction or to damage to the liver by malaria has not been demonstrated. Because of the different degrees of blood destruction in Vivax and Falciparum malaria, these observations are limited to proven Vivax cases. The following correlation has been made between serum bilirubin and hemoglobin levels in patients with Vivax malaria on admission to the hospital.

	SERUM BILIRUBIN						
Hemoglobin percent of 15.5 gm	0—0.5	0.6—0.7	0.8—1.0	over 1.0	Total cases	Total over 0.5	Percent over 0.5
over 110	0	1	0	0	1	1	
101-110	6	1	2	1	10	4	40.0
91-100	21	7	7	1	36	15	41.6
81- 90	34	18	16	11	79	45	56.9
71- 80	34	23	22	25	104	70	67.3
61- 70	9	9	7	9	34	25	73.5
under 61	1	1	1	3	6	5	83.4
Total	105	60	55	50	270	165	61.1

The increasing proportion of cases with elevated serum bilirubin levels as the anemia increases indicates that the two are related. It does not necessarily indicate direct causal relationship. The existence of high serum bilirubin levels in 40.0 and 41.6% of patients with hemoglobin levels within 10% (1.5 gm) above and below normal suggests that the two are not directly interdependent. This is also suggested by the number of cases with very low hemoglobin but normal bilirubin. Cases were sought in which the bilirubin level rose coincident with a rising hemoglobin or fell coincident with a falling hemoglobin. Two such cases were found, but in neither was the hemoglobin determination sufficiently accurate.

(c) It was thought that the level of serum bilirubin after treatment might bear some relationship to the probability of relapse. Value below are for cases of Vivax malaria after treatment:

Serum Bilirubin	Number of cases	Cases relapsing	Relapse rate
			%
0-0.5	34	8	23.5
0.6	7	3	42.8
0.7	9	4	44.5
0.8-0.9	6	3	50.0
1.0-0.2	5	3	60.0
0-0.5	34	8	23.5
over 0.5	27	13	48.1

The difference in the frequency of relapse in this instance is very striking in spite of the small numbers of cases.

(d) The thought was entertained that the patients with normal values for both sedimentation rates and serum bilirubin might be very much less subject to relapse than others. Values given below are in cases of Vivax malaria after treatment.

Serum bilirubin	Sedimentation rate	Number of cases	Cases relapsing	Relapse rate
				%
0-0.5	0-10	24	6	25.0
0-0.5	over 10	10	2	20.0
over 0.5	0-10	14	7	50.0
over 0.5	over 10	13	6	46.1

Attention is called to the maintenance of the relation of the relapse rate to the serum bilirubin level without regard to sedimentation rate. It can but be

concluded that the apparent relationship of sedimentation rate and relapse noted in par 5(b) above is in reality an expression of indirectly associated serum bilirubin levels.

7. (a) To determine whether the degree of anemia remaining after treatment bears any relation to the probability of relapse, the following tables were constructed. Values for hemoglobin were determined a variable period after treatment in cases of Vivax malaria. Data is separate for those patients who did not get blood transfusion and those who did.

Hemoglobin per cent of 15.5 gm	No Transfusion			Transfusion		
	Number of cases	Number relapsing	Relapse rate	Number of cases	Number relapsing	Relapse rate
			%			%
over 90	27	6	22.2	16	3	18.8
70-90	27	10	37.0	8	0	0.0
under 70	4	2	50.0	0		

A definite relation apparently exists with increasing probability of relapse with increasing degrees of anemia remaining after treatment. The relapse rate in those patients who had blood transfusion is difficult to interpret.

(b) Because of the above apparent relationship of residual anemia to relapse, a parallel between the rise or fall of hemoglobin during treatment and the relapse rate was sought in patients with Vivax malaria who had not received blood transfusion:

Hemoglobin	Number of cases	Number relapsing	Relapse rate
			%
Rising . . .	36	7	19.6
Constant . .	2	2	50.0
Falling . . .	10	4	

8. Damage to the liver in malaria is suggested by the elevated serum bilirubin levels, by the frequency of the occurrence of an enlarged tender liver in malaria, and by the abnormal cephalin-cholesterol flocculation and bromsulfalein retention in malaria as reported from the 182nd Station Hospital and 21st General Hospital. However, the absence of any reported pathology in the liver in autopsies and the absence of plasmodia from all types of cells of the biliary system in patients dying of malaria suggests that liver damage by malaria is not the cause of the bilirubinemia. The relationship of serum bilirubin to anemia (par 6 (b)) and of each of these to relapse (paragraphs 6 (c), 7 (a) & (b) suggests another mechanism: It is possible that the bilirubinemia is the result of blood destruction which in those cases with normal hemoglobin, is completely compensated for by parallel regeneration. Persistent bilirubinemia would, in this case, represent compensated blood destruction due to latent infection. There were no records of reticulocyte determinations after treatment with which to demonstrate this hypothesis by further correlation.

9. In summary, it may be concluded that:

(a) Short time follow-up is of value in the determination of the factors affecting malarial relapse.

(b) The frequency of relapse in primary malaria in this theatre is about 50% in the first year and it probably is progressively higher in recurrent malaria, as the number of attacks increases.

(c) The erythrocyte sedimentation rate is elevated in malaria but it probably has no relationship to relapse.

(d) The serum bilirubin is elevated in malaria. The cause of this elevation is unknown.

(e) Persistence of a serum bilirubin level above 0.5 mgm per cent after treatment indicates that malarial relapse is about twice as probable as when the bilirubin returns to normal.

(f) Persistence of anemia or failure of spontaneous rise in hemoglobin after treatment indicates that malarial relapse is more probable.

OBSERVATIONS ON MALARIA IN ITALY (1943-1944)

by

Lt.-Col. R. W. D. TURNER, RAMC

My remarks refer to observations made on over 5,000 cases of Malaria seen in 92nd British General Hospital in Italy, during the past 16 months. Particular reference will be made to M.T. infection from September to December, 1943, because we were in the middle of an epidemic and had special opportunities for clinical observation, and of B.T. relapsing malaria because we have been one of the collecting centres for these patients since last September.

No facilities have existed for special laboratory work or controlled experiments and as a consequence our experience is confined to the clinical side. This I would emphasise. Statistical difficulties have been enormous, owing to the changing seasons, shifting military populations, unreliable past histories (given by patients), and variations in treatment by different units. In the early days the proportion of clinical cases was high because most patients were treated by their units, or forward medical units, for a few days, before evacuation. In the summer and autumn it was impossible to differentiate relapses from fresh infections.

Different strains with presumably varying habits were also encountered. Perhaps the chief of the incalculable factors is the effect of suppressive mepacrine on the vivax and falciparum infection.

It will be readily appreciated how difficult is a follow up.

To provide a summary and avoid repetition and avoid the reading out of dull statistics, an Appendix has been prepared. It is suggested that this would be a suitable place for potential speakers to jot down their criticisms and remarks.

These opening remarks over a wide field are merely intended to set the ball rolling and stimulate discussion.

M.T. Malaria

During 1943 in North Africa, Sicily and Italy, deaths from M.T. Malaria were frequent. Such deaths must be to all intents and purposes avoidable, and are due to late diagnosis or inadequate treatment. One of the factors making early diagnosis difficult was the presence of a co-incidental epidemic of Infective Hepatitis. At such a season of the year when both conditions are occurring together, it is absolutely essential to establish at once, in every patient diagnosed as Infective Hepatitis, that bile is present in the Urine. This simple clinical observation, which was apt to be neglected, may be life-saving. It is true that many cases of M.T. Malaria arrived in Hospital with jaundice and dark urine. However, most of these had urobilin and not bilirubin in the urine, and when bile did occur in an occasional case there was very little. It is a convenient fact that the naked eye examination of the colour of the supernatant froth is as accurate as, and often more delicate than, the ordinary laboratory tests. Patients with M.T. malaria were often obviously seriously ill, but there were scarcely any cases of Infective Hepatitis who were ill in this way. Vomiting, of course, is common in M.T. malaria, and dangerous, but a patient with Infective Hepatitis tends to vomit in the early stages before he goes yellow or has bile in the urine. Another point is that on the whole in these M.T. patients splenomegaly is more marked than hepatomegaly. Finally, blood slides must be taken in every case with fever or which appears unduly ill.

An added difficulty is the arrival of patients diagnosed as Infective Hepatitis late at night, and in the rush they are liable to be left aside till morning unless examined with the object of this differential diagnosis specifically in view.

It often appeared that patients had become much worse during ambulance journeys down between the front line and the base and they arrived semi-conscious or even moribund. The giving of intravenous Quinine in Forward units before evacuation would undoubtedly have saved lives, but this was rarely done.

Again, many patients arrived grossly dehydrated, and the giving of drinks before and during evacuation is of vital importance too.

Everyone is agreed about the almost miraculous efficacy of intravenous Quinine, but during the period under consideration it was not in fact widely given, and it was found that many M.Os were afraid of reactions. Actually these must be very uncommon because we never saw anything alarming at all, nor have heard of anyone who has, when the injection has been slowly administered and properly diluted. If sterile solutions for dilution are not available under emergency conditions, dilution with the patients own blood in the barrel of the syringe is quite satisfactory. Intractable venous spasm was a difficulty in one case. If the patient is conscious and can swallow, 6 tabs. mepacrine (0.6 gms) repeated next morning, is usually equally efficacious, but intravenous Quinine is more certain and safe if it is evening time. If the patient is vomiting, intravenous Quinine should invariably be given, and it is usually best to set up a drip straight away to which further Quinine can be added if necessary. Intramuscular atebrin was not available at the time, but is said to be equally good. However, with peripheral circulatory failure it may not be quite so speedy in action.

To sum up, the treatment needs to be early and vigorous. This is one of the conditions where enthusiasm is needed.

Relapses

The other problem was that of relapse. From our figures it is evident that at the height of the season the minimum relapse rate was about 10% and may well have been considerably higher because it was not possible to follow up most cases. Some patients were remarkably resistant to treatment and relapsed at short intervals, frequently at the Con. Depot and even whilst still in hospital on mepacrine. They did this too even though mepacrine pigmentation was in the skin and a positive urine test was present. Good examples were Roberts, Marshall and Arthur. (See Appendix).

We formed the impression that on the more powerful course of Mepacrine they fared better, but once more statistical difficulties were great.

M.T. Malaria ceased to be a problem by the end of the year. In a group of 125 cases of M.T.(R) the interval between the fresh attack and the first relapse was less than one month in 75%. The subsequent relapse intervals tended to be even shorter. For details see appendix.

One other fact possibly worth mentioning was that M.T. gametocytes were cleared from the blood by three days Pamaquin except in one case.

As would be expected from the natural history of falciparum infection no comparable group of M.T. fresh cases to the B.T. fresh cases occurred in the Spring.

B.T. Malaria in the Spring

The expected incidence of B.T. Relapses in the Spring occurred as was customary in most parts of the world before suppressive mepacrine.

A most unexpected feature not so far as I am aware forecast by the experts was the large number of patients with B.T. infection in March, April and May, who had never had malaria before. We had over 400 of these. All of these patients were in malarious areas during the summer and autumn of the previous year, and very few could be persuaded to give a history of any febrile illness during this period, and were sure they had not been bitten by mosquitoes during the winter months. Thus there has been no evidence of any fresh case being recently infected and it can be assumed that all were infected some 4-9 months before the onset of symptoms. Presumably this group was due to the suppressive effect of mepacrine taken the year before causing a prolonged incubation period, or suppressing the primary attack—so that they were in reality comparable to relapses. Units stopped mepacrine at varying times from mid October till late November.

We had been warned that the cessation of taking suppressive mepacrine would be followed shortly by outbreaks of Malaria spaced according to the individual reaction. In actual fact, no such outbreaks occurred whatsoever.

An analysis of 1,000 cases of B.T. Malaria at this time showed that about 60% were relapses from known B.T. infection and 40% were so called fresh (i.e had never had malaria, or in most cases even a suspicious P.U.O).

Two groups each of 100 B.T. cases have been compared from a study of Follow-up cards returned 3 months after discharge from Hospital in March, April & May. These figures are minimal as many follow-up cards did not come back, but presumably the two groups are comparable.

Group (1) Spring — B.T.(F)
Group (2) Spring — B.T.(R)

Whereas 26% of the B.T. relapses had again relapsed, only 5% of the B.T. fresh cases had. The interest of this is that these spring mepacrine suppressed fresh cases behaved like normal B.T. fresh cases (and not like B.T.(R)), in their tendency not to relapse quickly. Whether a normal percentage relapsed later, we do not know.

Recurrent B.T. Relapses

This formed the principle Malaria problem after the Spring of 1944. Cases were transferred to 92nd British General Hospital from Medical Units in No. 3 District. For the purposes of this investigation, only those who had had four or more relapses were given special treatment. The majority of these had relapsed after repeated variations of the Q.A.P. theme including the previously recommended treatment "B" (Quinine plus Pamaquin for 10 days).

Numerically the problem is not a big one. Few, even of those who have had many relapses, have had complications such as significant anaemia, splenomegaly, general malaise or loss of weight. The striking fact about this group is that most of them recover normal health and vitality in between attacks, and there is rarely evidence of any marked constitutional disturbance. The symptom most frequently encountered is an anxiety state in individuals with these ever occurring attacks and subsequent admission to medical units. Out of the first 100 cases 72 were downgraded to Category B.1 or C.1 for 3-6 months. This was mainly to ensure that they were not employed in a malarious area. Latterly this has not been necessary as the Malaria season was to all intents and purposes over, but a few have been downgraded on account of their general condition.

Only three were evacuated to U.K., two of these having non-malarial complications as well.

One of the principle difficulties of course in assessing the value of any special treatment for relapsing malaria is the impossibility of knowing whether in fact the patient would have had another relapse without further treatment. In any case it is not known at what rate the natural tendency to relapse diminishes with modern treatment of attacks, nor the effect of Suppressive Mepacrine before and between attacks. Hence it is extremely difficult to assess the value of special courses.

In view of the various claims in the Journals of different countries it was decided to try the effect of N.A.B. in 100 cases. Accordingly injections of N.A.B., 0.3 gms., 0.45 gms., and 0.6 gms., were given intravenously at 4 day intervals during the 10 day course of Quinine and Pamaquin by mouth. In view of the fact that some patients arrived having already been treated with Quinine for a few days it was not always possible to give this at the beginning of the relapse and this may well be an all important factor. An attempt is being made to follow up these patients for three months. This naturally presents difficulties, but already, 6 weeks after the cessation of the series, 10 have been re-admitted with another attack (i.e. 10%). It is reasonable to assume that this is not an effective method of preventing relapse and it was abandoned at the end of November.

On the assumption that relapses may be due to the failure of the drugs in common use to reach a sufficient concentration in the blood it was next decided to treat a series of cases with Quinine or Atebrin by injection. The first group received Quinine gr. 5 intravenously each morning and Quinine gr. 5 intramuscularly each evening for 5 days.

The second group received Atebrin hydrochloride 0.4 gms. for 2 days, followed by 0.2 gms for 5 days. Again the difficulty of patients having received a few days treatment with Quinine before arrival was encountered. So far 30 have had a Quinine course and 44 the Atebrin course. Of the Quinine group 5 have relapsed, and of the atabrine group 3.

Perhaps the concentration of the drug in the blood is not the all important factor, but if it is it would seem that the only rational manner of dealing with these resistant cases is to give the drug by injection, and only in the acute phase of the infection when it may be presumed that the parasites are in the blood stream.

B.T. Relapse—Intervals

800 B.T.(Rs) have been studied and divided into 2 groups:—

(1) Those with no more than 2 relapses (who then petered out), and

(2) Those with more than 4 relapses (chronic B.T. relapses referred to above).

The part played by suppressive mepacrine is incalculable, but the interval between B.T.(F) and B.T.(R)1 varies from 1-12 months with a preponderance of 6-9 months. It is considered that had not 3 Divisions gone home to U.K. in the Spring this preponderance would have been greater.

In the chronic B.T. group the interval from B.T.(F) to B.T.(R)1 is usually shorter. In both groups (R)1 to (R)2 tends to be shorter than B.T.(F) to B.T.(R)1, and this is most marked in the chronic relapses.

If these statements are not easy to grasp on first hearing, graphs, details and difficulties of assessment, are available to anyone especially interested, and are summarised in the appendix.

On the whole most chronic relapses who had their B.T.(F) in the Autumn got their first relapse in the Spring and then tended to get attacks every month or so.

Criticism of M.R.C. Report

In the Lancet of November 18th 1944 there appeared two statements on Mepacrine for Malaria. One by the American Board for the Co-ordination of Malaria Studies, and the other by an M. R. C.

Committee. It was agreed that Mepacrine could replace Quinine with advantage, altogether, and that loss of world supplies of Quinine was no longer of importance.

The Americans then stated that the effective suppression of Malaria can be accomplished over long periods of time with the proper use of Mepacrine, and without danger; that Mepacrine has been demonstrated to prevent consistently the development of falciparum malaria when administered in proper dosage, before, during and after exposure, and that there is convincing evidence that Mepacrine not only suppresses the clinical symptoms of falciparum malaria but also cures the malignant form.

The British Committee stated that their experiences and investigations lead to the same conclusions as those reached in America and they too stated that Mepacrine if properly given will practically always cure falciparum malaria.

Doubtless there is much truth in these statements and the impression on our minds may have been exaggerated by the urgency of the problems, but in view of our experiences in Italy, these dogmatic statements must be challenged. We have no doubt that Suppressive Mepacrine did in fact fail to prevent the development of Malaria of both types in large numbers of patients, but in view of the fact that no controlled experiment was carried out, it is quite impossible to state what percentage of troops may have been so protected.

At Salerno six M.Os set themselves the task of gaining the confidence of Officers and men from various units with a view to finding out how many of them had in fact taken their suppressive mepacrine. It was explained to the individual that this was not an attempt to find defaulters but to establish a factor of vital medical importance, and that their units would not be reported. Unit discipline, of course, varied but we were all satisfied that most of the patients who had gone down with Malaria about this time had taken regular Mepacrine, and in a few instances had taken considerably more than the amount recommended. An analysis of 250 cases from 25 different units showed that 60% had taken four to six tablets a week for at least the previous four weeks.

It is clear that Malaria occurred in men who took regular suppressive mepacrine, and that M.T. infection even relapsed in some cases whilst they WERE in hospital under observation, and actually having mepacrine treatment. Also, in view of the number of cases of M.T. Malaria which relapsed after or during treatment it cannot be agreed that "Mepacrine practically always cures M.T. Malaria".

This much is certain; M.T. Malaria was the most urgent problem in a large General Hospital for several months during the season and gave rise to much anxiety. Moreover, these cases had been treated with Mepacrine and were being treated, and still relapsed, even on a larger dosage than officially recommended.

Mepacrine Administration

In this hospital, the daily dose of Mepacrine is invariably given in the morning in one dose. This is far easier from the administrative point of view, especially in busy wards where different treatments are being given, and it can be certain that the patient is actually swallowing the correct amount. No ill effects have ever been observed and an impression was formed that the patients re-acted better. Even a full dose of 8 tablets has always been given at one time. It is also most convenient when evacuations are taking place.

Two patients only have shown a real idiosyncracy to Mepacrine. One had intractable vomiting all night after one tablet, and had had this experience before. The other had copious blood stained vomiting apparently due to an acute hæmorrhagic gastritis, and he too had experienced this before. In neither case was there considered to be a psychological factor.

Mepacrine pigmentation was extremely variable. From observation on discharge parade by a number of different people over several months, all were satisfied that Mepacrine does stain the conjunctiva, though to a lesser extent than the skin. In some cases Mepacrine pigmentation has become very marked in a few days, and has persisted for months.

Proposed Scheme for the Management of Malaria in War

All things considered, in an Army at War when the conservation of manpower is essential, would it not be best in a highly malarious area to begin anti-malarial treatment at once in every case of fever, and then continue treatment according to the individual needs of the patient only until he feels fit, when he can return to duty? In most instances such treatment would not be needed for more than a few days. From observations made by selected individuals such as M.Os and experienced Officers who have in fact treated themselves for Malaria and remained on duty, and without apparent ill effect, the incidence of relapse may not be much increased, and at any rate they can be treated at a more convenient time later on.

The total period away from duty in the average malaria patient is considerable and includes the time taken to establish the diagnosis, evacuation to a suitable place for treatment, convalescence such as advised in this theatre of war, and time taken in Transit camps etc., returning to duty. This time was often about 30 days (for a 10 day illness). In the early days when evacuation of most cases from forward units was essential and even from general hospitals was insisted upon, such cases were frequently sent away from the mainland and in these instances the time away from the unit was even greater. Moreover, dislocation of units and absence of key personnel must be taken into account. In Italy, this avoidable loss of manpower must often have amounted to three battalions. A simple organisation such as an advanced Con. Depot, consisting of two M.Os, some tents and minimal staff could have prevented this enforced evacuation entirely. However, as has been suggested, the shortest effective treatment for each acute attack and return to duty may well be a practical proposition, and such an advanced Con. Depot would be a suitable organisation to deal with this.

These remarks do not refer to Malaria as it may occur in other parts of the world nor to what may have happened at some other period in history—but they do refer to what actually happened in Italy during this War.

Finally I would repeat that they cover a wide field and are merely intended to open up the subject and stimulate discussion.

MALARIA

Sept.—Oct. 1943. (SALERNO)

Malaria — Total 640

Quarter Ending 31 Dec. 43.	*October*	*November*	*December*	*Total*
Malaria, Clinical	1174	307	203	1684
Malaria, B.T.	251	100	91	442
Malaria, M.T.	116	96	116	328
	1541	503	410	2454

Quarter Ending 30 Mar. 44.	*January*	*February*	*March*	*Total*
Malaria, B.T. (F)	21	25	96	142
B.T. (R)	28	54	151	233
Malaria, M.T. (F)	5	—	2	7
M.T. (R)	10	9	10	29
Malaria, Clinical (F)	4	2	15	21
Clinical (R)	2	3	8	13
	70	93	282	445

Quarter Ending 30 Jun. 44.	*April*	*May*	*June*	*Total*
Malaria, B.T. (F)	174	142	32	348
B.T. (R)	194	204	69	467
Malaria, M.T. (F)	4	1	—	5
M.T. (R)	4	—	—	4
Malaria, Clinical (F)	28	6	15	49
Clinical (R)	6	1	—	7
Quartan (R)	1	—	—	1
	411	354	116	881

Quarter Ending 30 Sep. 44.	*July*	*August*	*September*	*Total*
Malaria, B.T. (F)	44	73	40	157
B.T. (R)	64	79	55	198
Malaria, Clinical (F)	1	6	3	10
Clinical (R)	3	1	—	4
Malaria, M.T. (R)	—	1	—	1
	112	160	98	370

Quarter Ending 31 Dec. 44.	*October*	*November*	*December*	*Total*
Malaria, B.T. (F)	18	8	16	42
B.T. (R)	69	62	81	212
Malaria, Clinical (F)	3	1	—	4
Clinical (R)	1	—	—	—
Malaria, M.T. (F)	—	—	2	2
M.T. (R)	1	—	1	2
	92	71	100	262

GRAND TOTAL ... 5052

APPENDIX

SUMMARY AND STATISTICS

1. *Introduction.*—Paper confined to observations on 5,000 cases in 92 B.G.H. in Italy in past 16 months.

2. *M.T. Malaria.*—(a) Fatalities—prevention of—diagnosis from Infective Hepatitis.

(b) Relapses — Intervals.

TABLE I

M.T. RELAPSE INTERVALS

Interval	0-14	15-28	29-42	42-56	Days
M.T. F—R.1	18	56	19	7	% of 125 cases
R.1—R.2	42	48	5	5	% of 40 cases

Case Summaries of 3 Chronic Relapsing M.Ts.

(i) Spr. ROBERTS: Re-admitted 4 days after 1st relapse. Treated with one day of Quinine gr. XXX and then 9 days of Mepacrine 0.3 gms. M.T. rings found on 4th, 8th & 11th days and again on 16th day after 2 more days Mepacrine.

(ii) Pte. MARSHALL: Admitted in 2nd. relapse. Given 2 days Mepacrine 0.6 gms and 5 days Mepacrine 0.3 gms. Still Febrile with M.T. rings, then given 5 days Quinine gr. XXX, and 5 days Mepacrine 0.3 gms. Relapsed 13 days later. Given 2 days mepacrine 0.8 gms and 5 days Mepacrine 0.3 gms. Relapsed 4 days later.

(iii) Dvr. ARTHUR: Relapsed (4th attack) after Mepacrine 0.6 X 2 plus 0.3 X 6 and again after Mepacrine 0.8 X 2 plus 0.3 X 5.

3. *B.T. Malaria*—(a) Unexpected Fresh Cases in Mar. Apl. May. 412 cases. Due to suppressive Mepacrine previous autumn.

(b) Behaviour as true Fresh case as regards Relapse. Comparison relapse rate—100 cases B.T.(F) and 100 cases B.T.(R) in Spring from Follow-up cards returned 3 months later.

TABLE II

	CASES	RELAPSED
B.T. (F)	100	5
B.T. (R)	100	26

(c) B.T. Relapse intervals—comparison B.T.(F)—B.T.(R) 1 with B.T.(R) 1—B.T.(R) 2.

TABLE III

Interval	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	MONTHS
BT(F)—R.1	8.1	8.5	7.4	6.8	7.6	10.3	11.7	13	10	7.1	3.9	3.5	1.1	.7	.3	% 710 cases
R.1—R.2	18	21	16	10	7	8	7	6	3	2	1	1	0	0	0	% 193 cases

Distribution affected among other things by shifting Military population and Suppressive Mepacrine.

(d) Chronic B.T. Relapses—Clinical State remarkably good.

TABLE IV

ANALYSIS OF 152 CASES CHRONIC B.T. RELAPSES

No. of Relapses	5	6	7	8	9	10	11	12	13	16	17	18
No. of cases	41	28	28	21	11	8	6	4	2	1	1	1

Sgt. LEE, 2 *Wilts* (*Age* 30)—21 attacks of Malaria in 26 months. After the last attack his general condition was good. Spleen and liver not palpable. H. B. 120%.

Cfm. FALLON, *REME* (*age* 23). *Poor response to heavy treatment.*—5th Relapse treated in N.A. with Quinine and Pamaquin for 17 days and then Mepacrine (0.3) for 19 days and then Mepacrine 0.1 for 30 days. After that he relapsed.

4. *Special courses of treatment*

	No. of cases	*Relapsed*
Intravenous N.A.B. gm. .3, .45 & .6 at 4-day intervals 10 days Quinine gr. XXX and Pamaquin .03 gm.	100	10
Intravenous Quinine gr. V a.m. Intramuscular Quinine gr. V p.m. } 5 days	3	5
Atebrin Hydrochloride 0.4 gms, 2 days & Atebrin Hydrochloride 0.2 gms. 5 days	44	3

5. *Mepacrine administration.*

Reasons for giving daily dose at one time.
Idiosyncracy.
Mepacrine staining of skin and sclera.
Remarks on Suppressive Mepacrine.
No outbreaks till the Spring.

6. *Comments on M.R.C. and American committee's resolution.*

Proposal for shortened treatment of Malaria in a theatre of War.

SOME ASPECTS OF EXPERIMENTAL MALARIA THERAPY

by

Major JAMES INNES, RAMC

I have been asked to talk for a few minutes about the Malaria Therapeutic Research on which I have been engaged since June of last year.

The Malaria Research Team in this theatre was formed by Brig. Boland at the suggestion of the War Office, to investigate the relative merits of a series of therapy courses laid down by the Malaria Committee of the Medical Research Council. The method of assessment of the courses was by daily parasite counts, whereby one course could be compared with another in terms of the numbers of parasites in relation to duration of treatment and dosage of drugs. Five courses were provided for cases of fresh infections, and there were two relapse courses. Cases were started on the various courses in strict rotation and were kept in hospital until the completion of treatment. A follow-up was done where possible.

Work was started at Bone, North Africa and has been continued in Rome since the beginning of last October. The number of cases suitable for investigation in this manner has so far been disappointingly small, being less than a total of 300, so that no definite conclusions can at present be drawn as to the relative value of the various courses. All but 29 of these cases have been B.T. infections. Though the number investigated may seem very insignificant, I would explain that an accurate parasite count takes about half an hour, and that such counts during therapy of 300 cases represent approximately 450 hours continuous microscope work alone so that with one laboratory assistant in the Team, eye strain becomes a definite limiting factor. The parasites are counted against the white blood cells in very thick films and expressed as numbers per c.mm. The accuracy of this method of counting has been compared with other methods and found most satisfactory and though repeated white cell counts are necessary, the actual counting time is as short as with other techniques. Thick blood films are used and stained by a modified Field Leishman stain which ensures complete dehaemoglobinisation of uniform films of up to 1 mm in thickness and this enables very small numbers of parasites to be detected.

The therapy courses all comprise variations of quinine, mepacrine, and pamaquin dosage and from the point of view of initial effect upon the parasites, can be divided into those starting with quinine, or quinine plus pamaquin, and those starting with mepacrine alone. The findings so far indicate that with a few exceptions all the courses result in a disappearance of asexual parasites from the peripheral blood within 72 hours of starting treatment and this time seems largely irrespective of the initial parasite count. Mepacrine dosage appears just as effective as quinine in reducing the initial parasitaemia and has in several cases been shown to be actually "quicker off the mark" than quinine. This is interesting when correlated with the clinical response, which, as has been found by most clinicians, favours quinine as being the more effective drug in the rapid reduction of pyrexia and improvement in the general condition of the patient. The general diaphoretic action of Quinine is probably responsible for this early lowering of temperature, acting independant of its specific parasitidal properties.

As regards curative merits of the various courses, only a follow-up of a large series of cases will provide the necessary evidence, although to date, the few cases of our series, whom I know to have relapsed, have all been treated with Mepacrine.

Arising out of the above main programme of work, have appeared many sideline investigations, some of which have proved interesting and worth following. I would like to say a little about these and show how they fit into the main picture.

It appeared that a daily study of blood films from Malaria cases during treatment might provide some microscopic evidence as to the effect of the drugs on the parasites themselves. It was therefore decided to do differential parasite counts which meant subdividing the asexual forms into various stages of their developmental cycle. 10 Sub Divisions were used representing 6 stages of trophozoite from the young ring form, to the large pre-schizont stage, 3 stages of schizont, and lastly the merocyte stage, just before it bursts to start a fresh cycle. Up to the present about 100 cases have been studied in this way. From such differential counts done on cases of both quotidian and tertian fevers, it would appear that both Mepacrine and Quinine cause a definite slowing in the development of the trophozoites and tend to produce an arrest at the pre-schizont stage. This form of parasite has been observed to persist until late in the course of treatment, being present along with young ring trophozoites which are the next generation offspring of schizonts that have escaped destruction.

As regards the visible changes in the parasites during treatment, three effects have been consistently noted due to Mepacrine. The most striking of these is the bunching up and rounding off of the trophozoite resulting from a disappearance of the vacuole and a collapse of the amoeboid ring form. It is suggested that the vacuole, which is a constant feature of all asexual malaria parasites before segmentation of their nucleus, is concerned with the metabolism of the growing trophozoite. The collapse of this vacuole during treatment may possibly be due to the interference by the drug with the metabolism of the parasite.

The second effect noted is an alteration in the pigment normally found in the asexual parasite. This would seem to result from the collecting together and extrusion of the pigment, and if the latter represents the waste products of parasite metabolism, such an effect might be expected when the metabolism of the parasite is being interfered with. It is this same pigment which is held by many authorities to be the cause of the pyrexial reaction in malaria when it is liberated into the circulation at the bursting of the merocytes.

The third abnormal appearance in parasites during therapy courses is the tendency towards irregularity of their cell outline. The parasites assume a ragged bedraggled appearance and seem to be on the point of cytoplasmic disruption. The latter is almost certainly their fate and they are then phagocyted by fixed or circulating reticulo-endothelial cells, although as previously stated some of the forms seem to struggle on valiantly in the face of a rising level of plasma Mepacrine.

The drug-affected late trophozoite that has just been described resembles very closely the female B.T. gametocyte with which it may readily be confused especially as the normal appearance of the latter is also altered by Mepacrine and the number of circulating gametocytes tends to vary from time to time. These points of microscopic differentiation have presented quite a problem in this work and we are now studying the distinguishing characteristics by encouraging the maximum formation of pre-schizonts by minimal Mepacrine dosage.

The effect of Pamaquin on asexual B.T. parasites, as shown by this differential counting, also appears interesting. When it was found that both Mepacrine and Quinine seemed to arrest the parasite development at the late trophozoite stage, a number of cases, small as yet, were started on treatment with 0.01 gm of Pamaquin T.I.D. for 5 days. This drug appears to be slower in initial action than the others but retards the parasite development without causing a hold-up at any particular stage. Pamaquin is also a powerful schizonticide.

It would therefore seem that Pamaquin would be a very good therapeutic agent in B.T. infections if its initial dosage and concentration could safely be made higher than is at present recommended. I have so far seen very few cases who have shown Pamaquin intolerance, and I would be very interested to hear from others with greater experience of its administration, whether they consider high dosage is safe to employ and also whether they have ever seen it used at the same time as Mepacrine.

The stage in the parasite cycle at which the drugs come into action appears to be of paramount importance in determining the rate of clearing parasites from the blood-stream. The work up to the present shows that Mepacrine and Pamaquin are schizonticides and at the same time exert some side action which tends to delay the parasites from reaching the stage at which they are most easily killed. If, therefore, the drugs could be given too late in the cycle to delay schizont formation and yet be ready in sufficient concentration to catch the schizonts as soon as they mature, they could reasonably be expected to produce the maximum destruction in the shortest time. The total duration of all phases of schizonts is in the region of 12 hours in B.T. parasites and the absorption time of Mepacrine taken orally has also to be considered in such an experiment. Cases having fairly high initial parasite counts and running only one definite parasite cycle, *i.e.* true tertian fevers, are suitable for such a demonstration and so far we have given the Mepacrine by intramuscular injection to ensure absorption in a minimum time. It has been found that, if these conditions are observed, the injection of 0.2 gm of Atebrine dihydrochloride at the late trophozoite stage of the parasite, will produce a complete clearance of a heavy parasitaemia within 12—24 hours and without further therapy. This means that, given to the right type of case and at the right time, the equivalent of 2 Mepacrine tablets can clear a heavy parasite count in less than one day. The clinical effect on the patient is usually to cause an increase in toxaemia with a prolonged cold stage and pyrexia occurring prematurely in a true tertian case, but after the first 24 hours the temperature remains normal.

Up to the present we have only treated a very few cases in this manner and it has only been regarded as an experiment of academic interest to substantiate our deductions about the importance of the stage at which Mepacrine could be expected to produce its optimum action. I feel that it is worth doing more of these cases with Mepacrine plasma estimations to compare with the parasite changes and we are going to try the same work using Quinine. It is obviously not a line of treatment to be advocated for general use as it requires special selection of cases and accurate microscopic parasite-watching for success. It does however show the potency of Mepacrine suitably used, and opens up side-lights on its mode of action and a basis for the building up of rational therapy courses with a wider application. It will be particularly interesting to follow-up these cases and see whether this rapid clearing of parasites during an attack, lessens the ability of the infection to produce subsequent relapses.

The immunity reaction of the host is always of great importance in the control and therapy of malaria infections. Among military cases in this theatre it is uncommon to find B.T. cases with initial parasite counts higher than 20,000 per cu mm, and such figures do not tend to increase even if no treatment is given. When it is considered that each B.T. merocyte usually gives rise to 16 merozoites, each of which is capable of starting a fresh generation in a red cell, it follows that theoretically the parasite count should multiply by 16 times each 48 hours. The fact that the count remains more or less constant implies that the immunity mechanism of the host is able to cope with 15/16 of the parasites without the aid of drugs. Any drug which slows the development rate of the parasites will thus enable the reticulo-endothelial system to control the infection, and in Mepacrine, Quinine and Pamaquin this action appears to be present in addition to their powerful schizonticidal effects.

In relapse cases the acquired immunity reaction is of course greater, so that a larger number of dividing parasites can be kept in check without the production of clinical symptoms, than is possible in fresh infections. An interesting study in this respect is to correlate the duration in days of clinical manifestations, with the first available parasite count. We have found that in general, fresh cases have low initial counts with several days of symptoms, and relapse cases have high initial counts with a very short duration of symptoms. If expressed as a relapse factor "R," obtained by dividing the initial parasite count by the days of symptoms multiplied by 100, it will be found that during the season for fresh infections, these will tend to have "R" values of less than 5, whereas relapse cases have much higher "R" values, *e.g.* 30. This is of course not universally true and

may be complicated by suppressive mepacrine resulting in fresh cases which remain latent and show themselves more like chronic infections after some months of suppression. We have, however, on occasions found this calculation a useful indication as to whether we were dealing with a recurrent or fresh infection.

A further important factor influencing the response to treatment in malaria cases, is undoubtedly the actual strain of the infecting parasite. This naturally varies with the locality in which the infection is contracted and is recognised as determining the clinical picture of the disease and such features as the degree of parasitaemia, the tendency to relapses, etc. There are, for instance, appreciable microscopic differences between the strains of B.T. and M.T. common in North Africa and those met with in Sicily and Italy, and there is evidence that small but important distinctions can be made between strains of parasites occurring in quite closely related localities in the same country.

It would appear, therefore, that there are 4 main considerations which together determine the response to therapy of B.T. malaria treated with Quinine, Mepacrine and Pamaquin, and there are quite likely to be more factors which further study will reveal. The 4 considerations known at present, and which in themselves need much more elucidation are:

(1) The immunity reaction of the host.

(2) The stage of the parasite cycle at which the drug administration is started.

(3) The concentration of the drug attained in the circulation or tissues, and

(4) The strain of the parasite involved.

From October until early in January we were co-operating with No. 1 Field Section of the Malaria Research Unit which came from Oxford to carry out Mepacrine estimations using a photo-electric fluorimeter. In addition to their main work, which was to determine the plasma Mepacrine levels of cases "breaking through" suppressive Mepacrine, we arranged for plasma levels to be estimated during the therapy courses of those cases that we were treating with Mepacrine. It was possible from this work to study the plasma levels attained in the various courses and to compare these with the diminishing parasite counts. The results obtained seem at present inconclusive and more may be required, but there would appear to be little obvious correlation between the plasma Mepacrine level and the rate of disappearance of parasites. In fact, several cases with high plasma levels continued to show parasites throughout the courses. Various associated investigations were done and further work is needed to elaborate this question, such as the whole blood levels, the levels attained by parenteral as distinct from oral administration, etc. It is hoped to continue this work now that we ourselves have the necessary apparatus and special reagents.

Another type of case suitable for study with Mepacrine estimations is the recurrent malaria case who relapses frequently in spite of numerous treatment courses and suppressive Mepacrine. These cases are being sent to us for investigation and in several so far studied there have been findings of very low plasma levels attained on the oral dosage of the standard C.M.F. treatment course. I am not prepared to argue at present as to whether this represents poor absorption, rapid breakdown or excretion, or fixation in the tissue cells. We have given these cases heavy dosage by injection after the oral course and sent them to the Convalescent Depot with a follow up form.

Most of what I have said refers only to B.T. infections which have constituted the great majority of our cases. Our parasite counts on M.T. infections are as yet limited to less than 30 cases studied last summer at Bone, but I feel that even this small number show a point of sufficient practical importance to mention. The parasite figures in fresh M.T. cases were found to follow the temperature charts with a tertian variation, and often with very high parasite counts corresponding exactly with the highest peak of temperature. Thus in cases having a continuous temperature the rise of one or two extra degrees every 48 hours was associated with a most striking soaring up of the numbers of trophozoites in the blood stream which often rose from about 5,000 to 300,000 per cu. mm. within a matter of a few hours and subsided as quickly once the peak of temperature was passed. The best time therefore for liagnostic demonstration of the parasite in blood films was thus at the extreme peak of the pyrexia, when their number was disproportionately high in relation to the temperature. I would suggest that this might be the optimum time for the start of treatment with intravenous Quinine or intramuscular Mepacrine, as then the infection is represented by a great number of circulating young ring forms and there would seem to be much less risk to the patient than when powerful schizonticides are injected to act on the schizonts which in M.T. Malaria lurk in the capillaries of the visceral organs.

Lastly, I would mention that we have studied the sternal marrows of malaria cases, a subject in which I took a very real and almost wishful interest. In Bone our patients were practically all subjected to a sternal puncture so that new arrivals almost regarded it as a routine part of our somewhat unusual treatment. Our results, so far, have been briefly as follows. We have never been able to demonstrate asexual parasites of either B.T. or M.T. malaria in the sternal marrow, when they were not demonstrable in thick films of the peripheral blood. When present in the marrow blood, the parasite count was never found to exceed that in the peripheral blood. The gametocytes of M.T. Malaria were found amongst sheets of marrow cells in several fresh cases on the third day of treatment, that is about three days before they appeared in the peripheral blood. It seems possible that in M.T. malaria the gametocytes may be formed among the cells of the reticulo-endothelial system, of which the sternal marrow is a sample. The initial leucopenia so commonly present in active malaria infections, is shown in sternal marrow smears to result from a maturation arrest at the metamyelocyte stage of the granular white cell precursors. I have searched diligently for any non-pigmented form of parasite that might represent an extra-erythrocytic phase, but have found nothing convincing. Several cases have shown small rounded bodies with red granules, which at first appear rather like parasites and which we called "curious bodies" for want

of a more apt description, but I cannot believe that they are anything but rounded granular cytoplasmic debris from damaged myelocytes, although if photographed they might easily be written up as very convincing extra-erythrocytic parasites.

I have attempted to describe some aspects of our work in Malaria therapeutic research and although so far the ground covered has been very little, I hope that you will agree that some of our investigations are worth continuing. I am grateful for this opportunity to have talked and am looking forward to the discussion and any suggestions or criticism that is offered.

Summary

A brief outline is given of the work of "A" Malaria Research Team*, C.M.F., who are comparing a series of therapy courses of Quinine, Mepacrine, and Pamaquin, by assessing their effects in reducing the parasite counts in the peripheral blood of malaria cases.

The microscopic changes seen in asexual B.T. parasites resulting from the administration of these drugs is described. Mepacrine and Pamaquin are powerful schizonticides and all three drugs produce a developmental retardation in the maturation of the trophozoites. The optimum time for administration of mepacrine is discussed and an experiment in illustration of this is described.

The four factors that appear to determine the rate of disappearance of asexual B.T. parasites from the blood during treatment are discussed. These are enumerated as (1) The immunity reaction of the host; (2) The stage of the parasite at which treatment is started; (3) The concentration of the drug attained; and (4) The strain of the infecting parasite.

A preliminary report is given of the findings of plasma Mepacrine levels in B.T. infections during treatment courses.

It is suggested by a study of parasite counts in fresh M.T. infections in North Africa that the exact peak of the pyrexial phase, is the optimum time for the diagnosis of the condition and possibly also for the administration of parenteral therapy.

The value of sternal marrow examination in the investigation of malaria infections is illustrated by examples and discussed.

MALARIA IN THE POLISH FORCES IN THE EAST AND IN ITALY

by

Major JUSTANOWSKI EUSTACHY, MD - Polish Medical Corps

The Summer of 1942 brought a great spread of Malaria amongst the Polish Forces in Russia. Some units quartered in the middle of the ricefields profusely irrigated. As a result of that, some units were totally infected with Malaria. In Autumn 1942, when the Polish Forces were transferred to Iran and later to Irak, I was appointed to arrange and carry through anti-malarial measures in the Forces.

My first step was to make a list of all men who were subject to infection during the two preceding years according to their history. They underwent standard treatment in the Winter 1942/43. However, there were many relapses in the Spring 1943.

The main features of the disease were as follows:—

(1) Relapses were usually mild.

(2) As the troops were stationed in Irak, which was a malarious country, part of the relapses should be considered as re-infections.

(3) The units where treatment was carried out accurately, and attention paid to 10-days rest, the number of relapses was half as large as those where the treatment was carried out less thoroughly and soldiers under treatment had to take part in training.

(4) In spite of numerous relapses, enlargement of the spleen was generally slight.

(5) Anaemia and cachexia occurred rarely, and as a passing complication.

(6) Malaria does not now exist in the Polish Forces. There are no chronic cases left by the epidemic. We do not know how much of our success in this fight with Malaria we owe to the nature of Russian Malaria (Genius Epidemicus), but, in my opinion, treatment of the patients without clinical symptoms, and not based on clinical observation, brought good results. We called that kind of treatment, "cold treatment". I intend to propose further experiments of this kind in the Winter period. Units, or groups of units, with the equal numbers of cases of Malaria during the last Summer should be chosen for the experiment. One group should undergo in Winter a course of treatment, the other should be left for comparison. During the next summer, the following points should be observed in both groups:—

(a) Number and features of relapses excluding possibly the cases of re-infection.
(b) Enlargement of the spleen with periodical estimation of the spleen, read possibly by one Medical Officer for both groups.
(c) Blood films should be examined, even of small parties, for example, fifty persons of each group.

The comparison of the results of the examination of both groups could give valuable material for setting down principles for our future dealing with Malaria in the Armed Forces. Treatment of large numbers of relapses compelled us to organise camps for Malaria patients. Mild and medium cases were treated in those camps, the grave and complicated were evacuated to General Hospitals.

* Now designated "No. 2 Malaria Research Team."

Well-trained laboratory workers examined in those camps blood slides of all patients. The examination was done immediately after the arrival of the patients, and, if the result was positive, treatment began at once. Patients with clinical symptoms and negative blood slides were evacuated to General Hospitals for further observation. Only cases with positive blood slides were treated in the camps. The camps sent out to Army units advanced teams for taking blood slides. Nearly all soldiers of the Polish Army in the East had their blood examined. Nearly a hundred thousand blood slides were examined in the laboratory of only one main camp. All soldiers with positive blood slides were treated.

Final deduction cannot yet be drawn. The verifying experiment as proposed above is still necessary. Theoretical grounds for "cold treatment" needs still more work and studies.

As regards the choice of the routine course of malaria treatment, we have to face the fact that, like in the specific treatment of Syphilis with Arsenic and Bismuth compounds, there is no routine treatment which gives the certainty of cure after only one course of treatment. Even such doses as 18 grms of quinine and 30 tablets of pamaquine in ten days will not always kill Malaria parasites in the patient's blood. Quick diagnosis, immediate and accurate treatment, climatic conditions and general diet are all very important. Even a very simple measure, like pouring out water on the hospital tents in Iraq, gave distinctly good results when this group was compared with the other when this was not done.

To end, please, if any experiments concerning above discussed problems will be carried out in the British and Imperial Forces, I would be most grateful for kind information about the results.

Major-General M. C. Stayer then declared the subject open for discussion.

DISCUSSION — Malaria

Colonel Perrin Long, M.C.

I was very much interested in the experience the British had in the questioning of individuals becoming infected with Malaria from the Salerno region. In July and August, at the time of the invasion, we had set up a mobile laboratory down there. We handled about 300 cases of fresh and relapsed cases of malaria in the Salerno area during that period. As soon as patients came into the unit their blood was taken and the Atebrin level determined. They were questioned as to whether they had taken suppressive therapy, 90% said "Yes." Roughly 60% showed inadequate levels of suppression, 6% were well below the suppressive level and there were very few instances in which they were near it. The results were taken back to the Medical Officer in charge and the patients were told that nothing was going to happen if they told the truth, and they then admitted that they had not been taking Atebrin. I would not believe a soldier's statement in that qualification but if you show him he has not been taking Atebrin by explaining how its presence or absence is determined, and explain a little about its pharmacology, the American soldier will generally "come clean"; some admitted they had taken a couple of tablets a week, some none, and that explains the findings. I am convinced that often a man is supposed to be taking six tablets a week, and he is not really taking them.

In the South-West Pacific early in 1942 there was a terrific rate of Malaria relapse. The men were all then trained in the taking of Atebrin. They were put back in a highly malarious area, and, as far as I am aware, well disciplined battalions went through without having an appreciable amount of Malaria. That is true of other units in the South-West Pacific, and once you have convinced everyone of the need for taking Atebrin you get that discipline. If all the tablets are taken there will be very few cases of Malaria.

Brigadier E. R. Boland.

Suggestions have been made that the treatment of Malaria is too long. A perfect treatment for Malaria has not been found, and all treatments have been rather disappointing. But bearing this in mind I must say that the standard treatment is on the whole satisfactory and a very large number of people are treated rapidly and returned to duty. In this theatre the treatment has been reduced from 13/15 days to 8 days. Colonel Turner says that it is a pity that these cases are not treated forward, but in actual fact, one of the reasons so few cases have been filtering through to the base is that they have mostly been treated in forward areas. We could probably cut treatment shorter without increasing the number of relapses and the treatment adopted in this theatre has already cut the period from 13/15 days and enables them to return to duty in 7/8 days. I do not see why a man who has had a primary attack of Malaria should be off duty for less than 7/8 days or even up to a fortnight. I think there is a limit to the brevity of treatment for Malaria. If a man has been ill, has had a high temperature, and constitutional disturbance, he should be off duty for a reasonable period. I know very well, if I cut treatment to one day, supposing I could do it, and return the man to duty on the third day, that no one would thereafter be allowed to be off only on account of Malaria for more than three days. I think one has to keep a sense of proportion.

As regards the treatment by Plasmaquin, Major Innes has said, and it has been pointed out that Plasmaquin also kills Schizonts. Whatever theoretical gain, in time, there may be by eliminating Plasmaquin from the scheme of treatment, the fact remains that in a large series of cases the percentage of relapses in people taking Plasmaquin was less than those who were not, and as Major Innes has emphasised in his address, the toxicity of Plasmaquin has been greatly exaggerated. The original treatment in M.E.F. was 3 days Quinine, 5 days Atebrin, 2 days free period, and then 3 days Plasmaquin. This interval was considered necessary because of the danger of combining Mepacrine and Plasmaquin. Later on the interval was increased to 3 days in M.E.F. because it was thought too dangerous for them to take Plasmaquin so soon after taking Atebrin. In this theatre I was proposing to cut out the interval altogether at the time when this decision was come to, but I left the period at two days rather than appear to move in the opposite direction. In actual fact we find there is no necessity to have this interval between Mepacrine and Plasmaquin and no interval is recommended in this theatre. The

number of toxic reactions was small in the Middle East in any case; I think they had had only six cases in all. Recently the War Office has recommended treatment for Malaria relapse which involved taking large doses of Plasmaquin over a long period in combination with Quinine, and although I expected a large number of toxic reactions, I am bound to say we had hardly any.

I am getting rather out of focus on Plasmaquin, there are lots of other subjects which I am sure you will wish to discuss.

Colonel J. K. Boyd—Consulting Physician, NZEF

I do not propose to deal with the clinical aspect of Malaria but I would like to tell you the practical experience of our New Zealand troops. In spite of the fact that right through the Malaria season our troops have lived constantly in malarious and in highly malarious districts, Malaria has been no problem to us at all; we have had 30,000 troops, and less than 50 cases of Malaria. We had no active Malaria precautions except nets, etc. We have to admit, and we often hear, that New Zealand troops are slack. The New Zealander does what is good for him. He appreciates that fact and sticks to it. Perhaps if other troops did the same, we would not have to spend so much time discussing them.

Lt.-Col. S. Alstead, RAMC

I am particularly interested in the cases of Plasmaquin poisoning mentioned by General Stayer. This series has particular interest and instruction in the light of our own experience, because I take it that the subjects of the experiments in that series were allowed to pursue their normal work. I gather that Plasmaquin was not issued to them at meal times, and that they carried out heavy work. I think it may be that the toxicity on the one hand was due to their undertaking vigorous exertion, and the lack of toxicity on the other hand in the ordinary therapeutic use is due to the fact that the patients are in bed or at least not working. One other point regarding Ascoli's diagnosis. A large number of his observations are based on general impressions and accordingly are unreliable, and the time has come to apply to this technique experimental methods which Major Innes has described.

Lt.-Col. A. Willcox, RAMC

I am not very certain what to think about the subject of Malarial Dysentery. The cases we had last summer were originally started on a course of Sulphaguanidine. They did not respond. It was a complete surprise when the first few cases were found to have a positive M.T. smear. I was not prepared for M.T. dysentery at that time of the year. They had responded very dramatically to Quinine. I think myself that these cases were not dysenteric infection, but were true Malarial Dysentery. I should like to have other opinions on this question.

Lt.-Col. C. B. Prowse, RAMC

I was interested to hear the previous remarks on Plasmaquin. It may be of interest to you in case you don't know that the standard German treatment seems to include a very considerable amount of Plasmaquin. I have heard of a case of a man in a P.W. hospital in Algiers who had what he called "Standard German Treatment," but I cannot say that it is 100% true. He started with 5 daily injections of Atebrin intramuscularly, follwed by Plasmaquin 3 tablets daily for 9 days. He then had 3 days rest from drugs, after which a further course of Plasmaquin 3 tablets daily for another 6 days. It is certainly a considerable quantity of Plasmaquin. I do not know the results, but Germany seems to do these things pretty well, and seems to have no doubt about giving Plasmaquin. A further point is one in connection with what Major Innes has said regarding the time in which Atebrin might be most effective. But I think in his discussion he suggested that Atebrin would be most effective if given in the early stages, at the same time perhaps our enemies have got on to this too if they are giving 5 doses intramuscularly as part of their routine course. I may say this man had had 14 relapses since July, 1943, so the Germans have their troubles as well as ourselves. He was captured in Salonika, and came to us looking like death. I have never seen anyone looking more like a ghost in my life, but since he has been in a British hospital he has shown no inclination to relapse in spite of having our therapy.

Lt.-Col. W. L. Ackerman, RAMC

Has any British Military Hospital treating Malaria relapses used Ascoli's treatment? I have not tried it. His theory is that relapses are due to parasites remaining in the spleen, unaffected by the usual anti-malarial treatment. By giving adrenalin, the corpuscles containing the parasites are expressed into the general circulation, where they are acted upon by the schizontocidal immune bodies. He gives increasing doses of adrenalin intravenously. For the first few days quinine is also given.

I have visited his clinic in Palermo, and his results appear impressive. I would be interested to know if there is any well founded objection to testing his treatment in our Military Hospitals. I have sometimes found subcutaneous adrenalin useful in the diagnosis of malaria. For example, I have a Nursing Officer as a patient at present, complaining of general malaise with no clinical findings or pyrexia, who showed B.T. Malarial parasites ¼ hour after adrenalin, when 4 earlier blood slides had been negative.

Lt.-Col. D. C. Macdonald, RAMC, spoke enthusiastically about Professor Ascoli's treatment of malaria by daily intravenous injections of adrenalin. The latter bases his treatment on the fact that the spleen is a reservoir of red blood cells where the malarial parasites lie in large numbers; that it is a contractible organ, and by contracting floods the general circulation with red cells; and that the stimulus for that contraction is supplied by the medullary hormone of the suprarenal glands. His supposition is that the natural protective power of the blood plasma of destroying parasites is nearly absent from the spleen and therefore they flourish and multiply. From time to time they reach the general circulation and cause symptoms when the stimulus for splenic contraction arises. If, however, the spleen is kept contracted by adrenalin, all the red cells in the spleen are thrust into the general circulation to be destroyed by the natural protective power of the plasma. Quinine is only given when there is a rise of temperature and then only in small doses.

Great success is claimed for this treatment and obviously a great saving of expense on drugs like quinine and Atebrin which Lt.-Col Macdonald states are dangerous because they are tissue destroyers and cause liver damage. Besides this they do not cure Malaria for neither of them has any effect on the parasites in the spleen.

Colonel Perrin Long, M.C.

We have been talking about Professor Ascoli's treatment of malaria. He knew little of the pharmacology of Quinine in his methods of determination of the therapeutic effect of Quinine. There is no reason to suppose this has not been developed since 1941. It is interesting to note that the concentration of Atebrin in the spleen runs from 47,000 times that in the blood.

One of our hospitals, the 59 Evacuation Hospital, had an extensive experience of Ascoli's method of treatment of Malaria for several months. At first there was much enthusiasm before reports came in of relapses, and the conclusion was reached that it was not more beneficial than any other type of treatment.

Lt.-Col. J. H. Hutchison, RAMC.

When my hospital opened up in December, 1942, in North Africa, we had no experience of Malaria. Within a few days we got an American pilot with M.T. which he contracted in West Africa. He did not seem very ill. We gave him 30 grains by mouth, and in spite of intravenous quinine he went into a coma. That case frightened us so much that we decided that future cases of M.T. Malaria would be given parenteral Quinine. He would be given 10 grains intramuscularly unless there was any change when it would be given intravenously. We have done that ever since, and we have had no deaths. Very frequently you are working with Medical Officers with no experience of Malaria, and who have just come out from England and this routine precaution is of the more value.

Colonel Perrin Long, M.C.

I would like to point out that in the first 8 months of 1944 our statistical forms showed 29,000 cases of Malaria and Clinical Malaria. There were two deaths in that time, one M.T., which was not recognised, the other B.T. who died of a ruptured spleen. I think this is rather interesting because in 1943 we had inexperienced Medical Officers in so far as Malaria is concerned, and we had less than one death per 1,000 diagnosed cases of Malaria. We did not then have the designation of Clinical Malaria. I think it is a tribute to earlier recognition and earlier intensive treatment that, although in 1944 we were dealing with far more B.T. and with far more relapsing Malaria than in 1943, yet according to our standard figures at home we could expect one death from Malaria in 2/500 cases, depending on the area. It seems that the record in 1944 has been excellent.

Major J. G. O'Sullivan, RAMC.

In the 1943 Malaria epidemic in Bone, the troops concerned were almost entirely fresh from U.K., without previous exposure to tropical disease. A large number of these with severe M.T. Malaria showed dysenteric stools, none of which yielded a positive culture for B. dysenteriae. I had a patient in Italy (1943) admitted with sub-normal temperature (96.6F), jaundice, frequent dysenteric stools and a heavy M.T. infection. He was put on intravenous quinine-saline drip and improved in the first 4—5 hours. His condition then suddenly deteriorated and presented signs of internal hæmorrhage. He was given 2 pints blood and improved quickly, to die suddenly later in the night. Autopsy showed a large quantity of blood in the caecum and colon with roughening of the mucosa; there was an ulcer with a bleeding point in its base in the terminal ileum.

Another point with reference to mepacrine. I am surprised that no one has referred to the change in clinical features of malaria seen in 1944 from that seen in 1943. I have noticed in 1944 a marked infrequency of the acute febrile picture, and an increase of low grade fever with vague ill-health, and have attributed the change to the action of increased weekly mepacrine dosage (0.6 gm. 1944—0.4 gm. 1943). I would be interested to know if my colleagues have noticed this change. On the other hand relapse in malaria under treatment usually occurs in 3rd or 4th mepacrine day and is quickly controlled by the addition or substitution of quinine. This variance in the value of oral mepacrine is probably due to different degrees of absorption and therefore blood-level as mentioned by another speaker. I hope today to hear more observations on the variation of mepacrine action.

Lt.Col. G. Slot, RAMC.

The danger of overlooking Typhoid Fever is sometimes present in cases sent in as Malaria or Dysentery. I remember a Flying Officer who was admitted in the Spring of 1943. He was sent in as a Dysentery patient as he had had Diarrhoea for 10 days previously. His very large spleen was thought to be due to an associated Malaria. He ran a temperature of 103°-105° all the time he was in hospital and a Blood Culture the day after admission proved positive for B. Typhosus. Before this he had a course of Quinine and Sulphaguanidine. He died from a fulminating Typhoid Fever confirmed by autopsy.

I have seen cases of Dysentery in Malaria. It is an uncommon complication. The patient passes pure blood in the first few days of the disease.

Atebrin does not cure Malaria but only suppresses it in some cases. I have seen a number of patients who have developed Malaria and whom I am quite certain have taken their prophylactic Atebrin conscientiously.

I have had patients who have been suppressed by Atebrin presumably and who have developed fresh Malaria in the early part of the year before the Anopheles are about. I have also had cases who have developed attacks during treatment, often at the end of the course. It is probable that these cases have not developed a high blood Mepacrine level. Cases of Malaria developing in Madagascar and Persia seem more difficult to cure and more likely to relapse than corresponding cases of Malaria contracted elsewhere. These strains would seem to be more resistant.

With regard to malarial discipline. I remember how a medical officer friend of mine was inspecting his unit about Mepacrine time and found that the

first man had none, the second had none either, nor the third; the fourth had about a hundred tablets, when asked about this large supply, he said that they had been playing poker!

Lt.-Col. J. G. McCrie, RAMC.

I wonder whether, in stressing that malaria may be present with dysenteric symptoms which do not clear up until anti-malarial treatment is started, Lt.-Col. Willcox was referring to M.T. or B.T. cases. The text books seem to describe dysenteric malaria as an M.T. manifestation. Though in North Africa a large number of patients admitted with dysentery were found to have B.T. malaria, I always thought of the two as being coincidental infections.

In connection with the question of whether "Spring" cases of malaria represent infections acquired during the previous autumn, the point has been mentioned that patients did not remember being bitten by mosquitoes during the winter. In my experience, patients rarely do seem to remember being bitten. The bite of an anopheline seems to be stealthy and painless, perhaps through thin clothes and rarely appreciated by the person bitten.

Brigadier E. R. Boland.

Malarial Dysentery appears to be having a prominence in this discussion out of all proportion to its relative importance. I believe there is perfectly good evidence that dysenteric symptoms can be produced as a result of malarial infection alone. Possibly Colonel Montgomery may give us information about this, but the only important thing to remember in this context is that some severe cases of M.T. present with symptoms suggestive of Dysentery, and if that fact is remembered cases are unlikely to die in the dysentery ward untreated.

Col. G. Montgomery, RAMC.

I am sorry I missed the early morning papers, I heard Brigadier Boland suggest I might say something about Malarial Dysentery or Dysentery due to Malaria. I do not know exactly what he meant by that statement, it is certainly not on my personal experience. In Italy I have seen very little of it. I think we should keep a thoroughly even keel. It is true that through P.M. examinations cases are described where there is some congestion of the intestinal tract, and the capillaries there are filled with parasites of M.T. Malaria. Whether or not these parasites are the cause of Dysentery it is difficult to say. It is obviously possible to get blockage of capillaries and consequently dysenteric signs, and perhaps dysenteric smears, but you must bear in mind that a great many of the reported cases have occurred in people who have a high basic immunity though they are not native people. They may have Malaria parasites in their blood in large numbers without their being responsible for their condition. That is one point. Another point we have to bear in mind is that very many of these cases of so-called Malarial dysentery were described before modern methods of bacteriological examination came into being. I feel that we should not accept a diagnosis of Malarial Dysentery unless modern bacteriological methods have been applied. It is a point we have to bear in mind and upon which we should keep a very even outlook. Whether or not this course might influence treatment is another matter altogether. There is one further point I might mention, the question of time interval between death and post-mortem. If post-mortem is delayed for some time after death, the intestinal capillaries become congested and thus you may have a large number of parasites collected there. I have no personal experience of this. I have seen one or two of Malaria associated with Dysentery, but only people with practical experience can speak with authority on the subject.

I should like to take this opportunity of congratulating Major Innes on the work he has done, and the manner he has presented it this morning. I have had frequent opportunity of seeing his work and I was very impressed with the way he went about it, particularly from my point of view, in that he set about first of all to establish an extremely high level of technical work. I have never seen more beautiful preparations than those which he has made. When a man sets about putting his work on that basis something is going to come of it. We have heard this morning what he has done on two or three very interesting lines of work, which I am sure will lead to something further. I shall not take up any more time, but I do want to pay this tribute to Major Innes; it has been a great pleasure to see his work develop in this way.

Summing-up by Opening Speakers

Lt.-Col. A. Willcox, RAMC.

The question of Malarial Dysentery has been well dealt with by Brigadier Boland and Col. Montgomery. I was very glad to hear Col. Hutchison's strong defence on the use of parenteral quinine in M.T. infections.

I was particularly interested to hear that Col. Turner gives his unusually large dose of mepacrine in one dose and that it stays down. I think that would be extremely useful.

Lt.-Col. James B. McLester, M.C.

We have discussed malaria at considerable length, but very few seem to have followed up to see whether or not the treatment was successful. We had an idea that certain little alterations in the standard form of treatment might be of benefit.

Major J. Innes, RAMC.

I have had no experience of Ascoli's treatment of malaria. I took half a dozen cases with a very large malaria spleen and X-rayed them, and continued to take X-ray photographs at about 10-minute intervals. The large spleens contracted to about a quarter of their size in 10 minutes and remained contracted for one to two hours. I am afraid I take a perverted attitude to malaria discipline, if too good, I might find myself out of a job.

Monday, 29th January, 1945

AFTERNOON SESSION

Subject: SHORT PAPERS

Presiding:

Brigadier E. R. Boland, Consulting Physician

Allied Force Headquarters.

WAR WOUNDS OF THE HEART

by

Lt.-Col. PAUL WOOD, RAMC

First, I wish to express my thanks for the honour you have done me in asking me to open this discussion; second, and in the same breath as it were, I would like to say that I feel unworthy of it, for I have only seen eight of these cases. In the series of 25 now presented, the great majority belong to Major Nicholson, who has most generously placed his material at my disposal.

In civil life we are more or less familiar with the various effects of cardiac trauma, as from direct and indirect blows, crush injuries, etc. These are not considered here. The present series deals entirely with injury from high velocity missiles, *e.g.*, bullets, and fragments from shells, mortars, bombs, etc., and in a very minor degree with stab wounds. Injuries of this kind may be classified into six groups:—

1. Near misses.
2. Grazes or tangential wounds.
3. Perforations.
4. Pericardial foreign bodies.
5. Myocardial foreign bodies.
6. Intravascular foreign bodies.

1. *Near Misses* (4 cases; fragments, 0.5—1.5 cms. diam).

The fragment entered the left thoracic wall posteriorly in all cases: in three, it lodged in the left lower lobe of the lungs, within ¼—½ an inch of the heart, where it showed transmitted pulsation; in the fourth it settled under the arch of the aorta.

Pericardial friction was heard within the first three or four days, and lasted 1-4 weeks; effusion developed in one, tachycardia in another, and praecordial pain in a third. An electrocardiogram taken on the 11th day in one case was said to be normal.

The foreign bodies were not removed, and the pericarditis settled down without incident in all cases. Two patients were observed for two months, and two for six months, and all remained well.

It is concluded that a near miss may cause early pericarditis which settles down without incident. From the cardiovascular point of view there is no need to remove a foreign body close to the heart.

2. *Grazes or tangential wounds* (4 cases; one bullet, 3 fragments, 0.5—3 cms).

It seemed highly probable, considering the site of the entrance wound, and the position of the foreign body, that the latter had grazed the heart in four instances.

All developed early pericarditis, lasting 1—3 weeks, and in three there was an effusion proved to be haemopericardium in two of them. One died on the 7th day, probably from cardiac compression, the venous pressure being elevated, and autopsy showing hæmopericardium and a tangential wound of the right ventricle posteriorly.

An electrocardiogram was taken in two cases and showed normal Q.R.S. complexes and simple inversion of the T waves in all leads. This type of graph may occur in all forms of pericarditis, rheumatic, tuberculous, malignant, pyogenic, or traumatic, whether there is effusion or not. I have called it elsewhere the pericardial T 2 pattern.

Of the three which survived, two patients recovered without further incident, but the third developed a sudden recurrence of pericarditis with effusion during the seventh week. There was fever, praecordial pain, considerable distress, tachycardia, gallop rhythm, and pericardial friction followed by effusion. An electrocardiogram showed the classic pericardial T 2 pattern just described. The attack, during which the patient was very ill, lasted about 10 days and then subsided spontaneously. A small foreign body was then discovered just below the diaphragm close to the right border of the vertebral column. There were no further incidents. This was the only case (of three which survived) in which the foreign body which grazed the heart lodged within a few cms. of it.

It is concluded that grazing wounds of the heart or pericardium cause early haemopericardium, which may kill by cardiac compression, or which may subside without incident. It would seem that surgical intervention, to relieve tamponade and to prevent further haemorrhage by suturing, might save cases which would otherwise die of cardiac compression. Paracentesis alone might be effective in a limited number of selected cases.

Attention is directed to the peculiar behaviour of the case which developed a second and later attack of pericarditis with effusion. This phenomenon, recurrent pericarditis, will be discussed in more detail later.

3. *Perforations.*

It might be thought that perforation of a cardiac chamber would prove rapidly fatal. In fact it is not always so. Just before the war an Italian was stabbed three times in the heart at White City Dog Stadium in London. He was taken to St. James' Hospital, Balham, where he arrived in a shocked and practically unconscious condition. Mr. Gissone saw him there and operated as soon as possible. He found a large haemopericardium and blood was spurting from three perforating wounds in the right ventricle. To facilitate exposure and suturing he inserted his forefinger through each of these perforations in turn, so that with the tip in the right ventricle he was able to hook the heart upwards. I saw this patient a day or two later, and was privileged to watch a remarkable and uneventful recovery in a matter of a few weeks. Serial electrocardiograms revealed the usual pattern and behaviour associated with haemopericardium. There are some two dozen similar cases in the literature, from which it may be concluded that perforating cardiac injuries are not always fatal, but may be successfully repaired in certain cases if the surgeon is quick enough.

In a second case in this series the position of the entrance and exit wounds strongly suggested a through and through perforation of the heart. There

was early pericardial friction and effusion, and bilateral haemopneumothorax, but the patient settled down without incident, and made an uninterrupted recovery in a few weeks.

4. *Pericardial Foreign Bodies* (7 cases; fragments; 0.5—3 cms).

In seven cases a foreign body was retained in the pericardium, or was sticking into it from without. The position of the entrance wounds suggested that myocardial damage was either absent or slight and of the grazing variety. In all cases, the foreign body was anterior or lateral to the heart: it was situated in the cardiophrenic angle in four, over the left ventricle towards the apex in two, and at the base between the right auricle and pulmonary artery in one.

Early pericarditis with friction and effusion was noted in two cases. The foreign body was removed on the 17th day in one of these, and the other is still under observation.

Delayed or recurrent pericarditis with effusion developed in three others, one on the 17th day, one on the 80th, and 102nd day, and one about three months after the date of the injury. These attacks were associated with fever, praecordial pain and distress, and with marked tachycardia; they lasted about 10 days or rather less. Electrocardiograms were taken in three cases and showed the characteristic T 2 pattern.

It may be remembered that a similar kind of incident was recounted in one of the cases in group 2, when a foreign body grazed the heart and lodged close to it, just below the diaphragm. Of the three in the present group, one was evacuated, and two had their foreign bodies removed in a quiescent phase, and have remained well since.

In the 6th case the foreign body was really outside the pericardium, in a pad of fat at the right cardiophrenic angle. It caused no trouble in five weeks when it was successfully removed. At operation it was seen to press against the right auricle during diastole.

In the seventh case the foreign body lay in the groove between the right auricle and the base of the pulmonary artery, on the surface of the right ventricle close to the right coronary artery. There were no incidents until the 55th day, when there was an attack resembling coronary thrombosis. The patient was taking things easily at a dance when he experienced a gradually increasing retro-sternal pain, radiating through the shoulders, down both arms to the wrists, there was associated dyspnoea and distress, and the pain lasted about two hours. An electrocardiogram taken four days later was normal. The foreign body was then successfuly removed, but no note was made as to the state of the right coronary artery. It is thought that the attack represented right coronary thrombosis without myocardial infarction.

It is concluded that pericardial foreign bodies are a menace. They may cause late and recurrent pericarditis with effusion, and if suitably situated they may cause coronary thrombosis. Of the four cases left alone, and observed for longer than six weeks, all went wrong. The presence or absence of early periocardial signs gave no guide to future behaviour. As these patients are critically ill during their attacks, removal of the foreign body if reasonably accessible, during a quiescent phase, would seem desirable. However, we do not yet know what would finally happen if they were left alone. Perhaps only one or two attacks would occur, and experience might prove them less dangerous than they appear. Nor is it absolutely certain that their occurrence depends upon a foreign body in the pericardium, or somehow connected with it, for the case in group 2 might have another interpretation, and as will be seen subsequently, one certain case and two possibles, occurred in association with myocardial foreign bodies.

5. *Myocardial Foreign Bodies* (4 fragments up to 1.5 cms., 3 bullets) 7 cases.

Four were in the left ventricular muscle, two in the right, and one was in the right auricle.

Five had early pericardial friction and effusion, proved to be due to haemopericardium in two cases, and one of these was noted to have signs of cardiac compression.

Two developed praecordial pain and a peculiar murmur which varied with respiration on the 17th and 30th days respectively. These two attacks were of doubtful significance, but may have represented the movements of a bubble of air between the heart and chest wall. In the last war they were known as "pericardial knock", while Scadding and I described them in 1937 as "systolic click", and showed that they were due to a small left sided pneumothorax.

The foreign body was removed from just under the surface of the left ventricle in one of these cases.

The final prognosis of a bullet left in the heart is well illustrated by a case seen by MacKenzie and Prof. Grey Turner in 1917. At the time an attempt was made to remove it, but it could not be located when the heart was exposed. Electrocardiagrams were taken by MacKenzie, and it is of some historical interest that he regarded the inverted T waves shown in all leads as within normal limits. I have seen these graphs, and they reveal the typical pericardial T 2 pattern. I saw the patient with Prof. Grey Turner in 1938, twenty-one years afterwards. The bullet was still there, and appeared to be embedded in the interventricular septum. The heart was normal in size and shape, limb and chest lead electrocardiograms were normal, and the officer was symptom free.

One case developed three severe attacks of pericarditis with effusion at approximately monthly intervals. This was S/Sgt. Michael, whom I saw at the 96th General Hospital, Algiers, early in 1943, and whose history has been well written up in one of the more popular American papers. As far as I could see, a bullet was lodged in the anterior wall of the right ventricle, and may have encroached upon the pericardium. The attacks were just like those we have associated with pericardial foreign bodies, and were characterised by fever, praecordial pain, pericardial friction, rapidly developing effusion, collapse of the left lower lobe, tachycardia, and great distress. Col. Churchill saw this case for us, and advised conservative management. He was evacuated to the States, and a note from him several months later indicated that he was then alive and well. He enclosed some recent electrocardiograms which were normal in all respects.

It is concluded that myocardial foreign bodies cause early haemopericardium, with or without cardiac compresion. They are less likely to prove

troublesome afterwards than pericardial foreign bodies, and it is possible that when they do, they may project into the pericardium. The last case described is of especial interest because it settled down without interference, yet the three attacks of pericarditis with effusion were the most severe I have yet seen. It is also evident that a foreign body in the wall of the heart may be successfully removed if it is in an accessible position. The right treatment remains uncertain.

6. *Intravascular Foreign Bodies.*

In two cases in the series the foreign body was thought to be whirling around within a cardiac chamber. This may or may not have been true, but if so it finally came to rest, and did not leave the heart. It is certain, however, that a foreign body may be intracardiac or intravascular, and may appear first here, and then there. As Churchill has said — "if there is an intrathoracic foreign body but no thoracic wound, think of intravascular foreign body". I have no experience of their behaviour.

So much for this series. No doubt there are other complications and manifestations of cardiac wounds from missiles, but we have had no experience of them. Major Nicholson will describe some of these cases in much greater detail, especially with regard to the operative procedure, and the post-operative course. I hope, too, he will fill in many of the gaps I have inadvertently left.

Summary and Conclusions

1. Cardiac wounds are not necessarily fatal, whether the agent grazes the heart, causes tangential injury, perforates a chamber, lodges in the heart or pericardium, or passes right through the heart.

2. If death is not immediate, early manifestations are due to hæmo-pericardium. The decision to operate and repair the wound should rest upon evidence of increasing cardiac compression, *i.e.*, upon a rising venous pressure. If there is no tamponade the immediate treatment should be conservative.

3. Early pericardial friction and effusion are common to all types of cardiac and pericardial injury, and may even occur with near misses.

4. Recurrent attacks of pericarditis with effusion, and sometimes without, may occur at any time up to three or four months after the wound. They seem to be a special feature of pericardial foreign bodies, or of foreign bodies elsewhere which project into, touch, or irritate the pericardium, or which are in some other way connected with it. Patients may appear very ill in these attacks, but none died. Seven such cases were seen in all. Four finally settled down without intervention, and three after successful removal of the foreign body. The evidence leaves us uncertain whether it is better to remove it, if accessible, or not.

5. Coronary thrombosis may occur if the foreign body is close to a major vessel. It would seem wise to remove such a foreign body before rather than after an attack.

6. When phenomena of the kind described occur in a patient with a thoracic wound, it is necessary to screen the heart, for cardiac foreign bodies may easily be overlooked in skiagrams, or indeed they may be invisible. This was so in several cases in this series.

7. Electrocardiographic changes are nearly always of the T 2 pericardial pattern, which appears to dominate any minor change which might be due to a local ventricular lesion. They are helpful, however, in proving the existence of abnormal pericardial events.

EXPERIMENTS IN DIPHTHERIA IMMUNIZATION

by

Lt.-Col. S. ALSTEAD, RAMC

The purpose of this brief communication is to invite your attention to the graduated Schick Test. The method is perfectly simple: the ordinary technique is adopted, but in addition to full strength Schick Test toxin, weak solutions are also used— ½ strength, ⅓ strength and ¼ strength. Positive results are further classified as strong, moderate or weak. One advantage of this procedure is that it provides a rough estimate of the degree of susceptibility. It is appreciated that this information is more accurately determined by laboratory methods, but these are not practicable for the clinician, especially under active service conditions.

In assessing the reliability of the graduated Schick Test, experiments were carried out to determine the consistency of the results. It was found that "sets" of positive reactions were repeatedly consistent in their relative intensity when performed at intervals over a considerable period, *e.g.*, 40 days.

The importance of this observation is twofold: first it indicates that the amount of toxin contained in the equivalent of 8 full-strength doses of Schick Test toxin does not act as an antigen which might invalidate the last results of a series; and secondly, these findings show that even ¼ strength toxin solution "keeps" for up to 10 weeks if it is stored in a refrigerator.

An obvious application of the graduated Schick Test in clinical research is to determine the potency of various antigens as immunizing agents. In the customary practice of using only full-strength toxin, it is necessary to wait for several months before an effect can be demonstrated. Using the graduated Schick Test, however, I was able to show that fol-

lowing the injection of 1 cc TAF intramuscularly, the rising concentration of antibody had "extinguished" a ¼ strength Schick positive reaction in six days and had converted a *moderate* positive reaction at ½ strength into a *weak* reaction. This result was confirmed repeatedly, and there can be no doubt that the method lends itself to the rapid determination of the optimum dosage and spacing of injections of immunizing agents.

The ease with which diphtheria toxin penetrates granulation tissue in ulcers infected with KLB suggested to me that it might be worthwhile to attempt to immunize susceptible subjects by the percutaneous route, using toxoid in a suitable ointment base. A mixture of lanoline and olive oil was prepared and TAF was incorporated lightly into it at body temperature. Three weekly inunctions were ordered, first using small doses of TAF, but later working up to 15 cc over a period of one week. No immunizing action could be demonstrated after 3 weeks in six men, nor after six months in two of them who were re-tested. In all cases the ¼ strength Schick Test remained positive.

Another application of the graduated Schick Test consisting in assessing the value of absorbents in preventing the absorption of toxin from wounds or ulcers infected with KLB. A direct approach to the problem was obviously out of the question, but the clinical conditions were initiated by dressing ulcers with an ointment containing TAF and noting the effect on the graduated Schick Test series. Subsequently, in other cases, 5% of activated carbon was incorporated into the TAF ointment and the effect of this addition was studied in the same way. As judged by the absence of any change in the intensity of reaction of the Schick Test at ¼ strength, it appeared that the activated carbon did in fact prevent any immunizing action of the TAF applied to the ulcer surface. Unfortunately, however, the number of suitable cases did not permit of furnishing satisfactory controls for this experiment. In any case, even if these results are confirmed, it is unlikely that they will ever be more than of academic interest.

Finally, in the reading of the graduated Schick Test—as with the ordinary test—there is an important phenomenon which is a fruitful source of fallacy unless it is carefully borne in mind, namely, the reactions of latent immunity. It has long been recognised that a positive Schick reaction does not necessarily mean that the individual is not immune. Sometimes, if the test be repeated after an interval of about one week, it is found to be negative. The interpretation of this which is generally accepted is that latent immunity exists and a positive reaction is obtained in the first test because the subject is, so to speak, caught off his guard. The minute amount of toxin contained in the preliminary test dose suffices however to sensitise his immunity mechanism, and by the time the second test is done sufficient antibody has been mobilised to render the Schick Test negative. This phenomenon was seen in about ten per cent of the subjects tested. It was suspected when, after the preliminary positive reaction at full strength, the weaker dilutions produced disproportionate reactions, *e.g.*, an unexpectedly negative S/3 and S/4 reaction. Confirmation of latent immunity was then obtained by repeating the test at full strength.

Summary

The technique of the graduated Schick Test is described and its advantages are mentioned as a time-saving method in carrying out clinical research on various aspects of diphtheria immunization.

FATTY DIARRHŒA

by

Lt.-Col. T. G. ARMSTRONG, RAMC

Fatty diarrhœa is not a common occurrence in this theatre of operation but when it does occur it necessitates long and continued treatment in hospital and a high proportion of these cases finally require evacuation to the U.K. Certainly a number of cases are overlooked because the Medical Officer in charge of a busy dysentery ward is sometimes not sufficiently wide awake to the implications of a putty-coloured stool even if formed and, strangely enough, the appropriate treatment of fat free diet is often started only very late. Early diagnosis is very important, for at least a percentage of these cases can be permanently cured if treatment is started early enough.

In the short time available it will not be possible to discuss the relationships of this condition to Sprue and idiopathic steatorrhœa both of which it closely resembles. I think the best thing is to describe the usual picture seen in this command and then press on to a brief description of its relationships and the results of treatment.

The condition may start acutely with a bacillary dysentery or it may have an insidious onset without blood or mucus ever been passed in the stools. About half the cases appear to start with an initial dysentery. I have never seen amœbic dysentery as a precipitating factor but it has been recorded in India. It is interesting that in 3 out of 11 cases recently seen the condition started while on board ship when the patient was coming out to the Mediterranean theatre from England.

The almost invariable complaint is that the patient is woken during the night often just before dawn to go to the lavatory. He passes a bulky, pale, porridgy stool and returns to bed often to be woken again perhaps 3 or 4 times. On the whole the majority of the stools are passed during the night but he is not usually exempt during the day. Quite often there

is a complaint of alternating constipation and diarrhœa, the stools sometimes being solid but always pale, and the patient may go for 3 or 4 days without a bowel action and then be woken several times a night for a few days. There is usually quite a considerable amount of colicky bellyache and much flatulence. These patients lose a great deal of weight and they become listless and demoralised and very easily bowel conscious—a difficult thing to avoid in a condition which depends for its diagnosis and assessment of treatment on careful attention to the stools.

In addition to these general symptoms vitamin deficiency states occur in a proportion of cases. Of the 11 recent cases, 10 complained of a sore tongue at one time or another and 4 had an angular stomatitis. The soreness of the tongue is by no means always due to vitamin deficiency though it certainly may be and can then easily be proved by its specific response to injectable vitamins. The soreness of the tongue is often a very fluctuating condition and may come and go without any relation to treatment. It is then usually of the aphthous type and small areas of denudation of papillæ will be seen set on an otherwise normally furry tongue. This condition is, of course, quite different from the general denudation seen in nicotinic acid and riboflavin deficiency which I will come to later.

Macrocytic anæmia was seen twice in the eleven recent cases and though definite was not very severe. As might be expected it responded to diet and liver therapy without a reticulocytic response owing to its relative mildness. The red cells did not fall below 3 millions.

No skin changes or neurological abnormalities attributable to vitamin deficiencies were seen.

Achlorhydria to Histamine was never seen in the cases that were investigated.

A glucose tolerance test was done on two cases. In one a completely flat curve was found, the other was normal.

The stools varied greatly. In some of the earlier cases the stools changed from day to day and were certainly not always fatty. They were always mushy or porridgy, but one day would produce a brown undigested stool with much identifiable food matter, while the next day a putty-coloured, obviously fatty stool would be passed. In those who always passed fatty stools they would sometimes be porridgy and sometimes formed like the solid stools seen in infective hepatitis. The typical frothy stool of sprue I have seen only once, and it is certainly not common. Owing to the tedium of estimations of fat content and the chronic overwork of the laboratory staff, but few estimations of fat have been done. Like the appearance of the stools, the fat contents varied from day to day in the same patient, and I have seen as wide variations as 5% to 48% in the same patient on different days. It is not all stools that look fatty that contain a high proportion of fat! From the practical point of view microscopy of the fæces for excess of fatty acids crystals is all that is required for diagnosis. It is simple and conclusive and throws no strain on the laboratory staff.

Apart from Giardia Lamblia which is almost invariably found, no parasites of any importance have been encountered in the stools. Contrary to some other reports I have not found Lamblia of any ætiological consequence. They are secondary invaders, for their destruction has no effect on the course of the disease. One case did show amœbic cysts, but appropriate treatment disposed of the cysts, leaving the steatorrhœa intact and unchecked.

The clinical picture is therefore quite clear cut and investigations have little or no place in its diagnosis except for academic purposes and for hazarding a guess at its ætiology. The Radiological side is interesting. It was pointed out by Brailsford and by Hurst that the normal feathery appearance seen in the small intestines following a barium meal is replaced in idiopathic steatorrhœa and tropical sprue by dense flocculating opacities sometimes apparently filling complete segments or loops of the small intestines. This appearance is also seen in the steatorrhœas occurring in this theatre and the appearances seem to be identical with that of sprue. In all the cases investigated no evidence of intestinal hurry has been found.

The tongue has in certain cases shown all the characteristics of both Riboflavin and nicotinic acid deficiency. The riboflavin deficient tongue is typically "magenta coloured" and quite smooth and rather atrophic but without any fiery red inflammatory reaction. I had occasion in Egypt to see many hundreds of cases of a pure ariboflavinosis in P.O.Ws. on a riboflavin deficient diet and I have seen identical tongues which responded quickly to riboflavin intramuscularly amongst these fatty diarrhœas. The fiery red tongue not often seen in pellagra is almost certainly a combination of the two deficiency conditions and is occasionally seen in this fatty diarrhœa, though it seems to be more common in sprue. The picture in circulation shows the tongue of one of these patients with a highly magnified picture of the central area of the tongue in the top left hand corner. The general appearance of the tongue is very faithfully shown in the picture. In the enlargement, note the absence of the filiform processes on the extremely flattened papillæ. This should be compared with the normal microscopic appearance of the tongue papillæ placed beside it. It is worth noting that the earliest vitamin deficiency change is a loss of filiform processes from the papillæ. This can only be seen with strong magnification. It is a very early diagnostic sign. During parenteral riboflavin and nicotinamide therapy these papillæ were observed to grow larger and finally sprout bud like projections which later became fully developed filiform processes. This reaction to vitamin therapy effectively establishes the reality of deficiency in this disease. The reaction is exactly similar both macroscopically and microscopically to what is seen in pellagra and riboflavin deficiency during parenteral vitamin therapy.

Pathogenes

In a paper written in 1942 Sir Arthur Hurst reviewed the present knowledge of fat absorption and its relations to idiopathic steatorrhoea and tropical sprue. Very briefly he states that with the aid of cinematography the villi can be seen to shorten and lengthen while food substances are passing over them. Their contraction squeezes out of the central lacteal of the villus the split fat and glycerine which has been taken up by the epithelial cells and passed on to the central lacteal. The pumping action of the villus is dependent on the activity of the muscularis

mucosae which is attached to the basement membrane of the villi themselves. Paralysis of the muscularis mucosae, which is activated by Meissner's plexus, results in inertia of the villi and an absence in the normal folding of the mucosa of the small intestine and disappearance of the valvulæ conniventes. This is of course, the explanation of the radiological findings.

The normal stimulus to Meissner's plexus which causes contraction of the villi is the passage of food. It has been shown that a substance of unknown composition named villikinin is present in acid extracts of the duodenum and is the normal stimulus to movements of the villi. A substance closely related to the vitamin B. complex which is however neither B1 nor B2 but is present in crude yeast and liver also causes contraction of the villi and may well be the same as villikinin. Thus the presence of another deficiency appears necessary to explain the syndrome. Certainly neither nicotinamide nor riboflavin have any demonstrable action on the intestinal symptoms. Manson Bahr, however, disagrees with this last statement. Crude yeast by mouth is equally ineffective, but I have thought that liver either in crude extract by injection or raw by the mouth has been of assistance.

Personally I doubt if this is the whole story. I am not really convinced that the condition is entirely dependent on the inertia of the villi. I am very struck by the absence of bile pigment in the stool and I feel that investigation of this side of the picture might well show that there is some deficiency of liver secretion as well.

Sir Arthur Hurst defines sprue as a disease with:

(1) Excess of split fat in stools.

(2) X-ray flocculation.

(3) No P.M. changes in the gut.

The resemblance of these cases to sprue and idiopathic steatorrhoea is very close. I do not myself believe they are identical. The stools are not frothy or offensive like the typical sprue stool. The disease is not generally so severe. In some cases when taken early it is completely cured and indeed permanently cured, by relatively short spells of fat free diet. After two months or so the patient is again able to eat fat without return of his symptoms. Occasionally, it recovers spontaneously. This condition may certainly be an early stage in the development of sprue and perhaps those who know sprue well might say it was. It would be interesting to know how many cases from Middle East and C.M.F., where sprue itself is not considered to be endemic, have been confidently diagnosed in England as "Tropical Sprue" after evacuation home. There is another condition, however, which has a much closer resemblance to the complaint seen out here—namely Hill Diarrhœa described by Manson Bahr as occurring in Europeans on their visiting the hill stations after living in the hot lowlands of India. It has been described as occurring in the highlands of Africa, New Zealand and Southern Europe. It appears to be associated with the low barometric pressure of mountainous districts and high water vapour content and is a complaint of definitely seasonal incidence. He describes it in the following words:—

"Without very obvious cause the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning sometimes between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious: very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half-a-dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience".

Manson Bahr states that hill diarrhœa is in a proportion of cases, a precursor of sprue. He gives as an effective treatment a strict milk diet.

Treatment

It would seem platitudinous to say that these patients should be given a fat free diet. It is quite often overlooked and I must confess at one time I thought myself that it was hardly rational to treat a symptom only when the underlying cause remained untreated and at large. Moreover the standard books on Tropical Medicine do not stress the importance of a strict fat free diet. In fact, Manson Bahr recommends in the acute phase of sprue 3 pints of fresh cow's milk daily; the Army Memorandum on Tropical diseases suggests 6 to 7 pints daily in certain phases. Manson Bahr also recommends 150-300 mgms of nicotinic acid daily stating that "The fiery redness of the tongue in advanced sprue tends to fade in 24 hours and is normal in 3 to 4 days. The diarrhœa ceases within 4 days without the aid of artificial drugs and the stools become normal in size and colour after 2 to 3 weeks. Under this treatment strict and prolonged dietetic precautions are no longer necessary".

If a fat free diet was given with good effect and then withdrawn, it would be unlikely that the patient would then be able to tolerate fat in normal amounts. For this reason most of my early patients were treated with a light low residue diet with added yeast and liver and vitamins by mouth. The results were very poor. The early patients whom I saw last year were nearly all suffering from vitamin deficiencies and I felt that one possible cause of the impotence of Vitamin treatment was the inability to absorb them. I therefore wrote home for injectable vitamins—nicotinamide and riboflavin—and in the interval before their arrival, I wrote to Sir Arthur Hurst for any information he could give me on this condition. The inevitable reply was "Have you tried a fat free diet". The answer was "No!" In a paper of his dated 1942 he quotes the case of a boy of 8 with 6 years history of severe cœliac disease commencing on board ship returning to England from Burma. He was given a fat free diet and responded at an amazing rate. After 3 months he was able to walk and after a year was playing normal games. After a year he was still on a fat free diet and was still upset by a single egg. Normal food caused a return of sprue symptoms. 13 years later in 1940 he was passed A.1 for the Army.

There is no doubt that this is a most effective treatment. Cases that have been ill for many months regain their health completely and put on weight

rapidly. But the strange thing is that at any rate in early cases 6 to 8 weeks of fat free diet is sufficient permanently to cure the condition—the patient can then return to a normal diet without suffering any ill effects. It must be realised that the normal fat free diet in use in military hospitals is quite inadequate. It is designed mainly for cases of Infective Hepatitis who are going to subsist on it at most for a week or ten days and is insufficient both in quantity and quality. The diet should be strictly fat free and should contain extra carbohydrate and extra protein. Meat, fish or cheese should be given with every meal and sufficient bread or potatoes to satisfy completely the patients desire for food. Raw or lightly cooked liver when available, if given to the extent of about ¼ lb. daily is, I think, really useful. Yeast should also be given. Multivite tablets even in large doses have not given satisfactory results and I have no idea why. Riboflavin, nicotinic acid and liver, preferably a crude extract, such as Campolon, which is very difficult to get now, are I am sure very useful particularly for replacing deficiencies which are not easily absorbed by the gut. If treated in this way many of these cases will respond and should be re-employable in a lower category after 6 to 8 weeks or even less. Officers are much easier as they can to some extent control their diets after discharge. The more serious cases will require evacuation home as their chances of relapse on Army diet are high.

In conclusion, there are one or two outstanding questions which appear to be as yet unanswerable. I would welcome any suggestions.

(1) Why does dysentery, a disease in the acute phase entirely of the large bowel later give sequelæ which are clearly due to small bowel disfunction?

(2) Why do some patients continue to pass pale stools—although not fatty—for some time after the institution of a fat free diet when there can be and is no fat in the stool?

There is an obvious deficiency of bile pigment in the stools.

Is this of any significance?

(3) Why does a short bout of fat free diet cure the disease as well as the symptoms?

DISCUSSION—Foreign Bodies in the Heart

Major J. W. Litchfield, R.A.M.C.

At 98 (Br) General Hospital we have had about 20 cases which fall into this group. We have had two cases which we have not quite understood and which probably fall into Col. Wood's group of "near misses". One case had pericardial friction and left ventricular dilatation which were associated with fever persisting from four to five weeks. He had a foreign body in the right lung about an inch away from the heart. He gradually improved, his heart returning to normal size and he is now perfectly well. The second case had a large foreign body in the left lower lobe and was found at autopsy to have a pericarditis.

We lost one case when early pericardiotomy was performed for what proved to be a cardiac foreign body, but apart from this case we have removed a number of pericardial foreign bodies without trouble.

There have been two or three patients with intracardial foreign bodies who developed pericardial friction and gallop rhythm and then made a gradual recovery, and I would like to mention one case, at present in hospital, who developed right heart failure and generalised œdema and has made a good recovery.

We have seen two intravascular foreign bodies—a small one in the auricle which we left and one in the axillary vein which was removed. We have not seen cardiac tamponade occur.

I would like to know what Col. Wood thinks the correct time for operation in these cases. My own feeling is that one should put off operation for at least two or three months.

Lt.-Col. Hayward has done the electrocardiographs on our cases and might like to tell us about them. I think Col. Wood has been misled about the Yugoslav and that the story is apocryphal.

Lt.-Col. G. W. Hayward, N.Z.M.C.

I agree with Lt.-Col. Wood that the electrocardiographic changes in wounds of the heart are usually those of the T_2 Pericardial pattern. In one patient the foreign body had lodged in the wall of the left ventricle, and no E.C.G. changes were seen at all.

Major W. R. Nicholson, R.A.M.C.

Only one or two points I wish to raise. First in answer to the question of time of operation. I agree that in general the longer you wait for the patient to settle the better, but the first problem we were confronted with was a patient who had a recurrent attack on the 80th day, another attack on the 100th day. It seemed reasonable to suppose that he might have one on the 120th day. Colonel Wood saw him and advised that we operate before the next expected attack and we only waited 10 days after he was settled after the second attack before operating. The other case on which I operated on was on a foreign body in the ventricle which Colonel Wood has already described. There was a weird noise which no one could define. Operation was indicated in any case because this patient not only had a right sided empyæma but also an infected pericardium which raised the question of when infection had set in. As Colonel Wood suggested the foreign body was removed. He eventually recovered and as far as I know is alive still.

THE DIAGNOSIS AND TREATMENT OF KALA AZAR

by

Lt.-Col. M. L. ROSENHEIM, RAMC

I feel very diffident at opening a discussion on the diagnosis and treatment of Kala Azar, for my experience of the disease is small. During the past year I have been fortunate enough to see five cases in the C.M.F.—three primary and two by transfer from other hospitals. You will appreciate, therefore, that I was rather loath to accept Brigadier Boland's invitation, but I will try to give a brief survey of the disease, in the hope that the subsequent discussion may add some new facts to our knowledge of the local aspects of the disease and its treatment.

While Infantile Kala Azar has long been recognised along the Mediterranean Littoral, and occasional adult cases have been reported from Malta and elsewhere, the occurrence of cases among British troops in Sicily and Italy came largely as a surprise. The disease has, fortunately, not proved common, but most hospitals have now seen cases. Malta, Sicily, Southern Italy and Greece are all potential sources of the disease. Of the five cases I have seen, three were in British troops, one almost certainly Sicilian, two probably Italian in origin. Of the remaining cases one was a Greek boy, aged 15, evacuated from Greece, the other was an African native. I have not heard of any proven cases arising during the North African campaign, and Kala Azar was never a major problem in the Middle East though series of cases occurred among troops in the Sudan, and the disease is not uncommon in Southern Abyssinia and Northern Kenya. The Sudanese Kala Azar is a somewhat different and resistant form of the disease and I hope that someone present, perhaps more nearly a "python" than myself, may have had some personal experience of these cases. The disease is, of course, widespread in certain parts of India, especially Assam and Madras, where considerable epidemics occur and where many of us may yet gain personal experience.

Kala Azar may be defined as a chronic protozoal infection of the reticulo-endothelial system, for it is in the cells of this system in the spleen, liver, bone, marrow and, to a lesser degree, in the lymph glands and the skin, that the parasite is mainly found. In these organs the parasite appears as the intra-cellular Leishman Donovan body, which I need not describe in detail. This Leishman Donovan body, in certain culture media, becomes a flagellate organism, a change which it also undergoes in the body of its intermediate host, the Sandfly.

It is now fairly well established that Kala Azar, as is Cutaneous Leishmaniasis, is spread by the phlebotomus, for not only does the geographical incidence of the disease closely follow the distribution of certain species of phlebotomus, but these sandflies can be infected by biting human patients and naturally occurring infected sandflies have been found. The transmission of the disease to human volunteers by the bite of an infected sandfly has recently been reported from India, where five volunteers were thus infected, the disease appearing 5-6 months after the infection. It is probable, though by no means certain, that certain mammals such as the dog in Sicily and the hamster in China may be secondary hosts or reservoirs for the parasite.

In the C.M.F. the disease has been met only as sporadic cases. It is important that its occurrence should always be borne in mind, for it is a disease that is readily diagnosed if thought of, while its often insidious onset and prolonged course may allow cases to become far advanced before the diagnosis is made. Some such undiagnosed cases have reached the UK, while, owing to its long incubation period, other troops have developed the disease only after their return to the UK. The exact incubation period is unknown, but is probably a matter of months. In the five human volunteers, the first cases appeared within 5-6 months of the infection. The disease is often insidious in its onset and even an apparently acute febrile commencement may be a relatively late manifestation of a symptomless illness.

The clinical picture is that of a chronic infection of the reticulo-endothelial system—a remittent and relapsing fever, with progressive enlargement of the spleen, often of the liver and occasionally of the lymph glands, with a progressive leucopenia, secondary anæmia and increasing cachexia, the whole disease span being measured in years rather than months.

The onset may be dramatic or slow and insidious. One patient, whom I saw in Sicily, had an acute onset with rigors and sweating, running a remittent fever for some ten days and being extremely ill. He had concurrent B.T. malaria, but his temperature was unaffected by quinine. His spleen was enlarged 2 f.b. below the Costal margin when first seen. Another British patient was admitted with a history of loss of weight and general weakness for three months, had been ordered to report sick by his officer and found to have a large spleen and liver with a low grade pyrexia. At the other extreme the Greek boy gave a history of only three weeks fever and shivering attacks, but was emaciated, anæmic and incontinent of fæces on admission, with a hard tender spleen enlarged almost to the umbilicus.

In the typical progress of the disease, the primary fever, after several weeks, gives way to a remission, often with clinical improvement and this is followed by irregular pyrexial periods, reminiscent of the Pel-Epstein form of chart or suggestive of undulant fever. Much has been made in the literature of the double rise or double crisis of the daily temperature. I have not seen a typical example of this. With the progress of the disease, the spleen becomes permanently and progressively enlarged. Kala Azar will produce a very large spleen though no bigger than those found in chronic malaria. Later in the disease the liver becomes enlarged and the lymph glands may be involved. The disease is progressive, emaciation and cachexia increase and the patient though often remarkably undisturbed by his disease, gradu-

ally goes down hill, succumbing usually to an intercurrent infection. Spontaneous recovery has, however, been described.

To this clinical picture of remittent fever with hepato-splenomegaly certain laboratory findings must be added. Leucopenia with a relative, though not absolute, lymphocytosis is an almost constant finding, though it may not be marked early in the disease. In four of the five cases, a leucocyte count of less than 3,000 was present before the diagnosis was finally made, but the initial counts in four of the patients was over 4,400 and in one case was 5,800 though only 45% of these cells were polymorphs. With this leucopenia is associated a gradually increasing secondary anæmia.

There are two further means by which the laboratory may assist in the diagnosis of Kala Azar, by the actual demonstration of the infecting organism and by certain serological reactions.

The Leishman Donovan bodies may be demonstrated in the tissues of the patient. Occasionally the diagnosis is made by finding the parasite in blood films, but more usually sternal or splenic puncture is required. Sternal puncture is a simple and safe procedure and should invariably be done in any patient in whom the disease is suspect. In four out of the five cases that I have seen, the parasite was, at some stage, found in the sternal marrow. I have never performed or seen a splenic puncture and, personally, would fight shy of doing one. While perfectly safe in expert hands, it has certain definite risks and I believe repeated sternal are preferable to a splenic puncture.

Leishman Donovan bodies can be cultured, in their flagellate form, on certain media, and the diagnosis can sometimes be confirmed by culture either of the blood or material from a sternal or splenic puncture. While citrated blood has been used for culture, the best medium is the N.N.N.—Novy, McNeal and Nicolle—medium containing rabbit blood. A slope is used and the organism is best found in the fluid of condensation. Culture is difficult except in specialised laboratories and I should be interested to hear whether any special media is available at the Central Path. Lab., and whether positive cultures have been obtained in the C.M.F.

If the organism cannot be demonstrated, its presence can often be recognised by the occurrence of a positive Formolgel or Aldehyde Test. In order to do this test a drop of commercial formaline is added to about 1 c.c. of the patient's serum.

Demonstration of Formol-Gel Test

In the course of minutes or hours the serum jellifies and then becomes opaque. In a strongly positive reaction this solidification and coagulation occurs very rapidly. If opacity occurs, the test is diagnostic of Kala Azar but minor changes of solidification of the serum have been reported in advanced tuberculosis, leprosy, trypanosomiasis and Egyptian splenomegaly. A more important point, however, is that a negative Formol-gel test does not rule out Kala Azar. It is not positive early in the disease and it should be repeated at intervals if a negative result is obtained. The test may be negative in quite advanced cases and a recent series reported by Napier, the test was positive in only 74 out of 100 cases in all but two of whom the parasite was demonstrated by punctures or culture.

I have no experience of the Chopra test in which a 4% solution of 'urea stibamine or stibamine glucoside is layered on to some of the patient's serum with a resultant heavy flucculent precipitate. This test is said to be about as reliable as the Formol-gel reaction, both probably depend on the alteration in the globulin albumin ratio that occurs in the disease.

With the characteristic clinical picture, with the leucopenia and with these laboratory aids, Kala Azar is not a difficult disease to diagnose. In its early stages it is almost invariably mistaken for malaria, either acute or chronic and an attempt made to treat the patient with quinine. It is important to remember that the two diseases often co-exist, and, even if malarial parasites have been found, the persistence of fever after the exhibition of quinine should always lead to further investigation. The remittent and relapsing fever may suggest the possibility of enteric, undulant fever or lymphadenoma while the considerable enlargement of the spleen may also suggest the latter disease, leukæmia of chronic malaria. Egyptian splenomegaly due to visceral schistosomiasis may occasionally be met in Native but is unlikely to come under consideration in British troops. Even in England the diagnosis of splenic anæmia is often made as a last resort and it should certainly never be entertained in the C.M.F. unless Kala Azar is one of the diseases that have been excluded. It is not necessary to labour the question of differential diagnosis further if the possibility of its occurrence is borne in mind, Kala Azar should rarely be missed.

Treatment

The original treatment of Kala Azar with tartar emetic has now given way to two very effective methods of treatment:—

a. With pentavalent antimonials.
b. With the new synthetic aromatic diamidine drugs.

1. *Pentavalent Antimonials.*

The British preparation — neostam-stibamine glucoside is the drug most generally used in this theatre. Other similar preparations of antimony are neostibosan, urea stibamine and solustibosan.

Neostam is given intravenously as a 5% solution. The powder must be freshly dissolved each time and the injection given slowly. It is not possible to lay down a standard course of the drug for the amount required will vary with the weight of the patient, the severity of the disease and the response to treatment. Usually between 2.5 and 4.0 grams are given in the course of 4—5 weeks, an injection being given every second day, starting with 0.05 or 0.1 g., increasing the dose by 0.05 g., each time until the dose of 0.3 g. is reached. Fifteen injections usually constitute a course of treatment.

The patient should be kept in bed. Nausea, vomiting, urticaria and other minor symptoms may occur following the injection. Laryngeal spasm with severe coughing may prove troublesome, but this responds readily to adrenalin. Using the above doses the

only ill effect observed has been occasional vomiting after the injection. Neostam is stated to be contra-indicated in pneumonia, nephritis, jaundice and ascites but no reason is given for this assortment. Neostam is a very efficient form of treatment but is not invariably successful, the Sudan form of Kala Azar, especially, being antimony resistant.

2. *Stilbamidine.*

The diamidine drugs were recently introduced by the Liverpool School of Tropical Medicine and have proved effective also in the treatment of trypanosomiasis. In addition to stilbamidine, used in the treatment of Leishmaniasis, pentamidine and propamidine are members of this new class of therapeutic agents.

Stilbamidine—M & B 744—diamidino-stilbene has proved very successful in the treatment of Kala Azar and cases resistant to antimony have responded readily to this drug. Stilbamidine was originally placed on the market as the dihydrochloride, but this proved difficult to dissolve and the drug is now issued as the isethionate, a more soluble compound. The dosage of this new compound is 50% higher than that of the original dihydrochloride, though containing the equivalent amount of active base. It is important therefore to make sure which form of the drug is supplied, further, this difference in the two products, makes it difficult to assess the exact dosage used in reported series of cases.

The following course of treatment—in terms of the new derivative—is based on the recommendation of Napier in '42 but again no standard course of the drug can be laid down. Starting with an initial dose of 40 milligrams, this is gradually increased up to 150 mg. or more, never exceeding the maximum single dose of 1.5 mg. per 1 lb. body weight. A course again usually consists of 10-15 injections which may be given daily or on alternate days. The course may be repeated after an interval of 7-10 days. The drug is given intravenously as a 1% solution, i.e. the required dose is usually dissolved in at least 10 ccs. of water. Intramuscular injection can be used but it is painful. The drug must be freshly dissolved and used within two hours of solution, since solutions of stilbamidine become toxic on exposure to light. The water should be neutral or faintly acid, otherwise turbidity may occur. Of 100 cases treated in India by Napier with this drug, ninety-eight were cured and two died. Of the cures two relapsed. This is an excellent result but unfortunately there were certain toxic effects. The immediate reactions following the administration of the drug are troublesome and may be alarming, though apparently free from danger. About one quarter of the cases had severe reactions, half mild reactions while the remainder were not wholly free from unpleasant sensations. These subjective symptoms flushing, breathlessness, giddiness, faintness, nausea, vomiting and occasional collapse are usually transient and appear to be associated with a marked drop in blood pressure. The reactions can be controlled by adrenalin and the preliminary administration of small doses of adrenalin is said to prevent their occurrence.

More serious are the late, and probably cumulative, toxic effects of the drug. Diamidino-stilbene neuropathy occurred in 17 of 104 patients treated with the drug. The symptoms, confined almost entirely to the face, first made their appearance 3-4 months after completion of the course of treatment. The main features were paraesthesiæ and anæsthesia, sometimes dissociated, in areas supplied by the trigeminal nerve with an absence of nerve lesions elsewhere. The condition is not dangerous to life and tends slowly to recover, but is troublesome and unpleasant. Peripheral neuritis and paraplegia are also mentioned by the manufacturers, but no reference to this has been found in the literature at my disposal. Hepatitis has also been described as a late toxic manifestation, but this may well prove to be the virus hepatitis which so frequently complicates other forms of intravenous therapy.

With our present state of knowledge, as in an area where the disease is not antimony resistant, stilbamidine should, in my opinion, be used only if neostam has failed or is not available. If it is used the suggested doses should not be exceeded and antimonials should not be given to the patient while he is receiving stilbamidine.

There remains but one point to discuss. How does one know when a patient is cured? This is, apparently a matter for prolonged observations. The Greek boy whom we were able to keep in hospital for nearly four months, first had a course of 3.75 g. of neostam, at the end of which though clinically improved, afebrile, and gaining weight, his spleen was still grossly enlarged and a Formol-gel test positive. He then had a course of 1.625 g. of stilbamidine, during which his Formol-gel became negative. At the time of his discharge, he was afebrile, had gained over two stone in weight, his white cell count had risen from 2,850 with 34% polymorphs to 7,700 with 46% polymorphs and his Formol-gel test was negative. The spleen was still easily palpable, though it had become somewhat smaller. Further sternal puncture was not considered justifiable. This patient had thus responded excellently to treatment, but whether he is permanently cured, only observation over a period of months can tell. It is for this reason that it has been recommended that all cases of Kala Azar should be returned to the UK.

Summary

A short account is given of the distribution and ætiology of Kala Azar with special reference to the incidence in C.M.F., followed by a discussion of its clinical course and of the laboratory aids to diagnosis. The treatment with pentavalent antimonials and with the new synthetic diamidines is described.

KALA AZAR

by

Major D. D. KEALL, RAMC

Among a small series of cases of Kala Azar which Lt.-Col. Willcox and I saw last year in Algiers, there were two in which treatment was very difficult, and in which sulphadiazine had an unexpectedly beneficial effect. After briefly discussing the treatment of Kala Azar I propose to describe our experiences with these two cases.

The most widely used drug is antimony in pentavalent form. There are many preparations, and some which have been used with success are stibosan, neostibosan, urea stibomine, and stibamine gluconate (or neostam). Sodium antimony gluconate (or solustibosan) has the advantage that it can be dispensed in solution and, with experimental animals, it is claimed that an oily suspension is capable of sterilising a Kala Azar infection with one dose.

The mode of action of the antimony is uncertain. The therapeutically effective preparations are said to be inactive in vitro, and an action of the cells of the reticulo endothelial system is suggested.

Pentavalent antimony has proved itself a very satisfactory drug for the treatment of Indian and Chinese Kala Azar, but the Mediterranean and Sudanese forms are more resistant and results have not been so good.

In recent years certain aromatic diamidines—stilbamidine, propanidine and pentamidine have been found to be active in Kala Azar. Stilbamidine has proved very effective in India and has given moderately good results in the Sudan, but it has certain disadvantages. Solutions become toxic if exposed to sunlight, and apart from this complications are not infrequent.

Immediate reactions associated with a fall in blood pressure are common, and may be very alarming. They can be controlled with adrenalin. Hepatic and renal drainage, polyneuritis and paraplegia may occur. A late complication involving the trigeminal nerve has been described in no less than 17 cases out of 104 in a series treated in India. Three to four months after the completion of treatment subjective sensory disturbances of face appear. There is a dissociated anæsthesia with loss of light touch, but normal pain sensation in variable parts of the fifth nerve area. The lesion is considered to be in the principle sensory nucleus of the fifth nerve. It tends to recover slowly.

Blood transfusion is sometimes of great assistance in treatment. In one case there was apparently no improvement after 8 injections of neostam, giving a dosage of 1.4 gm. A transfusion of one pint of fresh blood was given and after 48 hours the temperature fell to normal and improvement set in. It was considered that the blood had contributed to his beneficial response to antimony.

My first case, a man aged 25, had been treated for four months in another hospital before he came to us. The essentials of the history and previous findings were as follows. He was a life-long bronchitic, but apart from this had had no serious illness until he was suddenly taken ill with fever and headache on 24th January, 1944. He was admitted to hospital the next day, and during the next four months he had four bouts of irregular remittent fever, the first subsiding spontaneously after 16 days and the other three only after sulphadiazine had been given. Both the liver and spleen were markedly enlarged. W.B.C. counts were between 6,300 and 8,000, with polymorphs in the region of 5,000.

Seven blood cultures were done and of these 5 were sterile and two grew staph aureus, suggesting a diagnosis of staphylococcal septicæmia. Other features of the illness were severe bronchitis accompanying the fever, and the development of œdema of legs and a small sterile pleural effusion during one exacerbation.

Whenever sulphadiazine was exhibited the response was very rapid, but on the first two occasions, after 26 and 28 gms, relapses occurred within 3 days of stopping the drug. The fourth bout of fever was treated with 84 gms. of sulphadiazine during 32 days, and during this period the liver and spleen progressively reduced in size until they were no longer palpable. He appeared to have been cured and was transferred.

On the 26th May, he was admitted to us and at that time no abnormal signs were found. But on the 2nd June, 3 weeks after sulphadiazine had been stopped, and after a 7 weeks apyrexial interval, fever recurred. In a short time the liver was very greatly enlarged, forming an enormous tumour, and the spleen moderately enlarged. White blood cells were 5,000 with 3,700 polymorphs; two blood cultures were sterile; four sternal punctures were negative for Leishman-Donovan bodies, but these were finally found in smears from a liver puncture.

He had become emaciated and anæmic and had severe bronchitis with much dyspnœa. Diarrhœa developed.

Neostam was started with a dose of 0.05 gm. intravenously on 23rd June. Next day there was albuminuria, and a few days later the blood urea was 74 mgs. per cent. By this time he was very ill. A blood transfusion was given; sulphadiazine was started; and neostam cautiously continued. His condition improved rapidly; the fever settled, and the urine cleared. The sulphadiazine was stopped after 22 gms. but neostam injections were continued.

Nine days later on 13th July fever again recurred, and the patient's condition rapidly deteriorated despite 0.2 gms. doses of neostam on alternate days. Albuminuria developed; and as this persisted, and slight jaundice appeared, neostam was stopped after a total dosage of 1.9 gms. Sulphadiazine again caused an immediate termination of the fever, and apparently controlled the disease; he gained weight; his general health improved, the urine became normal and the icterus cleared; the liver became smaller and the spleen no longer palpable. The

drug was continued for 30 days and 74 gms. given, but at the end of this period a liver puncture still showed Leishman-Donovan bodies, though they were very scanty.

On 22nd August we stopped sulphadiazine and on 25th August gave him an intra-muscular injection of 0.075 gms. of stilbamidine. An hour later severe local pains developed and continued for some hours. Several hours after the injection he started vomiting.

Two days later 0.075 gms. was given intravenously. There was a very severe immediate reaction with sternal pain, severe headache, sweating, mistiness of vision and a poor tension pulse. Later in the day fever recommenced, albumin appeared in the urine, and he started vomiting.

After one further dose of stilbamidine and another severe reaction the drug was abandoned. In addition to the albuminuria and severe immediate reactions the appearance of thrombophlebitis after each injection made it almost impossible to continue.

Sulphadiazine was again exhibited and once again there was a rapid fall of temperature and amelioration of symptoms. Shortly after this he was transferred.

The next case, a South African airman aged 20 was admitted on 9th July, 1944. He gave a history of 6 months epigastric pain after food, and 2 weeks fever and headache. The liver was very markedly enlarged, forming a hard tumour extending down to the umbilicus and across to the left costal margin. The spleen was moderately enlarged. There was slight conjunctival icterus. Fever was remittent, rising to 102 to 104° each day. On admission the white cell count was 10,500; polymorphs 82% (8,610), lymphocytes 14%. Monocytes 1%, eosinophils 3%, and ten days later W.B.Cs were 16,500 with 90% polymorphs. Hæmoglobin was 69% and R.B.C. 3,110,000.

Leishman Donovan bodies were found in liver puncture smears on two occasions.

He was first treated with sulphamethazine, 42 gms. being given over a period of twelve days. Fever was markedly reduced but did not settle completely and relapsed immediately the drug was stopped. The jaundice disappeared, however.

Penicillin was tried but half a million units had no detectable effect.

Neostam was then given, but after two doses of 0.05 gms., there was albumin in the urine and icterus of the conjunctivæ.

Sulphadiazine was then started in doses of 6 gms. daily. After 48 hours the temperature was normal, and the jaundice and albuminuria quickly cleared. His general condition greatly improved but a course of 47 gms. of sulphadiazine in thirteen days had no effect on the size of the liver or spleen.

Stilbamidine was given. The initial dose was 0.075 gms. intravenously, rising to 0.15 gms. After four daily doses, totalling 0.475 gms. the urine contained albumin, pus cells, and granular casts so the drug was discontinued. Immediate reactions were similar to the last case but were not so severe.

These two cases had certain features in common. In both, the liver was the organ which appeared to have been most affected. Neither had leucopenia, and both rapidly developed albuminuria after neostam and stilbamidine.

Sulphadiazine had a dramatic effect, but in one case relapse occurred shortly after it was stopped and in the other the period of observation was too short for conclusions to be drawn. In neither case is the final result known as the hospital moved and the patients were lost sight of.

The source of infection was uncertain as both had been in Egypt and North Africa during their incubation periods.

Both cases were given emetine before a diagnosis of Kala Azar was made.

Summary

The treatment of Kala Azar has been briefly reviewed.

Two cases which were intolerant to neostam and stilbamidine have been described. In both sulphadiazine controlled the disease but one relapsed shortly after the drug was stopped, and the other could not be followed. Sulphamethazine was less effective. Both cases were notable in that there was disproportionate hepatomegaly and absence of leucopenia.

DISCUSSION — Kala Azar

Lieut.-Col. G. Slot, RAMC

I have a short note by Major F. D. HART which describes one case which presented itself as infective hepatitis.

Cultures from the blood are very valuable in Kala Azar and we have had two cases where this has proved successful and search for L.D. bodies in other tissues including sternal marrow was negative.

Our pathologist, Major PIKE, informs me the technique is easy and needs no special apparatus or medium not usually obtainable.

KALA AZAR

In the following case the condition was, on reasonable grounds, first confidently diagnosed as infective hepatitis.

Sapper Aged 40

Previously history irrelevant. On Jan 1st '43 entered N. Africa; in March he went into Tunisia; into Sicily in July and to the mainland of Italy in September of the same year. He was perfectly well in every way until March 29th '44 when he complained of sudden onset of shivering, headache and sweating. His temperature was 100°F. For the next 36 hours he had intermittent shivering turns which were followed by nausea and complete anorexia. He vomited once and was unable to face a cigarette. About midnight on the 30th, cramp-like pains came on under the R. costal margin keeping him awake. He was sent from the CCS to a general hospital where they found no icterus, no splenic enlargement, but a markedly tender and enlarged liver. T.99.8 P.90 R.20 low grade pyrexia, nausea, anorexia, flatulence and subcostal discomfort continued. The urine was " noted to be dark " on the 5th April but bile was not found. He was diagnosed as infective hepatitis in the preicteric stage and transferred to 93 Br G.H. on 8.4.44. On admission there was no icterus; he was a muddy sallow pale colour. The liver was enlarged to the umbilicus

and extremely tender; the left lobe was sufficiently enlarged to overlie any splenic enlargement there may have been at this stage. Urine was free from any abnormal constituents. Absolute anorexia, nausea and upper abdominal pain dominated the clinical picture. WBCs 4,000 (P.50 L.44 M.5 E 1%). X-ray= diaphragm moves evenly and well. Chest NAD. Stools normal. Blood slides all negative for MPs. He was afebrile on admission and remained so until 13th April when a low graded pyrexia presenting no particular pattern on two and four hourly charts.

In the next few weeks the liver gradually became smaller and nausea and anorexia slowly lessened. As the left lobe diminished in size the spleen became palpable 1 f.b. on full inspiration. It was never tender. Blood count on 21st April WBCs, 2,800 (P.64 L.29 M.5 E.1 Turk Cell 1%) toxic granulation present. On 1st May WBCs 3,600 (P.58 L.36 M.5 E.1%) Hb 74% Haldane) RBCs 3,410,000 CIO.84. RBCs showed some aniso-cytosis, many microcytes and slight polychromasia. Twenty days later the count was virtually the same. The general condition gradually improved though fever continued. Appetite became normal 5-6 weeks, though flatulence and abdominal fullness after meals was a constant symptom. His liver shrank to 2-3 f.bs. below the right costal margin and remained stationary at this size and only slightly tender for the month prior to evacuation. The spleen, never tender, remained enlarged 1½ f.bs. on full inspiration. Kahn Test and repeated agglutinations and blood cultures were all negative. The formol-gel test-ve on 7th May became positive on 20th, anopaque gel starting at 20 minutes was complete in 120 mins. Blood culture+ve for leptomonads on human blood NNN medium after 3 days incubation on 24th May. Neostam therapy was started on 29th May but was poorly tolerated and the patient's general condition was worse after it than before.

The case is of interest in that the whole picture was that of a hepatitis, and there was every reason in the early stages to think infective hepatitis the most likely diagnosis. Of interest also is the apparently acute onset after what would have been a minimum of six months incubation if the disease were contracted in Sicily. Of interest also is that according to the text books antimony intravenously is poorly tolerated if liver disease be present. This case was primarily hepatic and the drug was poorly tolerated.

Colonel Perrin Long, M.C.

I am very much interested in these two papers.

Back in 1940 I was asked to see a young woman. The story was as follows. She was the daughter of a Military Attache at Chungking, and 11 months before when there was trouble out there she was flown by China Clipper to USA, where she had perfect health for 11 months. At Baltimore she developed much fever. Unfortunately she had been vaccinated for typhoid a month before. The spleen was slightly enlarged. Two weeks later she developed fever again, and this time she had a lymphocytosis with a relative degree of leucopenia. Dr. Barker, who was in charge of her, had laboratory tests made and they were all negative. He asked me in to see if I thought we should give her sulphadiazine. Faced with a situation like that I said "Of course, give her some" and we started her off. Her temperature rose to about 103/105 and within 48 hours came right down to normal. Dr. Barker said to me "You are very lucky. Stop it and see what happens!" We stopped it, and the day we stopped it she had a sterile puncture. He came to me and I said "Start her on sulphadiazine again." It is very interesting after hearing Major Keall's paper to remember how quickly that girl's fever came down, also her initial attack began 11 months after she left the area in which she could have caught her infection.

This sulphadiazine interests me very much because I cannot see how it works. Why does it work in the various types of coccal infections when it doesn't work in other diseases? These are things we just do not know. We know, for instance, that sulphapyridine will bring under control cases of dermatitis herpetiformis right away while pencillin has no effect on them. I have had patients on sulphapyridine who have been on it constantly for 4 or 5 years now and nothing ever happens to them, except they remain very comfortable. Over four weeks the dose was first week 4 gr. initially and 1 gr. every four hours for 7 days. Then 1 gr. four times a day for the next four weeks, watching the white blood count between the 12th, 17th and 25th days, this is the only thing you have to worry about. Then after the 30th day, put them on 2 gr. a day, and then you can stop worrying. Certainly I would rather start out that way than have some of the shocking reactions I have just heard about.

Tuesday, 30th January, 1945

AFTERNOON SESSION

Subject: INFECTIVE HEPATITIS

Presiding:

Brigadier E. R. Cullinan, Consulting Physician

East Africa Command

INFECTIVE HEPATITIS

by

Lt.-Col. R. C. DICKSON, RCAMC

During the period between 25 July, 1943, and 31 December, 1944, 3,000 patients suffering from infective hepatitis were admitted to the Medical Division of No. 15 Gen. Hosp. RCAMC. About three-quarters of these contracted the disease in Sicily or Italy, the remainder in North Africa. These casualties, for the most part temporary, represent a loss to the army of 150,000 man days or the numerical equivalent of one division for ten days. Infective hepatitis thus has caused the most serious wastage in the Canadian Army of any non-venereal disease in this theatre. It is the purpose of this short paper to review some of the clinical findings in this group in an endeavour to clarify as much as possible the natural history of the disease, to assess the importance of this common disease to the individual affected and to the army as a whole and to evaluate any factors involved in the return of soldiers to full duty.

Clinical Manifestations

1. *Prodromal Stage or Pre-Icteric.* In all cases a prodromal or pre-icteric stage could be recognized which was manifested sooner or later by gastro-intestinal symptoms but in one-third of the cases these were preceded or accompanied by an acute febrile illness which dominated the clinical picture.

In febrile cases the onset was characterized by malaise, fatigue and lassitude, chilliness, occasionally a true rigor, frontal headache, body aches and often mental depression. Fever varied from 100° to 104° F. continuing usually from one to four days but occasionally to the tenth day and in 9 cases from 10—21 days (Table I).

TABLE I

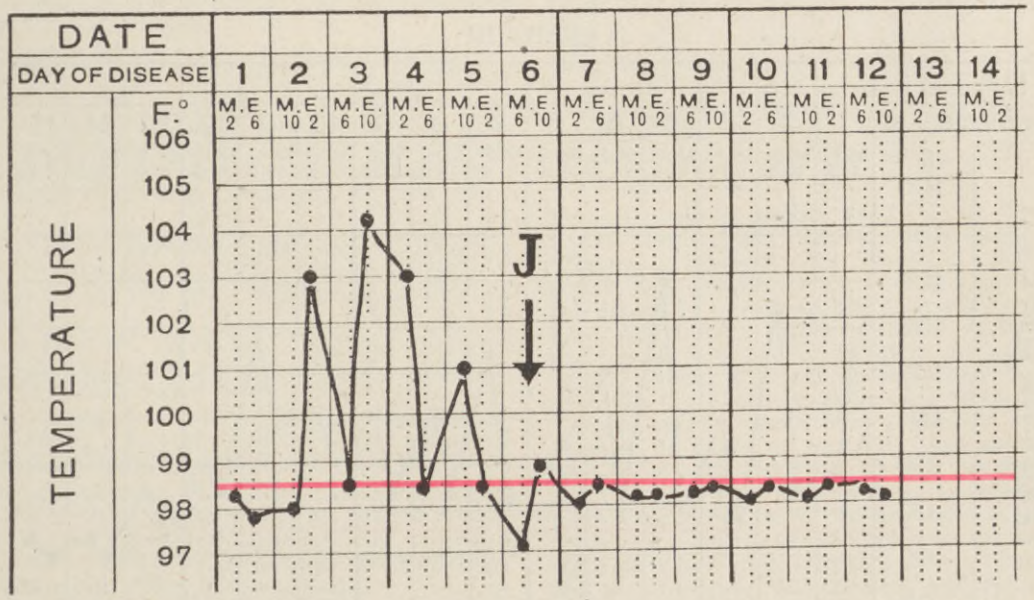
DURATION PRE-ICTERIC FEVER

355 Cases

1 day	— 55	10 days	— 4
2	— 97	11	— 1
3	— 90	12	— 2
4	— 43	13	— 1
5	— 16	14	— 2
6	— 20	16	— 1
7	— 9	20	— 1
8	— 9	21	— 1
9	— 3		

The course of the fever in this stage followed one of three quite distinct patterns. Most commonly the fever persisted until the appearance of jaundice then fell sharply to 99°—100° F. or to normal (Chart I).

CHART I



Less commonly after a short febrile period the temperature returned to normal and the patient apparently made a complete recovery. Then days or even two or three weeks later fever recurred for a day or two and jaundice developed (Chart II) (Table II).

CHART II

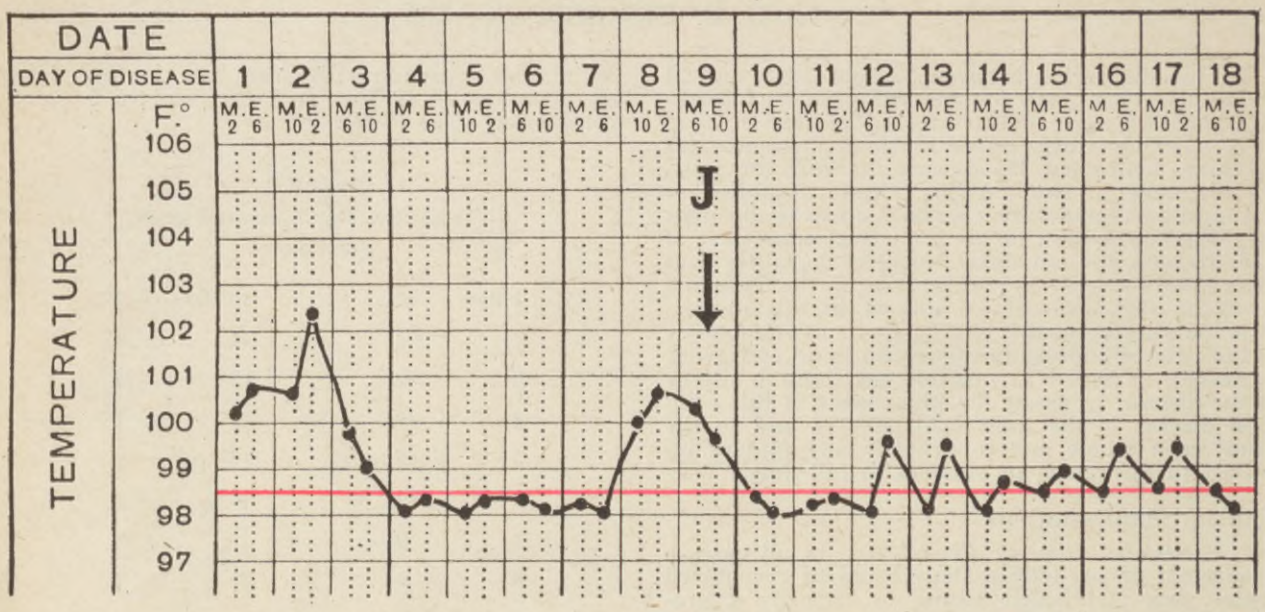


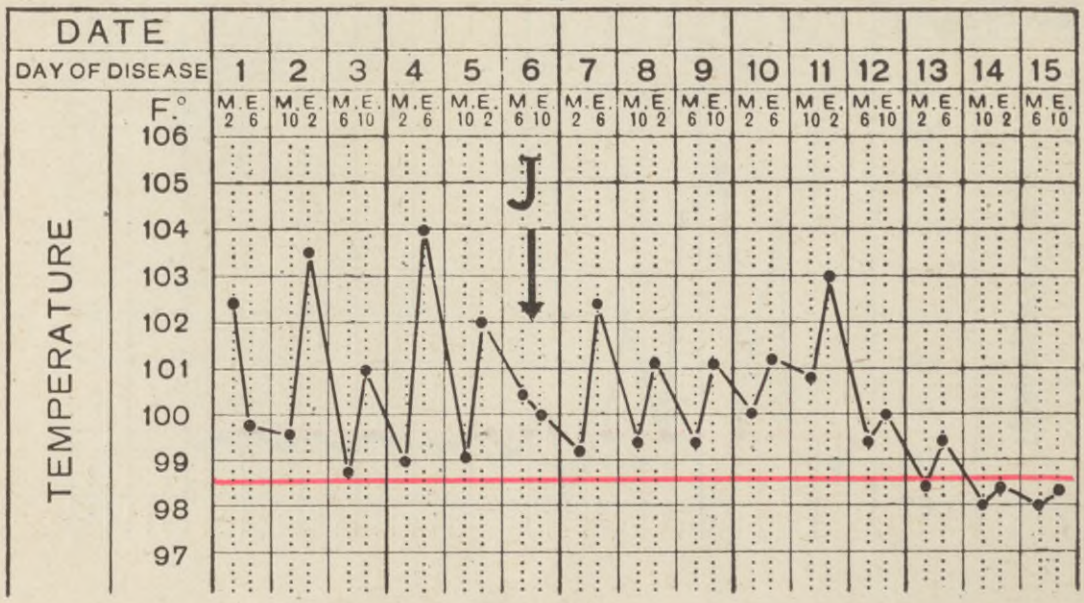
TABLE II

INTERVAL BETWEEN FEVER AND JAUNDICE—384 Cases

1 day	— 8	7 day	— 37	13 days	— 5	19 days	— 1
2	— 23	8	— 37	14	— 8	22	— 2
3	— 45	9	— 20	15	— 2	23	— 1
4	— 47	10	— 15	16	— 2	26	— 2
5	— 62	11	— 8	17	— 2	27	— 1
6	— 39	12	— 10	18	— 6	28	— 1

Very rarely the high fever of the pre-icteric period persisted for days after the appearance of jaundice (Chart III).

CHART III



The diagnosis of infective hepatitis during this pre-icteric febrile period was often most difficult and in an area where the differentiation of acute febrile illness constituted the greatest single diagnostic difficulty with which the physician was faced, added to an already big problem. The disease seen in this stage was not infreqently considered to be clinical malaria and treated as such. Commonly the patient was discharged apparently well under the diagnosis of P.U.O., only to be admitted later to the same or another medical installation with jaundice. As has been indicated, the symptoms during this phase were not specific. Three findings were noted, however, which, if present, were considered to be of definite value in diagnosis. The appetite might be impaired out of all proportion to the other symptoms, the liver might be enlarged and tender or the leucocyte count less than 5,000 c.mm. These findings occurring singly or in combination were strongly indicative of infective hepatitis.

All patients sooner or later developed gastro-intestinal symptoms and in two-thirds of the cases the first complaints were of such a nature. In others where the febrile features were mild the patient did not report sick until they appeared. Gastro-intestinal symptoms were present 1—14 days, prior to the appearance of jaundice, but most commonly the interval was 2—4 days.

Loss of appetite was almost invariable. In some mild cases it was the only symptom and never marked. In others it progressed to anorexia aggravated by the smell or sight of food. Two-thirds of the patients complained of nausea and about one-half vomited on one or more occasions. In a very few vomiting was so persistent as to necessitate the parenteral administration of fluids to prevent or correct dehydration.

Upper abdominal pain was common and of two types. Most frequent was vague right upper quadrant distress aggravated by movement or by pressure in that area and associated always with enlargement and tenderness of the liver. Less often the patient complained of the typical mid-epigastric discomfort of pylorospasm.

It is of some interest to note that diarrhœa occurred in 20% of the cases during the prodromal stage. In a few cases the stool was examined during this period and found to be loose, fecal and free from exudate and pathogenic bacteria. Constipation at this stage was not common although almost a constant symptom later in the disease.

2. *Icteric Stage.* With the appearance of jaundice the patient's general condition usually improved. The further course was remarkably constant in most instances.

Fever of 99°—100° continued in many cases for periods up to two weeks and occasionally persisted for a few days at a higher level.

Jaundice lasted from 1—64 days, averaging 16 days, in patients followed to clearing and measured to the time of disappearance of bile from the urine.

Hepatic enlargement associated with tenderness was present in 80% of the cases. By the time jaundice had cleared the liver had as a rule regained its normal size, but in a few patients some enlargement persisted for days or even weeks.

The spleen was palpable in only 6% of the cases. This is in striking contrast to a group of cases studied in this hospital in England and to sporadic cases admitted over a ten-year period to the Toronto General Hospital, where the incidence of palpable splenic enlargement was 25% and 50% respectively.

With mild illnesses no change in the appearance of the stools was noted. When more severe, they became pale and in the most severe cases they became acholic or clay-coloured. During this period in particular constipation was common.

Vomiting and nausea cleared gradually and usually disappeared in the first week of the icteric period. A sudden change in appetite was noted at the time jaundice started to clear. The appetite became much improved and even ravenous, but easily satisfied by a small amount of food. A few days later the appetite returned to normal.

Recovery of strength and energy was slow and quite inadequate for the performance of field duties until two or three weeks had elapsed after the disappearance of jaundice. 97.5% of the cases had, however, returned to full duty within an average period of 50 days from the onset of symptoms.

3. *Variations.* Certain variations of this, the usual course, were noted. The first occurred fairly frequently and might well be considered part of the normal course; indeed it almost certainly passed unnoticed quite frequently during busy times. In certain cases at about the time the patient was ready to get up, or soon after, a return of mild malaise and loss of appetite was noted by the patient. On examination, the liver, which had previously returned to normal size, was found to be palpable and tender. This phase subsided in a few days. The mild recrudescence might occur after the patient had reached the Convalescent Depot, where its occurrence was well recognized by the Medical Officers and where it was treated by a few days excused duty.

A more serious variation was the persistence of hepatic enlargement with or without jaundice for periods of six to eight weeks or longer. The average duration of jaundice in this group was known to be over 66 days. Twenty-one such cases were evacuated from this theatre and no follow-up has been possible as yet, but when last seen all complained of mild dyspepsia, loss of energy and frequently right upper quadrant discomfort. It would appear likely that in these patients severe liver damage had progressed to the stage of early cirrhosis.

Seventy-five patients, or 2.5% of the 3,000 admitted with infective hepatitis, were sent to hospital because of a relapse. By relapse is meant a second attack with jaundice occurring at some time within the arbitrary period of one year of the primary illness. Apart from these seventy-five cases only ten patients gave a history of previous jaundice. Such earlier attacks had usually occurred in childhood; never in the Mediterranean area. Relapses were, as a rule, more severe than primary attacks. The average duration of jaundice was something over 28 days as compared with 16 days for the latter. The exact duration is unknown as twenty-six patients were evacuated from the theatre. At the time of departure, never less than six weeks from the onset, eight still had gross hepatic enlargement, while 18 had gross hepatic enlargement and persisting jaundice. This increased severity of the relapse is indicated in Table III.

TABLE III

PRIMARY ATTACK . .	2925 Cases	
Death	2 ,,	0.06 %
Evac. to U.K. . .	21 ,,	0.7 %
To Duty	2904 ,,	99.2 %
RELAPSE	75 Cases	
Death	0 ,,	
Evac. to U.K. . .	26 ,,	34.6 %
To Duty	49 ,,	65.4 %

Relapses occurred most commonly within four months of the primary attack, and the longer the interval between attacks the less severe the relapse tended to be. This is well shown in Table IV.

TABLE IV
RELAPSE

	Cases	Duration Jaundice Days
Within 4 months . . .	60	34
4 — 8 months . . .	10	26
8 — 12 months . . .	2	14
Second Relapse	3	32

The most serious variation from the normal course, acute necrosis or acute yellow atrophy of the liver, occurred in two cases and accounted for the two deaths in this group. Several patients became very drowsy; a few became irrational. Such symptoms in conjunction with severity of the other manifestations of the disease suggested the onset of acute necrosis. However, in all but the two, noted improvement occurred after a few hours. One patient developed ascites, which cleared, although jaundice recurred and persisted until evacuation. The ultimate outcome is not known.

Hepatitis without jaundice has been described and there is no reason to doubt its occurrence. A few such cases were recognized and more suspected, but as no means was available by which the diagnosis could be established or disproved, they are not included in the series. Such cases usually presented with febrile symptoms and recovered without jaundice becoming apparent. All were mild, recovery was rapid and no serious medical problem was provided.

Treatment

No specific therapy was known for this disease and treatment was therefore directed to bringing about those conditions which would permit natural recovery to be as rapid and complete as possible. Bed rest was considered by far the most important of such conditions. This was continued except for bathroom privileges, which were permitted as soon as the acute phase had subsided, until the patients urine was free of bile, appetite and sense of well being had improved, hepatic tenderness had subsided and hepatic enlargement was not greater than one finger breadth below costal margin. Then following a short ambulant period, the patient was discharged to Convalescent Depot where it was found that graded exercise over a period of at least three weeks was necessary to bring the patient to fighting fitness.

Dietary treatment was limited by the food available. A light diet was used from which greasy food was eliminated but which was by no means "fat free", for instance those patients who so desired were permitted butter or margarine with their bread. Protein was not restricted but no special effort was made to increase the protein content of the diet. When the patients appetite demanded he was placed on full or ordinary hospital diet. In the early stage of the illness fluids, mainly sweetened fruit juice (synthetic!) were administered up to about 2500 cc. daily. Where necessary glucose saline was given intravenously particularly when vomiting was persistent. Latterly, a few patients have been given plasma in place of part of the glucose saline. No amogen or other protein digests have been available for use. Constipation was controlled by the use of saline laxatives. Patients on discharge were advised to abstain from alcohol for three months but it is highly doubtful if such advice was consistently followed.

Discussion

The natural history of the disease as exemplified by these cases appeared from the clinical course to be that of an acute systemic infection with evidence of selective damage to the parenchymal cells of the liver and exhibiting a strong natural tendency to spontaneous recovery. This is further borne out by the pathology of the disease which has been much clarified by recent work in Holland and later by McMichael and others on the study of material obtained by punch biopsy. These studies have clearly shown that the pathological picture is one of degenerative changes in hepatic cells varying in severity from cloudy swelling to necrosis and disorganization of the liver lobule. Mann's work in dogs indicates that at least 2/3 of the hepatic parenchyma must be removed before any evidence of bile pigment retention can be demonstrated either by increased pigment content of the blood or pigment excretion in the urine. These patients then display evidence of very extensive involvement of the hepatic parenchyma. Although this is of relatively short duration in most cases, the persistence of the disease for long periods in some and its recurrence in others within periods up to one year, would suggest that the etiological agent can persist in the body for months and that immunity is sometimes acquired very slowly. That immunity is developed is indicated by the rarity of second attacks after a period of one year has elapsed from the primary infection, and by the decreasing incidence and severity of relapses as time passes after the first attack.

Many factors must be evolved in the persistence of the disease, its effects and its tendency to relapse. One however, and one which can be controlled, is the duration of convalescence after the primary attack. Only too frequently, in the relapse cases, is the history obtained of an initial return to duty after little or no convalescence. In the Canadian Corps for instance the disease was taken too lightly at first and an attempt was made to treat patients

in forward medical installations and return them rapidly to combatant units. These men were found unfit for duty and had to be again evacuated for convalescence.

The management of patients suffering from this disease in 15 C.G.H. has been gradually evolved from consideration of all these factors and, as indeed is usual, it is remarkable how little discrepancy there is between a policy which serves best the interests of the individual and one which serves the best interests of the army. The object has been to return men to duty as soon as they were fit and likely to remain fit. The policy therefore has been:—

(1) Bed rest until the urine was free of bile and appetite recovered.

(2) Further ambulant treatment in hospital usually only for a few days, to allow the patient to regain strength and permit a little longer observation re early relapse.

(3) Discharge to Convalescent Depot when the above conditions were fulfilled, liver tenderness had subsided, and the liver edge was not more than one finger breadth below the costal margin.

(4) Graded exercises at Convalescent Depot for a minimum period of three weeks, weekly examination and where necessary prolonged convalescence. In all cases the successful completion of an eight mile route march up and down a mountain was required before the soldier was returned to duty.

Summary

(1) The clinical findings in 3000 cases of infective Hepatitis treated at No. 15 Canadian General Hospital between July 1943 and December 1944 are reviewed.

(2) The natural history of the disease as exemplified by these patients is outlined.

(3) The management, treatment and disposal of patients suffering from this disease is discussed.

A SUMMARY OF THE STUDIES ON INFECTIOUS HEPATITIS IN NATOUSA DURING 1944

by

Colonel MARION H. BARKER, MC

This symposium serves to punctuate the first year of the first major attack on infectious hepatitis by the U.S. Army Medical Corps.

Soon after German and Italian prisoners with jaundice were taken in Tunisia in the spring of 1943, our first experience with infectious hepatitis in this theatre began to develop as a major medical problem. Diarrhœa only partially explained, but possibly related to the great number of flies, involved the greater part of one of our combat divisions during June and the first half of July. The first large number of cases of jaundice began to appear in that division during the last week of July. Their attack rate of infectious hepatitis rapidly mounted and by the time our army was striking from Paestum towards Naples, large numbers had to fall out because of symptoms associated with jaundice, others with similar symptoms but without being jaundiced, and others became ill with relapses of their disease that had been suffered in Africa or Sicily. This and other organizations that had become similarly involved, contributed a large number of ill men which were necessarily hospitalized for various periods of time depending on their clinical and physical condition. A large per cent appeared able to return to combat duty in 17—30 days while a number remained ill or relapsed with or without jaundice, either while still in hospital or soon after returning to duty, combat or otherwise. A study on epidemiology had been initiated in Africa and Sicily during the fall but in January, one year ago, the study was enlarged and collaboration between Col. William S. Stone, Division of Preventive Medicine, NATOUSA, Col. Perrin H. Long, Consultant in Medicine, NATOUSA, and Col. Virgil H. Cornell of the 15th Medical General Laboratory permitted an extensive plan of study. The past year has been given to a combined study on the epidemiology, etiology, clinical recognition, course, therapy, pathology and disposition of soldiers suffering from infectious hepatitis.

Although the agent is not known, nor is the method of spread or its control or treatment more than hazily suggested, the following notes on progress are offered as reasons for encouragement and basis for continued study.

1. The obscure and bizarre nature of the disease has been sufficiently observed to reach a high degree of accuracy in the clinical recognition and the many problems of differential diagnosis.

2. Experience with a large number of cases during the prodromal, acute, chronic or relapsing stages of the disease has been sufficient to adopt a general clinical classification or nomenclature which has served as a basis for disposition and discussion, mutually helpful to the medical officers in this theatre.

3. Nutrition in the care of those sick with acute and prolonged infectious hepatitis has made a great advance by shortening the course and by controlling the wasting usually attending this disease. This improved dietary support has resulted in the safe, early return of a high per cent of soldiers to combat duty.

4. A standard graduated physical reconditioning programme has been evolved and generally employed by all hospitals so that the patient's medical officer has had a controlled evaluation of the patient's adequate physical capacity which better insured his ability to assume the full responsibilities of combat with his fellow soldiers.

5. A substantial and varied study on liver function in the normal and abnormal state of many diseases has resulted in a broader understanding of liver physiology which may be increasingly valuable when war is done.

6. Peritoneoscopy and the removal of liver biopsies at the various stages of the disease is under way which, when completed, should be a most valuable addition to our meagre understanding of the clinical manifestations and the correlation of liver function studies.

7. Although the agent is not known nor is the chief manner of spread clearly understood, at least three different workers have demonstrated that icterogenic serum injected subcutaneously into a donor often results in hepatitis with jaundice in 56—100 days. Further, the stools from patients ill with hepatitis with jaundice produce the disease in 21—30 days in 80% of the volunteers when taken in capsules or by stomach tube. Such evidence speaks strongly for the incubation period of injected or ingested icterogenic agents and serves as a warning to general sanitation and to the care of our needles and syringes.

8. Local theatre attempts at recovering a virus have included the injection of blood, stools, liver emulsion and pharyngeal washings into baby chicks, rabbits, hamsters, pigs and chimpanzees. The chick and rabbit embryo have been injected with icterogenic specimens. These and pieces of liver removed by the peritoneoscope, lymph glands and mosquitoes fed on icteric patients have been shipped to workers in the Zone of Interior that are collaborating with the Surgeon General in this study.

This brief summary of the past 12 months study of infectious hepatitis in the North African Theatre of Operations is presented for the information of anyone not familiar with the advance in the knowledge about infectious hepatitis and to indicate lines of attack immediately applicable to injectible and ingestible aspects of transfer of this disease. This opportunity to express appreciation to General Stayer, his commanding officers, the many medical officers, nurses, dieticians, enlisted men, mess officers, sanitary supply and quartermaster officers and the Air Corps who have made this programme possible is most welcomed.

(Ed.—Colonel H. Perrin Long and Colonel Marion H. Barker left for a visit to the United States immediately after the Conference and before we could secure their contributions.

The paper which is included is a brief summary of the work which is being done by Colonel Barker and his group and is not an account of what he said in Rome.)

INFECTIVE HEPATITIS

by

Major S. C. TRUELOVE, RAMC

I very much regret that the work which Major McKinlay and I are doing on the epidemiology of infective hepatitis is not yet ready for presentation. In consequence, I propose to make a rapid survey of the more important epidemiological features of the disease, in the hope that it may serve as a basis for discussion.

I. Brief History

Under a variety of names, such as epidemic catarrhal jaundice, epidemic jaundice of campaigns and camp jaundice, numerous outbreaks of this disease have been described during the past two hundred years. The first recorded outbreak occurred at Minorca in 1745. Descriptions of outbreaks become more frequent after 1850. Military garrisons appear to have been particularly subject to outbreaks, but really large-scale epidemics have occurred only during wars.

A large outbreak occurred in the American Civil War in the Federal Army, and among its 2¼ million men there were 42,569 cases of jaundice with 161 deaths.

In the last war, jaundice broke out in 1915 in Alexandria and spread around the shores of the Mediterranean to Gallipoli, Salonika and Mesopotamia. Some of these epidemics were on a large scale. Thus, at Suvla Bay, in 1915, during the period 19th August to 1st December, the 53rd Division had 456 cases. Small outbreaks occurred in France and Flanders, but the disease never became epidemic there.

During the present war, there has been a notable rise in infective hepatitis in many regions of the world. Large scale epidemics have once again occurred in the Mediterranean area. As far as I know, no major epidemic has occurred in north-east Europe.

There has certainly been a great increase of infective hepatitis in the U.K. since the beginning of the present war. Since the disease has not been notifiable, it is impossible to say how great the increase has been.

II. Evidence Concerning the Mode of Spread of the Disease

1. EXPERIMENTAL.

Experimental work has been limited by the inability to find any suitable susceptible animal. In consequence, it has been necessary to employ human volunteers to gain knowledge of possible modes of spread of the disease. A brief summary of the successful transmissions is as follows:—

Cameron (1941) transmitted the disease by intramuscular injections of serum from pre-icteric and early icteric cases.

Voegt (1942) transmitted the disease by the use of duodenal washings given per os, and also by the injection of serum subcutaneously.

Martin and Findlay (1943), employing nasal washings from a case of homologous serum jaundice following yellow-fever inoculation, produced jaundice in three human volunteers.

Recently, Paul in America and MacCallum in England, in the course of work which is still in progress, have shown that faeces are infective, but, to date, have not found naso-pharyngeal washings to be so.

2. EPIDEMIOLOGICAL.

(a) *Droplet Spread.*

Most of the civilian observers of epidemics have felt that the disease was transmitted by droplets from the naso-pharynx. Thus, for example, Pickles, in his classical observations on epidemics in 1929 and 1935 among village communities in Wensleydale, was able to trace a "case to case" spread, often as a result of only the most casual contacts. Similarly, Newman (1942) was of the opinion that "all the evidence points to direct spread from case to case," although some of his evidence pointed against a droplet method of spread. In tracing the chain of infection, he was forced to conclude that a headmaster of a school infected four children merely by passing through a class-room in which they were sitting. He concludes:—"In the light of this, we are forced back to the rather unsatisfying explanation—if it can be called an explanation — of the disease being air-borne."

Cameron, studying infective hepatitis among the Army in the Middle East in 1941, also traced "chains of infection" where the disease behaved as though spread by droplets.

Some observers have produced evidence against the droplet spread theory. In the last war, the general impression was that the infection came from some common source. The association of the disease with dysentery was stressed by Willcox and others. The peak of the jaundice outbreak usually came a few weeks after the dysentery peak.

Spooner, in the Middle East in 1942, cited, among other evidence, the following: In an Italian P.o.W. Camp, there were 500 Italian O.Rs., who had spent the summer there. In November, 1,120 newly-captured Italian officers were admitted. Hundred and one of these subsequently developed the disease, but none of the old prisoners who were waiting on them.

Boyd, reporting on a N.Z. Division, which had a very high rate of jaundice at Alamein in 1942, pointed out that the brunt of the disease fell on forward troops who were not nearly so congested in their living and sleeping conditions as rear troops. Moreover, 1,500 cases of infective hepatitis were treated in a N.Z. General Hospital, but only one nursing sister and three nursing orderlies developed the disease, and they, as it happened, were not employed in the wards.

Trotter and I observed a curious feature in an American Field Service unit situated in Naples during the 1943 epidemic. Eighty members, approximately a half of the total unit, had been attached in small parties for varying lengths of time to a number of forward medical units. These small parties were constantly returning to their base whenever each period of duty came to an end. Among these 80 members, there were 26 cases of infective hepatitis during the epidemic period. In the other half of the unit, there was not a single case of jaundice by the middle of February 1944, when the epidemic season had passed.

(b) *Ingestional.*

In the literature, there are several accounts of water-borne spread of the disease. Perhaps the most striking is that given by Halgren (1942) in his description of an outbreak in a sanatorium. The essential facts were these:— 178 cases of jaundice occurred among an exposed population of 549 — an attack rate of 32%. "The water conduit of the sanatorium had become polluted from a defective drain. Thirty-four days after the infected well had been excluded, the epidemic came to an end, a few odd cases only occurring during the following 18 days .....Among 188 persons who had joined the sanatorium population either as patients or personnel after the exclusion of the well, no case of the disease occurred although the new arrivals came into contact with a large number of unisolated cases. This indicates definitely that the disease with which we have to deal here is not transmitted by contact."

(c) *Blood-Sucking Insects,*

The possibility of blood-sucking insects acting as vectors for the disease in suggested by

(i) Transmission experiments already quoted;

(ii) The occurrence of post homologous serum jaundice and post-arsphenamine jaundice.

No constant vector has been described. The only experimental work of which I am aware is that carried out by Cameron in 1941 in the Middle East. He applied bed-bugs to infective hepatitis in the pre-icteric stage, and then allowed them to bite human volunteers. The results were negative.

III. Factors Influencing the Development and Magnitude of an Epidemic

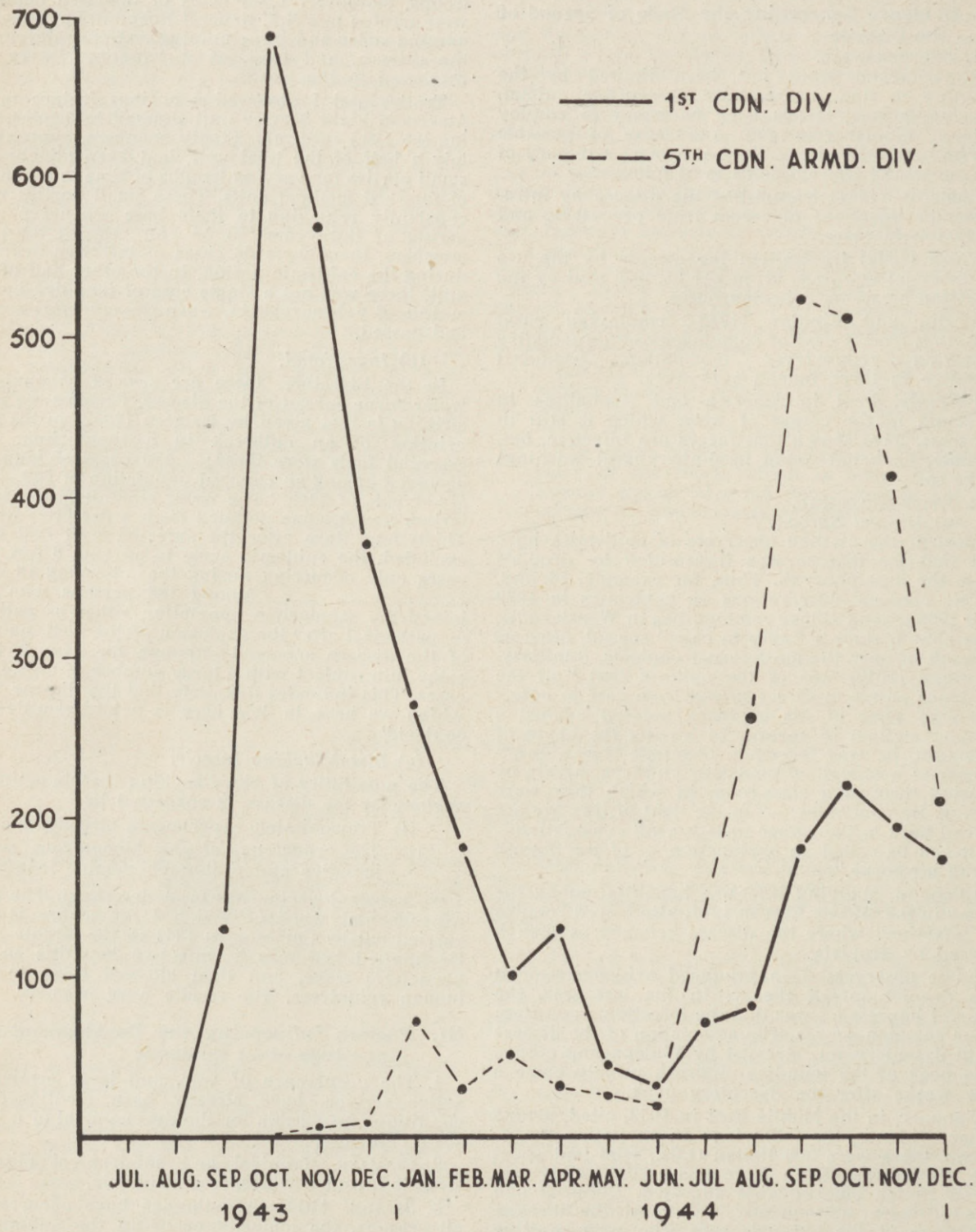
1. The occurrence of war, and large armies on active service, have already been mentioned as conditions favourable for the development of a large scale epidemic.

2. CLIMATE. Tropical and sub-tropical climates seem to favour a widespread epidemic.

3. SEASON. Although outbreaks have occurred at all seasons, the majority occur in the autumn or early winter (Stallybrass, 1931).

FIG. I

Infective Hepatitis among two Canadian Divisions after their arrival in C.M.F.

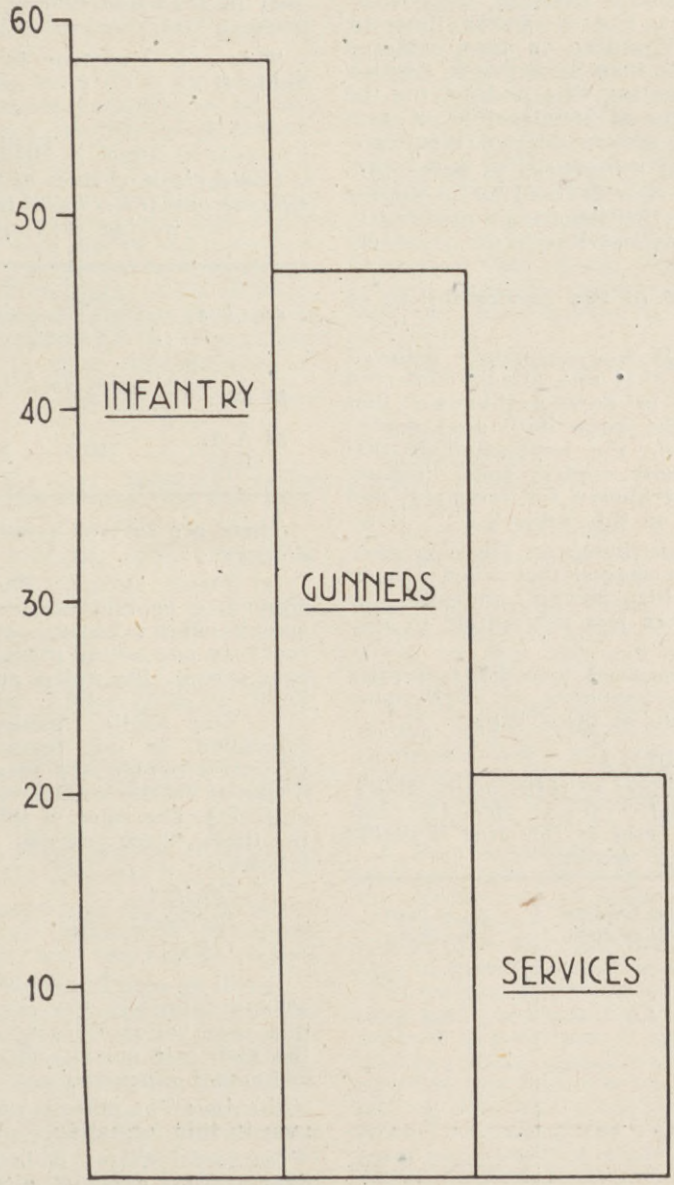


During the present war, there has been a very marked seasonal variation in the incidence of the disease, with the peaks occurring in the autumn or early winter.

The experience of two Canadian Divisions in the C.M.F. is of interest (see Fig. I.) 1 Canadian Division landed in Sicily on 10th July 1943. Six weeks later it began a jaundice epidemic, which climbed rapidly to its peak in October, from thence declining to its summer endemic level by March. The 5 Canadian Armoured Division landed at Naples early in November 1943 and remained in the Naples area for some weeks. At that time, there was a general jaundice epidemic in progress in the Naples area, as indeed there was in the whole of the C.M.F., and the epidemic was at its peak. This Division developed cases of jaundice after a few weeks, but there was no real epidemic until the 1944 epidemic

FIG. II

Breakdown of 1 Canadian Division to show rates of infective hepatitis in Infantry, Artillery Regts., and services (Aug.-Dec. 44 incl.)



season arrived, when a major epidemic occurred. It is interesting to speculate on the reasons, for this highly susceptible group of men escaping a major epidemic when they first arrived. The disease occurred, but apparently by that time in the epidemic season conditions did not favour a wide dissemination of the infective agent.

4. Forward and Rear Troops. In 1942, the forward troops in the Alamein outbreak were much more heavily affected than rear troops.

In 1943, in the C.M.F., there was a general epidemic, in which no such difference was apparent.

In 1944, in the C.M.F., the disease has reverted to 1942 pattern, and the bulk of the cases have occurred among forward troops.

Even within 1 Canadian Division, this same discrepancy is apparent. Fig. II shows that the infantry battalions of the division have suffered from much more jaundice than the services. Caution must be used in interpreting this finding, for the age-composition and rate of immigration of new troops among the three groups are not identical.

5. Race. Marked racial differences in susceptibility exist. Canadian and New Zealand forces appear to be highly susceptible, British troops moderately susceptible, while Indians and Maoris are relatively immune.

IV. Factors Concerned in the Susceptibility of Individuals

1. Previous Attack. It was commonly believed before the present war that one attack conferred life-long immunity. It is now well-known that attacks may occur in the same individual during successive seasons. While the impression is that a previous attack normally confers some measure of immunity, this is not known for certainty, and further work is needed on this subject.

2. Passing Through an Epidemic. There is some inconclusive evidence to suggest that when a body of individuals passes through an epidemic, the body as a whole becomes less susceptible to subsequent epidemics.

Thus, Trotter and I observed very different rates among the three Field Regiments of 56 Division during the 1943 epidemic in the C.M.F.

TABLE I

Rates of Infective Hepatitis in O.Rs. of Fd. Regts. of 56 Div. during period 5 Sep-11 Dec 43, compared with numbers of cases of Infective Hepatitis during previous epidemic season.

Unit	Average O.R. Strength	Infective hepatitis per 1000 per week	No. of Cases in 1942/3
113 Fd. Regt.	535	4.6	Nil
64 Fd. Regt.	570	4.1	4
65 Fd. Regt.	572	0.3	70

The most satisfactory explanation seemed to be that the difference was due to their previous experience of the disease. If so, there is the possibility that very large numbers of sub-icteric and subclinical attacks occur during an epidemic, and confer immunity on the group as a whole. We were, unfortunately, unable to proceed to the obvious corollary of analysing the outbreak within 65 Fd. Regt., to determine whether or not the second epidemic had chiefly affected persons who had joined the unit since the end of the first epidemic.

3. Age. Within the Army, the younger an individual, the more susceptible he is to a clinical attack of infective hepatitis.

4. British Officers. It was noted in the Middle East in 1942 that British Officers were much more prone to infective hepatitis than were O.Rs.

This was also true in 1943 in the C.M.F. (see Table II).

TABLE II

Comparison of rates of infective hepatitis among Officers and O.Rs. in 56 Division and 22 A.A.Bde. during 1943 epidemic period.

Formation	Officers: Infective hepatitis per 1000 per week	O.Rs. Infective hepatitis per 1000 per week	Officer/O.R. ratio
56 Div.	8.4	2.1	4.0
22 A.A. Bde.	10.7	2.3	4.7

There are several possible causes of this striking difference:—

(a) *Easier spread*: The most attractive theory seemed to be that the disease spreads more easily among officers because of their use of communal crockery and eating utensils in officers' messes. For comparison, the rates among serjeants of H.A.A. Regts. in 22 A.A. Bde., who lived in small messes in a very similar fashion to their officers, were calculated. In this formation the food eaten by officers, serjeants and men was the same, and was prepared in the single cookhouses of each gun-site or B.H.Q. The rates of infective hepatitis per 1,000 in these three classes of individual were as follows:—

Officers	147.4
Serjeants	38.8
O.Rs.	32.8

It will be seen from this that the serjeants suffered at approximately the same rate as the men, and this observation does not support the theory that the high rate among officers is due to their use of communal crockery.

(b) *Age*: The officers were not younger than their men in this formation.

(c) *Social Class*: It is possible that officers are drawn from a social class which has been little exposed to the virus of infective hepatitis. Against this is the fact that in the Royal Navy, officers are not more affected than ratings.

(d) *Drinking Habits*: Officers are said to drink more heavily than their men, and their susceptibility to infective hepatitis has frequently been attributed to this. There is no positive evidence to support this view. Officers who are teetotal or very light drinkers appear to be as susceptible as the remainder.

5. Alcohol. The consumption of alcoholic liquors is often assumed to predispose to infective hepatitis. Such an attack upon an old-established social custom is malicious and unfounded. A recent paper attributed the relative immunity of Indian troops to their teetotal habits. It would be equally logical to attribute the recent increase in infective hepatitis in England to the war-time restrictions on the manufacture of alcoholic drinks.

6. Fatigue, Mental stress, and Chill have been put forward as contributory factors, but I know of no good evidence in favour.

7. Food. Much work has been done on the relationship between diet and susceptibility to hepatic damage. I shall mention only one interesting feature, with the deliberate intention of being provocative. We have seen that infective hepatitis has shown a great tendency to attack armies during the past century. I am told that tinned food was introduced about 150 years ago, and that one of the main reasons for its introduction was the military necessity to feed armies in the field. Certainly, at the moment, a very large proportion of the soldier's food comes out of tins. Can there possibly be any connection between this fact and the great susceptibility of soldiers to infective hepatitis?

Summary

1. A rapid survey of the more important epidemiological features of infective hepatitis has been put forward as a basis for discussion.

2. A very brief history of the epidemiology of the disease has been given.

3. Evidence from experimental work and epidemiological observations bearing on the mode of spread has been mentioned.

4. Some of the factors which affect the development and magnitude of epidemics have been discussed.

5. Some of the factors influencing the susceptibility of individuals to attack by infective hepatitis have also been discussed.

Presented on request by Major George M. Brother, M.C., Epidemiologist, 15th Air Force.

Brief Preliminary Report on Epidemiological Observations in Current Infectious Hepatitis Season of 15th Air Force, and the Use of Gamma Globulin.

1. The incidence of this entity in 15th A.F. has been much lower this year than last, as attested by the November 1943 rate (cases per 1000 per annum) of 310 in contrast to the November 1944 rate of 43.

2. The 1944 season was marked by a great preponderance of cases in one Bomb Group. One third of all the air force cases during the last four months of 1944 were in this group which comprised less than 1/40th of the A.F. strength. The rate for the A.F. during this four months' period was 31 as contrasted with the rate for the group of 324.

3. This same location (of the highly infected group) was used by another group during November and December 43 who experienced rates of 250 and 510 for those months respectively.

4. Special studies have been carried on in this group during this outbreak in an effort to control it and also to determine the unusual preponderance of cases in this particular locality. The field occupied by the group was also used for an Italian air force unit of approximately 1600 personnel. No other groups of the air force were under similar conditions, and a special study and physical examination of the Italian troops was made in an effort to ascertain any association between them and the high incidence of hepatitis in the air force group. Evidence of acute infective hepatitis could not be found in the Italian soldiers nor in civilians in a nearby large town. The water supply was suspected as a possible mode of transmission of the virus but the weight of evidence did not substantiate this possibility. In the absence of other explanations for the high incidence in this group it seems most logical to assume that the disease is endemic in the local population in that area, notwithstanding the negative results of efforts to demonstrate this assumption.

5. Twelve per cent of the personnel of this group were infected between 23rd August 1944 and 29th December 1944. Three peaks occurring at approximately monthly intervals were observed during the outbreak. Attack rates in various categories were as follows:—

A. Personnel over 30 yrs of age	70	(per 1000 for the 4 mths period)
" under " " " "	128	
B. Officers	141	
Enlisted men	115	
C. Flying Personnel	150	
Ground "	102	
D. Seasoned personnel	103	
Non-seasoned personnel	135	

(Arrival in the theatre prior to 1st May 1944 was used as an arbitary date to qualify as a "seasoned" person, since no cases occurred in this group between 1st May 1944 and the beginning of the outbreak under discussion).

It is of interest to note that when the attack rates in the above categories are co-related the most significant factor appears to be whether the individual has been in the Mediterranean theatre over Six months. "Non-seasoned" were much more susceptible to this particular outbreak.

6. Representatives from the epidemiology board of the surgeon general's office attempted to evaluate the effectiveness of gamma globulin in the control of this disease. Their work will undoubtedly be published in the near future and no effort is made here to describe this research project. It would seem worth while, however, to report the early observations made as a result of injecting 10 cc of this blood product as a temporary prophylactic against infective hepatitis. Approximately half of the personnel received this injection and the remaining half were left as controls. During the four weeks following no cases occurred in the injected group, whereas 18 cases have occurred in the non-injected group. These preliminary results in this small experience certainly do not warrant definite conclusions but do seem to throw a ray of hope on the future potentialities in the control of this disease.

DISCUSSION — Infective Hepatitis

Lt. Commander Kaswell, R.N.R.

With regard to the incidence of infective hepatitis amongst naval personnel in the Mediterranean there is one interesting observation. We divided personnel into two groups mentally—one, shore-based personnel (those who man small ships attached to bases and who spend the majority of their time in harbour), and the second group composed of ships' personnel or sea-going personnel. The men who belong to shore-based personnel live under rather trying conditions, whilst ship personnel live in overcrowded conditions such as happen in war-time, although sanitary conditions on board are fairly good. If we compare the incidence of infective hepatitis as reported amongst these two groups, we find a rather odd comparison in that the rate among shore-based personnel for the first three-quarters of 1944 was approximately three times that of ship-based personnel. I do not offer any particular explanation for it, but these are the figures and I think they may be of interest.

Major H. B. Jackson, R.A.M.C.

During the winter of 1942-3 a large number of troops were in Middle East where there is an incidence of infective hepatitis, and moved up to Syria where there is little. At that time I was working in 11 CCS and I carried out a series of blood counts in the cases that came in. I started off by doing blood counts on these cases and one was struck by the fact that, in the early stages of the disease, in about 30% of the cases, there was a leucopenia, but in several cases when blood was taken during the first two or three days after appearance of jaundice, there was an increase of monocytes which formed 10 to 20% of the total white cell count. We carried out a very small series of white cell blood counts on cases in the pre-icteric stage of hepatitis and in these cases there was definite monocytosis and these did not rise until the onset of jaundice, and then fell a week after onset of jaundice, and in most cases soon reached normal. I feel that is a definite help in diagnosis and it certainly helped us. In some cases we found malaria parasites in the blood smear. In these cases there was no increase in the monocyte count. I just offer that as a possible suggestion as a help for diagnosis of jaundice.

American Officer.

At one time we were impressed by the fact that many of our patients showed considerable weight loss previous to the onset of jaundice. That was the time when the supply of rations was deplorably inadequate and they were not very palatable and it was nothing unusual for a weight loss of 10, 15, and 20 lbs throughout a unit. We suspected that malnutrition was one of the conducive factors in rendering this group of patients more susceptible to the disease. We have known from several hospitals that the incidence of hepatitis in infections amongst arsenic treated patients was always quite high. I would like to know from people who have had an opportunity of studying this disease in large numbers whether the incidence of jaundice in the arsenic treated group of syphilitic patients is higher than in the ordinary army population. I cannot help feeling that at times poor physical standard does not necessarily entail weight loss but it might be one of the producing factors.

Colonel J. H. Palmer, Consulting Physician, Canadian Corps

I was very much interested in those cases of non-icteric hepatitis which Colonel Barker referred to. As Colonel Dickson has pointed out in his opening paper we have had very few of these in the Canadian patients, and amongst the PUOs we have had we have attempted to see if some might fall into this group. May I ask if Colonel Barker would tell us a little more of these cases and what the percentage was compared with infective cases and describe a little bit more of the various groups into which he places them.

Lt.-Col. Harold H. Golz, M.C.

We have made a few studies in the Naples area in which you may be interested. Last fall we ran a cephalin cholesterol flocculation test for control purposes on 202 patients selected at random from the Venereal Disease and Orthopædic wards of the 182nd Station Hospital; of these, 17, or about 8.5%, gave positive results. We were able to follow up 13 of these 17 positive cases and found that 10 showed other evidence of disturbed liver physiology such as impaired bromsulfalein excretion, a recent history of hepatitis, etc.

As a result of this study it became obvious that the number of "false positives" was disproportionately large in those patients with primary and secondary syphilis. With the co-operation of Lt.-Col. John Hughes, 69 cases of early syphilis were gathered from the Venereal Disease wards of the 225th and 182nd Station Hospitals. When the test was done on these patients, positive results were obtained in 28% as compared with 5% in non-syphilitic controls.

In Malaria we have found the cephalin cholesterol flocculation test to be positive in every case. It becomes positive on the average on the 7th day of the disease regardless of whether or not the disease had been controlled by treatment and it remains positive for an average period of 30 days. In individual cases the duration of the positive test ranged between 11 and 59 days.

Finally, I would like to bring to your attention some studies that we have made on post arsenical jaundice. There has been much difference of opinion in the literature as to the etiological role of arsenic in these cases. Dible and McMichael studied a series of such cases (liver biopsies were done in several cases) and concluded that they represented cases of infectious hepatitis. Hanger and Gutman divided cases of post-arsenical jaundice into 2 groups: those coming after the first few doses of arsenic and those coming on later in the course of treatment. In the first group the serum phosphatase level was uniformly very high, that is, over 10 Bodansky units, and the cephalin cholesterol flocculation test was persistently negative. In the second group the serum phosphatase level was only moderately elevated, that is between 4 and 10 Bodansky units and the cephalin flocculation test was uniformly positive. These authors concluded that the jaundice in the first group was attributable to arsenotherapy and probably represented drug idiosyncrasy while in the second group the jaundice was a manifestation of "catarrhal jaundice" in liver sensitized by arsenic.

We have seen 24 cases of post arsenical jaundice and have continued to treat them through their icteric phase with mapharsen. Six of our patients fell into the first group just described. In 5 of these patients continued arsenotherapy had no untoward effect whatever, while the sixth man seemed to have an idiosyncrasy to the drug and became worse whenever mapharsen was given. In the second group of 18 cases coming on after the 10th injection of mapharsen and in which the cephalin flocculation test was positive and the serum phosphatase only moderately elevated, continued treatment with mapharsen had no deleterious effect whatever. These patients had a clinical course in no way different from non-syphilitic patients with acute infectious hepatitis.

Brigadier E. R. Boland.

As far as the treatment in our hospitals is concerned, it is of the cottage or garden variety. We keep our patients in bed and on as high a protein diet as we can manage and on the whole they do very well. For various reasons we would be unable to do all the liver function tests even if their value were not in doubt. We have to go by the feeling of well-being on the part of the patient. If he feels fit he goes back to duty. We cannot control him in the same way as Colonel Barker does. How far the patient's fitness conforms our clinical impression we do not yet know. The only change in treatment of hepatitis in our hospitals this year is probably that we give them a fuller diet than the year before. That brings one to the question of the very high protein diet which Colonel Barker has been giving to American soldiers and that brings us back to the question of steaks. I am not certain whether all our patients, not only cases of infective hepatitis, but also convalescents from other illnesses would not return to duty better and more ready to fight if they had a pound of steak a day. But unfortunately we are not able to supply that and are not likely to be able to. On the whole in 42 to 50 days most of our patients are able to return to duty and ready and fit to fight at the end of that period.

Brigadier E. R. Cullinan, Consulting Physician, East Africa Command.

One or two points I would like to raise as questions.

In the series I saw, one outstanding symptom was inability to eat. The patient would like to eat but could not. That, in a fairly large series, was the outstanding symptom—in 94% of the cases. Personally I think fever is a very deceptive method of diagnosis. It comes on at various times, is by no means constant, and it is very difficult to determine what it is. An officer at present in this hall had monthly attacks of fever. Nobody could make out to what it was due and then finally he turned yellow. Another point I want to ask about is the enlarged spleen. My experience has been that 5% is the figure. I think everyone agrees that the more you go into the question of hepatitis the harder it becomes instead of easier. I think it has been said that this is a disease of forward troops. It was not entirely so at the time of Alamein. At the time there was a considerable epidemic in the 9th Army in Syria. It was an interesting epidemic because the men were living in ideal conditions with excellent food, well nourished and housed and in a large variety of situations and had a variety of water supply so that one could put water out of the question. Altogether they had a variety of food supplies with the exception of the bulk foods. They were not exposed to undue fatigue, chills, dysentery, or anything when they got their attacks of jaundice. The question was raised of biting insects but all the bites these men were getting were from ordinary biting insects. The peak of the epidemic was two months after the peak of the secondary dysentery epidemic of the year. After the first epidemic there was no increase in jaundice. There were not a lot of flies. It was too cold. One thing that was interesting was that it certainly was not a dormitory spread. Men were sleeping in one brigade in dormitories of 20 at a time, with one case per dormitory. I want to ask a question about one more point and that is about the escape of new troops or people coming into a camp where there is an epidemic. That has been seen in many places in the Middle East and was originally pointed out at an agricultural school in Jerusalem. What is difficult to understand is that the length of time in a given theatre does not seem to matter. In one brigade in Syria, one battalion had just come out from home, one had just come back from Libya, most of the men had been out for a couple of years. One of the battalions had been in the Middle East for three years and hardly had any reinforcements. Suddenly they had 50 cases in that battalion. It seems to be a very difficult thing to explain. One more point—it has been suggested that the place was infected. If so, how does this happen? At the end of 1943 there was a camp really very dirty into which troops entered, got no jaundice and then left. A battalion came in which had been in the Middle East for some time and they immediately got jaundice, and hadn't had it before. In about six weeks or two months the whole battalion moved away and another came straight in who had had no jaundice. There was not a single case in that battalion.

Major D. Prieskel, RAMC

There are one or two suggestions one could make. One is that infective hepatitis seems to occur at a time of the year when the days are still warm and the nights are cold. It is possible, therefore, that short exposure to chill plays a large part. In October the days are still warm but at night we tend to go around in day clothes and we feel cold. The difference between the soldier and the officer is that whereas the soldier goes to bed in his clothes, that is his underclothes, the officer strips and for a short time he is exposed to chill. He gets into a camp bed and it is some time before it is warmed up. I suggest it is this exposure to chill which helps to activate the virus which may have been present in the blood for months. In other words it is similar in many ways to rheumatism. You get the virus and keep it for a long time, but it only becomes activated by certain climatic effects. In this respect it would be interesting to know regarding Brigadier Cullinan's remark regarding the second unit which came in and didn't develop jaundice on the same site whether they came in at a time of the year when it was not prevalent.

Answer by Brigadier Cullinan—They came in at the peak of the epidemic.

Lt.-Col. J. E. Caughey, NZMC

During the past 6 months we have had 784 cases of infective hepatitis. There have been no deaths. Eighteen have had to be regraded Category E and returned to New Zeland. We have followed a series of the severe cases with serial investigations of the blood, the urine, and stool.

Our tests of liver function have been the cephalin flocculation, Britton's modification of the Takata Ara test, albumin-globulin ratio and serum protein.

The blood picture in severe cases has been that of a moderate anæmia with a slight macrocytosis generally. The counts usually ranged between 3.5 million and 4.5 million reds. The Mean Corpuscular Volume on the high side of normal 95-100. Sternal puncture on three cases was normal. One showed an early erythroblastic marrow picture.

Intramuscular campolon gave no notable reticulocyte response in one case with a red count just below 4 million. The anæmia has improved synchronously with the recovery of the hepatitis.

In some of the long term cases we have seen various degrees of avitaminosis—perleche, sore tongue, tender calves, exaggeration of deep reflexes have been the chief features. In some a patchy sensory loss of common sensation over the legs or arms. There has been subjective glove and stocking impairment but no objective loss.

Our impression from a short experience is that the Takata Ara test as modified by Britton gives a reliable indication of the liver function. In our experience the cephalin flocculation test has not proved as satisfactory. Most of the severe cases at some time have an obstructive jaundice as evidenced by an immediate direct Van Den Bergh and an absence of stercobilin in the stool.

We have used a strict fat free diet, with high protein content, a total caloric intake of approximately 3500. We give 60 ozs. of dried skimmed milk daily. Extra vitamins are given in the form of multi-vite tablets and yeast 1 drachm in 5 ozs. of water daily to every patient. Our clinical impression is that our cases do well under this treatment. There is no complaint of hunger as previously noticed and there is a steady notable increase in body weight in almost all cases. The patients appear much more fit to resume duty than those who have been treated with lower protein diets in our previous epidemics in the Middle East.

Colonel Perrin Long, M.C., spoke about jaundice after yellow fever inoculations and said that it had been found that men who had had this, were twice as likely to get infective hepatitis afterwards as those who had had the inoculations without getting jaundice. (ED: It is regretted that Colonel Perrin Long's remarks were not recorded at the time by the stenographer).

Colonel John P. Williams, M.C.

The excellent results obtained by our British Allies are just a shade better than those which we have to report—96% to full duty and an average period of hospitalization of 51 days. We feel reasonably sure that our own figure for return to full duty is too high since it is based on our experience in the disposition of 250 cases during the past four months and is heavily loaded with the milder cases. Many of the more severe and the relapsing cases are among the more than 300 still hospitalized and still to be disposed of. On the other hand, our average period of hospitalization has diminished each month and should diminish still further. During the first three months we did not take full advantage of the much more rapid improvement under the new dietary regime and furthermore because of the very large number of cases, laboratory check-ups were done by roster at 10-day intervals which meant that almost all patients received at least 3 weeks of bed rest, 1 week ambulatory about the hospital area and finally 2 weeks in the Reconditioning Section on general hospital diet. Under this plan the minimum period of hospitalization was 6 weeks.

During December and January we have varied this considerably so that now about 30% are discharged within 5 weeks and another 20% by the end of the 6th week. We are convinced that these percentages can be safely increased until 80% to 90% can be returned to full duty within 6 weeks, but we are going ahead slowly, keeping in mind the basic principle stated by Brigadier Boland yesterday in discussing malaria, that we save nothing by sending unfit men to duty.

Our reconditioning period is designed to give the liver a good shaking-up so as to bring out latent activity and precipitate a relapse in the hospital if one is to occur. By the end of the first week of this final period these soldiers are required to take 25 minutes of callisthenics including "side straddle hop" and double time, close order drill and a 5 mile hike, and 40 minutes of volley ball in addition to assignment to duties about the hospital in the afternoon. Experience has shown that soldiers who pass this exercise tolerance test asymptomatically rarely have recurrences after return to duty.

There may be some question as to the specific effect of our high protein, high methionine, low fat diet on liver metabolism and it might be claimed with much truth that such a diet would be good for whatever ailed anybody. As a matter of fact even our surgeons are convinced that when skin grafting is done in these patients the donor areas heal in 1/3 less time than in their own patients on general hospital diet. Whatever the mechanism of its therapeutic effect may be the results have furnished a striking contrast to those obtained in a group of 40 unselected cases which was treated by the old method of rest, low fat diet and multivitamin capsules. This study was undertaken both as a check on the comparative severity of the 1944-1945 epidemic and on our statistics for the previous year. So far, the results would seem to indicate that the disease this year is at least as severe as last year and probably more so as the following incomplete data show:

(a) At the end of 60 days of hospitalization only one of the forty has been well enough to return to combat duty. The rest are still sick in hospital.

(b) Symptoms have persisted, the return of appetite has been slow with the result that caloric intake has been low and weight gain negligible in many cases, and less than 1 pound per week for the group.

(c) Relapses have been frequent even while on the ward as bed patients. The larger group on the hepatitis diet showed the following:

(i) Disappearance of symptoms and return of appetite was markedly accelerated so that by the third or fourth day the vast majority were taking the full diet and asking for more.

(ii) The gain in weight has averaged 2.5 pounds per week (including all patients).

(iii) The general sense of well-being is very striking and morale has been maintained at a high level in spite of prolonged hospitalization.

(iv) Relapses have occurred very rarely on the ward and have been reduced to one-third or one-quarter their previous frequency during the exercise tolerance test.

(v) As compared with last year's figures, 25% more men have returned to combat duty.

(vi) The period of hospitalization has already been reduced 25% and will almost certainly be reduced another 10%.

(vii) The 96% returned to their units for full duty were actually fit for combat.

Only one other thing occurs to me which might be worth mentioning. We have had two desperately ill patients who in spite of what appeared to be a perfectly hopeless prognosis, began to show improvement immediately following the transfusion of whole blood from convalescent patients. The first was one of our own nurses who remained comatose for 6 days, whose prothrombin time dropped to 15% of normal with hæmorrhages into the skin, sclera, retinæ, and from all mucous membranes. In addition to 2000 c.c. of glucose and 4 units of plasma daily she received in all 10 transfusions of 500 c.c. of whole blood, the last 4 of which were from convalescent donors. She made a good recovery and was evacuated to the Zone of the Interior on full diet on the 36th day of her illness. Incidentally her hæmaglobin went to 17.5 gms., R.B.C. to 6,000,000 and the volume of packed cells was 60%.

The second of these was a battle casualty who came down with hepatitis while a patient on one of our surgical wards. During the next two days he became very drowsy and the icterus index mounted rapidly to 150 units. Coma supervened and persisted for 12 days during which time he received plasma, glucose, whole blood and 300 c.c. of gamma globulin which was available at this time. Since there was no improvement and prognosis seemed hopeless, he was given 3 transfusions of convalescent blood (500 c.c. each) as a final gesture. Following the third transfusion he could be aroused and began to take fluids. From that time onward he has made steady improvement and is now taking the full diet.

We realize that such clinical observations are notoriously unreliable, and that the virus of hepatitis probably persists in the blood of most convalescent patients so that the routine use of such a procedure is certainly not justified. On the other hand in acutely toxic patients either in coma or verging on it where the outlook is extremely grave, our inclination is to resort to it considerably earlier than we did in the cases cited.

Lt.-Col. C. B. Schoemperlen, RCAMC

I would like to endorse the remarks of Major Truelove, about the epidemic amongst the Canadians in Sicily in 1943. Our hospital arrived in Sicily on 19th July 1943, nine days after the 'Y' Division. During the first six weeks, i.e. to the end of August only twelve cases of hepatitis were admitted. In September there was a sudden increase to 278 cases and in October to 500. Admissions kept on a fairly even keel until March 1944, when the epidemic began to subside.

In 1944 however we found that according to our admissions the epidemic started somewhat earlier; i.e. at the end of July and early part of August and that there was a marked decrease in December and January. Thus the epidemic started this year had shown a marked shift to the left.

Another point noted was that the majority of troops who arrived in C.M.F. in July 1943, who contracted the disease, did so that fall or early in 1944, or not at all. This was exemplified by reviewing 700 cases admitted to this hospital from June to October 1944. Only 100 of these came to this theatre in July 1943 or before, the remaining 600 came in November 1943 or later.

We have admitted a similar number of cases to Colonel Dickson, i.e. 3,000, with only one death; a soldier, 23 years old. It is our impression that the epidemic was more severe this year than it was in 1943. We have more cases of deep jaundice and more cases seriously ill and we feel that the morbidity is higher than in 1943. I would like to know if anyone else has noticed this.

Summing-up by Opening Speakers

Lt.-Col. R. C. Dickson, RCAMC

A question has been asked regarding the incidence of jaundice in patients receiving the routine arsenical treatment for syphilis. Lt.-Col. Mitchell, then Officer i/c Medical Division No. 1 Cdn. General Hospital, reviewed this problem in Canadian troops stationed in England about two years ago. He found that the incidence of jaundice in men receiving arsenical treatment was thirty times that in the remainder of the troops.

Brigadier Cullinan described the incident of a fresh unit taking over a camp site from a battery which had sustained a high incidence of infective hepatitis. The incidence of the disease in the new unit did not rise although it arrived in the new site at the peak of the epidemic. The situation corresponds closely to that provided by the arrival of the 'X' Cdn. Division in Italy in November 1943 when the epidemic in 'Y' Cdn. Division was at its height. The incidence of infective hepatitis in the 'X' Division remained low until the 1944 epidemic. It was felt that although the 'X' Division arrived at the peak of the epidemic, it escaped because the peak of infection, if the incubation period is considered, occurred four to six weeks earlier.

Colonel Marion H. Barker, M.C.

We have many reasons to believe that patients may come in after illness extending over many months. One can carry this virus over a long time before clinical manifestation. The same is true in the convalescent period.

With regard to Brigadier Boland's remark that all patients would be better off with more steak I am sure that is true, and surgical patients would do better in the hepatitis programme! Regarding vitamin K, our experience last year was that vitamin K did not do very much for us, and we could not derive much benefit from it. We gave quite a bit of it, but we were forced to feel if a man had enough liver to work with perhaps vitamin K will do some good. I do not think we can depend on it.

I would like to tell you that in 1942 we experienced our first study of hepatitis. There were two short of 700 cases admitted to the hospital with jaundice. We went into the unit set-up and found continual cases of men who were complaining but who would not go into dock. When we went into the group we found that we had a condition of 2300 cases of hepatitis without jaundice. It seemed to us then that we must look upon them as having an incidence of about 3 to 1. I know from hospital experience that men seem to get to duty much quicker at the end of each season when the disease seems to be a little milder. We have had more relapse rates in that later stage of what we call hepatitis without jaundice than at any other.

In that matter of insects we have no evidence.

The question of alcohol I gather is not taken seriously, from the smiles which greeted the remark. I might tell you we have looked into this and find that the men who were sick with jaundice and were teetotal were in higher proportion than the men who admitted to getting really drunk twice a week, as a minimum standard. We find from the results of last year's study that they show an attack rate in teetotallers of 68 per thousand as compared with 18 imbibers.

Regarding sex, it is interesting to me that married couples who live together in the full sense catch the disease out of proportion to those only dining together.

Major S. C. Truelove, RAMC

I was interested to hear Colonel Perrin Long's remarks about Colonel Keall's investigations into the susceptibility to infective hepatitis in soldiers who were suffering from a post yellow fever jaundice. I did know of various figures, but it seems to me that the point Colonel Long makes is not necessarily true. Although it is probable, it is not certain that the agent is the same in the two diseases, and even if it is the same we do know that in the case of the natural disease the incubation period does vary apparently according to whether the agent is given by mouth or injected, and it seems to me quite conceivable that if you get one you might quite easily get another. Therefore I think that this particular observation in relation to the identity of jaundice is not necessarily proved. I was also interested in the observation that the time of onset of an epidemic might bear some relation to the endemic level of the disease. It is quite true that the highly susceptible troops, the New Zealanders and Canadians, have taken the epidemic very early this year and it is also true they had run a high endemic level. They may run it because they are susceptible, and if you have taken figures for the New Zealand force (and their figures are extremely good and are given right back to the time they came to Middle East), you find there has been a steadily rising endemic rate ever since 1941. Whereas their epidemic was early in August 1942, if I remember myself, this rising endemic rate beginning just about the end of June this year, last year they had a small endemic rate which occurred almost entirely in January, though their endemic level was high the year before. Therefore I personally am not particularly convinced by these observations. Further, sir, I would like to say it does me a lot of good to hear a person of your experience put forward so many posers which you are unable to answer.

Brigadier E. R. Cullinan, Consulting Physician, East Africa Command.

There was an epidemic among Somali Scouts, but no epidemic among British troops in that area. They all get exactly the same food from the same source and the same canned food, but the Somali Scouts did not get very much canned food. Before closing I would like to thank the speakers for their opening papers and others who have brought valuable experience.

Wednesday, 31st January, 1945

MORNING SESSION

Subject:

Penetrating Wounds of the Chest

Presiding:

Brigadier E. R. Boland, Consulting Physician

Allied Force Headquarters

WAR WOUNDS OF THE CHEST ON THE ADRIATIC SECTOR

by

Lt.-Col. A. L. d'ABREU, RAMC

(*Read by Major J. W. Litchfield, RAMC*)

It is a pleasure to be able to report a very considerable improvement in the prognosis of serious war wounds of the chest on the Adriatic sector. In the last year we have received nearly 1,000 cases: in this short paper two series of casualties are reported.

(1) Those admitted from the Sangro battle at the close of 1943.

(2) Those from the Gothic Line battle at the close of 1944.

An analysis (Table I) is of interest.

TABLE I

ANALYSIS

	Number Admitted	*Empyema Rate*	*Deaths*
SANGRO			
Oct., Nov., Dec.	260	77 (33%)	15 (5.7%)
GOTHIC LINE			
Oct., Nov., Dec.	373	31 (12%)	5 (1.4%)

1. The Deaths

In the first series 13 were chiefly due to gross empyemata, some associated with serious lesions such as paraplegia (1), a large diaphragmatic hernia (1), severe multiple wounds (1), a shell fragment embedded in the aorta (secondary hæmorrhage) (1). These figures (reported in the Lancet (Lieut-Colonel d'Abreu, Major Litchfield, and Major Hodson)) emphasize the gravity of war wound empyemata.

The contrast in the second series (5 deaths—1.4%) is striking. Three were suffering from complete paraplegia with hæmothorax: one was a death six days after the closure of a large œsophageal tear and the fifth had a shell wound brain abscess (drained) together with a pericarditis and a huge lung foreign body (removed). No patient died from empyema alone.

2. The Decrease in Empyema Rate. This can be attributed to several factors.

(a) *Improved Evacuation.*

In spite of the lengthy line of communication, patients have reached the centre earlier because of an excellent air evacuation service. There is no doubt that penetrating chest wounds that arrive early at a hospital provided with a specialist chest service, which includes facilities for thorough radiological and bacteriological examinations, a special thoracic surgical equipment including cyclopropane anæsthesia and the apparatus for its administration, have a better chance of recovery than when held at units lacking these advantages. It can be reported confidently that these casualties have travelled extremely well by air after their early physiological derangements have been corrected in the first 24-48 hours by resuscitation, the closure of open sucking wounds and the aspiration of blood and air. The worst travellers are those with developed or developing empyemata and those who have just undergone rib resection and drainage: such arrive in far worse condition than those with a large simple hæmothorax. The chief function of the forward unit lies in the correction of the disordered physiology of the chest.

(b) *Improved Surgical Treatment in the Forward Centres.*

In the Sangro battle many more patients were admitted with open sucking wounds, often infected, than was the case in the Gothic Line operations. The improvement is due to a change in the forward surgical policy: wounds are now excised in accordance with accepted general surgical principle and the suck closed by suture of the muscles with the skin left open for delayed primary suture to be done at the Centre. This is infinitely preferable to the vaseline gauze occlusion method.

(c) *More Thorough Aspirations.*

Hæmothoraces are aspirated adequately and early in the forward centres. This has had two notable effects—patients arrive with less dyspnœa and the incidence of infected clotted hæmothorax and of frank empyema has notably diminished. If blood is removed early it is not there to clot and if lung re-expansion is obtained there is less space in which purulent empyemata can develop.

(d) *The Routine Use of Penicillin—Intra-Pleural Instillations.*

From figures gathered at this Centre the instillation of 60,000-120,000 units of penicillin in 10 c.c.s. saline at the first two aspirations has greatly reduced the infection rate of hæmothoraces. The local instillation is in every way preferable to the general parenteral administration: the pleura is a most effective barrier against the passage of penicillin into a hæmothorax cavity.

(Lt.-Col. d'Abreu, Major Litchfield, Major Scott Thomson).

From these observations an outline of treatment (1) at Forward units and (2) at Base can be suggested.

1. FORWARD AREA TREATMENT.

The two stage conception of the treatment of wounds has become accepted in this theatre of war. At the primary excision operation no detailed attempt is made to remove foreign bodies or to correct anatomical defects unless this is easily done—the main aim is to render the wound safe. The principle is extended to the thoracic casualty and in spite of the success of many brilliantly executed major thoracic operations in the first 24 hours it is generally accepted that it is unwise to further embarrass the shocked dyspœic patient by major thoracotomy. A search for lung foreign bodies is unjustifiable unless it is readily seen through the wound or good radiology is available. The ideal forward operation is excision of muscle, and shattered rib fragments followed by suture of the muscles by catgut and skin being left open. Penicillin powder and vaseline gauze is then applied and the patient should reach the Base Centre within 4-8 days to make de-

layed primary suture possible. If the patient is held longer than this, opportunities may be lost. If there is a hæmothorax present this should be aspirated once or twice, 60,000-120,000 units of penicillin in 10-20 c.c.'s saline injected, and the patient then sent off by air.

2. Management at Base Hospital Level.

(a) *Investigation.*

A routine assessment of the patient starts with a mental and written synopsis of the history. The site and number of the wounds are noted and this information must be available to the radiologist as on it is chiefly based his decision as to whether more than the routine postero-antero and lateral views is caused for. For example—one entry wound on the chest or surrounding areas and no visible metallic body on the plain radiograph demands a screening examination to exclude retained missiles in the mediastinum and heart (small fragments being frequently overlooked if this precaution is not observed). Previous notes which indicate the type of wounds and type of hæmothorax are of great value. A clinical examination is followed the morning after admission by a routine postero-antero and lateral radiograph; this is quite essential and is never omitted except under exceptional circumstances and is regarded as important as any surgical operation. These radiographs are essential for successful aspiration to be carried out with the minimum number of "negative" aspirations. The number of anterior hæmothorax collections shown up by the lateral radiograph is high.

(b) *Treatment—Chest wall wounds.*

A high priority is given to the early closure of wounds by delayed primary suture. If the wounds are clean simple suture is done, if 'dirty' and including fractures of ribs or scapula requiring re-excision they are closed by the penicillin tube technique. This is of the greatest importance because the gravest pye-pneumo-thoraces seen are those with broken down, septic sucking wounds.

A short analysis of the type of work done is of interest. To given a fair estimate the patients discharged during the months October, November, and December, 1944 are analysed. The cases include the Gothic Line casualties that have been discharged and also cases received from Yugo-Slavia.

TABLE II

Total number of Chest wounds discharged or died — October, November, December, 1944 — 402.

Hæmothorax	143
Lung abscess (3 around foreign bodies)	9
Pleural foreign bodies (All removed)	14
Mediastinal foreign bodies (7 removed)	10
Pyothorax (British)	37
(Yugo-Slavs)	16
Lung foreign bodies (31 removed by operation)	51
Cardiac foreign bodies (None removed)	4
Endothoracic foreign bodies (All removed)	9
Deaths	5

Major Hodson will describe later our experience of atelectasis. It is only possible to indicate briefly the salient parts in treatment.

3. Hæmothorax

The arguments in favour of careful thorough aspirations are too overwhelming and too well known to require reiteration. It is important to regard this operation as important enough to make special arrangements for its efficient performance; only the most seriously ill are aspirated in bed, the remainder are carried to a special aspiration room in the charge of a trained nursing orderly who is responsible for the care of apparatus, the supply of penicillin. The notes and radiographs always accompany the patients: the operation is a deliberate unhurried one. A note is made of the site of aspiration, the type of fluid obtained, and a specimen of every aspiration is sent for bacteriological examination: this essential allows an intelligent use to be made of penicillin and avoids useless instillations. If at the first aspiration the fluid is apparently infected penicillin is injected but all later therapy is controlled by the bacteriological findings. The patients undergoing aspiration are radiographed at frequent intervals to estimate their progress and to eliminate the possibility of overlooking loculations.

In the three months under consideration nine operations have been done for the evacuation of clotted, multilocular hæmothoraces, (3-5 weeks after wounding). As Major Nicholson is to consider this subject in detail little need be said here except a few words in favour of a little conservatism. Certain cases are absolute indications for this operation. We do not favour operation for small basal clotted effusions that are running an apyrexial course for most of these do very well on breathing exercises and frequently show a surprisingly rapid return to normal on the radiograph.

4. Pyothorax and Infected Hæmothorax

The Place for Penicillin

This drug is of great benefit in the sterilization of a pleural cavity infected by penicillin sensitive organs and many patients can be cured entirely by its use combined with aspiration, 120,000 units for large cavities and 60,000 units for smaller in 10-20 c.s.s are injected on alternate days until three specimens of the fluid have been reported to contain no pyogenic organisms on smear or culture. Frequent radiological estimations of the cavity are necessary. Towards the end of the treatment the fluid becomes serous and the interval between the aspirations can be lengthened to once or twice a week. Full breathing exercises are necessary coincidents. General parenteral penicillin therapy is only indicated when pulmonary suppuration or severe lung infection exists together with the infected hæmothorax.

The Place for Surgery

Rib resection and closed drainage are indicated as follows:—

(i) For large empyemata associated with total lung collapse—if these are left undrained the deposit of fibrin hampers lung re-expansion and chest wall movements.

(ii) For persistent gram negative effusions.

(iii) For cases with large broncho-pleural fistula.

(iv) Septic sucking chest wall wounds with an associated empyema call for rib resection and drainage in association with re-excision and penicillin closure of the "sucking" wound.

(v) For most empyemata associated with pleural missiles or peripherally placed lung missiles. Some such empyemata are curable by aspiration and penicillin instillation after thoracotomy without drainage.

(vi) For empyemata shown radiologically to contain fibrin masses, clot clearance is indicated. If the cavity is small and the organisms penicillin sensitive, again the chest is closed without drainage and is treated by the aspiration-penicillin-instillation technique.

(vii) Bile empyemata associated with right thoraco-abdominal wounds.

We have completely disregarded the text book advice that empyemata are not to be drained until the lung re-expansion has left a loculised pocket. Such a happy natural history is rare in war wound empyemata. It is important to remember that war wound empyemata are far more complicated than peace time empyemata and require very close radiological checking because of the bizarre shapes of the cavity due to uneven lung re-expansion, the commonly associated bronch-pleural fistula and the unpredictable formation of adhesions and loculi.

5. Intra-Thoracic Missiles

We have removed nearly 200 in the last year. In the quarter under review 60 were removed by operation, 31 from the lung, 14 from the pleura, 7 from the mediastinum and 8 from the endothoracic fascia. There was one death, a soldier with an associated cerebral abscess (due to a missile and not embolic). Four cardiac foreign bodies were seen but none was operated on—these all showed clinical evidence of cardiac dilatation and muscle damage on the electro-cardiograph. They all made good immediate recovery on the strictest bed rest.

Indications for Missile Removal

It is our practice to remove all intra-thoracic foreign bodies of 1 c.m. or more in size. Our experience has shown that pleural foreign bodies if not removed are very common associates of empyema—they should all be screened on the day of operation. We remove lung foreign bodies to prevent the complications of infection, (lung abscess and subsequent bronchiectasis) and hæmoptysis: it is in keeping with the general surgical principle that if possible foreign bodies should be removed. In the case of the mediastinum the removal of foreign bodies is wise—in view of the danger to the structures there: infection around them has been common especially those that have injured the vertebral column. It would be out of place at a meeting of this type to discuss technique. Three facts of interest may be given:

(I) The need for expert radiological localisation.

(II) The need for anæsthesia of a high skill.

(III) The avoidance of post operative drainage except in exceptional circumstances.

Instead of reliance being placed on tube drainage we prefer aspirations and where indicated the use of penicillin instillations.

6. Lung Abscess

Nine were discharged in the three months under review.

Three were clinically mild and were around lung foreign bodies—these are cured early by the removal of the foreign body. The others due to infection in collapsed lobes, in air containing missile tracks or breaking down lung hæmatomata have been treated by postural drainage and general penicillin; the addition of the latter has led to surprisingly good results. Two were cured by surgical drainage: surgery is indicated if improvement is not rapid under the expectant regime. The course of the disease requires constant radiological checking.

Conclusion

An attempt has been made to describe the management of the common conditions. It is impossible to discuss the many other fascinating conditions seen—such ones observed include blast phenomena, patchy atelectasis, œsophageal and other mediastinal lesions. Over 80 thoraco-abdominal wounds have been treated and in passing it may be mentioned that over 33% have had empyemata.

In conclusion stress must be placed on the value of breathing exercises at all stages: these are carried out under the supervision of the physiotherapy staff, the emphasis being placed on the inspiratory type of exercises as taught by MacMahon which are in every way preferable to the forced expiratory ones encouraged by the blowing type.

Summary

1. A marked improvement in the results of war wound of the chest is presented: this is reflected in a fall of death rate from 5.7% to 1.4% and of the empyema rate of 33% to 12% in two comparable series of casualties on the Adriatic front.

2. An analysis of the deaths and the factors responsible for the diminished incidence of these and of the empyema rate are described.

3. A suggested outline of treatment for (a) Forward, (b) Base units is submitted.

CLOTTED HÆMOTHORAX

by

Major W. F. NICHOLSON, RAMC

Introduction

The clotted, multilocular or "organising" hæmothorax is a condition which is sufficiently common to demand our attention. Though spontaneous absorption does occur slowly in some cases, in the vast majority infection is present and the neglected clotted hæmothorax is a common cause of empyema. The infection is often low grade in these cases, so that pus is slow to form; penicillin still further delays the onset of suppuration. But in many cases an empyema eventually is formed. Evacuation of the clot and local chemotherapy will frequently prevent an empyema from developing especially if the operation is done in good time. It is therefore important that these patients should be evacuated to the Base as soon as they are fit to travel, if possible, not later than the tenth day. Once suppuration occurs, though surgery may still be of value in limiting the infection, it is unusual to avoid drainage of the pleural cavity.

Incidence

There were 93 clotted or loculated cases in 1,027 consecutive hæmothoraces (9%). Though there were other small basal clots which were never confirmed by operation, these raised no special problem and have not been included.

Pathogenesis

Clotting is twice as frequent on the right as on the left side. There were 61 right and 32 left clotted hæmothoraces. Though there is a higher percentage of fluid hæmothorax on the right, owing to the greater mortality in left-sided wounds, it is only 56% right to 44% left, so that there is a real increase in the incidence of clotting on the right side. We have been impressed with the association of clotting with thoraco-abdominal wounds on the right. It may be that it is only the greater tissue damage that favours clotting, but the most likely explanation is the low grade infection associated with liver wounds. Though it did not appear at first that infection favoured clotting, there is now do doubt that low grade infection is very common. In over three-quarters of the cases in which we have evacuated clot, organisms have been found in either the clot or fluid, or fibrin peeled away from the lung surface; the organism most frequently found is the staph. aureus. This is an organism which produces no fibrinolysin, so that it is not surprising to find it present in these cases. Low grade infection is therefore common in the clotted hæmothorax, not infrequently associated with a retained foreign body.

Morbid Anatomy

There are two distinct types:—

(a) The multilocular hæmothorax in which fibrin webs divide up the pleural cavity into many loculi, each containing a little liquid blood. Here aspiration is tedious and frequently unsatisfactory, moreover some loculi may be infected and others sterile, till later on the whole pleural cavity becomes infected.

(b) The rarer type—a hæmatoma, in which the blood forms a solid clot usually in the postero-basal part of the pleural cavity; serum which separates from the clot floats to form a separate loculus in front.

Diagnosis

This depends on a difficult or failed attempt at aspiration, both posteriorly and in the axilla. In the loculated type fluid may be tapped, but very soon ceases to flow; perhaps 20 to 30 ccs is as much as can be aspirated at each site. The fibrin webs block the needle. Even with a wide-bore needle, though more fluid can be aspirated it is rare for the hæmothorax to be completely evacuated. Clots in the aspirated fluid are good evidence of other clots remaining in the pleaural cavity. In the hæmatoma, aspiration is usually unsuccessful except for serous fluid from an anterior puncture. Sometimes the needle can be felt to impinge on a solid clot. X-rays of the loculated hæmothorax are so typical that they are readily recognised.

Case Report

(*Hopewell*, 18.) This patient was wounded at El Alamein in October, entry wound in the neck in the right posterior triangle, the missile retained behind the lower end of the sternum. One month later, when he came to us, he had a loculated hæmothorax. He continued with low fever until the hæmothorax was evacuated. The X-rays show a typical loculated hæmothorax. No organisms grown from the clot or fluid in this case.

It is the solid clot which is more frequently missed. Here there is basal opacity, typically extending up in the posterior gutter so that it tails off above. This is frequently thought to be thickened pleura, or a thin layer of fluid; but irregular air spaces in the opacity are typical of clot. The pleura is not sufficiently thickened at this stage to cause such a dense opacity, which must be either due to fluid or clot. If no fluid can be aspirated, it must be clot.

Case Report

(*Capt Booth*, 5.) This Officer was wounded in February 1944, a perforating GSW on the right from the 6th space in the mid-axillary line to the 10th space in the scapular line. X-rays show a clotted hæmothorax—this was chiefly solid clot. Three aspirations, all difficult, yielded only a little fluid, and clots. Gram $+^{ve}$ bacilli and pus cells were present. Operation showed a solid hæmatoma. Evacuation of clot and decortication.

Fever to 100° is usual, and does not necessarily indicate that infection is present, though it is common enough.

Treatment

Conservative

There is no doubt that some clots are absorbed slowly; twelve of the larger and many small basal clots have been treated conservatively: but absorption of large clots is slow and usually leaves pleural

thickening with limitation of movement. This is not surprising when we consider the frequency of low grade infection in such cases. The tragedy of conservative treatment when generally applied is that many cases will ultimately develop empyemata, at a stage when the chest wall is already "frozen" by thickened pleura. As Col. D'Abreu and his colleagues have stressed in a recent article, fibrin is very excessive in these empyemata, which are often very loculated. Drainage is therefore difficult and may be impossible without breaking down some of the fibrinous septa.

Operative Measures

Though penicillin may sterilise many of the loculi in a loculated hæmothorax, it does not always reach the centre of fibrin clots. These, therefore, remain a source of infection. It is therefore generally agreed, amongst surgeons, that the clots should be removed. Thoracotomy with evacuation of all clot and fluid greatly decreases the risk of an empyema developing. The controversy arises over the treatment of the empty pleural space, and here there are two policies. One is to close the chest, leaving penicillin in the dead space, repeating aspirations with penicillin replacement till the lung expands to obliterate the dead space. The other is a more radical operation, by which the lung is encouraged to expand immediately so that no dead space remains. This is decortication. At our Centre we have favoured decortication because we have been impressed with the toughness of the fibrin lying on the visceral pleura. When this is stripped away a normal thin shiny visceral pleura is displayed and the lung expands easily. Moreover, organisms are frequently grown from this fibrin "peel" even when they are not present in the clot or fluid.

Case Report

(*Pte Hall*, 6.) This man was wounded in May, 1944, with GSW entry over the left shoulder and the missile retained in the body of the 7th dorsal vertebra. Complete collapse of the left lung with an uninfected hæmothorax. Thoracotomy for removal of the missile two weeks after wounding; a decortication was done at the same time, although the fibrin was not very thick on the lung surface. A pure growth of hæm. staph. aureus was obtained from the fibrin "peel". X-rays show post-operative result, no empyema, and at Con. Depot 6 weeks later.

Thus, a more complete operation not only allows immediate lung expansion, but also removes more infected material. If a pulmonary foreign body has to be removed, or a broncho-pleural fistula requires repair, suturing of the lung is much more satisfactory after the fibrin has been stripped from its surface. When the operation has been completed, the lung is expanded by the anæsthetist and the chest is closed with temporary intercostal drainage for the first 2 or 3 days.

Case Reports

(*Cpl. Earl.*) Wounded end of October, 1944, by mortar, entry in 7th space left paravertebral line, a small foreign body retained in the lingula lobe. Four aspirations with penicillin replacement, getting increasingly difficult, before operation 3 weeks after wounding. Large basal hæmatoma (2 pints) with an anterior collection of fluid and fibrin. Staph. aureus grown from the blood clot, "peel" and fibrin clot, but not from the fluid. Decortication, fever settled promptly, Con. Depot 6 weeks later. X-rays before and after operation.

(*Gdsm. Jago.*) Wounded end of September, 1944, entry in right anterior axillary fold, a fragment being retained in the right posterior chest wall. Four small aspirations of a loculated partly clotted right hæmothorax, the fluid containing pus cells, but sterile. Six weeks after wounding, thoracotomy. A loculated hæmothorax with the lung adherent along the oblique fissure (site of entry) but elsewhere collapsed. Clot in the basal cavity and loculated clot and fluid in the upper. Decortication and temporary drainage (4 days). Though the clot and fluid were sterile, non-hæm. streptococci were grown from the "peel". X-rays show subsequent expansion of the lung, no empyema developed, and as will be seen from the temperature chart, fever settled very soon after operation.

One criticism of the method is that there is a theoretical danger of insufflating septic material into remote bronchioles when pressure is applied by the anæsthetist; we believe that this is not a real danger in most of these cases; the lungs are not wet, and are in no way comparable to the septic bronchiectasis of civilian practice. Routine post-operative bronchoscopy in a series of cases showed so little secretion that it was considered unnecessary.

Another criticism is that a wounded lung requires time to heal and it may be better to leave it collapsed until healing is complete.

The experimental work of Montgomery suggests, on the contrary, that the process of repair in lung wounds will be quicker and more complete in the fully expanded lobe. The conditions which encourage healing in a tuberculous focus are not necessarily of equal value in war wounds.

Unfortunately in so many of these cases it is the lower lobe which bears the burden, even when the wound has been of the upper lobe alone. Often the upper lobe is expanded, but the hæmothorax has prevented the lower lobe from expanding. So that the healthy lobe remains collapsed till the clot is removed; but even with a wounded lobe, if it is collapsed, by the time the decortication is done—not usually till three to four weeks after wounding—the wound track will not be disrupted by the pressure necessary to expand the remaining lung. That this is true we have observed many times, when a waist-like constriction, corresponding with the healed wound has appeared in a lobe which has otherwise expanded satisfactorily.

A further criticism is that to disturb the walls of an abscess cavity is bad surgery, and that to do so invites dissemination of the infection. It may be that here penicillin (both local and systematic) has enabled our patients to withstand our onslaughts; but there are certain features of the fibrin coat on the surface of the lung which are quite different from the walls of an abscess cavity. The fibrin settles on visceral pleura long before infection occurs in every hæmothorax, infected or sterile, fibrin is deposited on the lung. As infection progresses (especially if fibrolysins are absent as in staph. aureus infection) more fibrin is deposited together with other inflammatory products. But in the majority of cases the pre-septic deposit of fibrin forms a barrier between the visceral pleura and the empyema cavity; microscopical sections of the fibrin

coat show such a concentration of fibrin on the lung side of the preparation. This explains why in many cases it strips so easily from the lung with very little bleeding, leaving a normal shiny visceral pleura beneath; so that when it is removed new capillaries and lymphatics are not laid open to infection as they would be if a wall of an abscess cavity was excised.

Finally, although decortication may expand the lung, it may leave pleural pockets where pus may accumulate if an empyema forms. This is true; unless complete expansion occurs such pockets may remain. They are usually small and situated commonly at the apex, at the anterior costo-phrenic angle, and at the base. Even if one or all these pockets required drainage it is still true that the patient may be more fortunate than he would be waiting for spontaneous re-expansion to occur with a total empyema. We drain the pleural cavity with intercostal drains at these three sites, so that if an empyema does form it is usually quite small. But in the majority of cases (30 in 47) an empyema has not formed after thoracotomy and decortication in the clotted hæmothorax.

CASE REPORTS

(*Tpr Hart.*) This man was wounded on 20 July, 1944. Left thoraco-abdominal with wound of the stomach. One month later arrived at the Chest Centre with a clotted pyothorax. Rib resection, clot scooped out and water-sealed drainage. Pneumococcus only grown from the pus. Two weeks later there was no appreciable expansion of the atelectatic lung. Decortication was easy. Intercostal drainage in 4th space in front and posterior drain replaced. Streptococci grown from the peel. The lung expanded well, the anterior drain being removed after two months, when a sinogram showed no remaining cavity. There was still a posterior tube track, so that a small basal tube was required.

X-rays show condition before rib resection, just before decortication, two months later, and a final sinogram. General condition excellent. This is a case in which drainage was not avoided, but re-expansion accelerated.

(*Pte. Magee.*) Wounded 12 December, 1944, entry 6th space anterior axillary line on the left, the fragment perforating the upper lobe, and lying in the posterior triangle of the neck on the left. Aspirated five times before arrival at the Chest Centre on 30 December. He now had a loculated pyothorax, with a pleural hernia into the neck. Thin pus was aspirated from the anterior loculus, yielding coliforms and diphtheroids. Thoracotomy on 6 January 1945, evacuation of basal clot and anterior clot and pus. The upper lobe was adherent at the entry wound, otherwise the lung was quite flat. Rib fragments embedded in the upper lobe were removed. Easy decortication and complete expansion. Temporary drainage in front in the 2nd and 6th spaces, and behind in the 9th space. The front drains were removed on the 5th day and the posterior on the 9th, when the foreign body was removed from the neck.

X-rays show loculation before operation and the result of decortication. Temperature chart shows improvement after operation.

Simple evacuation of clot and closure is successful in the basal clotted hæmothorax, but where a whole lung is collapsed there is a great advantage in getting the upper lobe expanded as soon as possible. Return of the lung to full activity is thereby effected at a much earlier stage than can be attained with conservative treatment.

Summary

(1) 9% of all hæmothoraces are clotted.
(2) Infection is common—often low grade. 75% of clotted hæmothoraces were infected.
(3) There are two types—the multilocular, partly fluid; and the solid hæmatoma.
(4) The diagnosis is discussed.
(5) Evacuation of clot by thoracotomy and decortication is recommended for large clots.
(6) The arguments for and against decortication are reviewed.

MEDICAL ASPECTS OF PENETRATING WOUNDS OF THE CHEST

by

Major O. H. J. M. TELLING, RAMC

"The point of view that holds a chest injury to be progressing satisfactorily so long as pleural infection has not developed is no longer tenable. Every consideration is now given to the restoration of full lung function. The change of the focus of attention from the pleural space to the lung stands as one of the important achievements of the military surgeons in this war." Colonel Edward D. Churchill, Surgical Consultant to the U.S. Army, Mediterranean Theatre.

Hæmothorax

It is essential to remember that a hæmothorax may often accompany blast and other injuries to the chest although no wound is visible, such as fractured ribs, and cardiac wounds. But by far the largest number are due to penetrating wounds.

The uncomplicated hæmothorax is reflected clinically in two stages. (1) The reaction to injury; characterised by acute onset, pain, dyspnœa, apprehension, a varying degree of hæmorrhage and of shock, fever rising in 24 hours from subnormal to 102°-103° F. with a corresponding rise in pulse rate, and lasting 24-60 hours. (2) The stage of quiescence, associated with lessening of the acute mental and physical distress, and with physiological compensation by the body. It is quite usual for these patients to have a sustained fever of say 100°-102° F. for the first 2-5 days after injury followed by an evening rise to 99° or 100° F. for a further week; the pulse rate tends to settle earlier than the temperature. Less commonly, fever may persist for more than two weeks in the absence of infection.

TREATMENT. This may be summed up in three words—efficient early aspiration. Certain objections to this procedure have been raised: that there is a risk of introducing sepsis, of restarting bleeding from the wound, or of causing a new hæmorrhage, and that some effusions will absorb completely if left alone.

Now it is quite impossible to tell which effusions will absorb uneventfully and how quickly; sepsis or hæmorrhage due to aspiration is a reflection upon the operator and not upon the method; there is no danger of restarting bleeding from the wound. It is generally agreed that clotting occurs within 6-12 hours, so the surgeon may safely empty the chest during the initial operation and perhaps thereby obviate any further tapping.

Further, the return to normal function of the lung, diaphragm, and chest wall, is enormously accelerated, and the time spent in hospital and convalescence greatly curtailed with consequent conservation of manpower, etc. If the fluid is not removed, it may clot—a calamity. 5% to 10% will clot any way (Major W. F. Nicholson). If it does not clot, it may become infected, being an excellent culture medium.

Finally, what happens if the fluid is left and does not clot?

(1) It is said some fibrin is always deposited on the lung and pleura; this is probably true.

(2) Hæmothorax fluid is an irritant causing thickening of parietal and visceral pleura if left.

(3) The slow unaided absorption of fluid leads to inspissation which renders futher absorption even more difficult. The blood is slowly replaced by fluid rich in cholesterin crystal. The shaggy walls of the cyst may calcify while the fluid is still present: if sepsis develops in the years following, treatment is difficult. (T. Edwards).

(4) The lung and chest wall are immobilised (quite unnecessarily) for a varying length of time, and in time the lung, chest wall, and absorbed hæmothorax, may be bound together in an almost iron-hard mass of fibrous tissue, which may calcify or even ossify in the years to come. The so-called frozen chest.

It is opportune here to dwell upon the evils of the infected hæmothorax—d'Abreu (Lancet, 1944) had a mortality rate of 17%.

The sepsis rate varies with different authors: Ryle (quoted by T. Edwards, British Journal of Surgery, 1943) gives 80%, Tudor Edwards (Lancet, 1943), in 204 patients found 11.3% with closed, and 22% with penetrating injuries becoming infected. Of 434 hæmothoraces from 1.4.44—30.9.44, 15½% became infected (W. F. Nicholson), Tudor Edwards also found that the earlier the hæmothoraces are aspirated, the fewer became infected.

Remember, the commonest cause of invaliding in chest injuries in the last war was chronic empyema; Clifford Hoyle (Lancet, 1940) found 50% were permanently invalided, 33% became infected, and of this 33% nearly half died. Conservatism was then in vogue.

Infection becomes evident early or late: from the fourth to the seventh day is a common time. It should be suspected when there is an unexpected rise in pulse rate or temperature, which is sustained, or a decline in condition, return of dyspnœa, or when the temperature keeps rising again after each aspiration. Low-grade infection may declare itself in the second or third weeks by persistent irregular fever and lack of expected progress in the patient. A white cell count is sometimes valuable. The patient does not always look ill and toxic.

TECHNIQUE OF ASPIRATION. This should be a simple and painless procedure.

1. Explain to the patient what you are going to do, and why.

2. A separate room is desirable, but not always available except in Chest Centres. In the ward use screens. Preliminary morphia is rarely needed.

3. The patient must be sitting up, or at least well propped up with back rest and pillows.

4. Physical signs. There is always reduced movement, T.V.F., impaired P.N., weak or absent B.S., and often stony dullness. There may be much more fluid present than the signs and X-ray indicate.

Good breath sounds, and even bronchial breathing may be heard through a layer of fluid. Clinically it is often quite impossible to differentiate between residual fluid or mere pleural thickening, even with X-ray help. Needling is essential.

5. The site or sites of election should be decided beforehand by examination and X-ray in two planes. The site should be memorised or marked; the tendency is to go too low. This is important because in many patients the diaphragm on the injured side is raised, and fibrinous sludge collects in the costophrenic gutter.

6. A three-inch needle with Rotanda syringe or one with a two-way tap should be used. I do not favour the use of Novutox as a local anæsthetic or a Potain's apparatus or blood transfusion needle for the aspiration.

7. Aspiration should be performed 24-36 hours after initial operation or wounding and then daily.

8. Quantity aspirated varies from one to three pints at a session, and the time from 10-45 minutes. There are so many variables which I need not stress here.

I would like to condemn the practice of air replacement. It is unnecessary and quite inaccurate unless controlled manometrically, because no one can foretell the mediastinal vagaries of any particular patient. Apical collapse is inevitably ensured, all possibility of the upper lobe becoming adherent is temporarily removed, and lung expansion effectively delayed. Should infection supervene, it is sad to think that what might have been a basal empyema is now a total pyopneumothorax.

Only on rare occasions such as the outlining or localisation of fluid pockets in a clotted or loculated hæmothorax, would I advocate air replacement, and then 52-100 c.cs. is enough. Another point which is often forgotten by the people who stress the risk of introducing sepsis with the needle is that both lung and pleura have already been penetrated by a missile; a potential source of infection which should itself command aspiration, in view of the known empyema rate of 15-33%. Furthermore, the clotting rate is 5-10% (Major W. F. Nicholson's series).

Serial radiological control is essential in all aspiration work owing to the vagaries of the physical signs.

That there is a slight risk in aspiration I do not deny. The possibility of infection has already been mentioned, and pleural shock is a familiar bogy. True secondary hæmorrhage is a rare occurrence. Major W. F. Nicholson, in 1027 patients has met this complication eight times in three years—0.77%: in only four patients was there any possible connection with the aspiration, and in none of the eight would air replacement have prevented it. The bleeding is usually from the internal mammary or intercostal arteries, but occasionally torrential hæmorrhage from the lung vessels is met.

The specimen should always be sent for cytology and culture (anærobic as well if necessary), and the results recorded in the notes. The normal appearance of the fluid changes from frank blood to clear yellow serous fluid, as absorption progresses; sometimes it becomes thick, tarry, and inspissated. Blood is a pleural irritant, and in the pleural cavity is diluted by the fluid whose secretion it provokes. At first the Hb may be as high as 70% and R.B.C. 3,000,000; the R.B.C. and polymorphs rapidly diminish in number and later the lymphocytes and macrophages dominate the picture: in the second or third week the latter are filled with pigment.

An infected fluid may be recognised by the smell, the colour, which ranges from dark purple to brown, turbidity, and change in consistency. Microscopically the pus cells are sharply increased in number, and smear and culture may yield an organism.

It is a wise policy to leave 30,000 units of penicillin in 40-50 c.c.s of saline in the chest after each aspiration. I have never seen any reaction to this.

It is not generally recognised how greatly pentothal (05-1.0 grammes) facilitates multiple aspirations to establish the presence of loculation or to find an elusive pocket. An æsthetist is essential. The patient should be arranged in the desired position, sitting up, leaning forward on an adjustable instrument tray or pillows on a heart table: in this position, and only when the physician is completely ready, the injection is made.

The value of a blood transfusion is obvious, but it is not generally appreciated how much a hæmothorax may deplete the blood (Hb 60-70%). I always transfuse if the Hb (Haldane) is under 80%, or the hæmatocrit under 40%. The best laboratory technique is the copper sulphate series, for the plasma proteins can be estimated at the same time; they may need replenishing if there is much infection present. It is the duty of the first holding unit where good laboratory assistance is available, to "top up" the patient. Though I cannot produce factual evidence, it is my strong conviction that wound healing and resistance to infection are greatly enhanced by adequate transfusion.

Pulmonary Contusion

This is associated with direct blast, or violence therefrom, or with wounds of the chest wall, perhaps with fractured ribs or scapula. In 1,100 admissions from 1.4.44 to 30.9.44, 139 patients had pulmonary contusion (Major W. F. Nicholson's series).

Pathologically there is more or less localised interstitial and intra-alveolar hæmorrhage, occasionally scattered, with a varying degree of atelectasis which is usually patchy and slight. Sometimes infection from the respiratory tract develops.

The physical signs are hæmoptysis, cough, sputum (which is bloody, and mucoid or purulent), and pleurisy causing local pain. The temperature usually settles in a few days, the pulse and respiration rates being little raised.

More severely wounded patients may be cyanosed, shocked, and dyspœic. Reduced movement, local râles, and occasionally a friction rub, are evident. The skiagram shows patchy opacity usually confined to the site of trauma, but sometimes, and in more severe examples, the radiological signs are far more extensive than the physical.

It is evident that pulmonary contusion resembles the less severe degrees of blast lung; this is also met. The moving of severely blasted patients should be cautiously undertaken as any premature disturbance may start more bleeding.

The prognosis is good and treatment is by sitting up the patient, sedation, and chemotherapy.

Pulmonary Hæmatoma

Despite certain differences this may blend with contusion. It is classically seen in patients with through and through wounds, with clean entrance wounds, or penetrating entrance only wounds of lung. Naturally an effusion is often present, but I am excluding this group here.

Pathologically there is frank trauma with hæmorrhage into the lung tissue around the track. The degree of atelectasis varies—usually it is small in extent.

Clinically there is hæmoptysis, often considerable, or actual clots, cough, pain, surgical emphysema and fever. The patient may be quite ill for a few days, dyspnœic, and locally there are reduced movement, râles, weak B.S., and friction.

The skiagram shows an irreguar roughly circular opacity which surrounds the track; this is often relatively clear in the centre; it may vary greatly in extent. A lateral view is rarely taken but shows the track well (at operation the wound track may be felt).

The treatment is essentially the same as in contusion. The prognosis is good, allowing for possible complications from the F.B.

Both pulmonary contusion and hæmatoma may break down into an abscess with the usual signs. This is best treated by postural drainage, chemotherapy or penicillin, rarely by surgery. The abscess usually settles down uneventfully although the F.B. may have to be removed later.

Dry Pneumothorax

This is often found as a result of (1) Blast and violence. (2) Chest wall wounds. (3) Small penetrating wounds (F.B. may remain in the lung).

Local wound toilet, a short course of chemotherapy, and early breathing exercises, comprise the necessary treatment.

Convalescence and Rehabilitation

(Summary of Remarks)

Aim. (1) Restore lungs to full and normal function.
(2) Restore chest wall to full and normal function.
(3) Reduce time off duty.

Snags. Local limitation of movement due to wound (or other wounds). Internal adhesion of lung, chest wall and diaphragm. Resultant pain in sneezing, stretching, deep breathing, coughing.

Resultant and apprehensive dyspnœa on exertion.

Explain everything to the patient, what is the aim of physiotherapy? Get his trust.

Breathing Exercises.

Value undisputed — { Good Physiotherapist. / Sex appeal and personality.

When to start Breathing exercises.

Too soon may cause.

i. Undue pain.
ii. Recurrence of fever.
iii. Recurrence of effusion. { Clear / Bloody

1. Uncomplicated hæmo-or-pneumothorax: After temperature normal 48 hours. Keep in bed 2-3 days before up.

2. Infected hæmothorax: 48 hours after drainage is satisfactorily established (or as soon as patient is fit).

3. Clean thoractomy: 12-18 days after operation (needle and X-ray control essential) T. is settled.

4. Thoracotomy for infected hæmothorax: As soon as patient is fit.

5. Drainage of pyopneumothorax: As in 2.

6. Medical empyema: 24-48 hours after operation.

7. Pulmonary contusion: Very early. As soon as clinical and X-ray allow.

8. Pulmonary atelectasis: As soon as recognised. Tell patient to cough and breathe himself all day.

9. Pulmonary hæmatoma: As in 7.

10. Larger chest wall wounds: 10-15 days. As soon as wound allows. Usually up patients to up class for short course. Massage to scar.

Occupational therapy. Fresh air. Sequelæ of chest wounds: prognosis: Grading by Convalescent Depot Staff is essential.

Summary

The causes, physical signs, and clinical behaviour, of traumatic hæmothorax have been discussed. The treatment of uncomplicated hæmothorax is efficient early aspiration. The objections to, and risks of, aspiration have been set forth, and the practice of air replacement condemned. The irreparable damage to the thoracic mechanism caused by leaving the fluid *in situ*, the risk of infection and its attendant evils, and the correct technique of aspiration, have been emphasised.

Adequate early transfusion with blood, or plasma when sepsis is extensive, is valuable. The causes, clinical and radiological aspects, and treatment, of pulmonary contusion and hæmatoma have been elaborated. Breathing exercises are most valuable: the risks of starting physiotherapy too soon have been mentioned, and the value of good nursing is again stressed.

RADIOLOGY IN TRAUMATIC CHEST CASES

by

Major C. J. HODSON, RAMC

(*Read by Major J. W. Litchfield, RAMC*)

Approach to the Problem

The simplest and most straightforward way of considering traumatic chest radiographs is to decide the course of the missile (or type of damage in the case of non-penetrating injuries) and what structures it must have involved on its course. Subsequently damage along this path can be assessed and the various findings correlated.

For this purpose the Radiologist requires from the Clinician the date of wounding, the type of missile, the exact site of entry and exit wounds and the gross clinical findings. From these data he can build up his picture.

Postero anterior films of a penetration such that the vertebral column is just visible through the heart shadow have been found to be the most valuable for both initial and subsequent examinations. An initial lateral film is usually essential. The following routine is then carried out:—

System of Examination

1. Rib and other bony damage is first carefully estimated.

2. The state and position of mediastinum and diaphragm then noted.

3. Pneumothorax, hæmothorax or other pleural lesion is then assessed and localised. Postero anterior and lateral films usually suffice for this.

4. The state of each lobe of both lungs hetero- as well as homo-lateral sides, is then examined. Particular search is made for the presence of missile tracks, atelectasis, contusion and lung abscess.

5. Heart size and outline is noted.

6. The position of any F.B.s is then guaged as accurately as possible and decision made as to whether this is sufficient, or screening will be necessary for further localisation.

7. The condition of other structures, *e.g.*, œsophagus, which might have been damaged is then considered and further investigations carried out if necessary.

8. Any other coincident or abnormal features are lastly noted and any complications commented upon.

Only by a regular routine such as the above can the complexity of findings be sorted out and diag-

nosed. A discrepancy between number of wounds and F.B.s should always lead to fluoroscopy as small intracardiac F.B.s are, as a rule, invisible on the films owing to movement.

My own experience is that rib damage, the position of diaphragm, mediastinum and interlobar fissures, and the site of the F.B.s are the main points to assess, other things such as effusions or collapse are then easily estimated.

Subsequent Examinations

Once the original pathology has been decided, subsequent films are used to observe the effects of treatment. Usually postero anterior films alone are enough for this but laterals are occasionally necessary to discover the size of pleural pockets or effusions.

For localisation of peripheral, paradiaphragmatic and para- or intra-mediastinal F.B.s, fluroscopy is essential. The *depth* of the FB to the structure in question is first found by tangential screening, *i.e.*, rotating the patient until the perpendicular plane from the F.B. to the surface in question lies on the screen.

The position of the chest wall F.B. is then marked by skin mark, needle localisation, or plotting it off by counting rib level and distance from midline. If mediastinal, the F.B.s relation to the various big structures around it must be determined and its anatomical position given as accurately as possible. As regards the diaphragm all the surgeon wants to know is, is the F.B. above or below the diaphragm and in which quadrant does it lie?

Empyemata

The early diagnosis of empyema lies with the Clinician, but occasionally X-ray evidence is of value in suggesting the condition. Three signs are of use:—

i. The presence of multiple fluid levels in a hitherto straightforward hæmothorax is often followed by frank infection.

ii. A rapid increase in fibrin deposit on the parietal pleura is again suggestive of infection.

iii. The reticular fibrin shadow seen covering the lung when infected fluid is aspirated. (An example of this is shown.)

The part played by Radiology in the Chronic Empyema is both extensive and complicated because of the large variations met with in this condition. The first object is usually to localise the pocket and give the optimum site for drainage. This can usually be done from two deep penetration postero anterior and lateral films, but screening is occasionally of value. An aid in a limited number of cases is the instillation of a few c.c.s of lipiodol into the empyema cavity with the object of outlining its lower border on subsequent films. There are drawbacks to this procedure in some cases.

Once rib resection and drainage have been carried out the main problem is to assess the degree of expansion of the lung and to control the tube position. In the early stages this is fairly straightforward, blockage of the tube being indicated by the presence of a fluid level, providing always it has been placed at the most dependant point.

But in the late stages, particularly when uneven expansion of the lung occurs, the recognition of the position, shape, and size of the cavity becomes more difficult. For instance, it is common for a lung to expand right across the thoracic cavity in its anterior or posterior half leaving the other half unfilled but giving an appearance on the postero anterior film of a fully expanded lung. A lateral view will usually demonstrate this state of affairs.

Another appearance which is a tremendous help is the outlining of the empyema space on the film by the difference in translucency to X-rays between its contained air and the surrounding fibrin-covered lung. This is often striking and the cavity can be directly visualised without the aid of opaque media. (An example of this is shown.)

But in cases of difficulty or doubt opaque oil must be used.

This is instilled through the empyema tube (the latter always being left *in situ*), with the patient lying tube uppermost. On cases of big cavities one bottle (20 c.c.s) is used and the patient postured to spread it round the walls of the cavity. Postero anterior and lateral films are then taken. With small cavities a complete filling is essential and oil is put in until it is squeezed out between tube and chest wall, only then can it be assumed that all pockets and fistulæ have been entered. The tube must be clipped off after filling to ensure no oil runs out and all surface oil removed before the films are taken.

Points to notice are that non-filling of a cavity does not mean its obliteration necessarily, and that in big cavities the oil will pool in dependant furrows and holes giving the impression of small loculated cavities.

Finally, opaque oil control is the only safe way of judging the final removal of the tube. The tendency always is to remove the latter too quickly.

The remaining task of the Radiologist is to describe the final state of the patient with particular reference to scoliosis, flattening of the chest wall, lung expansion, and position and movement of the diaphragms.

2. ATELECTASIS IN THE TRAUMATIC CHEST

Many of the estimations involved in the building up of the radiological picture of traumatic chests depend upon the recognition of atelectasis. And by atelectasis is meant "active" collapse or "aspiration" collapse, or "plug" collapse as compared with "passive" or "compression" collapse.

In a series of 400 consecutive cases of chest injury in which there was radiological evidence of a definite intra-thoracic lesion, a conservative estimate showed that in 54% of cases atelectasis of one or more lower lobes was present at some time or other. The duration of this condition varied from four to over seventy days and the graph shown gives a rough indication of the periods involved.

The estimation of atelectasis can at the best of times only be rough under Service conditions, and many of these figures are admittedly inaccurate, but the error is a conservative one and I believe the correct findings to be even more striking still.

Because of this large figure and the difficulties of assessing atelectasis in the traumatic chest, both clinically and radiologically, but more still because of the complications to which, if untreated, the condition can undoubtedly give rise, it is considered advisable to deal specifically with this subject.

X-ray Diagnosis of Atelectasis

The Radiological signs of atelectasis of a lobe can be divided into two groups. Definite signs and Suggestive signs.

(a) *Definite Signs of Atelectasis.*

i. Triangular "jib" shadow in the para-cardiac region denoting total collapse of a lower lobe.
ii. Definite shift of the interlobar septa indicating decreased volume of the lower lobe.
iii. Bronchographical findings of "bunched" bronchi.
iv. The observed re-expansion of the suspected lobe at a later date.

(b) *Indefinite Signs of Atelectasis.*

i. Mediastinal shift to the same side or absence of shift in the opposite direction when space-filling pathology is also present on the same side.
ii. Elevation of the homolateral diaphragm. Often found apart from collapse in the traumatic chest. In cases of bilateral collapse in the traumatic chest, elevation of both diaphragms may be the only abnormal finding.
iii. Depression of the homolateral hilar shadow.
iv. Flattening of the chest wall on the same side—an equivocal sign in chest injuries.
v. Increased translucency of the upper lobe with "fanning out" of the upper lobe lung markings indicating emphysema.

Each of these signs by itself is unreliable owing to the fact that its appearance can be simulated by other conditions, or because though present its cause may be other than atelectasis. But where several are present in one case the probability becomes almost a certainly. Even then diagnosis in some cases remains extremely hard owing chiefly to the presence of other lesion such as fluid, pleural thickening or empyemata.

In the figures quoted the diagnosis was made only in cases where definite appearances were present or where indefinite ones were supported by clinical signs, i.e., bronchial breathing.

Aetiology

The ætiology of this atelectasis is uncertain. There are these probable factors:—

i. An impaired diaphragmatic function due to injury.
ii. Inhaled bronchial secretions.
iii. Inhaled blood.

It has been impossible to ascertain which factor is chiefly responsible or whether there are other mechanisms involved.

The causes for re-expansion are equally obscure. All patients are given breathing exercises as soon as their general condition allows, as a routine, but there is no evidence yet as to the changes leading up to re-expansion. Once it commences it continues rapidly as a rule, the lobe re-aerating in 2-3 days. But there are exceptions when it occurs much more slowly.

Clinical Signs

When positive these are diagnostic, when absent, they in no way exclude the condition, being upset by intervening fluid and air and the presence of secretions, etc., in the bronchus.

When bronchial breathing is heard, however, it is taken to indicate collapse or consolidation, but it comes and goes in many cases from day to day, even though the lobe may remain obviously collapsed.

To recapitulate then, there is radiological evidence of active atelectasis in just over 50% of all traumatic chest cases showing some intra-thoracic change. The estimation of this condition is usually a difficult one in the early stages and is sometimes only proved by the passage of time. The presense of atelectasis of one or more lobes has considerable significance in the correct assessment of the general intra-thoracic state particularly with regard to foreign body localisation and the behaviour of the lung associated with an empyema. The factors causing both collapse and re-expansion are largely unknown.

It is suggested that collapse of a lower lobe should always be assumed until it is proved otherwise in doubtful cases. By this means treatment is ensured, unwelcome complications averted, and in any case no harm is done.

3. TRAUMATIC CAVITATION

An intra-pulmonary lesion peculiar to the traumatic chest is the damage caused by a missile passing through lung tissue—the so-called "Missile track". One variety of these lesions demands attention because of its important complications. It is the cavitated missile track.

Pathology

When a missile passes through the lung it leaves a path of torn and bleeding tissue. This forms a lesion which may well be described as a central core of hæmatoma surrounded by ecchymotic and œdematous lung. But if a bronchus is involved in this path it appears that the contents of the hæmatoma may drain away leaving an air-containing cavity behind.

Morphology

These cavities assume a variety of shapes, but characteristically they are elongated or sausage-shaped rather than circular and may traverse the lung horizontally or obliquely according to the direction of the missile. They may or may not contain a fluid level.

Radiological Appearances

These depend on the age, site and direction of the cavity. In the early case the walls are hazy and ill-defined but become more distinct as time passes and surrounding damage is absorbed. They are roughly parallel and may be either hardly visible or 2-3mms wide. When seen sideways on the lesion appears cigar-shaped but in the end-on position is usually circular. It follows the path of the missile but may be distorted by collapse of part of the lung or effusions. Sometimes it occurs partly along the length of an otherwise solid track. It may contain a fluid level, and this may come and go from day to day presumably as drainage occurs.

As time goes on lesions slowly become smaller, usually both in diameter and length, until the space is obliterated and a solid linear shadow remains. Very often by this time they become very indistinct. The process is prolonged and has been followed up to 82 days.

Clinical Signs

The uncomplicated condition has not yet produced any clinical sign that we have been able to elicit.

Complications

These lesions are for the most part of academic interest only and heal without incident, but a certain number are of great importance to the clinician because they become infected and give a clinical and radiological picture typical of lung abscess, an example of which, of course, they then are.

There is pyrexia, cough, and purulent sputum and the X-ray reveals a parenchymal cavity usually with a fluid level, and with surrounding inflammatory shadowing. There may be local pain.

So far we have had three such infected cavities. Two were open through fistulae to the outside in the region of the entrance or exit wound and also to a bronchus. The third was closed to the outside and connected to a bronchus only.

All three cases were treated conservatively, i.e. by postural drainage and chemotherapy and responded very dramatically with eventual complete recovery as far as we could follow them. This benign course is stressed as it may be a characteristic of the condition and if so may contra-indicate operative treatment.

Treatment

The uncomplicated lesion calls for no special therapeutic measures. If infection occurs as mentioned above, it has responded very readily to postural drainage and chemotherapy.

Remarks

In two of the cases we have been able to introduce lipiodol into the cavity through the external fistula. In each case a broncho-pleural fistula was demonstrated. Attempts to outline them by bronchography have so far proved unsuccessful. The incidence of these lesions is 1-2% of all cases showing intrathoracic damage.

Conclusion

Cavitation may occur along the path of a pulmonary missile track. The lesion gives no peculiar signs or symptoms and normally resolves slowly, apparently by fibrosis and contraction of the walls. In a number of cases infection has occurred giving the signs and symptoms of lung abscess. These have responded rapidly and well to treatment by postural drainage and chemotherapy.

Summary

1. An outline of the routine interpretation of the traumatic chest X-ray is first given, stressing the importance of determining the exact path of the missile and estimating the damage to each structure it must have involved. A brief reference is given to F.B. localisation and Radiology of empyemata.

2. The incidence of atelectasis in traumatic chest cases is given.

The radiological features of this condition are briefly discussed and the difficulty of its recognition stressed.

Its ætiology is commented upon and the average course the condition runs.

3. Traumatic cavitation is described. An account of its pathology, morphology, radiological appearances and complications is submitted. The importance of recognising these lesions when infected, and their benign prognosis with treatment by chemotherapy and postural drainage is emphasised.

Discussion — Penetrating Wounds of the Chest — Brigadier E. R. Boland

Major Nicholson and Major Litchfield (on behalf of Col. d'Abreu) have given a very clear exposition and demonstration of what can be done by teamwork. Major Litchfield has given a special exposition of team work. He has very successfully impersonated first Lt.-Col. d'Abreu and then Major Hodson and he would have included the anæsthetist in his impersonation had he been asked to, and had it been possible to include a physiotherapist, he would have no doubt shown the necessary sex appeal stated to be desirable in such persons by a previous speaker. Unfortunately there are not a great number of Col. d'Abreus and Major Nicholsons in this theatre. There is a demand for chest surgeons all over the world and the number of trained and skilled chest surgeons is small. Taking the over-all picture we have got as many as we can hope to get and therefore most of the chest surgery really devolves on the forward surgeon. Teams can deal with more serious cases but the quality of the chest surgery depends on the skill of the forward surgeons. That there have been changes in chest surgery in this theatre during the past 12 months and that improvement has taken place is shown by the improved figures which Major Litchfield has given. Prognosis is better and cases are arriving at the chest centres now in much better condition than formerly. This is due to the work of the forward surgeons and forward physicians. Forward physicians and surgeons have realised the necessity of frequent aspiration. They are aspirating frequently and are sending cases back more or less dry and much less liable to become infected. At one time forward surgeons in the British Army tended to do as little as possible to chest cases and evacuate them to the special chest centre. In many cases they treated chest wounds in quite a different way from that in which they treated other wounds. One used to see a number of cases with fragments of ribs which had not been excised and which might even have been driven into the lung. The chest teams naturally set their face against wholesale removal of foreign bodies in the forward areas but sometimes gross foreign bodies were left in positions from which they could have easily have been removed, sometimes dead tissue and bits of cloth were left in the wounds — the aim was to cover up the wound and evacuate the patient as quickly as possible. All that is changed now.

There are several officers here with a knowledge of chest wounds in forward areas, they may be able to speak on the difficulties they have in dealing with them and for that reason this subject was included in this meeting. Sometimes there is not enough liaison between forward areas and the base. The forward areas do not know what the base is doing and sometimes people at the base are not clear regarding the difficulties of the forward areas. As there are several people with such knowledge I hope they will contribute to this discussion.

I would like to ask Major Nicholson his views as to prognosis regarding chest wounds. Patients with

chest wounds who do not die in the early stages, on the whole do extremely well so far as survival is concerned. First-class surgery materially affects the completeness of their eventual recovery but survival would take place in any case in most cases with normal luck, if you like to leave it to that. What I would like to know is how many of these men with chest wounds can be usefully returned and made into fighting soldiers. A man who has been wounded and returned to the line tends to feel abnormally fragile for a definite period; nobody likes being shot at, and if already wounded once dislikes the idea of being wounded again. Being shot through the chest sounds very much worse than being wounded in the leg. The soldier is liable to feel when he goes back to the line that the chest is a very large exposed part of his body.

Further, I would like to know how far Major Nicholson thinks penicillin has really affected prognosis and treatment of these chest cases.

At the same time that surgery has improved penicillin has been used on a wholesale scale. One feels that at the beginning we expected rather too much of penicillin and now the time has come to evaluate its use. I would like Major Nicholson to give us his impression. This subject is now open for discussion.

Air Commodore R. N. Ironside, RAF Medical Services:

I would like to thank the speakers for their very excellent presentation on this subject and as an appendix to what they have said I would like to say a word on the evacuation of these cases at the acute stage of the illness. I cordially agree with the two speakers who mentioned the subject this morning, that most of these cases can go very well by air and the risks in the past have probably been over-estimated. At the same time there are three groups of cases that should make one think, particularly when the question of urgency of treatment or question of other means of transport being available are under consideration and are being weighed in the balance.

The first group of cases are those with air in the pleural cavity. If you take a patient with a closed pneumothorax into a decompression chamber and take him up to between 6-10,000 feet you will see that a very rapid mediasternal shift occurs. This is no mere theoretical danger. You cannot dictate to a pilot the height at which he is to fly. Terrain or weather might necessitate him going up to a considerable height when evacuating patients by air. Air ambulances often travel at 2,000 feet but they may under certain weather conditions be forced very much higher than that. This is a point which has to be borne in mind. That is the first point.

The second group of cases are those with severe hæmorrhage and suffering from shock. Most of these patients perhaps do not travel well by air.

The third group are those who are apprehensive and particularly if they are nervous of air travel or have a tendency to air-sickness. Their condition is likely to be worsened rather than improved by air transport. One sees a certain number of closed head injuries who have blood and air in the chest undiagnosed and, what is worse, unsuspected. These are points that I think everyone should bear in mind when a decision has to be made whether a case should be evacuated by air or not is being weighed in the balance.

Lt.-Col. A. W. Spence, RAMC

My recent experience is limited to only twelve cases and it is probably a presumption on my part to say anything about this subject. We had, however, at 97th General Hospital an opportunity of seeing and treating these 12 cases within half an hour of their being wounded. You will probably know 97th General Hospital was in a district in Athens where there was a spot of bother and fighting was going on in the hospital precincts. These cases were admitted at once to the hospital. They consisted of 6 O.R.s, 4 British officers, one Greek girl aged 12 who was shot by the E.L.A.S., and a boy aged 14 who was a prisoner of war and had been shot when attempting to escape by one of the British guards. When these cases were admitted they were taken at once to the resuscitation ward and about half of them were in a severe degree of collapse, and were resuscitated by the usual method of plasma or whole blood. At the same time they were seen by the Medical Specialist or myself. I feel that I was learning from the previous speakers and what struck me most was the great importance of X-rays. You could not always rely on the physical signs. For instance, quite a large hæmathorax would give no impairment of percussion note. The reason was that there was surgical emphysema or extra pleura pneumothorax which would change a dull note into a resonant one. This is one reason why I feel that in chest wounds one should not rely greatly on the physical signs but have the patient X-rayed as soon as possible. These cases were treated by aspiration as previous speakers have described and 40,000 units of penicillin were introduced into the pleura after each aspiration. They were also given sulphonamides for about 4 or 5 days. The previous speakers have already described fever occurring in a number of these cases and in about 8 of them the temperature subsided in about a week or a fortnight, but in 2 cases the fever continued and it was noted that the sulphonamide treatment and penicillin had had no effect whatever on the fever. Specimens of blood stained fluid which were aspirated were cultured and in every case were negative. Two cases required rib resection and in them the fluid which was withdrawn was sterile on culture. As has been shown by the previous speaker a positive culture was obtained from the fibrin removed from the surface of the lung. I should like to ask Major Nicholson to help me. I understand during the operation fibrin is peeled off the lung only, whereas I presume there is also fibrin left on the parietal pleura, and *that* fibrin is infected so that you are only removing fibrin from the lung to enable it to expand. You still leave behind the fibrin which is lining the parietal pleura. What I would like to know is why you don't take away fibrin from the parietal pleura and if that is true why do they clear up so well after the operation?

Lt.-Col. O. A. Savage, RAMC

Col. Spence has just emphasised the importance of X-rays in chest injuries and I would like to emphasise myself the importance of X-rays in relation to casualties which have been exposed to blast. In a series of autopsies which we had a chance of

doing from Cassino, Col. Ascroft and I found in 87 autopsies (none of them chest injuries) that 30 showed blast lung. This was so common that we began to doubt if it were correct. At that time Dr. Joan Ross arrived from England. She had seen blast cases in London and confirmed that this was so. We then continued our investigations on these cases. Radiologically they were quite clear, and we found that in all these cases where history of injury was forthcoming they had been exposed to blast and the conclusion we came to was that if there is a history of blast if possible X-rays should be taken.

Major McDermott, RCAMC

I have recently seen a number of these cases for the first time. I think they are important in that they show a problem we had in the C.C.S. The time it took to get our people in was approximately 5 or 6 hours from time of wounding and with one exception they all survived. Now there are two things I want to ask, one of which has already been mentioned, and that is the question of penicillin in the pleura. We made a practice at first of introducing penicillin. In three instances we had collapse and shock following the introduction of penicillin. I wonder if it is true that certain forms of penicillin particularly do not create trouble while other forms do. I would like an opinion about that. The question was raised about oxygen. I am as great a believer in oxygen as anyone. We have great trouble in getting supplies. I think the use of oxygen if it could be procured would be very helpful.

Lt.-Col. C. B. Prowse, RAMC

Brigadier Boland has asked people who have had opportunity of seeing these cases to speak about them. Possibly I am a little out of date in my remarks. I have not been in a forward area for about a year, but there are certain things which I think spring to mind, and the first is that one must realise that the cases which are sent in to a C.C.S. are generally mixed up with other casualties so that it is difficult to examine the chest thoroughly. You can imagihe yourself in a reception tent with perhaps 50 or 100 wounded; you have to sort them out as quickly as you can so that is is impossible to make fine distinctions or to X-ray all chest cases as Major Litchfield (for Major Hodson) has stressed. I would emphasise the importance of making a proper clinical investigation by all the standard methods rather than depend so very much on the interpretation of X-rays which will come afterwards. I say that one doesn't get very much help in the interpretation of the X-rays because as you know in the C.C.S. there is no radiologist available and therefore the physician must be his own radiologist and he is not always as good at it as he would like to be. I won't dwell too long on that. The next point is that there is a great variation in the distress which patients with chest injuries show, and how distressed they are is not necessarily an indication of the severity of the wound. There is here of course the psychological factor. One finds to begin with that some people are unusually distressed, but closer observation leads to the belief that the degree of distress is apparently dependent very often on the mentality of the patients.

Major Telling has emphasised the importance of blood transfusion for persons with chest wounds and I must say I would like to endorse his opinion that it is valuable help to the shocked severe cases, and it is I think most important from the point of the physician who is watching the case to be able to observe the subsequent response after transfusion has taken place, because in a certain number of cases, although responding unusually well, they can go down very rapidly and it is at that point that the physician has to be prepared to advise the surgeon whether or not the chest operation has to be done. I remember one case at the C.C.S. where I was working, and this man had passed through the phases I have described, and he had then become again extremely collapsed. Col. d'Abreu did a thoracotomy. He sutured and closed the chest and during the course of time that patient was in the C.C.S. (it was about six days only) he did not produce any further indication of blood in the pleural cavity at all. His lung was expanded at the end of that time. Except to those who are acquainted with that fact it seems amazing but it is true. The value of morphia for cases recently wounded in the chest cannot be over-emphasised. There was great prejudice against it which I think everyone has now overcome and in my experience it has done nothing but good. Pneumonia has been cited as a danger to be looked out for and I think perhaps its importance has been over-emphasised. In the course of my term in the C.C.S. I saw only one case of pneumonia in a very large number of chest injuries. Col. Spence has mentioned the presence of surgical emphysema as a difficulty and I have experienced that difficulty as well because it does unduly interfere with the interpretation of the physical signs. The temperature which follows a chest injury I have observed, as he has, is not an indication that sepsis is taking place for it always settles unless sepsis does supervene within a matter of 10 days or so. A large number of cases are found to have a pneumothorax present by taking clinical observations as well as radiological study, but it is remarkable how quickly these pneumothoraces will absorb most of them within 48 hours of the patient's admission to a C.C.S. That is of course probably if he gets to the C.C.S. 6 to 12 hours after wounding or earlier. I think he is going to reabsorb a small pneumothorax within two or three days. Finally, there are one or two things I would like to ask from the experience of others, firstly, whether there is any difference in the prognosis according to the part of the lung that is injured. I have had it said to me that the prognosis in the upper lobe is not so good as when the other lobes are damaged, but I have no evidence of my own to tell me whether this is so or not. Secondly I would like to ask Major Litchfield if he can perhaps give me some idea of how to differentiate the symptoms met with between the operations he has described when the lung contracts and those which may be associated with what has been termed cold hæmothorax. There are symptoms often similar and I would be glad if he could tell me about that. And finally before I sit down there is one thing I left out before, when I was talking of the cases in forward areas and that is the extraordinary difficulty which there is and which is always placed on the shoulders of the physician to decide whether or not the injury is above or below the diaphragm. The extraordinary rigidity of the upper abdomen which is noted in cases in which the chest lining is injured needs to be seen to be believed. Physicians are only human just as surgeons are, and it is a great compliment that the decision is left in their hands but it does not make it any easier to deal with.

Lt.-Col. K. Shirley Smith, RAMC

While damage to the lungs and the risk of infection are outstanding considerations in penetrating chest injuries, embarrassment of the circulation has also to be taken into account. I dealt with more than 60 such injuries at 72 (Br) General Hospital (which was in a forward position during the Tunisian campaign) and I observed that patients with hæmothorax commonly had pulsus paradoxus. This abnormality corresponded approximately to the degree of respiratory distress and depression of blood pressure. Aspiration of the hæmothorax relieved the dyspnœa, raised the blood pressure and abolished or greatly reduced the pulsus paradoxus.

In two or three patients who had had repeated aspirations for hæmothorax or empyema conspicuous œdema developed over the back and legs. This was regarded as partly due to protein loss and partly to impairment of the circulation.

Major F. C. Dornhurst, RAMC

I would like to say a few words regarding the difficulties in dealing with wounds in forward areas. The reason, I think, is to be found in what was stressed by Col. d'Abreu's paper that the first phase of a lung injury is one of disturbed physiology. Its exact nature is obscure but very real. Distress may be great but is not proportionate to the amount of lung damage. Patients as a rule arrive at the forward C.C.S. in such a state. In spite of the usual assumption that the patients travel well in this state many of them arrive looking very sick. At that stage they are unfit for operation. As a rule the condition improves on conservative treatment consisting of good posturing and making the patient comfortable, the administration of small doses of morphia and if necessary oxygen and the condition is considerably improved at the end of 24 to 48 hours. By that time many surgeons will feel that the time for doing wound toilet has passed. The surgeon feels he is not a priority case for by that time several bellies and other things where the patient's life is actually threatened have come in, and so it often happens that after holding him, he is evacuated unoperated. This looks bad but that is the reason. I would like to make one observation about this distress and that is I think œdema of the lung plays a part. I believe there is such a thing as traumatic œdema. I have only seen it mentioned in one paper. It is a common observation to all in the forward areas that the lung is dull on the affected side. This may be due to blood, but it does not always follow that this is a sign of effusion. Occasionally moist signs spread over the whole lung field and I have had one such case in this theatre on which I was able to do an autopsy and that definitely showed an œdema of both lungs and a primary hæmatoma on one side. I have more recently had a case which also died on which I had no time to do an autopsy, but on which I took a couple of X-rays which showed a spread to the other side. This case died in spite of extensive therapy although his chest was clear and it was proved in the end that he died of long standing anoxæmia. I think therefore in some of these cases of chest injuries in the early stage oxygen is life saving and I have seen cases looking very grave, put on oxygen for 24 hours, and wetness of the lung passed off. Another reason for the reluctance of the surgeon to operate is undoubtedly that he is afraid of converting a non-sucking wound into a sucking wound and many surgeons feel it is not a fair risk for them to take particularly as the anæsthetist may not be equipped to deal with the emergency. With regard to the point raised about penicillin I have not seen any collapse following penicillin.

Summing-up by Opening Speakers

Major W. R. Nicholson, RAMC

I was asked about the chance of a man being returned to the line. Our experience of course is that that depends on how quickly we have evacuated patients, but in the quarter October to end December, which has been the quoted quarter, we have been able to return our patients in the Naples area, send them to the local convalescent depot and there they are really tested out. Two-fifths of our hæmothorax cases pass the test and return to duty but most of them are seen back after a month there. We review them and most of them, over three-quarters, probably five-sixths, were down graded to B for three-months and we do not see them again. My impression is that not more than one in 10 hæmothorax cases goes back to the line in six months. In officers it is noticably easier to get them back to the line. They make more effort than the majority of the men. Regarding penicillin therapy. In the Middle East and Sicily before we used penicillin our empyema rate in hæmothorax cases was about 30%. When we came to Naples we got about 25% and at that time we were only using penicillin in the infected cases. Subsequent quarters from April until now, it has dropped to 15-16% in the hæmathoraces and since March in this group penicillin therapy as a prophylactic has been generally employed so that there is no associated drop in the empyema rate coincident with the use of penicillin. Unfortunately for statistical purposes it coincides with a much better wound excision and with a short line of evacuation. It has not increased with a long line of evacuation. In my own opinion penicillin has done more to boost aspiration than anything else and it is impossible to introduce penicillin without going through the motions of aspiration. I think penicillin is of value. Regarding Lt.-Col. Spence's inquiry about the fibrin left on the parietal pleura: we do not remove it; I agree it would appear to be logical to do so. Unfortunately to strip it often leads to more bleeding than to strip the fibrin from off the lungs. It is very easy to start tearing so we leave it strictly alone. In April we were using penicillin in tablet form when we had trouble. Since we have had the general issue of penicillin in ampoules we have had no further trouble since we stopped using tablets. Regarding oxygen, during the Cassino Battle we got most of our casualties within 12 to 24 hours and we were practically the first unit to hold them. I was not surprised we had used more oxygen then than before but even then it was small. One is surprised at how little oxygen is needed after the first 24 hours, in chest wounds.

When oxygen is needed our slogan is "think of a needle".

Major O. H. J. M. Telling, RAMC

I have one or two things to say. One point is sucking wounds. Sucking wounds are wounds which are sucking on the battlefield or when they reach

the RAP. The wound which only sucks in the course of the operation should not be called a sucking wound. The definition of sucking wounds is not as clear as it should be. One other point I would like to stress is the question of removal of foreign bodies. The first point is which is the more dangerous, the presence of a foreign body or the operation to remove it. This is not an easy thing to assess, but we do know that the foreign bodies which cause least trouble are peripheral and therefore easiest to remove. The nearer the hilum they are, the more frequently do they cause trouble, and early removal is advised. The optimum time is not too early, say 6-8 weeks after injury, when the lung has recovered fully: if done before there is a very great danger of infection. Pleural foreign bodies should always come out.

Major L. W. Litchfield, RAMC

In answer to Col. Prowse's question about lung tracks. I do not think there is any difficulty in distinguishing them from clotted hæmothorax as there is only one air containing cavity and the track always leads from the point of entry to the point of exit or to a retained foreign body. As regards penicillin, I have seen no ill effects from intra-pleural injection but there is usually a layer of fibrin over the pleura by the time cases reach us and this may have something to do with it. We clear up about 30% of our infected hæmothoraces with penicillin and aspiration alone. As far as the anæmia of hæmothorax is concerned we make a practice of giving all our patients full doses of iron as a routine. I have always regarded the œdema seen in these patients as due to hypoprotenæmia from protein loss in the exudate.

Thursday, 1st February, 1945

MORNING SESSION

Subject: AMOEBIASIS
and
Foot Conditions due to Cold and Wet

Presiding

Colonel H. Perrin Long, Consulting Physician

Mediterranean Theatre of Operations, United States Army

DIAGNOSIS & TREATMENT OF AMOEBIASIS

by

Lt.-Col. W. L. ACKERMAN, RAMC

In common wth the other diseases already discussed at this conference, amœbiasis is such a large subject with a voluminous rapidly increasing literature that only a few points in the diagnosis and treatment of this condition can be lightly touched in a paper of 20 minutes.

Diagnosis

Amœbic dysentery may sometimes be so acute as to be indistinguishable clinically from bacillary dysentery, furthermore the possible coexistence of the 2 diseases should be remembered. The failure of the dysenteric symptoms to respond rapidly to sulphonamide therapy makes amœbiasis the probable diagnosis particularly if microscopical blood in the stools persists. The absolute diagnosis of amœbic dysentery rests on finding active amœbæ containing ingested red blood cells, moving across the field of the microscope as with a set purpose. There is no evidence that any strain of E.H. is avirulent although their virulence may vary.

Some authorities suggest that E.H. (and similarly other intestinal protozoa) may be harmless commensuals and that the large conventional active amœba is not an indispensable stage in the life history of this species. The E.H. minuta (I2u) — usually called the precystic stage—it is thought by some, can live harmlessly in the bowels producing cysts. Different habits are given to these two forms. The active pathogenic variety ingest R.B.C.s, whilst the precystic (" minuta " or " lumen ") are content with bacteria.

It is wise to assume that cysts and these precystic forms mean active disease somewhere in the bowel. They are often disassociated with any symptoms and seem to live in symbiosis with their host, but their presence denotes a potential focus for exacerbations of diarrhœa or secondary amœbic manifestations particularly if any existing factor such as fatigue, malnutrition or acute intestinal disorders appear. Experimentally the susceptibility of animals to infection is much greater in warm weather and may partially explain the increased prevalence and greater severity of the disease in hot climates.

A reliable complement fixation test is not yet available, although that perfected by Craig, using an alcoholic extract of cultures of E.H. as antigen, is said to give 90% accuracy.

Collectively, the unusual manifestations of amœbiasis account for an appreciable proportion of cases seen.

P.U.O.

So called amœbic fever with high temperature is recognised, but considered very rare. I have notes of 5 cases who had no other symptoms but pyrexia and malaise—2 on close questioning gave a history of a mild, short-lived diarrhœa. In the first case I recognised, the symptomless pyrexia lasted 2 weeks. All investigations were negative. At the end of this time E.H. were found in the stools. After the 4th injection of emetine the temperature was normal and remained so. There was never anything to suggest an amœbic hepatitis. The fever may be due to toxæmia from a localised area of amœbiasis high up in the bowel not causing diarrhœa. As I have already mentioned I have seen other cases of P.U.O., due to this cause, and it should always be considered in an unexplained prolonged pyrexia.

Rectal Amœbiasis

An ulcerating granulomatous mass in the rectum should always make one think of amœbiasis. Of the 5 cases I have had, all had long histories of diarrhœa. In none were we able to find E.H. Much of the granuloma may be due to superadded infection with the amœbæ nestling at the base. Anti-amœbic treatment causes the complete disappearance of the mass. Two cases are described briefly:—

(A) Had had intermittent diarrhœa for some weeks with a recent acute exacerbation. Stool examined showed a bacillary exudate. The diarrhœa persisted in spite of sulphaguanidine. Sigmoidoscopy showed 8 inches from anus a sessile mass with an œdematous and nodular surface encircling and narrowing the lumen — no ulceration seen. Below this mass the mucosa was abnormal with numerous small nodules and superficial ulceration.

4 weeks later — mucous membrane redundant — otherwise normal.

(B) This man had an ulcerating mass protuding from the anus covered by dirty slough — diphtheria organisms were grown from this (as also from an ulcer inside his lower lip). He received both antidiphtheritic and amœbic treatment. I have not seen the single indurated ulcer similating carcinoma which is described. Conversely one series of cases has been recorded of carcinoma of the colon occurring some years after amœbic dysentery.

Appendicitis

As is well known, appendicitis can occasionally commence with diarrhœa or more commonly diarrhœa may develop during the disease, particularly if the appendix is pelvic in position, but amœbiasis should *always* be considered when a lump is palpable in the R.I.F.—it is usually more extensive than is compatible with the stage of appendicitis and the whole cæcum feels thickened. Furthermore, tenderness and muscle rigidity are usually less marked. If in doubt an expectant Oschner-Sherren regime should be instituted. In the Chicago epidemic there was a high mortality rate from misguided appendicectomy. Amœbic appendicitis and typhlitis will not resolve without specific anti-amœbic treatment.

Anal Condition

Surgeons are well aware of the inadvisability of operating on fissures in ano, hæmorrhoids and suchlike without first eliminating amœbiasis.

Amœbic Hepatitis—Amœbic Hepatic Abscess

These are grouped together as there is not one infallible sign (except of course the rupture of the abscess) which will distinguish the two conditions —not pyrexia, pain, tenderness over liver, either diffuse or more localised, leucocytosis, raising of the diaphragm or even bulging of the ribs, or bulging from under the costal margin. (Any or several of these signs may be absent.) All gradations from amœbic hepatitis to amœbic abscess are seen and cases which one feels certain have abscesses respond dramatically to emetine. I have had recently two such cases; so certain was I, that when one had recovered clinically I attempted aspiration lest I should miss a quiescent abscess. (The Consultant in Tropical Medicine to M.E.F. told us that there was one thing the Army Medical Services did not forgive, and that was missing a hepatitic abscess.) A liver abscess may almost silently eat away a large part of the liver. A mere recitation of the differential diagnosis of hepatic abscess would take too long — practically every disease would have to be included. To remember amœbiasis is halfway to the correct diagnosis. Amœbæ are more often absent than present in stools. If a localised area of tenderness is discovered it should always be marked on the skin as it may not be so obvious after the patient has had emetine — but it is usually the most successful site for the exploring needle. One often finds the dome of the diaphragm remains somewhat raised when the patient is cured. This, possibly due to adhesions, can be safely ignored.

Signs at the Right Base

This trap is well known. The signs of congestion, collapse or effusion may be the predominating signs of an hepatic abscess, but if amœbiasis is considered, almost invariably in my experience, signs of hepatic involvement can be elicited. Usually there is doming or limitation of movement of the diaphragm.

Perforated Gastric Ulcer

"Only the novice makes this mistake". I have made it and in a similar case would probably repeat the error.

The Case:—A man aged 36 was admitted with a history of very severe continuous epigastric pain. He almost knew the precise moment of its onset.

On Examination—Tenderness and rigidity upper abdomen.

Diagnosis—Perforation of peptic ulcer into lesser sac. The surgeons were somewhat wary of operating, but the tenderness and rigidity increased in area and severity, and 3 days later he was operated upon.

Report — Large abscess cavity bounded by liver and elsewhere by granulations. Blood stained pus — Gall bladder not identified, but some threads of tissue which might have been gall bladder removed.

Drained. *Diagnosis* — Acute gangrenous cholecystitis.

Progress — Pyrexia persisted — man became very ill, and when I saw him 6 days later there were large unhealthy granulations in wound. From the pus, active E. H. were identified. Responded to anti-amœbic treatment. Even with this information, cross questioning failed to disclose any previous ill-health, diarrhœa, pain over liver, etc., but of course the cause must have been a ruptured hepatic abscess.

Clinical Amœbic Dysentery

This is sometimes an even more unsatisfactory diagnosis than clinical malaria — any worthwhile course of treatment for amœbiasis means fairly long hospitalization and the use of drugs such as quinoxyl, which may be in short supply. I have seen it made in the slender support of an unexplained raising of the Rt dome of the diaphragm and of course frequently when chronic diarrhœa responds to emetine. But this response is no real proof. Let me please quote a case still under my care:—

An Indian Army Officer was admitted with severe abdominal colicky pain in the R.I.F., of a few hours duration. He gave a history of diarrhœa for some months past. On examination he had a slightly tender, actively contracting sausage-shaped swelling in the R.I.F. There was no abdominal distension, and flatus was passed readily. At home in England, there would have been no hesitation in diagnosing subacute intestinal obstruction due probably to a carcinoma of the colon or a band. He was however investigated. A barium enema showed extensive ulceration of the cæcum. (Amœbic granulomatous masses in the cæcum have been known to cause intestinal obstruction.) Sigmoidoscopy was normal. In spite of the failure to find E. H. in his stools he was given anti-amœbic treatment. His symptoms disappeared and furthermore the radiological appearance of the cæcum returned to normal. However, occasionally one could cause by palpation and observe, active peristalsis with a contractile swelling in the R.I.F. Four weeks after admission when he thought he was nearly cured, the original signs and symptoms of subacute intestinal obstruction reappeared, a laparatomy was performed and a carcinoma of the transverse colon near the hepatic flexure found. The explanation of this temporary clinical recovery is the same no doubt as in many cases of so called clinical amœbic dysentery that respond to anti-amœbic treatment, viz., bed, warmth, and a suitable diet. This recent case has made me even less satisfied with the diagnosis of clinical amœbic dysentery.

As for regarding general ill-health as possibly due to amœbiasis, when there are very slight colonic disturbances and no positive findings on clinical laboratory or radiological investigations, one should always maintain a healthy scepticism although most authorities on tropical medicine stress how it may be the only manifestation of latent amœbiasis and how it responds to anti-amœbic treatment given empirically. But once again this treatment is combined with rest and suitable diet.

Treatment

The toxic effects of emetine are well known, but I suggest that the dangers, particularly in therapeutic doses, and given intramuscularly are rather exaggerated. Napier states "the most disastrous consequences may result from the ill-advised administration of emetine. The most dangerous effect is on the heart in which it produces myocardial degenerative changes and alterations in the conductivity with a fall of blood pressure, cardiac irregularity and acute dilation as the result of undue effort". On the other hand Brown, of Mayo Clinic, in 15 years experience of 554 cases had seen no untoward cardiovascular reactions and his conclusions were

"a 12 grain course by the intramuscular route had no damaging effect on the myocardium, even if some myocardial effects exist at the commencement of medication". My own experience is naturally very small compared with Napier's. I have rarely recognised any toxic effects from a 12 grain course. In experimental animals an overdose of emetine causes ventricular fibrillation. As a precautionary measure all patients having emetine must remain strictly in bed.

Many combinations of emetine, E.B.I., quinoxyl and an arsenic preparation are used, but no treatment at present known guarantees against a recurrence. To obtain good results with any of these drugs, singularly or collectively, attention to details is essential, e.g. (1) Do not sterilise solutions of emetine by boiling (except in ampoules); (2) Ensure that the E.B.I. pills are not old and insoluble; (3) Persist in the use of E.B.I. in spite of vomiting or diarrhœa; (4) Precede the quinoxyl retention enema by a sod. bicarbonate washout.

The treatment I would suggest is almost that recommended by Brig. Boland, which is emetine gr. I daily for 3 days, E.B.I. gr. III for 12 days concurrently with quinoxyl retention enema, followed by carbarsone tds for 12 days; except that the course should be opened by at least 6 daily injections of gr. 1 emetine intramuscularly, as there is no doubt that emetine has a dramatic effect on the symptoms of an acute amœbic dysentery and hepatitis. Since using the recommended standard treatment (i.e. 3 grams of emetine) for the past 6 months the immediate results have been excellent. Every case has responded to treatment. Clearance tests have been satisfactory and sigmoidoscopy normal. It is, of course, too early to state that they are permanently cured, but no patient has been re-admitted with a recurrence of symptoms. (In Sicily we are the only hospital and the military population is relatively static.) Cyst passers have had this course.

Yatren tablets have been tried prophylactically but not on a scale sufficiently large to make its value certain. In endemic areas the administration of a 4 grain tablet of Quinoxyl twice weekly might have marked beneficial results particularly reducing the number of cysts passers.

I have seen many patients who have had course after course of emetine, a practice rightly condemned. Experimentally E. H. can become emetine resistant and this certainly occurs in man. There are explanations for this abuse of emetine (1) At one time (not in C.M.F.) it was the only drug available, and (2) there was a lack of appreciation that a person cured of amœbic dysentery is often liable for some months to abnormal irritability of the colon, causing diarrhœa. It is a mistake to retain such patients in hospital or allow them to be readmitted frequently for further investigations. If the body weight does not diminish unduly, such diarrhœa should be ignored, otherwise post amœbic neurasthenia or an unhealthy interest in the bowels may rapidly follow. On the other hand a spine like syndrome may be a sequelæ of amœbic dysentery.

Diet

This is of fundamental importance. A non-residue diet should be maintained during treatment, and persisted in as far as possible for some months afterwards. I feel that some of the poor results of treatment are due to the neglect of this factor. A liver abscess does not develop in every case in which amœbæ are carried to the liver. Experimentally in dogs, raw liver or liver juice given by the mouth acts as a amœbostatic, or even amœbocidal agent. If this is so, raw liver might with benefit be given to patients with amœbic dysentery.

As regards the treatment of hepatic abscess a preliminary course of emetine, if necessary aspiration which may have to be repeated, the injection of emetine into the abscess and the avoidance of open operation, are essential. I have not had the opportunity of observing the effects of penicillin injected into the abscess cavity. The possibility of more than one abscess must be remembered if symptoms, particularly pyrexia, persist after emetine and apparently successful drainage.

A new German arsenic bismuth compound called Wia (I.G. preparation 9659A) is reported to be very effective and furthermore there is no difference in response between ambulatory patients and those confined to bed. The few failures responded to Wia combined with emetine. I am hoping to hear more about this drug.

I have skimmed inadequately over a very large subject.

Among the points touched are:—

(1) The suggestion that a life cycle of E.H. may exist in which the active conventional amœbæ is not essential.

(2) There is no evidence that any strain of E.H. is virulent.

(3) All cysts passers should be treated.

(4) Unusual manifestations of amœbiasis may suggest P.U.O., carcinoma of rectum, appendicitis, perforated peptic ulcer.

(5) All gradations from hepatitis to hepatic abscess may be seen. At first it may be impossible to know whether or not an abscess is present.

(6) The diagnosis of clinical amœbic dysentery or amœbiasis should be avoided if possible, and that it is a fallacy to assume that response to anti-amœbic treatment is a proof of the accuracy of the diagnosis.

(7) That possibly the dangers of emetine are exaggerated.

(8) A combination of emetine, E.B.I., quinoxyl and carbarsone has been recommended.

(9) The importance of diet in this disease and the suggestion that raw liver would be beneficial.

AMŒBIASIS

by

Lt.-Col. J. H. HUTCHISON, RAMC

I think that a suitable title for this paper might be "The Voice of Inexperience". My experience of the dysenteries was obtained in North Africa where amœbic diseases are rare and in Italy since September, 1944, i.e., after the dysentery season had passed. I regard amœbiasis in its varied guises as the most difficult infection I have ever attempted to master as a clinician, and I feel that only a physician with many years of experience in "amœbic" countries and also with experience of the resistant, relapse, and "missed" cases seen in tropical wards of U.K. is qualified to speak with authority on this disease. Even then his experience would probably not be directly applicable to amœbiasis in soldiers, because all chronic intestinal diseases become inextricably mixed up with the autonomic nervous system and the psyche and in no type of human are the nervous system and the psyche more trying and even uncooperative than in the "browned-off" British soldier.

I personally am still trying to make my confused, fearful, and at times sceptical way towards the final goal, that of understanding this infection, which may not always be a disease; a little public confession of these confusions, fears, and scepticisms, while I doubt if they will do my soul much good, may at least serve to promote discussion which is the object of this paper. I propose to confine my remarks to the diagnosis of intestinal amœbiasis and other bowel abnormalities which may simulate it, leaving the discussion of treatment, hepatitis, etc., to others.

In the first place, I think it is necessary to realise that amœbic infection and amoebic disease, like tuberculous infection and tuberculous disease, are two different things. As has been pointed out by Dobell, the aim of the parasite is to infect man without causing death or even deterioration of health; the production of grave symptoms—dysentery or hepatitis—is as inimical to the parasite as to its host. And so it is, that amœbic dysentery is not, probably, the most common expression of amœbiasis; more often the amœbæ live and multiply at the expense of the host who is, however, usually capable of compensating for the ravages of the parasites without detriment to health, and without suffering from symptoms of disease. Such a carrier cannot, however, be regarded as normal — no more than can the apparently healthy individual harbouring a primary tuberculous complex, be regarded as normal—there are always some lesions (probably microscopic) in the intestinal canal. Under certain conditions, however, these lesions may, as may the Ghön's focus, awaken into an activity which terminates in a fatal disease. It is as difficult to decide whether to treat and how to treat the "healthy" man with amœbic infection as it is to make a comparable decision in regard to the "healthy" child with tuberculous infection. The analogy with tuberculosis can, however, be pushed too far. Tuberculosis in its primary stage tends to heal spontaneously leaving certain helpful serological evidence of its passage that way. Amœbic infection probably never heals and tends to hide its presence most effectively, at least from the staffs of overworked military hospitals.

The pathogenesis of amœbic disease seems to be that the amœbæ suddenly start destroying the tissues more rapidly than the host can repair them, and all degrees of intestinal ulceration may occur from minimal lesions producing mild intermittent diarrhœa to necrosis of large areas of mucous membrane associated with severe local and general disturbance.

The common type of case with onset of diarrhœa of moderate severity, stools often containing some blood and mucus and associated with some degree of malaise, necessitates treatment, and if the soldier is sent into hospital at this stage it is my impression that diagnosis is not difficult, most of the stools containing entamœbæ in reasonable numbers. If however, the unit M.O. treats such a case empirically with sulphaguanidine—and frequently, repeated courses are used—the patient finally reaches hospital with several months' history of diarrhœa, often alternating with periods of constipation and it is in this type of case which we have experienced most difficulty in establishing the diagnosis. The same difficulty is found also with cases in which the onset of diarrhœa—frequently months before—of mild degree has not caused the patient to report sick until finally he is worried because of the long duration of diarrhœa or it may be that he finally uses his mild diarrhœa which so far had not worried him to escape from an unpleasant or tiresome situation. These mild cases of chronic diarrhœa have been the subject of much discussion in my hospital in recent months between the clinicians and the pathologist, and the cause of not a little anxiety; how intensive should the hunt for amœbæ or cysts be; how long should investigation be continued in terms of period off-duty; how serious is it to miss an occasional case of amœbiasis among the large number of chronic diarrhœas investigated; what are the other possible ætiological factors in producing chronic diarrhœa; is Manson-Bahr wrong when he states that 80% of cases of amœbic disease have visible lesions at the sigmoidoscope level; are all cases of mild but long-continued diarrhœa associated with otherwise good health but in which evidence of amœbiasis is found due to the amœbiasis; may it be that some of the so-called treatment resistent cases are really instances of diarrhœa associated with amœbiasis but not due to this infection?

I cannot pretend to know the answer to these questions but in the consideration of them lies the answer to an understanding of amœbiasis; the secondary amœbic diseases—hepatitis, abscess, pulmonary disease, cutaneous, etc., while often present as diagnostic teasers, are distinct easily understood pathological entities, whereas primary amœbiasis which is the precursor of them all has a widely variable pathology, an unpredictable course, a little understood pathogenesis.

I think perhaps that if I outline the experience of one hospital in Italy during 4 months (September-December, 1944) this would form as good a basis as any on which to discuss the clinical and diagnostic

problems. During this period 544 cases of diarrhœa, of which 275 cases were dysentery (i.e., exudate in stools), were investigated—this excludes cases evacuated for investigation elsewhere and excluding cases of secondary amœbiasis. From that number a diagnosis of amœbic dysentery was confirmed by finding vegetative E. histolytica in 19 cases, i.e. 3.6% of all cases of diarrhœa, and 7% of all cases of dysentery. Of the 19 cases of amœbic dysentery, 13 were fresh cases with moderately severe diarrhœa, some colic and enough malaise to indicate admission to hospital after periods varying from a few days to one month of illness; 2 were relapses; in the remaining 4 the diarrhœa was mild, chronic and associated with reasonably good general health. The diagnosis was confirmed by the laboratory in the fresh cases after examination of the first few stools after admission, whereas in the 4 chronic mild cases the amœbæ were only found after the examination of many stools; in one case actually the diagnosis rested on typical sigmoidoscopic appearances of mild ulceration and the finding of sluggish amœbæ containing red cells. None the less, among the 544 cases of diarrhœa was a very considerable number of chronic cases—very different from our experience in North Africa, where chronic diarrhœa was much less frequently seen. We were naturally worried over our inability to find evidence of amœbiasis in these cases because their pathogenesis was by no means obvious or well-defined, and at first it was felt that amœbiasis must be the most probable ætiological basis. We therefore surveyed our diagnostic routine. It is agreed by all the experts that certain essentials must be observed in diagnosing amœbic disease; 1. The stools must be examined fresh and warm. 2. The pathologist is better presented with the whole specimen in an antiseptic-free bed-pan than with an aliquot portion in a container. 3. The clinician and the pathologist must liaise in the ward and in the laboratory. 4. Sigmoidoscopy must be regarded as a *sine qua non* in diagnosis and the microscope should be regarded as part of the sigmoidoscopy " set-up ". We felt that we were in fact, adhering to all these essentials. Our routine is as follows:— routine specs of stools from new cases—direct to the laboratory from the ward—a matter of 5 minutes, or thereabouts in a well heated building. On 3 mornings per week the pathologist brings his microscope to the ward; patients are prepared for these mornings by calomel and salts—normally they are the more chronic, less acute cases (straightforward dysentery B.E. and amœbic dysentery are spotted on routine stools) and stools are examined within a matter of seconds of being voided. The micro-findings are often discussed against the clinical picture by pathologist and clinician. Sigmoidoscopy is done in every case of diarrhœa which does not clear within 10 days, and in every case with a long history, and in any case in which the aetiology remains obscure. However as already stated, we were *not finding* amœbiasis to be a cause of more than a very occasional case among the many chronic diarrhœas being investigated under these circumstances. Our findings in these mild chronic sufferers might be summarised as follows:—

History. Several months duration of mild diarrhœa sometimes alternating with constipation, mucus often seen, blood rarely. Colic from time to time, not severe; no tenesmus.

Prev. History. Diarrhœa or dysentery in N. Africa, M.E., Sicily, etc., almost invariably.

Prev. Treatment. Sulphaguanidine had been administered by unit M.O. in almost every case; often repeated short courses had been given; response had been either partial recovery or no change.

Examination. These patients were generally fit looking, well-nourished healthy men with excellent appetites, clean tongues. Their personalities were varied but colon-consciousness, lack of sense of humour, and a pessimistic outlook on life generally were often obvious.

Stools. Exudate was either indefinite or more often completely lacking even after trauma with calomel and salts. In passing, I might say that if repeated stools after purging were without exudate we felt that amœbiasis was a very remote possibility. Culture was done in over 50 cases—only one was positive (Flexner A2).

Sigmoidoscopy. The mucous membrane to distances of 6-12 inches was either quite normal or mildly injected. In the 4 cases of chronic diarrhœa showing evidence of ulceration we found amœbæ in due course.

I feel that the routine just outlined will, given accurate and informed observers, detect the very great majority of cases of amœbiasis. None the less, we have felt happier in stating that amœbiasis had been excluded since we have given thought as to what—if not amœbiasis, are the causal factors in these mild chronic cases. Stools microscopy is negative: culture is negative; sigmoidoscopy is negative; the patient is negative, physically and often in personality, but his bowel frequency is positive. What then is the pathogenesis? We feel that several causal factors are concerned, not all being present in each case, and not always occupying the same order of importance. The use of sulphaguanidine in short courses and without other therapeutic measures (rest, diet, etc.) was an almost universal part of the history; possibly S/G so diminishes general malaise and acute ileo-colitis that men are enabled to remain on duty with subacute ileo-colitis which, however, does not resolve under service conditions—exertion, rough diet, exposure to damp and cold, etc. In some cases the condition is undoubtedly a functional instability of the colon following repeated attacks of bacillary dysentery each rapidly controlled but not always completely cured by sulphaguanidine, in fact this is probably the major factor in most cases, and on such a basis it would be explicable why we should see more chronic diarrhœas now than in N. Africa when the patients were all new to dysenteric disorders. In a proportion of patients psychological factors are prominent the " unwilling " soldier colon-conscious, depressed and pessimistic, minutely examining his stools, is a phenomenon reminiscent of similar personalities with effort syndrome, nervous dyspepsia, functional frequency of micturition, etc., and equally difficult to deal with. Provided that amœbiasis is excluded by thorough fæces examination, etc., the disposal of these cases is R.T.U. or Conv. Depot. In most cases the diarrhœa ceases with a short period of rest and light diet, plus chemotherapy which, however, rarely seems to help; in the others reassurance is given that the passing of 3-4 semi-formed stools daily is nothing to be worried about after several " goes " of dysentery.

To return to the diagnosis of intestinal amœbiasis; we feel in my hospital that there is only one satisfactory basis on which a diagnosis of intestinal amœbiasis can be made, the finding of vegetative E. Entamœbæ; I think it is correct to treat the chronic type of case in which sigmoidoscopy reveals typical amœbic ulceration of pitting of m.m. and in which amœbæ or cysts cannot be found, but the use of emetine as a therapeutic test in cases of chronic diarrhœa in which sigmoidoscopy is negative or in which it has not been done is agreed by experienced people to be not only unhelpful but unsound; such a course of action means that the poor patient is almost inevitably doomed to further emetine treatment every time he develops diarrhœa from whatever cause. Regarding the importance to be attached to the demonstration of cysts, opinions in my hospital may be summarised as follows:— 1. It is doubtful if any but the most experienced pathologists can often say with certainty as to whether a cyst is Coli or Histolytica. 2. The findings of probable Histolytica cysts from a patient with some other objective evidence of amœbiasis sigmoidoscopic appearances of amœbic disease, hepatitis, or with a history of amœbiasis and present diarrhœa justifies a diagnosis of amœbic disease and therefore treatment. 3. The presence of cysts alone, in the absence of +ve sigmoidoscopic, X-ray or clinical findings, does not justify a diagnosis of active amœbic disease whether or not the patient has diarrhœa. We feel that it is as wrong to base a diagnosis, especially one implying an unpleasant treatment, on one pathological finding, especially a somewhat dubious one, in this disease as it is in any other.

I feel that this paper has been more of a survey of the problems of clinicians in one hospital meeting a difficult and on the whole an uncommon disease for the first time rather than a statement containing easy method of diagnosis. Yet I imagine that our problems cannot differ greatly from those of other hospitals in Italy. Our experience might be summarised thus:— Amœbic dysentery seen early is not often a difficult diagnosis, and given a proper diagnostic routine will rarely be missed; amœbic dysentery seen late is a most difficult diagnosis, but if the clinical, microscopic and sigmoidoscopic evidence is added together it is unlikely that many cases will be missed; chronic diarrhœa in this force is most often not due to amœbiasis. We have not seen cases of chronic amœbic dysentery in poor condition following repeatedly unsuccessful courses of treatment although I believe such cases are a problem in U.K.; in fact we have been impressed by the efficacy of the present routine treatment in amœbic dysentery. We have, however, been worried by a few patients with chronic diarrhœa previously treated with emetine, etc., without pathological confirmation of the diagnosis and without much benefit and in whom we could find little to suggest that amœbiasis was or had been a causal factor. I feel, personally, that anti-amœbic treatment in a case of diarrhœa should not be employed unless the evidence in favour of amœbiasis either constitutes proof or is overwhelming, and that once started it should be completed. It is my impression—I do not speak from wide experience—that it is less dangerous to miss an occasional case of mild chronic amœbiasis, than to treat a non-amœbic diarrhœa with emetine.

Summary

This paper is confined to the diagnosis of intestinal amœbiasis, and discusses diseases which may simulate it. Amœbic infection and amœbic disease are two separate things. The apparently healthy carrier of this infection cannot be regarded as normal; intestinal lesions always exist; but it is most difficult to know how to treat him. Secondary amœbic diseases are distinct pathological entities but primary amœbiasis it is pointed out has a widely variable pathology, an unpredictable course, and a little understood pathogenesis. It is in fact a condition on which many questions remain unanswered; how intensive should the hunt for amœbæ be and how long should it go on? How dangerous a disease is mild chronic intestinal amœbiasis? What are the other factors in producing mild chronic diarrhœa in this theatre? What percentage of cases of amœbic diarrhœa have lesions at sigmoidoscopic level? Are all cases of diarrhœa with evidence of amœbic infection due to this infection, etc. etc.?

The experience of one hospital in Italy from September to December, 1944, is discussed. 544 cases of diarrhœa were investigated, of which 275 had exudate in the stools. Included in these were 19 cases of *proved* amœbic dysentery (this excludes cases with secondary amœbiasis — hepatitis, etc.) — 13 fresh cases easily diagonosed, 2 relapses, and 4 chronic cases in which diagnosis was difficult. The great majority of cases of *chronic* diarrhœa were not due to amœbiasis. Their pathogenesis is discussed. Factors involved were (1) repeated courses of sulphaguanidine in ambulant patients not given other therapy, e.g., rest, diet, etc., exposed to exertion; the elements, etc.; (2) functional irritability of the colon after repeated attacks of bacillary dysentery in N.A., M.E., etc.; (3) psychosomatic disturbances. The opinion at this hospital may be summarised thus:

(1) Demonstration of vegetative E. histolytica is the only really satisfactory basis for diagnosis. (2) It is correct to treat chronic cases with positive sigmoidoscopy findings without proving the diagnosis pathologically; it is wrong to treat chronic diarrhœa with emetine if thorough fæces examinations and sigmoidoscopy are quite negative. The repeated absence of exudate in stools is against an amœbic basis. (3) The presence of cysts in the fæces in conjunction with positive sigmoidoscopic appearances or with a previous history of amœbiasis is an indication for treatment; the findings of cysts in the absence of positive clinical, sigmoidoscopic, or X-ray findings is not an indication for treatment—unless the pathologist is experienced and quite certain the cysts are histolytica—by no means an easy distinction from coli cysts. (4) The use of emetine as a therapeutic test in cases of chronic diarrhœa in which microscopy and sigmoidoscopy are negative is to be discouraged; it is rarely helpful and may be harmful.

DIAGNOSIS AND TREATMENT OF AMŒBIASIS

by

Lt.-Col. R. KAUNTZE, RAMC

In actual number the cases of diagnosed amœbiasis in this theatre have not been great; yet because of their chronicity, quiescent periods, tendency to recurrence and important sequelæ, these patients present a problem. The chronicity and often relatively slight indisposition occasioned by the disease are, in themselves, a danger, for they may delay investigation and adequate treatment. Of 31,000 British troops returned from the Middle East after the last war no less than 9.8% were found to be infected with entamœbia histolytica (quoted from Stitt).

During the period April to December, 1944, cases of amœbiasis in 104 General Hospital numbered 110, comprising 69 dysenteric (74% E.H. +), 39 hepatic (12% E.H. +) and 2 of liver abscess. That the disease is frequently associated with or brought out by catarrhal or bacillary affections of the colon is illustrated by the occurrence of 83 cases (75%) during the summer months. Bearing on this is the experiment of Westphall (1937), who infected himself with washed cysts of entamœba histolytica; two days later cysts and trophozoites were present in the stools. He remained symptomless for eight months, when he further infected himself with a mild dysenteric colitis. Another worker similarly infected cleared up, as did Westphall, in a few days, yet one month later Westphall developed frank amœbic dysentery. It seems probable that some synergic action is necessary to start off an amœbic dysentery, as opposed to the mere symptomless passage of cysts. Walker and Sellards fed 20 men with E.H. Eighteen became parasitized, passing typical cysts, but only four developed dysentery. Thus it would seem that there is some explanation of the frequently disappointing previous histories of patients presenting amœbic hepatitis.

Typically the history in amœbic dysentery may be of relatively mild yet recurrent bouts of diarrhœa, frequently long continued, with a flatulent aspect both of the gut and on life itself. Fulminant cases with pyrexia do occur and are difficult to differentiate from bacillary dysentery until stool and proctoscopy supply the answer; often there are mixed infections, but the passage of almost pure blood is always suggestive. The duration of symptoms is most variable—of the last 60 cases of amœbic dysentery seen by me six had histories of 4 to 10 days only, yet the majority ranged from 2—24 months. Stools in this series numbered from 3 to 18 in the 24 hours. However, amœbiasis of the gut is not always associated with diarrhœa, and previously symptomless yet extensive ulceration of the bowel wall may be revealed at autopsy. At certain periods brown mucus may be passed with the motions; this, which is due to degenerated blood, is of some diagnostic importance.

On the whole the dysentery lives up to its name of "walking dysentery"; and it is this history of recurrent mild diarrhœa which even in the absence of positive stool or sigmoidoscopic findings makes, *on occasion*, treatment with emetine in some form advisable. If this needs justification then it must be considered in the nature of a therapeutic test, furthermore in proven cases the earlier treatment is instituted the more successful are its results.

Achlorhydria and a food relationship may too easily lull suspicion; and the label of lienteric diarrhœa may obscure an amœbic basis.

In hepatitis the history although vague is of major importance, for its very indeterminate character will serve to direct attention to the liver; exacerbation from a "surcharge of aliment and alcohol" is a common story as is discomfort from wearing equipment around the waist; there is often preference for sleeping on the right side. Periods of well-being are usual between the exacerbations. Low fever of intermittent type is of frequent occurrence, the rise in temperature occurring during the afternoon.

Case 1. A well-built officer aged 37 — overseas for 3 years — had experienced during the previous 2 years, bouts of fever, malaise, flatulence, and upper abdominal discomfort associated with mild diarrhœa. Lack of energy and loss of weight had also been noted. The stools in the last attack contained brown mucus. During previous periods in hospital he had been labelled malaria and sandfly fever; latterly 3 molars had been extracted as a possible cause of the symptoms.

There was diminished air entry at the right base with restriction of the diaphragmatic movement on this side. The liver was enlarged 2 fingers breadth downwards and was somewhat tender. Stools, sigmoidoscopy, and agglutinations against the brucella group were all negative.

After emetine his general condition has greatly improved, there has not been further fever and although it is early to be certain, I do not think there is doubt but that this is a case of amœbic hepatitis.

A more definite history:

Case 2. Corporal M., aged 32 — overseas since October, 1943.

In February, 1944 he first complained of a dull aching pain in the right subcostal area, "as though he had strained himself". Primarily noticed in the early hours, made worse by wearing equipment or bending down, without food relationship. Diarrhœa for 2 days in February, 1944 and again in June, 1944.

Cæcal thickening and tenderness were present; the liver was enlarged 3 fingers breadth downwards. Apyrexial.

Sigmoidoscopy showed mild hyperæmia and a few submucosal hæmorrhages. Stools yielded E.H. W.B.C. 7,500. P.55%. L.39%. M.6%.

He received 12 × gr. i Emetine I.M. after which sigmoidoscopy was negative but the stools still showed E.H. After E.B.I. and Yatren the stools were negative.

Finally he was discharged well, although the liver was still palpable one-finger breadth below the costal margin.

By far the most frequent causes of confusion in the diagnosis of amœbic hepatitis are cholecystitis and low-grade inflammatory conditions at the bases of the lungs, usually the right. Although malaria, undulant fever, subphrenic abscess, Kala Azar and even gastric neoplasm may at times present difficulties.

Case 3. A welfare-worker, aged 55, with an ill-defined history of dyspepsia complaining of pain in the right upper abdominal quadrant of 2 days duration with fever was diagnosed acute cholecystitis. Later basal signs were present in the chest and the diagnosis of bronchopneumonia was added. For this he received 29 gms sulphapyridine with improvement and he was transferred to 104 General Hospital.

At this time there was some tender enlargement of the whole lower surface of the liver. W.B.C. 11,400 and the X-ray which accompanied him showed a raised right diaphragm. Stool examination revealed E.H.

He has reacted well to emetine, during treatment with which there was a further low-grade bronchopneumonia.

We have diagnosed as amœbic hepatitis certain cases which might be classed as "Infective Hepatitis without Jaundice" in which there has been well-marked and persistent hepatomegaly — especially were leucocytosis present and low fever an occasional episode. Response to treatment has in many instances been most satisfactory, and perhaps has made us more elastic in our criteria. For it must be emphasised that amœbic hepatitis is sometimes a rather vague syndrome. But with the remedy to hand, if a few patients are unnecessarily subjected to emetine I hardly think it matters greatly; any more than diphtheria antitoxin to the suspicious yet not definite diphtheritic throat. It is an insurance policy. It is also salutary to remember that 20% of untreated amœbiasis in men is said to be followed by tropical abscess.

As a coincident event we have seen infective hepatitis and amœbiasis concurrent.

Thickening of and tenderness over the cæcum or colon has seemed a most helpful sign. Tumour of the cæcal region or an apparent appendix abscess with a history of previous diarrhœa should call for a scrutiny of the stools. One recent patient with amœbic dysentery developed a typical picture of acute appendicitis; as this subsided without surgical intervention it was impossible to say if it was an amœbic typhlitis or a catarrhal appendicitis.

Diagnosis is much a matter of patient stool examination, and I cannot speak too highly of the efficacy of adequate magnesium sulphate for displacing the lurking amœba. Sometimes a positive stool may even be obtained after the first or second injection of emetine.

The stools are frequently alkaline as opposed to the acid motions of bacterial dysentery, of loose consistency, sometimes with dark or bright blood. This latter may be in association with hæmorrhoids which are not infrequently present in amœbiasis. The finding of Charcot-Leyden Crystals is a pointer, but they are also described in ulcerative colitis, etc.

Sigmoidoscopy is an invaluable aid to diagnosis and progress but negative findings in the presence of intestinal amœbiasis are frequent, in a small recent series there were 16% of negative sigmoidoscopies in which stool examination showed E.H. This is readily understandable. Out of 186 fatal cases Clark found ulceration of the cæcum in 87.3% of the ascending colon in 57.1%, and of the rectum 39.6% only.

Carcinoma of the rectum may present as an acute diarrhœa and here sigmoidoscopy is of vital importance. One such patient with a seven weeks history of intermittent diarrhœa had been treated with sulphaguanidine. Examination revealed an annular carcinoma of the ampulla.

In the acute stages proctoscopy is possible and usually suffices, but in the chronic phases sigmoidoscopy may be an undignified but is not a painful procedure. I remember during the passage of the instrument in an officer looking up to see a cloud of smoke, but on a second glance I was reassured to see that he was contentedly smoking his pipe. And that in the knee-elbow position which is the best and least uncomfortable.

The following sigmoidoscopic appearances in amoebic dysentery have been observed:

1. A voluminous, redundant mucosa.
2. Flame-shaped submucous hæmorrhages.
3. Small discrete white-capped ulcers with or without a zone of surrounding hyperæmia.
4. Thin fissured ulcers in the rectum.
5. Single or rarely multiple large ulcers, sometimes hard and fixed with excavation, seemingly like carcinoma.
6. A polypoid mass.
7. Nodules on the valves.
8. Granular proctitis.
9. The pitted mucosa of healed lesions, especially around the valves.

It is always worth while taking mucosal scrapings for the lesions are sometimes quite minute and easily overlooked. An apparently normal mucosa may yield a positive result. Johnson (1941) found that the gut of monkeys infected with E.H. showed no macroscopic lesions, yet in 7 of 10, microscopy revealed positive evidence. The scraping of areas of submucosal hæmorrhage is often successful.

Usually the amœbæ, like clumps of bright stars under the 2/3, exhibit their two main diagnostic characteristics of included red cells and amœboid movement; the latter has been nicely described by Dobell as that "of a slug travelling at express speed." Sometimes precystic forms alone are present; these are small and sluggish, and again there may be apparently typical E.H. which do not show any movement. Gently warming the slide may produce the desired effect.

The white cell count in amœbiasis is not often of great help.

Radiography is of assistance in hepatitis and liver abscess. Diminished movement, paralysis or doming being frequent.

The following case is illustrative:—

CASE 4. A poorly nourished soldier, aged 30, in the Mediteranean Area since May 1941 was admitted to hospital on 20th April 1944. He had noted right chest pain on deep breathing, cough with scanty sputum and dyspnœa on exertion for one month. During this time he had lost 8 lbs. in weight.

His previous history was of diarrhœa for 5 days in Egypt in April 1943—right pleuritic pain for one month in December 1943 and again in March 1944 following coryza; also at this time pain at the point of the right shoulder.

T.101.P.132 Clinically there were signs of a large right pleural effusion with marked displacement of cardiac impulse. The liver was not palpable and there was no superficial tenderness.

Diagnostic aspiration produced yellow-green pus, which showed a few pus cells, many R.B.Cs., macrophages and Charcot-Leyden crystals, sterile on culture.

X-ray of the chest showed the right diaphragm much elevated and the right lower lung field relatively normal, *without* evidence of effusion.

W.B.C. 13,200. P.77%.

Forty-eight ozs of anchovy coloured pus were aspirated from the liver on one occasion.

The patient received 12 x gr.i and later 6 x gr.i emetine, and apart from a ? small hæmorrhage into the abscess cavity in June 1944 following a bout of immoderate laughter, made an otherwise uninterrupted recovery. The first specimens of pus aspirated did not entail going deeply, the absence of movement in the needle was presumably because the right diaphragm was immobile.

The main lessons of this case were that on purely clinical grounds a diagnosis of empyema would have been acceptable, treatment along those lines harmful, and X-ray assistance diagnostic. The first symptom of probable hepatitis was present 5 months before the abscess was found.

I have had little experience of examination of the colon with barium and X-rays in amœbiasis—I cannot imagine that it holds a high place in diagnosis.

Craig has described a complement fixation test using an alcholic extract of cultured amœbæ as antigen. Out of 175 positive reactors he reported later finding 90% E.H. or cyst positive.

Treatment

Long before the isolation of emetine, ipecacuanha had been recognised in China as a remedy for amœbic dysentery.

That injected emetine is a specific for amœbic hepatitis there is little doubt, and it is this favourable and rapid reaction to treatment which frequently confirms or disproves the diagnosis; even in cases with localised tenderness and leucocytosis, where perhaps a small abscess exists—recovery can often be expected without needling. Consequently if conditions allow it is desirable to observe the result of injected emetine before liver puncture is attempted. In liver abscess in association with paracentesis the results of emetine seem excellent. It has been our practice in the majority of cases of stool negative amœbic hepatitis to give 12 x gr.i emetine injections and two or three weeks later 6 x gr.i, a few cases have had more and a few less—stool positive cases presenting as hepatitis have been treated with intramuscular injection and after an interval a course of E.B.I.

Emetine by injection appears to have little effect in sterilising a well-marked intestinal infection, and E.B.I. has the desired result in most instances. Even so after 30 grs. E.B.I. relapse occurs occasionally.

Manson-Bahr quotes his combined E.B.I.-Yatren treatment of 300 cases of amœbic dysentery as showing 2 relapses. Of the last 60 cases admitted to 104(Br) General Hospital 12% had had previous amœbiasis, not all of which, however, had had E.B.I. I am convinced that early treatment lowers the relapse incidence, but this is an impression rather than a fact.

Manson-Bahr stresses that the patient vomits nightly some 4 hours or so after administration of E.B.I. thus showing adequate absorption of the drug. This has not been our experience, although nausea was a complaint in 55%; only 20% vomited and those not every night. All our dysenteric cases of amœbiasis have had the standard emetine, E.B.I. Yatren Course, yet I think that the three preliminary injections of emetine might well be omitted from the course.

The side effects of emetine or E.B.I. have been asthenia, depression sometimes marked, loss of appetite, loss of weight, and not infrequently an exacerbation of the diarrhœa at the beginning of the course. Premature beats have been frequently observed and some lowering of the blood pressure is usual.

With emetine a non-suppurative reaction has occurred around the site of injection on some occasions. One officer had reaction to each injection, all deeply sited, and with adequate regard to sterility, each further injection causing an exacerbation at the previous sites. The result of these injection-reactions may be most painful and although no permanent disability results, their effect may take 2 weeks or more to wear off. Intramuscular injection is however far preferable to subcutaneous.

I have seen one case of serratus palsy occur during emetine injection.

Yatren or oxyquinoline has been of great value as an adjuvant. Certainly it is efficacious psychologically!

Carbarsone or stovarsol have been given to dysenteries only; they appear to improve the appetite.

A low residue diet is advisable in the early stages of treatment and extreme moderation in alcohol after recovery is essential.

During the past year we have had only two cases of amœbic abscess of the liver. The finding of pus in those cases was not difficult. In each instance the abscess was unilocular and one aspiration combined with emetine sufficed. The usual site of abscess formation is in the upper part of the right lobe and if there is no helpful indication such as localised tenderness or surface œdema then puncture should be made in the eighth interspace in the anterior axillary line.

Amongst our cases of amœbic hepatitis there have been some in which by virtue of continued pyrexia,

localised tenderness and perhaps leucocytosis, abscess has seemed likely. In these needling has been attempted without success. Yet in two cases there has been dramatic and remarkable improvement following this hepatic phlebotomy—for nothing but blood was evacuated. This apparently coincidental improvement I have not been able to explain.

The question of treating cyst passers is fraught with difficulty. Yorke noted 5% of cyst passers amongst lunatics and army recruits in England; but amœbiasis indigenous to England is rare. Reichenow thinks E.H. a normal inhabitant of the gut and only under certain tropical conditions invasive.

Ideally I think that cyst passers should be treated with E.B.I.

Finally, continuity of treatment by one person is essential for success. And after-care with a gradual return to full physical status has been made possible by the efficiency of the Convalescent Depot.

The majority of these cases have been protected by a temporary lowering of category and this we have hoped would ensure re-examination and if necessary further treatment.

Summary

The role of associated intestinal infection in the precipitation of amœbic dysentery is noted.

Typical histories, differential diagnosis and sigmoidoscopic appearances are given.

Response to emetine and E.B.I. is discussed.

DISCUSSION — Amœbiasis

Lt.-Col. W. A. Loewenthal, SAMC

Three small points based on 10 years tropical experience before the war. The first is amœbiasis of the colon. Radiological amœboma of the colon is indistinguishable from carcinoma of the colon, dependent on the age of the patient and very often on the previous history of dysentery within six months. I have only seen two. They both had that. The second point is diagnosis in the settled case of intestinal amœbiasis, rather than giving purgatives such as mag. sulph. in large doses it is quite convenient to give 5 per cent soda sulph. enemas and the result of that is usually a large blob of mucus in which you find the amœba. I have seen cases of hepatitis which clinically are indistinguishable from amœbic hepatitis which are associated with enormous quantities of lamblia guardia in the stool. Those hepatitis cases responded very well to a 5-day course of atebrine. They will not be so commonly found in this theatre where atebrine is a routine.

Lt. Dr. Braun, Polish Medical Corps.

In the past two years I have observed in No. 1 Polish General Hospital 25 cases of amœbic hepatitis. They have varied in their clinical symptoms, but none of them had signs of hepatic abscess. I would like to point out one very typical and always present symptom in this disease. It is the behaviour of the right diaphragm.

In all cases without exception by physical examination, and much easier and more exactly by X-raying, we have found that the right diaphragm is flattened and raised. The difference in the level of the right and left diaphragm is 2—5 cm. Then the right diaphragm is not so mobile as the left one. Especially the inner part of the right diaphragm is completely immobile one has a paradoxical movement, sometimes the inner part is protuberant.

The signs are so characteristic that the X-ray Specialist by routine examination of the chest in several cases has drawn the attention of physicians to the diagnosis of amœbic hepatitis.

The syndrome is very similar to that very well known amœbic abscess. I must stress that in all our cases the clinical course and the good results of emetine treatment have excluded quite certainly the possibility of abscess. The diaphragm syndrome disappears after emetine course.

I think it may be very helpful in the early detection of amœbic hepatitis and in preventing the bad consequences of abscess.

Lt.-Col. I. D. Easton, RAMC

Regarding diagnosis of clinical amœbiasis. In our hospital we have had a large turnover especially during the last 15 months, and many cases of chronic diarrhœa. These cases of chronic diarrhœa are extremely tedious. They are very difficult to diagnose as we are all prepared to admit. In the summer of 1943 our laboratory started reporting a non-specific exudate. The physicians were extremely sceptical, and challenged the laboratory findings but in my opinion they proved their case. After subsequent investigation they were able to show the presence of a long standing infection. We would receive reports from the laboratory on two or three specimens. All these would have "amœbic exudates." I want to stress this, for if the laboratory findings fitted the clinical picture particularly the history, then we would treat such a case as a case of amœbiasis and give it a full course. Now that appeared very wrong but the proof of the pudding is in the eating of it, and there is no doubt about it that we did in point of fact clear up most of these cases of chronic diarrhœa. We were ourselves convinced that they were cases of amœbiasis. Another great problem we have found is the case of chronic hepatitis, and we ourselves have not recognised the condition described the other afternoon as infective hepatitis. We have found that no case of hepatitis which would appear to be infective hepatitis with jaundice, failed to clear up in a reasonable period of 6 or 7 weeks. If we investigated the case more closely and investigated the fæces we very frequently have found the actual parasite or we found cysts or again this amœbic exudate. Our routine for taking specimens was almost identical with that outlined by Col. Hutchison. The laboratory would not accept any specimen unless it was warm, and we produced those specimens with calomel or salts. There was another group of cases with liver enlargement and tenderness where we have not been able to obtain very satisfactory evidence of amœbic infection. There I am afraid we have had to confess that on many occasions we have resorted to the use of emetine and with a large measure of success. This of course may be purely a coincidence, but I maintain that in an area where amœbic infection is so extremely common as to be so frequently missed we are entitled to assume that that very common infection is responsible for the condition.

Lt.-Col. J. B. Harman, RAMC.

One point I would like to raise and that is the question of German literature which I understand is being sent over to the troops on how to simulate illness. I am told amœbic dysentery is one of those suggested. I think it would be rather important to hear about this because it would be quite interesting to see what the Germans say and whether it could be used for our own needs. If anyone here has been circulated with this literature I am looking forward to hearing from him.

Brigadier E. R. Boland.

I have a copy here.

Lt.-Col. T. G. Armstrong, RAMC.

I want to raise a therapeutic point which may be a heresy. I believe strongly that three doses of emetine injection is not really quite sufficient. In the last two years I have seen three cases of proved amœbiasis (by sigmoidoscope and microscope) which were given emetine by injection and one of these showed amœbæ after 10 days, another active after 12 days, and a third active after 15 days. These cases were all treated by 21 days of emetine and had no toxic effects. I think emetine by injection is usually taken as having more effect in the acute phase than E.B.I. and if this is so I do feel a three days' dose is rather inadequate. Another point; in the Middle East some of us were rather concerned about the relapse rate from the usual course and some of us gave more emetine by injection than had been given before. Since we came to Italy I have followed up as many cases as I could. Ten cases have given me a six months follow-up and 2 a year's follow-up, that is of the cases that I treated. These cases were treated with E.B.I. Out of 10 cases not one had a relapse after 6 months. I think it is only right to say that these were all cases which occurred in Italy. One point I would like to ask: it often happens that in a case which looks typically an amœbic dysentery by sigmoidoscopic examination, no amœbæ can be seen and yet cysts are present. I have always doubted this and would like to ask if anybody has any experience whether it is really possible for cysts to be produced in a stool from a gut which is actively inflamed and full of blood and mucus.

(Here Brigadier Boland read document from German sources already referred to.—Ed.)

ENEMY PROPAGANDA

World War No. 2 Is Almost Over.

Nobody can say that as a good soldier you haven't done your duty. But no man in the world will ever blame you for not wishing to be one of its last victims. It is far better for you to be a few weeks ill than all your life dead. You don't know how to do it? Well, we're going to teach you the "rules of the game."

1. The doctor should feel straight away: "Here is a good soldier who has the misfortune of being ill against his will." Therefore you shouldn't exaggerate your illness.

2. Make up your mind for one kind of disease and stick to it.

3. Above all, you mustn't tell the doctor the name of the disease you pretend to be suffering from. Don't use any technical terms, doctors don't like that. You will never be found out if you say too little, but you might easily be caught if you say too much.

Never forget: Better a few weeks ill than all your life dead!

Dysentery.

Take a laxative, preferably castor oil. (In Italian: Olio di ricini). When it has begun to work report to your doctor with the following complaints: Tell him that you had a severe attack of dysentery some months ago in Africa, South Italy or some such place with slime and blood in your motions. Since that time you notice that heavy foods, such as pork and beans, fat meats, etc., produce violent pains in your stomach and diarrhœa. Occasionally your motions have been slimy with red streaks and lumps in them. Tell the doctor that you nearly always suffer from mild gnawing pains in your abdomen high up, especially on the right side, but sometimes also lower down on the left side. Say that you feel weak and run down.

When the doctor examines you, show painful response to pressure on the right side immediately below the ribs, also during examination of the right kidney.

Stick to your story at the hospital, and don't forget to take a laxative from time to time.

A few weeks after leaving hospital you might try the whole thing again.

Colonel J. K. Boyd, Consulting Physician, NZEF.

I will only touch on two points. First—How should we deal with the symptomless cyst-carrier?

In the latter part of 1940 in Cairo the then Director of Pathology gave an interesting address on amœbiasis. He stressed the opinion that for an individual to become the victim of amœbiasis, something more than the swallowing of the parasite was required. What that additional factor was he did not say, but he was convinced that many people had the cysts of E. histolytica in their stools but did not have clinical amœbiasis.

My feeling is that we have no guarantee that this condition of immunity will last throughout that individual's life. May not a symptomless cyst-carrier eventually develop the disease in one or other of its forms?

I recently went into a small series of cases of amœbic hepatitis and found that 20% insisted that they had never had any bowel disorder of any kind during their service in the M.E., a fact which calls for congratulation considering the frequency of such disorders in these countries.

It therefore seems to me to be hardly reasonable to say that a man known to be a symptomless cyst-carrier should receive no treatment. I think he should get full courses of treatment in an attempt to rid him of the infection. If unsuccessful this case, on return home, should be handled in the same way as is done with a typhoid carrier—notified to the Health Authorities and his occupation controlled to the extent that he will not be permitted to do any work involving the handling of food and so on.

My other point is this—are we not inclined to over-accentuate the question of the toxicity of emetine?

I remember my own experience. In 1918, towards the end of the last war, I had an amœbic abscess in my liver which was aspirated. I had 3 months in hospital and was given an injection of 1 grain of emetine every day of these three months. During the last month I was up and allowed to go out in Cairo, and it was a case of emetine in the morning and alcohol in the evening—with no ill effects!

Col. Craib, Consulting Physician, United Defence Forces.

I should like to quote one case in my experience which has a bearing on the toxicity of emetine. A sister at my hospital complained of persistent diarrhœa. She was investigated very fully, and amœbic cysts were found in her stools. It was considered a suitable case for emetine. After the fourth injection of emetine she complained of exhaustion. In spite of this, the course was continued. After the next injection she complained that she could not walk upstairs without being extremely uncomfortable, and it was then that I was asked to see her. She had the symptoms of effort syndrome and I thought probably she did not like injections. However an electro cardigram revealed a flat T. wave in lead I, inverted P in lead 2. We decided then that she should have no further emetine and it took two months for the T. wave to become normal. Two months later she was perfectly normal. I feel that although this may have been a case of what you might call "myocardial idiosyncracy" to emetine, the evidence suggests that in certain cases the drug may affect the myocardium.

Summing-up by Opening Speakers

Lt.-Col. W. L. Ackerman, RAMC.

I was interested and surprised to hear of the frequency of amœbiasis in resistant cases of infective hepatitis. It is generally recognised that jaundice is extremely uncommon even in extensive amœbic hepatitis and hepatic abscess.

Lt.-Col. J. H. Hutchison, RAMC.

I feel only qualified to answer one or two points. As regards this question of clinical amœbiasis I should like to say that I think amœbic hepatitis is a different thing from amœbic dysentery. One must make the diagnosis frequently without finding the amœba. I think to diagnose clinical amœbic dysentery is a very different matter. It is probably justified when you find sigmoidoscopic appearances of active inflammation, but to use emetine in a case of diarrhœa where there are no amœbæ and negative sigmoidoscopic appearance must be wrong. As regards Col. Boyd's remarks about cysts. I would like to point out that there is a difference between a cyst carrier and a typhoid carrier. A typhoid carrier is always known to be so. A pathologist will tell you with a hundred per cent. certainty that he is a typhoid carrier whereas many a pathologist is unwilling to say the same about cysts. With regard to Lt.-Col. Harman's mention of German literature, the only patient who showed us one of these pamphlets had actually amœbic hepatitis and amœbic dysentery.

Lt.-Col. G. Kauntze, RAMC.

I have nothing to say.

FOOT CONDITIONS DUE TO COLD AND WET

by

Lt.-Col. G.A. ELLIOTT, SAMC

My experience of foot conditions due to cold and wet is confined to 55 cases of Trench Foot admitted to 106 S.A.C.G.H. during November—December, 1944. These cases have been handled in one ward under the care of one medical officer in a standard conservative manner which I shall describe, and having formed a base-line of observations of clinical signs and symptoms and general course under these conditions of observation, it was intended to modify the management of the next batch of cases—a batch which never arrived, there being only two admissions during January, 1945. The failure to arrive was apparently due to a change in the line of evacuation of casualties.

All cases have been or will be followed up at Convalescent Depot up to and in many cases beyond the stage at which they are fit for some restricted form of duty. By beyond, I infer that cases are being held for purposes of follow up—with the approval of administrative authority.

In addition to these 55 cases, I have been able to see a handful of cases at the R.A.P.—Field Ambulance level when the exposure conditions were muddy wet cold.

The follow up is not yet complete and I shall avoid figures as statistical deductions from such a small number of cases, so far incompletely studied, are likely to be misleading.

Etiology

Predisposing Factors

Age and length of service. The majority of cases were youthful, aged 16 to 22. Short service with the infantry was the rule, to which of course there were exceptions, service being from 2 weeks to 4 months. Short service happened to coincide with youthful age. Whether the short service man was less tough, or whether the short service man who was usually youthful was less responsible and failed to take the necessary precautions, accounts for the age-short service incidence, I do not know. As the winter progresses, the age-service factor may alter.

Previous history of effects of cold. A previous history of habitual sensitivity to cold under peace time living conditions was exceptional. One case usually suffered from chilblains in the winter, one from what he considered to be unusually cold feet, and one from cold blue hands. The series included a fair percentage of men from the colder parts of South Africa. On the other hand, there were examples of men who under exceptional war time conditions of exposure had previously suffered from trench feet or related conditions and who contracted severe grades of trench feet after a short second exposure, e.g. an ex P.O.W. who for two previous winters in Italy had had "bad feet" and two cases who during October 1944 had been rested from the forward line for cold effect on the feet (details not known) before contracting quite severe trench feet after short exposure in December.

Exposure

In one group of 22 cases, the exposure period was as standardised as it could be. For a period of 9 days in October they lived and fought night and day on an exposed feature with no cover and no chance of relief or of taking proper preventive measures. At the end of the time, they were carried or hobbled down the hill. The majority first experienced foot symptoms from the sixth to the last day. A minority had symptoms from the third day on. The period of symptoms did not appear to have any direct relationship to the ultimate severity of the condition. The remaining 33 cases had periods of less continuous exposure for up to 4 weeks. Where there was a previous history of cold effect on the feet (i.e. the cases referred to under heading "predisposing factors"), a short period of exposure to mud-cold precipitated their present condition—in one case, a period of 24 hours. The type of exposure in the vast majority of cases was cold mud and water. In the few cases admitted since, the exposure has been to snow, the onset has been sudden and the period of exposure short, e.g., one night at a listening post. The clinical picture of the snow-cold cases has been somewhat different, toes being mainly affected.

One might summarise the period of exposure by saying that a period of 4 to 5 weeks intermittent water/mud-cold exposure, a period of 4 to 5 days continuous water/mud-cold exposure, and a period of 4 to 5 hours snow/freezing exposure produced the condition.

Precautions for Prevention

Under the heading of predisposing causes one might include failure to take adequate preventive measures. It is not difficult to set down on paper the details of measures to be taken to prevent trench foot. In practice, it is not quite so simple to carry these measures into effect. It is as much a matter of instruction, discipline and co-operation between the medical officer, combatant officers and men as it is of supply of footwear, socks, warm body clothing, dubbin, powder, etc. There is no wonderful boot or overboot or other form of panacea the general issue of which in itself is the answer to the problem. One must also bear in mind that there is a degree of exposure which will break through the finest precautions carried out in the most conscientious manner possible. I shall leave the details of prevention to others taking part in the discussion.

Pathogenesis

I can but give a brief outline of the contemporary views, sometimes rather contradictory, of the pathogenesis of trench foot. The views are based on deductions from physiology, on animal experimental work (where one must remember that rats' tails, cats' hind legs, rabbits' ears and dogs' bodies subjected to wet and dry cold of various grades are not necessarily comparable to soldiers' feet exposed to the Italian winter) and on histological investigations on human cases.

The basic principles of the pathogenesis of trench foot, immersion foot, frost-bite appear to be accepted in the main as similar, the different clinical pictures being determined conditions of exposure and the anatomy of the parts affected. Pathogenesis can be considered under two main headings:—

A. The Phase of Cooling

During this phase there is, presumably as a result of stimulation of the cold receptors of the skin which reflexly stimulates vaso-constriction through the medium of vaso-constrictor nerves, a diminished blood flow with closure of capillaries of the corium and contraction of varying degree of arterioles and larger arteries such as the dorsalis pedis, showing clinically as pallor, and coldness with or without impairment of sensation and pain. During this phase, one good thing and several bad things happen.

The good thing is the reduction of the metabolic demands of the tissues by cold. The cold tissues have their vitality preserved whilst waiting for the circulation to be re-established. It is known for instance that limbs ischæmic from cold recover better than limbs ischæmic from other causes, e.g. embolism or thrombosis.

The bad things that are observed to happen are: (a) œdema, which is the less serious of the bad things, and (b) tissues are damaged with a certain degree of selectivity. The tissues that are specially liable to damage are nerves and muscles. In experimental work (rats' tails immersed at 4 to 5 degrees C) nerves show Wallerian degeneration after 2 or 3 days exposure and muscles show gross degeneration. At these temperatures, skin, subcutis and vessels show no histological changes. In immersion foot from a case dying during exposure, nerves and muscles showed similar degenerative changes, the muscles having an appearance similar to that of Zenker's degeneration; the vessels showed minimal changes to be referred to in a later paragraph. At freezing temperatures (minus 67 F) experimentally there are vascular changes, also slight-constriction of the caudal artery, and in the areas destined to become gangrenous some swelling of the endothelium with clumped shrunken red cells in the lumen but no thrombosis. It should, however, be noted that in late cases due to very low temperatures (Germany and Russia), arterial thrombosis is described. With regard to nerve degeneration, it is *assumed* that sympathetic vaso-constrictor fibres are damaged along with peripheral nerves, or if not the fibres then the nerve endings, during the stage of cooling.

The cause of the observed damage to tissues is apparently not settled. The two factors that are held responsible are ischæmia and the direct damaging effect of cold.

In the case of œdema, metabolites are assumed to collect in the tissue spaces owing to the poor circula-

tion, the osmotic pressure of the tissue fluid is raised as is the protein content, and transudation from vessels occurs with consequent œdema. Damage to capillary endothelium by cold, with increased permeability, is also claimed as a factor.

The ischæmic factor is reduced by the concomitant reduction in the metabolic demands of the cooled tissues. Nevertheless there must be a point beyond which ischæmia and oxygen debt will result in irreversible damage. It has been suggested that there is a selective inactivation of tissue enzymes, those most requiring oxygen suffering first—nerves and muscles. However important or unimportant the ischæmic factor may be, it is produced in this the cooling phase mainly if not altogether by a functional disorder of the vessels, namely, vasospasm. Organic histological changes in the vessels at this stage are conspicuous by their absence, with the exception of the changes described during gross freezing described in an earlier paragraph. The clumped red cells are considered to be the result of loss of intra-vascular fluid by transudation. It is of interest that experimentally, mechanical constriction of the circulation of a rabbit's ear renders the part of the ear distal to the constriction far more susceptible to cold effect.

Cold as such can also damage tissues. It has been mentioned that cold œdema is considered to be primarily due to damage to the capillary endothelium. Many authors assume that the damage to nerve and muscle is due to the direct effect of cold. I have not had access to the investigations of this property of cold. It is remarkable that solidification of a digit by cold, if not of too long duration may not be followed by any signs of tissue destruction such as blisters or gangrene, the digit resolving to normal when the circulation has been re-established.

B. The Phase following Cooling

Following complete occlusion of the circulation of a normal limb by tourniquet for say 5 minutes there is a reactive hyperæmia the degree and duration of which is dependent upon the duration of the occlusion. The hyperæmia does not recur spontaneously and does not persist indefinitely.

In the case of vaso-constriction due to cold a comparable hyperæmia may follow and persist at first continuously and later intermittently in the remarkable manner which we see in trench foot. Later, a persistent or intermittent algid state lasting weeks, months or years may follow the hyperæmic phase. These vascular phenomena have not been satisfactorily explained. In the early post-cooling phase histological abnormality of the vessels has not been noted. Later, histological abnormalities have been noted. In cases of immersion foot, arteries examined 4 to 12 months after exposure showed slight degrees of intimal and/medial fibrosis but not differing significantly from arteries of " normal hard living men ". Continental workers (Russian, German), dealing with the effects of much lower temperatures, describe more extensive arterial abnormalities not unlike those in Buerger's disease and associated with thrombosis (thrombosis not being a feature in cases of immersion foot). These are considered to be due to organisation of the exudation within the walls of the vessels and are noted not in the gangrenous parts but more proximally, e.g., in demarcated gangrene of the toes, changes are found in the vessels of the dorsum and the sole of the foot—this is understandable, since there is no vitality in the gangrenous part and therefore organisation cannot take place. The capillaries in immersion foot (late) show no abnormalities histologically. I have not had access to reports on the capillaries in those conditions caused by exposure to excessive cold.

Organic changes in the vessels do not account for the dilatation of the hyperæmic phase, nor for the algid state in immersion foot. They may in part account for the algid state in late cases of exposure to excessive cold, although even where organic partial occlusion is known to be present the algid state varies in degree from time to time and an element of spasm must be postulated. The hyperæmic stage has been likened to the state of the circulation following novocaine sympathetic block (although it is not exactly comparable) suggesting that the hyperæmia is due to damage to vaso-constrictors. To account for the algid state at least in cases of immersion foot it has been suggested that there is partial denervation of skin vessels which are thereby made more sensitive to adrenalin, all denervated tissues being adrenalin sensitive.

Detailed study of the effect of autonomic drugs on the vaso-motor disorders following cooling offers scope—I shall not have time to deal with this aspect in relation to pathogenesis.

Amongst the latest effects observed histologically are fibrosis of muscles, accounting largely for the orthopædic disabilities that follow immersion foot and trench foot, and perineural and endoneural fibrosis which accounts for the persistent defects of peripheral nerve function as shown clinically by loss of power and sensory disorders.

As a matter of curiosity, we estimated the cold agglutinin titre of the venous blood of 25 cases of trench foot at various stages of their hospitalisation, and 25 controls, members of the unit. All results were within normal limits with the exception of one case of trench foot who agglutinated to a titre of 1/256 in his fifth week. No explanation of the exception can be offered.

Before proceeding with the clinical syndromes due to cold and from the point of view of correlating pathogenesis with the clinical picture, I would suggest that fundamentally the pathogenesis of the clinical syndromes described as trench foot, immersion foot, frost bite and chilblains is similar. To complete the picture, one might include the cold foot syndrome, to be described. The clinical differences are determined by the conditions of exposure mainly. In trench feet and immersion feet, the period of exposure is relatively long and the temperature not excessively low, possibly a few degrees above or below 5° C—the foot is chilled gradually " through and through " so to speak; in frost bite, the period of exposure is short and the temperature excessively low, down to minus 50° C—parts with a relatively large skin surface such as digits, ears, nose take the brunt of the chilling and having deeper damage done: in chilblains, only a superficial area of skin is affected (capillaries and arterioles of skin), the deeper circulation being unaffected; and the cold foot syndrome is the stage of vaso-constriction due to spasm induced by cold which may resolve on removal from exposure or pass on to trench foot, immersion foot or frost bite if sufficiently persistent.

Clinical Aspects

For purposes of discussion I propose to classify the clinical syndromes due to cold as follows:—

Cold foot syndrome
Trench foot, immersion foot, frost bite
Chilblains

1. Cold Foot Syndrome.

In this condition, the whole foot, or a toe or toes, during exposure becomes numb, white and cold, with or without defect of sensation and with or without pain. We have all experienced this in some degree. If the cold stimulus is of sufficient grade or duration (the lower the temperature the shorter the necessary exposure), resolution on removal from exposure may be delayed for many hours or may not occur, selective damage to tissues occurring and the condition passing on to what is called trench foot, immersion foot or frost bite.

In practice, when the "cold foot syndrome" persists on removal from exposure and return to normal fails to occur following such simple measures as removing boots, keeping in a warmer atmosphere, exercise and possibly judicious warming of unaffected limbs in warm water (measures to re-establish the circulation from "within out"), the decision as to whether to return the man to duty, or to hold him for observation either at the R.A.P. level or at some other forward medical unit is the problem of the R.M.O or other forward medical officer. In general one may say that if the condition returns to normal and does not pass into a hyperæmic phase, the man may be returned to duty and observed for recurrence. The hyperæmia may be delayed an awkwardly long time, as in the case of an infantryman who after his feet had become cold and numb for several days on and off, slept on his right side in a slit trench half full of water and at once developed a moderately severe trench foot on the right; the numbness and coldness passed off on the left, and seven days after admission to base hospital he developed hyperæmia of the left foot for the first time which persisted for ten days. Such cases can hardly be of sufficient frequency to give an R.M.O. sleepless nights concerning his disposal of cold feet!

2. Trench Foot.

The salient features of an average case as we have seen them at 106 S.A.G.H. are that during a period of exposure the feet become numb and cold, sometimes intermittently for a week or two sometimes continuously for a day or two or less. Swelling may be noted at this stage. This passes on to the hyperæmic phase either during exposure or more usually within an hour or two after reporting sick. The hyperæmic phase may be continuous or intermittent and gradually fades, leaving the part at normal temperature or in a cold algid state. The swelling lasts a few days and the hyperæmia one to four weeks. Pain of a burning throbbing character is worse with the onset of the hyperæmia and is eased or completely relieved when the feet are cooled by exposure to the air or by artificial means. Pain of a bruised or stabbing type may occur when the feet are cool or cold and is a feature of a severe initial cold numb phase. In the later stages, when the patient is walking, another type of pain may be experienced—aching pain on exertion across the ankles, across the dorsum, under the instep or across the transverse metatarsal arch, presumably due to arch defects. Paræsthesiæ may be felt in the numb stage and persist intermittently for some weeks. A peculiar pricking sensation on pressure of the balls of the feet, severe in the early stages, persists after the hyperæmic stage for one to four weeks and is one of the guides as to when the patient should be allowed up. Sensory defects, superficial and kinæsthenic, are bizarre in their characters. There is usually defect to pin prick and light touch in the cold numb phase which may clear as the foot heats up. Such changes, however, often persist through the hyperæmic phase, and if involving the whole skin surface of the foot, gradually recede towards the toes, the defect over the toes persisting for many weeks. There are many peculiar features of the sensory defects which I shall not describe now. Power may not be limited at all except by the initial pain produced on movement but 8 cases showed weakness of toe movements persisting up to 4 weeks. In these cases there was weak response to faradism sometimes of an isolated muscle such as the extensor hallucis longus, or a group of muscles such as all the long flexors or extensors. Gangrene was not observed in any of the cases, although blisters on the toes occurred in 7. These tended to make their appearance after the onset of the hyperæmic phase according to the records and gradually resolved without opening.

Following the hyperæmic phase, a cold algid state remained and has persisted in 5 up to about 6 weeks to date. This does not constitute a serious disability, being more of a nuisance than a serious disability. A typical case is one who in his tenth week states that his feet "are always cold" and the toes are sometimes painful when cold; as long as he gets his feet warm by running his feet feel perfectly normal. Excessive sweating has not been a feature of the cases yet, although some do complain that their feet sweat more than they did on exertion.

Observations on the hyperæmia deserve further comment. Hyperæmia of the foot is one of the few objective physical signs of the condition, and in doubtful cases indicates in my view that the case must be disposed of as a case of trench foot. Two observations have some practical importance—its occasional delayed appearance and its nocturnal phasic character.

I have already referred to an example of delayed appearance.

Its phasic character was sometimes striking. Feet that on a morning round of the ward are very cold, blue but comfortable begin to heat up in the evening and on a night ward round at 10 or 11 o'clock they are unrecognisable as the same feet, being red, tense, "flaming" hot and extremely painful (pain, however, was not prominent in all such cases). In bilateral cases, one foot may heat up one night and the other the next. This may go on for a week or two before the feet settle down to an even day and night temperature. It is difficult to account for this variation. Ward temperatures taken 2 hourly showed a maximum of 4° F variation in a 24 hour period. That the patient curls up when asleep and pulls his legs up under the blankets (all cases being treated with feet exposed to the room air night and day) may account for some cases, but the grossest cases began to heat up long before they thought of going to sleep and the pain if severe kept them awake.

Whether the excessive cold spasm of the day, a feature in these cases, whatever it may be due to, exhausts the vaso-constrictors so that the slight afternoon rise of body and room temperature acts as a trigger setting off an exhaustion vaso-dilatation in the evening, I do not know. It was intended to attempt to eliminate this rather unphysiological behaviour in the batch of cases that failed to arrive in January by keeping the feet when cold exposed to a temperature rather warmer than room temperature and to expose and cool them only when hyperæmic.

The objective demonstration of the physical sign of hyperæmia at night may relieve one of the feeling that the patient whose feet appear normal by day is trying to put a fast one across. The failure to demonstrate a hyperæmic phase is evidence against but not exclusive of a disabling cold effect—I shall refer to such a case in a later paragraph.

A peculiar feature in two cases was the insistence of the patient that his feet had felt cold throughout the course of the condition even at times when the feet were objectively extremely hot—a point to bear in mind when assessing the significance of symptons as described by the patient.

Swelling as an objective sign in the earlier stages is usual. In all cases in this series, gross swelling as described in the case records from forward had subsided in the 4 to 10 day period of evacuation, leaving a peculiar diffuse " waxy " thickening rather than œdema of the toes. In a small number of cases there was no swelling reported from forward medical units, yet considerable hyperæmia was present. The presence of swelling does not necessarily signify that the case is one of trench foot, as in the case of an officer with severe chilblains of the fingers and toes with considerable pitting œdema of the distal third of the foot which subsided rapidly with rest and was not followed by the vaso-motor disorders or other symptoms of trench foot, the course being short and the chilblains resolving.

Localised Trench Foot. I use this rather loose term to describe a type of case in which certain regions bear the brunt of the cold effect, especially the toes. The condition does not conform to my conception of frost bite nor is it chilblains. A case in point is one who after exposure to mud cold complained of painful toes and a painful right heel. The observations at the R.A.P. and down the line were that the toes were red, hot, swollen and anæsthetic, and the right heel discoloured and anæsthetic. The foot as a whole was described as normal. From the time of admission to 106 S.A.G.H. the toes had the appearance of trench foot toes in the algid phase, with tenderness on pressure and prickling paræsthesiæ. The heel returned to normal in a few days and no hyperæmia of the feet has been noted night or day. The feet have actually remained unduly cold. Another case had similar types of toes with blistering, the body of the feet never being hyperæmic nor unduly cold. These toes are mentioned as a stage between trench foot and one's conception of frost bite.

3. Immersion Foot.

I have had no experience of immersion foot as it occurs in ship-wrecked mariners, but from all accounts it differs in no essential particulars from trench foot.

4. Frost Bite.

Frost bite too appears to differ in no essential particulars from trench foot or immersion foot, the differences being the greater degree of cold, the tendency to affect digits, ears, although whole feet and hands can be affected, and the greater depth of gangrene. Tradition demands its inclusion as a separate entity.

5. Chilblains.

In the early stage of chilblains, difficulty may be experienced in differentiating them from the severer condition of trench foot in all its varieties, and a wait-and-see policy may have to be followed. Helpful in the differential diagnosis are the facts that chilblains are more superficial, affecting certain localised areas, e.g. the lateral aspects of the digits, are itchy rather than painful when warm at rest, affect fingers and toes, are not preceded by any dramatic cold numb phase, and resolve at rest or without rest leaving patchy superficial well defined areas of redness. They are not associated at any stage with vaso-motor disorders more extensively distributed than their own limits, nor with any of the other symptoms of trench foot already described.

Treatment

Before considering the details of treatment, certain elementary facts must be remembered:

(a) By the time the case is correctly diagnosed, damage, sometimes reversible sometimes irreversible, has been done to tissues, which nature will attempt to cure, helped or hindered by our ministrations.

(b) The assessment of the efficacy of any assisttance we give nature which we call treatment, is dependent upon an accurate diagnosis and upon a follow-up to the end result. In a condition which changes its clinical characters from hour to hour and day to day especially in the early stages, during which stages half a dozen medical units see the case, an accurate account of the findings at each unit is of extreme importance to the unit finally handling the case. Our standards of the assessment of the final result will vary according to the personal opinions of different medical officers whose opinions are largely dependent on the symptoms of the patient for at this stage the condition is one of symptoms rather than physical signs.

The treatment and general management of the series at 106 S.A.G.H. has been as follows:—

The case is put to bed with the legs elevated by one pillow and exposed to the air from the lower third of the leg down. The temperature of the air has varied from something just below 50°F to 58°F. The biggest variation in 24 hours, taken 2-hourly, was 4°F. Toe and foot movements are encouraged at regular intervals from as early as possible, pain being the limiting factor. Movements if defective through weakness are assisted with passive movements. Hyperæmia, whether continous or intermittent is regarded as an indication for continued rest in bed. When the hyperæmic phase has passed (which it had sometimes by the time of admission, in other cases persisting intermittently for up to 5 weeks), decreasing tenderness and prickle sensations on pressure on the balls of the

feet, ability to sleep comfortably under blankets and ability to hang the feet down without discomfort were taken as the indications for getting up. Colour changes on dependency in themselves were not regarded as an indication for further rest, as these may persist for weeks and be associated with no symptoms when the case is active at the Convalescent Depot stage. At the late hospital stage and Convalescent Depot stage, exercises, graded P.T. are carried out. In cases in a cold sensitive state, short wave diathermy to the body (the lumbar region) has been given daily. One case claimed no change in his cold sensations during the application of S.W.D. over a ten-day period. In the others, the feet warmed up during treatment and reverted to coldness after varying intervals—from 10 minutes to several hours. In two cases the period of warmth tended to increase over a period of 2 weeks. I am not able to say whether improvement in the cold sensitive state was part of the natural course of the condition, or a response to treatment. Faradism at this stage certainly does no harm and the patients like it. At the earlier stages, say soon after the subsidence of the hyperæmia, faradism (used in testing electrical reactions) was very painful.

One has been impressed by the variations in day and night limb temperatures in some cases, and if we had had any fresh cases during January showing this variation, it was intended to keep the limbs warmer when cold with cradles covered by sheets or blankets and if necessary to warm up the affected parts by applying heat to unaffected parts (limbs or body), and, as heretofore, cool when hot. It was also intended to keep the affected parts warmer as soon as they settled into a cold algid state. Amongst cooling methods I should have mentioned the use of electric fans placed about 18 inches from the feet; these were if necessary supplemented by lint soaked with 50% alcohol placed on the feet (the alcohol alone, without fans, lost its cooling effect after a few minutes owing to its being heated up by the hot feet.)

If the patient's symptoms are any indication of the correctness of cooling treatment, then cooling in the hyperæmic phase is the correct treatment. I have already mentioned that when the feet are in the cold algid phase and still exposed to room temperature they remain comfortable.

The follow-up is as yet incomplete. To date, it is estimated that roughly three quarters are or will be fit for restricted duty in 6 to 8 weeks from the onset. Of these, some feel "A1" but nevertheless have been or will be regraded B1 for the period of the winter. Residual symptoms include a persistent cold sensitive state (in 5) not of a disabling degree, pains across the arches of the feet on exercise, a tendency for the feet to become hot and sweaty on exercise, a tenderness of the soles of the feet on exercise, the skin being "thin" and pink, and troublesome hyperkeratosis.

Prolonged hospitalisation (10 to 12 weeks) can be accounted for in some cases, for example a history of previous cold effect on the feet as described under heading "Predisposing Causes," a previous softening up period of 8 weeks in hospital immediately prior to exposure.

All cases are being regraded B1 for the period of the winter and the diagnosis entered in the pay book. It is not possible to say at this stage how many of the cases will be fit for A1 duties eventually.

Various controversial views have been expressed on the treatment of trench foot.

The consensus of American, British and a fair proportion of continental opinion is that treatment in the early stages, including part at least of the period during which we handle the cases in hospital should be conservative by cooling. The most experienced workers are emphatic in advocating cooling and condemning the practice of warming which they state is actually harmful. Methods of cooling include exposure to room temperature, application of ice bags to the affected parts, placing the feet in special "refrigerator" boxes. Undoubtedly, warming increases œdema which is a further restriction to the circulation. It is stated that in the case of immersion foot treated by application of ice bags œdema increases notably if the ice bags are removed, the limbs being kept in the same elevated position. Although many arguments which I shall not discuss now are used in the condemnation of warming, I have not been able to find any controlled series comparing the final results of cooling and warming in the 40 odd publications to which I have been able to refer.

The opinion that advocates cooling, condemns novocaine sympathetic block as an early form of treatment. Again, I shall not discuss all the arguments for and against. The sympathetic block enthusiasts go so far as to advise that R.M.O's should institute the treatment almost on the field of battle. Three cases of my series were treated by novocaine lumber sympathetic block in the early hyperæmic œdematous phase. Careful records accompanied these cases to hospital. Two cases claimed immediate relief from pain following block; there was no record of increased hyperæmia or œdema following block. The end result in the three cases does not however differ significantly from the end result of cases treated conservatively. After 2½ months, one is free of symptoms, one is in a persistent cold sensitive state, and one is troubled by sensitive soles with hyperkeratosis. The series is too small to suggest that the end result is not quite as satisfactory as in cases treated conservatively. From my small experience, and from discussions which I have had with colleagues who have used block treatment and abandoned it, I do not think that it has any place in the early treatment of trench foot.

In the later stages, interference with the sympathetic may have a place in treatment. In cases with necrosis, it is reported that repeated sympathetic block speeds up the line of demarcation. In cases with severe persistent algid cold sensitive state with "Raynaud's" episodes or with chronic non-healing ulcers, improvement considerable or slight following sympathectomy is reported. The most ardent antagonists of novocaine block in early hyperæmic cases admit the possible value of sympathectomy in the late cold sensitive type of case.

In cases with necrosis, of which I have seen none, all surgeons are agreed on the importance of the principles of keeping the affected parts dry, combating infection, and avoiding early amputation. Nature must be allowed to demarcate the final and inevitable loss of tissue.

Passive vascular exercises of Buerger type have been recommended in the mildest early cases but where necrosis is expected all forms of congestion must be avoided. The reports are vague. I have had no experience of such treatment. It is possible I suppose that they might result in some improvement in the late cold sensitive stage. Other forms of vascular exercise described include suction in an air-tight cylinder followed by hot-air baths; and alternate heating and cooling of the unaffected limbs in the hyperæmic phase, which however is reported to produce no vaso-motor or symptomatic alterations in the affected limbs.

There are not many tricks of treatment that have not been tried. All the evidence favours cooling as the correct treatment in the stage of hyperæmia. Heating of unaffected parts, *e.g.* by hot arm baths, in the early cold numb stage, with a view to re-establishing the circulation from within out may be of some diagnostic value—if the part returns to normal, the man can be returned to duty, but if the part passes into an hyperæmic phase he must be evacuated. Apart from this use of heat, I can see no reason for carrying out any but the orthodox treatment by cooling during the hyperæmic stage.

TRENCH FOOT

by

Lt.-Col. F. A. SIMEONE, MC

INTRODUCTION

The winter campaign of 1943-1944 in Italy confronted us with the problems of the treatment and prevention of cold injury to the feet which for want of a better simple term we are calling Trench Foot. The incidence of the disease was unexpectedly high, averaging about 25 per 1000 per annum. This was slightly lower than the figure for the British Expeditionary Force during the first 2 years of World War I, but at least 3 times the incidence occurring in the British 10th Corps during the winter campaign in Italy, 1943-44.

Clinical Aspects

The large number of cases provided many of us with abundant material for learning something of the clinical features of the disease both with regards to prevention and what one must not do in the treatment of it. The clinical appearance of trench foot in the pre-inflammatory,inflammatory, and post-inflammatory stages is illustrated in the slides presented. (Lt.-Col. Simeone showed a series of colour-photographs of trench foot on the screen which illustrated very well the stages and degrees of severity of this condition). Its clinical differentiation from frost-bite is not always easily made. Typically, the latter results from exposure to below-freezing temperatures, is more highly localized and, generally, far less painful.

Treatment

The treatment of trench foot, insofar as lowering the morbidity of the disease is concerned, has been generally disappointing. Local application of heat during the early stages of the disease is very definitely contra-indicated. On the other hand, difficulty has arisen in cases that remained cold too long because of persistent spasm of the peripheral vessels. Therefore, in cases where the feet do not begin to warm up within 6 or 8 hours, active measures have been recommended to induce vasodilation.

During the inflammatory stage, the application of cold has been beneficial. Extreme cold has not been recommended, however, and an optimum skin temperature of 65 to 70°F has been suggested.

A number of measures have been employed in treating the later stages of the disease. Warm or cool baths have brought temporary symptomatic relief but have had no readily demonstrable effect upon the course of the disease. Whirl-pool baths and intravenous concentrated saline have similarly had little real influence upon the course of the disease. Gentle massage of the feet, Buerger exercises and a gradually increased regimen of active foot and toe exercises have helped keep to a minimum the general progressive atrophy of the feet resultant from inactivity added to the cold injury. During rehabilitation, properly fitted soft sponge rubber arch supports will be of some benefit. Amputation for gangrene is delayed as long as possible.

In the vast majority of cases, return to duty is prevented by the presence of a deep-seated ache in the metatarso-phalangeal joints (particularly the first), in the longitudinal arch of the foot and in the ankle. Novocaine block of the lumbar sympathetic trunk has been tried in sufficient cases to warrant doubt as to its efficacy. Actual ganglionectomies have been performed in 13 cases with the hope of abolishing or diminishing pain and of speeding the healing process. Neither of these effects were realized. Cold, blue, and sweaty feet were changed to more comfortable warm, pink, dry feet. The ache persisted, however, and kept the patients from duty. It has had value in treating late cases with actual or impending gangrene.

Disposition

The disposition of soldiers hospitalized for trench foot presented a serious problem, particularly when most of us were not aware of the prognosis in these cases. We wanted to keep forward installations from being crowded with cases of trench foot; yet we did not want to evacuate cases to the rear unnecessarily. Before long, it became apparent that the degree and duration of œdema was the best criterion of the severity of injury and the expected minimum of

hospitalization. On the average, patients with any œdema do not return to duty in less than two weeks. If the œdema persists 12 or 14 days, return to duty is not expected in less than 6 weeks of hospitalization. Using such a yardstick, the evacuation policy was adjusted to the tactical situation. There is little point in keeping patients in the forward area whose œdema lasts 2 weeks. They are best evacuated to the base. Oedema seldom lasts more than 3 weeks, but symptoms may persist much longer. Those who complain of aches after 3 months of hospitalization are best evacuated to the Zone of the Interior after careful psychiatric appraisal. Patients should not be returned to duty until they have passed vigorous physical examination and exercise tests. By following this policy it has been possible to return two thirds to three fourths of the cases to full duty after an average hospital stay of about two months.

There have been recurrences. Accurate figures on the rate of recurrence are unfortunately not available. They have been at least 10% and probably closer to 15 or 20% of cases returned to front line duty.

Prevention

In view of the morbidity of the disease and its attendant high rate of ineffectiveness, the prevention of trench foot assumes special importance. The object in prevention is to conserve body heat and to maintain the feet warm and dry. To accomplish this two things are necessary. First, the soldiers must be equipped with suitable clothing and foot gear. Second, they must be taught to use properly such equipment as is provided. The first should be made a command quartermaster function. Heavy woollen socks should be provided so that the soldier can change to dry socks at least daily. Shoes must be of sufficient size to avoid compressing the foot when heavy socks are used. When shoe-pacs are issued, sufficient inner soles must be provided so that the soldier can have a dry pair always available. Ointment may be provided to induce soldiers to remove their shoes, rub their feet, and change to dry socks daily.

Any amount of equipment, however, will not prevent trench foot if the soldier is not taught to use it well. Proper understanding of foot hygiene and of the nature of trench foot should be made an important part of the soldier's training. This teaching should be the responsibility of the company commander. The soldier must be taught to take measures to promote his peripheral circulation and not to impede it. He must be taught that whereas it is not dangerous to hike or fight with wet shoes and feet it is imperative to change to heavy dry socks as soon as activity ceases. Trench foot will almost certainly result if the soldier is allowed to rest or sleep in the cold with wet shoes and socks. Rest periods as frequently as possible would help maintain foot discipline and prevent trench foot. The lowering of the incidence of trench foot in the British Expeditionary Force during the second half of World War I to half of what it was during the first two years perhaps reflects the effectiveness of instituting preventive measures. Whether the striking decrease in the incidence of trench foot in Fifth Army this winter (about ¼ the incidence during the winter of 1943-1944) is due to effective prevention or to a change in the kind of warfare, one cannot say with certainty. Perhaps both are playing a role. It is realized, further, that tactical situations may not allow the practice of all the mentioned principles of prevention. However, the more closely these principles are applied the lower will be the incidence of trench foot.

Summary

1. The incidence of trench foot was unexpectedly high in American Fifth Army troops during the winter campaign of 1943-1944 in Italy.

2. The disease results from exposure to wetness and moderate cold. It passes through 3 phases; a pre-inflammatory, an inflammatory and a post-inflammatory phase. It is characterized by the signs and symptoms of inflammation, peripheral neuritis, and dysfunction of the peripheral vessels and sudomotor apparatus.

3. Various methods of treatment have had little influence upon the morbidity of the disease. It has been learned, however, that the local application of heat is injurious early in the disease, and the application of cold during the inflammatory stage has decreased the amount of tissue loss from gangrene. The value of interference with the sympathetic nervous system is very limited. Amputation for gangrene must be delayed as long as possible.

4. The best index of the severity of injury has been the degree of œdema. It has helped determine which patients to retain and which to evacuate from forward area.

5. Prevention is of special importance in a disease with such morbidity. It depends upon supplying soldiers with suitable clothing and footgear, and, most important, upon teaching them how to use the equipment properly.

TRENCH FOOT

by

Capt. G. N. RANKING, SAMC

163 cases of Trench Foot passed through my Battalion R.A.P. in the 3 months, November, December, and January, and I would like to describe my observations of these cases and to make some crude deductions from them and finally to ask a question.

The cases occurred in 3 series. Firstly, a group of 27 cases in wet fairly warm weather where the Bn. was exposed for 9 days after a particularly severe spell of 6 weeks in the line under bad weather conditions and before any precautions had been taken. The next month was spent in an intensive course of foot discipline so that the Bn. next entered the line 100% foot-conscious and employing all preventive measures available.

The second series of cases began very dramatically after about 3 days in the line and just under 100 cases occurred in about a month. The second rest period was spent in a frantic effort to remedy the boot position and the Regiment entered the line for the third time a week later, practically 100% re-shod, with dubbin and duckboards being used.

A steady decline in the number of cases was apparent and in the last week I was in the Regiment no case was admitted to hospital, although conditions were still very severe.

In reviewing these cases certain interesting facts emerge:—

(1) 91 cases occurred in men who were in the Bn. during its initial severe exposure to trench foot conditions. Of this number, 35 came to Italy with the Bn.

72 cases occurred in new recruits who had joined subsequently so that prolonged exposure appears unnecessary for the onset of the condition although prodomal symptoms of toe anæsthesia and mild metatarsalgia were forthcoming in the histories of a large number of the 91 cases. These symptoms dated from October and these cases were, on the whole, worse when they occurred after a precipitating long route march followed by further exposure.

(2) Of the 72 cases occurring in new recruits, 35 were admitted within a month of arrival in the Bn.

11 „ „ „ 10 days „ „ „ „ „
3 „ „ „ 4 days „ „ „ „ „
1 was „ „ 3 days „ „ „ „ „

(3) Symptoms of trench foot appear to be rapid in onset and as the weather got colder the fully developed syndrome would be present after an exposure of only 24-48 hours.

(4) Clinically a vasomotor disturbance was the most noticeable feature.

(5) Oedema was slight in all cases.

(6) Pain was rarely severe.

(7) Actual tissue damage was minimal and only 1 case of gangrene was seen, in which the R. Foot was completely black and showed what appeared to be a well-marked line of demarcation in the tarso-metatarsal area. Pain in this case was acute and amputation appeared inevitable, but the case history reveals that no tissue was lost and only superficial blistering occurred. The tissue damage, when it does occur, then appears to be very superficial.

(8) Of all the cases evacuated, only 1 has since returned to unit.

(9) After the onset of snow the type of case became different and instead of the classical picture of trench foot the cases could almost be described as trench foot of the toes with numbed, painful, swollen, very cold toes which cleared up readily after a few days rest in bed plus warmth and toe exercises.

(10) No cases of chilblains plus trench foot were seen in the same patient but a few men who complained of chilblains developed trench foot later on.

(11) Only 1 case of frostbite was seen and this in an Italian, although a few men reported with frozen toes which became completely normal after gradual re-warming.

(12) 5 cases of trench foot were seen in 3 weeks in a group of 500 Italian pioneers.

Causes of these conditions

(1) Frostbite would appear to be caused by exposure of a tissue to severe cold for sufficiently long to cause death of superficial tissue.

(2) Chilblains appear to be caused by a degree of cold acting on a normal vasomotor system sufficiently severe to produce localised damage to capillaries with subsequent exudation of serum and blood pigment. This can lead to skin necrosis and ulceration later on and often does.

(3) For the development of trench foot what appears to be necessary is a fairly prolonged exposure to a moderate degree of cold of a tissue in which there is a certain stasis of circulation due either to gravity or direct compression. Dampness appears unessential except in so far as it lowers the temperature. (Witness the cases which have occurred in men who have never had their feet wet.)

The effect of this exposure appears to be to produce a spasm of vessels. This spasm can behave in 3 ways:—

(a) It may pass off once the cause is removed and the limb may return to normal. This was often seen in the snow type of trench foot of rapid course.

(b) Spasm may be so prolonged as to produce superficial tissue death so much so as to simulate gangrene due to vessel thrombosis.

(c) The vast bulk of cases so exposed appear to result in spasm of sufficient duration — or repetition — as to produce minor tissue damage. This does not appear to affect the blood vessels which are apparently healthy even in fully developed cases of trench foot but appears to be confined to nerve tissue

to produce damage to cutaneous nerves but chiefly nerves of the vasomotor system leading to an upset of the normal vasoconstriction and dilatation mechanism. This would explain the characteristic appearence of the alternately blanching and flushing limb. It is possible that the damage, when it occurs, occurs during the stage of vascular spasm and is due to ischæmia and that is ischæmia is progressive with each successive period of vascular spasm even after the exciting cause is removed and the patient is in hospital. Permanent damage to, not only the vasomotor nerves, but muscle tissue and, in some cases, vascular tissue then results.

Treatment

Following the above line of reasoning, a rational form of treatment would appear to be to aim at prolonging the hot stage from the earliest moment the patient is seen so as to prevent as far as possible further vessel spasm. The use of parasympathetic-stimulant drugs from early on might not be irrational.

Pain could be readily controlled by sedatives and oedema, which would appear to be incidental and due to minor damage of an ischæmic nature to vascular endothelium, could be controlled, if necessary, by postural treatment. It should clear up once blood supply is permanently re-established.

Many cases of so-called snow trench foot have responded to this regime.

Nineteen cases (2 officers and 17 other ranks) of mild trench foot have also been so treated in the R.A.P., albeit crudely, in the last 6 weeks and returned to duty. Treatment varied from 4—20 days. None of these cases has relapsed over the last 6 weeks.

Prevention

It is obvious that with proper equipment and footwear trench foot should not occur. The most essential preventive factors are:—

(1) Discipline.
(2) Correct footwear—preferably an overboot.
(3) Rapid rotation of exposed troops depending on weather conditions.

Preventive measures at present in force in my Bn. comprise:—

(1) Duckboards in all forward and muddy trenches.
(2) Sacks over the boots as a substitute for overboots.
(3) Sound, dubbined boots with a minimum of studding to prevent leaking.
(4) Insoles of two layers of felt with a thick intervening layer of greaseproof paper.
(5) Very rigid foot drill comprising exercise, and massage with oil and powder.
(6) Frequent rotation of forward troops.
(7) Provision of frequent hot meals and beverages.
(8) Wearing of long underpants because it is felt that leg covering is important where vessel spasm is the main pathology.

Foot Soap

My impression of foot soap as a permanent foot application in forward areas where water is not available has reached the conviction that it is undesirable. Many cases of dry, scaly feet have been seen and very many men complain that it actually makes the feet cold. This seems quite likely if one assumes that the natural fat content of the skin is partly an insulating mechanism. Soap must certainly dissolve this natural secretion and cause dryness and softening of the skin.

A very satisfactory substitute has been found in margarine plus olive oil, and men volunteer the information that it makes the feet feel warmer. It certainly makes the skin look healthier.

Question

It is generally accepted that trench feet should be treated by cooling and that warming of these limbs is dangerous. Are there any facts to show what harm results from keeping a flushed foot warm, apart from œdema and pain, when the clinical picture of such a limb appears to indicate a complete and functioning vascular system?

DISCUSSION—Conditions due to Cold and Wet

Lt.-Col. W. A. Loewenthal, SAMC.

The Presence of Cold Agglutinins in 24 Cases of Trench Foot.

True cold agglutinins are substances which produce agglutination of red cells at temperatures varying from 0°—25° C., the reaction being reversible by warming to blood temperature. They are distinct from the iso-agglutinins which determine blood-group, and have nothing to do with pseudo-agglutination or rouleau formation, and pan-agglutination, which is the result of a bacterial product.

Cold agglutinins are of two kinds: one is non-specific and will agglutinate any suspension of human (or even animal) red cells at the appropriate temperature. The other is strictly specific to the host's own red cells and is, in the true sense, an auto-agglutinin.

The first variety is present in the blood serum of normal individuals, but in such low concentration that they are not often shown by a direct slide test in the cold, using an equal quantity of Sod. Citrate to prevent clotting. In fact, Shone and Passmore, who found this type of cold agglutination constant in cases of primary atypical pneumonia (as have other workers), saw it only rarely in other diseases, and never in a batch of 60 healthy Indian troops in the Middle East.

The British Medical Journal has an excellent review of a recent article by Stats and Wasserman, elaborating the above facts. It contains the following possibly significant sentence: "When a patient with a high titre of cold agglutinins is exposed to cold, the temperature in the extremities may fall low enough for agglutination of red cells to occur locally and block the circulation of the digital vessels. Long continued exposure in such cases will lead to gangrene".

The preceding remarks apply exclusively to cold agglutinins circulating in the blood serum, and absorbable from that medium. The conception of cold

agglutinins fixed in the tissues is, so far as I know, a new one. A remark in the British Medical Journal Editorial, quoted above, seems to render the idea less fantastic than one would at first believe: ". . . the possibility that when tissue proteins are damaged . . . they are altered in such a way as to produce an auto-immunization, of which the cold agglutinins are a manifestation". The reference here is to circulating agglutinins, the result of such conditions as trypanosomiasis and primary atypical pneumonia, but the elaboration of cold agglutinins which remain fixed at the site of tissue damage would appear to be a reasonable corollary.

Technique

Because of the impossibility of using elaborate laboratory methods at the RAP, where the investigation was begun, a simple form of slide agglutination was used. This needed only some glass slides, citrate solution and plenty of snow and ice; this equipment was available in generous amounts. Blood was obtained by pin-prick from both great toes and both thumbs, each drop mixed with roughly an equal amount of 3.8% sod. citrate on a slide, the whole cooled to just above freezing point, and the reading taken immediately. Further drops of blood were squeezed from the same punctures at roughly 5-minute intervals and examined in the same way, until either agglutination was observed or no more blood could be expressed. Records were taken (a) from the immediate drop of blood and (b) from the last drop that could be obtained. Cold agglutination was checked by warming to (roughly) body temperature, which abolished the phenomenon, and cooling again, which restored it.

As it was impossible to do quantitative tests, results were simply recorded as positive or negative, irrespective of their apparent degree of agglutination. *The only criterion was whether a donor would have been accepted or rejected on a similar slide in a direct compatibility test.*

Results

Using this technique, the following results were obtained from toe blood of one foot in eight fresh cases of trench foot, and in eleven controls from the same battalion.

	No.	*Immediate positive*	*Delayed positive*
Trench foot cases	8	2	8
Controls	11	3	4

On my return to Bari, 16 further cases of trench foot of about four weeks' duration, and 11 more controls, were examined by the same method:—

	No.	*Immediate positive*	*Delayed positive*
Trench foot cases	16	7	16
Controls	11	0	3

In addition, among the 24 trench foot cases, 14 showed a delayed thumb blood positive and 3 controls did the same.

Among the interesting results seen in more than one case, and repeated to avoid the possibility of experimental error, were a positive delayed agglutination in one great toe or thumb, but not in the other (6 cases).

Blood groups were determined in the Bari cases, and showed a normal type of distribution.

Comment

(i) Treated statistically, the differences in delayed reactions between control and trench foot cases show an extremely high significance.

(ii) The presence of agglutinins in tissue juice expressed some time after the puncture, seemed to be supported by the instances of positive reactions occurring in only one limb, on repeated examination. Such a phenomenon cannot be explained satisfactorily if the agglutinin is present in the circulating blood. The following experiment has therefore been made on 4 cases:—

A group of small superficial punctures was made in one toe, and the blood wiped away. After a while a clear serum exuded and was collected. This serum, diluted up to 1:25, agglutinated the patient's own red cells, washed in citrate and at a low temperature, but not those of stock red cells of the same blood group. Further, the patient's own blood serum, undiluted, did not produce cold agglutination of his own or other red cells.

I submit this as presumptive evidence of cold agglutinins held in the tissues in certain areas, while absent from the circulating blood. Further, these agglutinins would appear to be highly specific, *i.e.* true auto-agglutinins.

So far the observed facts. What is their significance in the œtiology of trench foot? Nothing that has been found so far incriminates cold-agglutinins as causative factors; on the other hand, a highly speculative hypothesis devised before the investigations were begun has become a reasonable theory.

If intravascular agglutination is substituted for vascular spasm, then the accepted type of theory of causation (*e.g.* Goldstone and Corbett, B.M.J., 12.2.44) becomes acceptable. It explains, which "angliospasm" does not, why lesions are patchy in distribution and do not always affect the most peripheral parts of the foot. It explains that every common finding in the early case: a cold, blanched or livid foot associated with bounding tibial arteries; and it is, of course, highly compatible with the sudden reversibility of the whole clinical picture, which is one of the cardinal signs of trench foot. It provides a link between trench foot and certain cases of Raynaud's phenomenon, acrocyanosis and the common chilblain.

Future work may show how these tissue cold agglutinins come into existence; whether their presence in controls is a part of their normal make-up or the result of some external cause; in fact, whether they will clear up the problem of causation of trench foot, or prove to be merely a by-effect of that condition.

The erythromelalgic type of reaction is, to my mind merely the effect of Nature's over-exertion. Her first reaction to chill is blanching; when the temperature of the foot has fallen sufficiently for agglutination to happen, and ischæmia of tissues sets in, she tries to increase the blood supply by the only method she knows—vaso-dilatation. But so long as vessels are blocked, this will not alter the pallor, or lividity, or temperature of the foot. It

will produce merely bounding arteries without corresponding benefit. When the agglutination reverses, as it should do from external warming, the full effect of vaso-dilatation becomes suddenly apparent and the picture of erythromelalgia, which we have seen so often in troops in North Africa, supervenes. As Allen and Barker have shown, this condition is remarkably responsive to aspirin, hence possibly the benefit derived by these patients from indirect warming plus aspirin.

Lt.-Col. J. R. Fleming, RAMC.

Early in 1940 I was in Iceland. In the garrison where I was stationed we had no acute trench feet, but we did have a good many men who had what I like to call chronic trench foot. Early in 1940 a bunch of Pioneers came to Iceland and about half of them came for Medical Boards. My medical specialist was astonished that they were downgraded to C. A month before the foot complaint these men had worked fairly well, and then some began to get trench foot. When they came to our medical boards practically every one of them had. This trench foot had been described as flat foot. Some had flat foot, most had flattened feet, and they were swollen and red. The vast majority had foot difficulties such as ingrowing toe nails and so on. Now, as regards the more acute type I am in agreement with our friend who spoke earlier about the young patient being more susceptible to this than the old.

I remember a case of shipwrecked mariners. 36 men had been in an open boat for 14 days, in January, and among them were two elderly men, one 73 and the other 75. The rest of the group were 20 to 40. Three of them had to have amputations of the toe or other part of the foot, practically all the remainder had to lie up with bad feet for two or three weeks, but the two elderly men sat up next morning to attack their ham and eggs and never turned a hair. My experience is that if you are going to be shipwrecked you should be over 70. Personally, I would like to endorse what the other speakers have said on conservatism in the treatment of trench foot both from the medical and surgical point of view.

Col. John P. Williams, MC.

When we first arrived in the Naples area the latter part of December, 1944, the need for hospital beds was so acute that a 30-day limit was necessarily imposed on us, which meant that all trench foot cases save the mildest were immediately evacuated to North Africa. This condition persisted until the latter part of February, when we were permitted to hold cases for 90 days, but even then, as soon as they were able to hobble about sufficiently to go to the latrine and mess hall we transferred them to convalescent hospitals. Beginning in April, when the peak of the season had passed, we set up our own convalescent section and followed them all the way through to final disposition. I may have seemed to digress, but the purpose was to impress on this conference the fact that the 260 cases to be discussed were of the milder types, chiefly grades I and II.

During the first three months of the year we sent only 5% to full duty and 7% to limited assignment. During the next two months (April and May) we discharged a goodly number to A2 duty to what was commonly known as the Trench Foot College, a kind of convalescent or reconditioning depot. Up to this time the ratio of dispositions was:—

1. Full Duty and Trench Foot College, 59%.
2. Limited Assignment, 28.5%.
3. Zone of Interior, 12.5%.

At this time we did not realize what has been brought home so forcibly to us since. All acute symptoms had passed and on superficial examination the feet looked like pretty good civilian feet which just needed a little toughening.

During June and July they began trooping back from the Trench Foot College for a post-graduate course in the hospital, and this kept up right on through August and September. Curiously enough, we got only 2 of our own patients back, but some other hospital in the area was very probably taking care of them. For the first time we began to look critically at these feet and found the following very obvious and significant changes: (1) The skin was as delicate as a baby's and in some cases even atrophic. (2) There was marked hyperhidrosis pedis, and short hikes caused maceration of the delicate skin, blister formation and repeated attacks of disabling trichophytosis. (3) In many there was no tendency whatsoever to reform good plantar callouses in spite of soaking in brine and alum and hiking to the limit of tolerance. (4) The feet were stiff and weak with inability to flex and spread the toes normally, and atrophy of the small muscles. (5) In most cases there was persistence of anaesthesia of one or more toes and deep pain along either the longitudinal or transverse arch or both on varying degrees of exertion.

We went to work correcting our previous errors and made the following rather arbitrary lines of division:

1. (a) 5 mile hike without undue discomfort.
   (b) Reasonable regeneration of plantar callouses.
   (c) History of progressive improvement in sensory and motor impairment.
   (d) Strong desire to return to his unit.
2. (a) Ability to hike 2 — 3 miles without undue discomfort.
   (b) Some plantar callous formation even though poor.
   (c) Hyperhidrosis of not more than moderate degree.
   (d) Reasonably resistant skin which from past history had shown itself capable of sustaining moderate trauma without blistering or infection.

3. All others in which residual changes were apparently permanent were sent home. The final ratio of dispositions for the 1943-44 season was:

   1. Duty—36%.
   2. Limited Assignment—39%.
   3. Zone of Interior—25%.

Of these sent to Limited Assignment, a large number were subsequently sent home administratively after varying periods in Replacement Depots since it was difficult to find duties for them which they were capable of performing.

The final denoument came with the equinoctial storms in the mountains of Southern France. From 20th September to 20th October, 1944, we received 57 recurrent cases of trench foot. These were the most hopeful cases that we had sent back to their units the previous spring and summer and their story was most interesting and can be told in summary:

1. Average period between first hospitalization and final boarding for the Zone of Interior: 9.2 months.

2. Average period of hospitalization and reconditioning: 4.5 months.

3. Per cent time unfit for any duty: 49.0.

4. Per cent of soldiers able to perform full duty on return to unit: 30.0.

5. Per cent of soldiers unable to perform full duty on return to unit who were excused from hikes and rigorous training, were allowed to ride trucks on unit movements or given light work about the kitchen areas: 70.0.

6. The weather which had precipitated recurrence had been excessively wet but not particularly cold, the lowest recorded temperature being 40°F. on 21st September at 0300 hours.

7. These men had been able to keep going as long as their various units carried them on what really amounted to limited assignment, but as soon as the pinch came and it was necessary for them to perform the duties of a foot soldier, they found themselves unable to meet the demands. Another very significant thing is that in this relatively mild period of exposure, 90% of all trench foot cases admitted were recurrent and only 10% were primary. All of this latter group were very mild but were retained on temporary limited assignment since in the light of past experience it seemed useless to attempt to return them to combat with the bitter winter weather before them.

So far this season we have disposed of 239 cases and the ratio has been as follows:

1. Duty—2%.
2. Limited Assignment—43%.
3. Zone of Interior—55%.

It is to be hoped that some of the 43% on limited assignment may be able to be reclassified to full duty with the advent of warmer weather but we are not sanguine and have the very definite impression that only a few of these cases will ever be able to perform adequately as foot soldiers again. These are good combat soldiers and physically sound save for their feet. The sooner we begin to realize this and begin to give them combat assignments which do not require excessive use or exposure of the feet, such as with tanks, tank destroyers or transport, the sooner is our immediate problem solved. Lacking such assignments, the protected environment of the rear areas is the next choice and finally if these are not available evacuation to the Zone of the Interior for use in industry is the final choice.

Summing Up by Opening Speakers

Lt.-Col. G. Elliott, SAMC.

Col. Williams has stressed the importance of the complete follow-up of these cases. We have had this advantage also in a small series of cases. One gets the impression that our experience would be the same as Col. Williams. These cases one is following up were sent to the convalescent depot and had these symptoms which he describes. We have graded them all B to keep them away from the exposure conditions for the duration of the winter, then grade them for three months with a view to retesting. One hopes to be able to follow them up. My impression is that our results are not dissimilar from what Col. Williams has described. These fellows can do odd jobs about the place but when it comes to stress and strain they are not standing up to this just as well as the normal person. With regard to the subject of cold agglutinins I will not go into that at length but one can say first of all that in the conditions in which cold agglutinins and circulatory disorders are described the agglutinins are part of the circulating blood. The other point is are these agglutinates in the tissue cause or effect, and I would like to hear the results of control tests on the tissue fluids. The question of treatment by cooling. Strangely enough I have been unable to find any controlled series. Capt. Ranking mentioned the question of using warmth in the early trench foot. My impression is he was referring to what I call persistent cold feet. I think it could be quite reasonably done by using artificial means to re-establish circulation not by application of anything to the affected parts but rather by hot baths or by heating the body generally.

Lt.-Col. F. A. Simeone, MC.

Regarding re-establishment of circulation. Experiments have been conducted on rabbits in trench foot caused by immersion in cold water, and it has been found that one side gave better results than the side which had no vascular interference. Whether this experience is typical of man I do not know. My experience is the sooner you start circulation going through the whole foot the better it is. Our general policy is to wait 6 to 8 hours before installation and if the foot has not begun to warm up by that time we take more active measures. We believe in warming the foot from within, and getting circulation through the foot and not heating it. Last winter we studied some cases at the 300th General Hospital where one foot was treated with application of cold and the other not; we had 3 or 4 cases where we could show that the side which had local application of cold did better. There was less loss of tissue. Cold did not reduce skin temperature very much. Col. Williams brings up the problem of disposition. We have learned enough from experience not to fall into the same trap as last year. We have no good follow up figures but we did have an opportunity of following up 10 cases which had been sent back to front line duties, and of these 10 cases only one had had a recurrence. Another was evacuated having been wounded later and 8 cases were still in the front line.

Friday, 2nd February, 1945

MORNING SESSION

Subject: DIPHTHERIA

Presiding:

Brigadier E. Bedford, Consulting Physician

Middle East Forces.

DIPHTHERIA

by

Lt.-Col. J. H. HUTCHISON, RAMC

It is impossible in the time available to do more than discuss certain aspects of this huge subject. Diphtheria in my opinion should be regarded as a serious disease.

I have tried to find in the literature available to me some reflections as to how serious a disease it really is in terms of the mortality and complication rates. Diphtheria unfortunately varies greatly in virulence from place to place and year to year unless one can talk in thousands, figures are of doubtful value.

Before the use of antitoxin, in Boston City Hospital, the death rate only once fell below 40%; in the same hospital after the advent of antitoxin (1895), the mortality over 6,000 cases was 7.8%. In England and Wales, 47,000 odd cases were notified in 1939 with a mortality of 4.5%. In children in Scotland the mortality is around 10%. In the Army in M.E.F. on the other hand the mortality has been just over 2%. The figures for my own hospital for what they are worth, for cases treated in the hospital from the outset during the past 2 years are 264 with one death. During the past 12 years there have been some alarming but fortunately localised outbreaks of hyper-toxic diphtheria on the Continent and in Ireland in some of which even with the use of anti-toxin the mortality has been 60%. The incidence of nervous complications like the mortality is widely variable. In civil life it is rarely below 10% usually nearer 20%. My own figures over 264 cases is 8%. Brig. Hunt in 96 (Br) General Hospital, N.A., gave a figure of 5%. J. D. S. Cameron on the other hand in an outbreak among British Troops in Palestine in 1940 reported polyneuritis in 17% of cases.

I think there is evidence to show that the problem of diphtheria in the Army will increase in the future. The Lancet recently published some rather striking figures; thus in Germany, the only European country in which the incidence of diphtheria had been rising for some years before the war, the rate per 100,000 of population has jumped from 181 in 1939 to 287 in 1943; in France the rate has risen from 36 to 119; in Holland from 17 to 639; and in Norway from 2 to 753. It can be assumed that this trend will be accelerated during the period of chaos which will follow the collapse of Germany and before the Allies can establish control. This spread of diphtheria among the peoples of Western Europe must be considered in relation to its possible effects on the occupying Allied Armies. In the M.E.F. an annual incidence among British Troops of 4-5 per 1,000 indicates that it has not been a negligible infection, and in Europe a much higher incidence may be expected, especially in British Troops, few of whom have been immunised in childhood.

In the Army, therefore, diphtheria is an infection to be regarded with respect; it is likely to carry a significant mortality, it implies a long period of ineffectiveness, complications may be serious. Unless we embark on the formidable task of immunising the whole Army, the only way in which the problem can be met is by early diagnosis and adequate treatment. Unfortunately it is a disease in which the average M.O. is little experienced and it presents special difficulties in diagnosis and treatment under active service conditions. I shall therefore confine the rest of my remarks to the diagnosis and treatment of diphtheria of the upper respiratory passages where it is most dangerous, and leave the discussion of cutaneous diphtheria, carrier-state and its treatment, etc., to subsequent speakers.

Diagnosis

It is a commonplace to say that early diagnosis and therefore treatment is all-important. Yet in my own hospital the average day of illness on which antitoxin is given is the third day, and in a recent 6/52 period during which cases were admitted from forward medical units, of 40 faucial cases only 17 had received antitoxin before admission to us although the diagnosis ? diphtheria appeared on many W.3118's. Obviously M.Os must be made more diphtheria-conscious and be trained to recognise the disease at an earlier stage.

While the majority of faucial cases appear as typical diphtheritic throats from the onset, none the less a reasonable proportion are far from typical. Many cases in the first 48 hrs. appear like typical follicular tonsillitis—such cases usually grow H.S. ++ as well as K.L.B. I have seen more than a few cases in which peritonsillitis was gross—these are mixed diphtheritic and streptococcal infections requiring Sulphonamide as well as serum—and two cases in which an undoubted quinsy burst with liberation of pus. Such cases in which H.S. is playing a large ætiological role, of course, ultimately develop appearances, pathognomonic of diphtheria but often not until the fourth day of illness and it is necessary to make every effort to give serum before that stage.

There are some clinical features which I think worthy of note; although not pathognomonic of diphtheria I think they nearly always indicate the admin. of antitoxin.

1. Fœtor. Some clinicians undoubtedly can smell diphtheria.

2. Much faucial œdema often with less hyperæmia than would be expected in a streptococcal infection.

3. A marked degree of adenitis—not common in H.S. infection.

4. Unilateral sore-throat—Vincent's may cause difficulty but an underlying ulcer usually obvious on swabbing the slough and in adults ulcerative gingivitis usually also present in Vincent's Angina.

5. Absence of previous history of sore-throats should cause one to think—but not too hard!

The T. and P.R. levels in adults are of no importance where concomitant H.S. infections are so

common. I think that the text-books descriptions should not be read too literally in regard to adults; in children one sees uncomplicated disease, in adults concomitant disease—in this instance streptococcal infection—is common. Nasal diphtheria is not a difficult diagnosis once the possibility is in the M.Os mind. Blood staining of the discharge is less common in adults than children. Laryngeal diphtheria is very rare in adults. The main features of laryngeal diphtheria in adults are dysphagia, cough, fever. Stridor is almost unknown. Laryngoscopy should be done in every case of dysphagia with fever.

In fever hospitals it is reckoned by Cruickshank that even the experts with full lab. facilities have a diagnostic error rate of 10%. Provided the error is on the side of giving antitoxin too often this is of little importance.

Treatment

There are only two essentials in the management of this disease: 1. Early and enough antitoxin. 2. Absolute physical and mental rest, both of which can be amply justified on the pathology of the disease.

1. *Antitoxin.* Diphtheria is a disease due to a diffusible toxin which once fixed to the tissues produces damage directly proportional to the amount fixed. Three tissues are more severely damaged than the others—the myocardium, the suprarenals and the nervous system. Antitoxin will only neutralise free circulating toxin, it will do nothing to minimise damage produced by already fixed toxin. It is therefore obvious that antitoxin must be given before irreparable tissue damage has occurred, and in sufficient quantity to neutralise all free circulating toxin; antitoxin alters the course of the disease little if given after the fifth day and not at all if the membrane has already separated.

Dosage varies greatly from centre to centre depending partly on the local strains of K.L.B. There is a tendency to give larger doses now than some years ago. The doses recommended in the Army are appreciably greater than those recommended by most civil health authorities; whether these very large doses are necessary I do not know —there is some evidence that they may diminish mortality and complication incidences—at any rate they can do nothing but good. It is desirable that the whole dose be given at once; an insufficient dose at first can never entirely be made up by subsequent administration. Daily injections over the course of some days as one sees frequently is unscientific. The scheme of dosage used in my hospital is:—

Nasal only—24,000 U. I.M.

Faucial—membrane unilateral or small patch each side 48,000 U. I.M.

Faucial—bilateral tonsillar membrane—72,000 U. I.M.

Faucial + bilateral + adenitis ++ and/or toxæmia—96,000 U. I.M.

Late cases or if much toxæmia or bull-neck 160—240,000 U. of which at least 100,000 I.V. preferably in 1/2 pint glucose-saline. We have not found that the I.M. injection of the large volumes implied in these dosages causes any serious discomfort. Using modern pepsin treated sera the risk of anaphylactic shock is negligible even in allergic subjects. We always have adrenalin on the serum tray, but only twice in 2 years have we done intradermal sensitivity tests in men who had had horse-serum recently; one was negative, one +ve, with him we went through the so-called desensitisation ritual, probably unnecessarily.

2. Rest is fully justified by the pathology. In even the mildest case of diphtheria the myocardium is probably damaged to some extent most marked in the bundle of His which may virtually be disorganised. In severe cases the muscle fibres show swelling with loss of striation; areas of focal necrosis with hyalinisation are numerous; perivascular leucocyte aggregations occur. Healing takes place slowly by phagocytic infiltration, fibroblastic proliferation, and finally replacement fibrosis.

I believe that the orthodox teaching of absolute rest is correct. We nurse our cases on one pillow only for two weeks in nasal cases, three weeks in faucial, and often considerably longer in toxic cases. The patient is then allowed one extra pillow daily for a week and is then allowed out of bed for gradually increasing periods. It is quite possible to do this with a fever-trained nursing staff without mentioning heart-disease or otherwise frightening the timid ones, and it is a good plan to keep "flat" patients and "up" patients in separate wards or tents.

Sudden death is not uncommon—at any rate in children. During the first week peripheral vascular failure is the common catastrophe—the suprarenals probably play a part in this; later in the disease, usually towards the end of the second week or later if vagal neuritis occurs, acute myocardial failure may cause death within a matter of minutes or days. I have seen two children die suddenly—both had sat up when nurse's back was turned—neither had been regarded as particularly in danger. If cardio-vascular accidents do occur I think morphine given freely is the mainstay with possibly some benefit from adrenalin and glucose. Raising the foot of the bed and analeptics (nicamide, strychnine, etc.) are useless. Tachycardia, bradycardia, and arrhythmia (other than of sinus type) should be looked upon with the greatest respect. A falling diastolic B.P. fills me with acute anxiety.

Polyneuritis

Instability of the pulse ratio frequently occurs some days before the appearance of neuritic manifestations—in no disease are 1 min. pulse-readings more worth-while. The advent of neuritis indicates further bed-rest or return to bed until the P.R. is stable and until all new signs of spreading neuritis have ceased to appear.

Convalescence

Should be gradual and in the absence of heart-block and fibrillation which may be permanent, the soldier should be reassured that complete recovery will take place. Threats of heart-disease, etc., have no place in the management of this disease at any age. An attitude of confidence in recovery is remarkably easy to culture in diphtheria wards given a trained staff.

Some of you may think that experience of the more dangerous diphtheria of childhood has made

me over-rate its danger in the adult. I do not believe that this is so and hope I have produced enough factual data to convince the sceptics.

Summary

An attempt is made to assess the severity of diphtheria in terms of mortality and complication rates. It is noted that this disease varies in virulence from place to place and year to year and that figures should be interpreted with this in mind. Evidence is brought forward to suggest a probable increasing incidence of the disease in the Allied Armies in Europe.

Diagnosis of upper respiratory diphtheria is discussed, stress being laid on the importance of early treatment, the frequency of concomitant streptococcal infection in adults and several clinical observations found to be of value in differential diagnosis.

Treatment is based on the pathology; the importance of giving adequate amounts of antitoxin before toxin is fixed in the tissues is the basis of modern treatment. Complete prolonged rest is justified on the myocardial pathology and occurrence of cardiac catastrophies in carelessly nursed patients.

DIPHTHERIA

by

Lt.-Col. PAUL WOOD, RAMC

The few observations I have to make concerning diphtheria are based on a series of 251 cases seen in their active phase at 103 (Br) General Hospital during 1944, and upon 53 cases of diphtheritic polyneuritis seen during the same period. The great majority (80% in both groups) were direct admissions. I wish to confine my remarks to three aspects of diphtheria, namely: skin diphtheria, circulatory collapse, and the effect of exercise on polyneuritis.

A. SKIN DIPHTHERIA

During the whole of 1943 and 1944 I have had but two deaths from diphtheria in my division, and both have been cases of skin diphtheria.

In the series of 251 active cases seen in 1944, 20% were cutaneous. In the series of 53 cases of diphtheritic polyneuritis seen during the same period, 40% were due to cutaneous infection. The figures express the danger.

An analysis was made of all cases of skin diphtheria with adequate records: of such there were 31 uncomplicated cases seen and treated in the active stage, and 17 with polyneuritis (six of which were still active), making 48 in all.

Site of Lesions

In all but 4 of the 48 cases, the lesions were in the extremities. Of the four exceptions, one was in the scalp and three were in the penis. There was a notable difference in the site according to whether the case was uncomplicated or whether it was followed by polyneuritis. In the uncomplicated group eleven out of 31 had their lesion in the fingers or toes, compared with one out of 17 in the group with polyneuritis. Again, in the uncomplicated group, the lesions were in the arms or legs in 9 out 31, whereas in the series with polyneuritis they were in the arms or legs in 12 out of 17.

The lesion was single in 22 of the 31 uncomplicated cases, but in only 4 of the 17 with polyneuritis; the lesions were multiple (more than 3) in 3 of the former, and in 8 of the latter. Considering the number of lesions and their size it was found that the total area involved could be called extensive in only 3 of the 31 uncomplicated cases, but in 10 of the 17 with polyneuritis.

Nature of the Initial Skin Lesion

In 37 cases the initial lesion was established: in 17 it was an abrasion or bruise; in 4 a pimple or boil, in 3 desert sores, in 3 infected scabies, in 4 tinea, in 2 burns, and in 2 others blisters. One followed on seborrhœic dermatitis of the scalp, and one appeared to arise spontaneously.

Appearances of Diphtheritic Ulceration

The diphtheritic ulcer is usually punched out and angular, while its base is covered by a dirty slough. It is indolent in behaviour.

Of the 31 seen in the active phase, 21 were diagnosed clinically, and four others were thought suspicious. The remaining 6 did not look like diphtheria, but swabs were positive. The diagnostic problem is therefore very similar to that of sore throat, and routine swabs of indolent ulcers are advised.

Treatment

(1) UNCOMPLICATED CASES (31)

15 received on the average 48,000 units A.D.S. within the first week.

7 received the same amount during the second week.

9 were treated late; it is difficult to say how late. Sores or ulcers had been present for 1 — 4 months in 8 of them, but it is impossible to say how long they had been diphtheritic. They received 64,000 units A.D.S. each on the average (32,000 — 96,000).

(1) CASES WITH POLYNEURITIS (17)

Thirteen were missed altogether elsewhere, and received no treatment. Three were missed elsewhere, diagnosed on their arrival at 103 G.H., and received 48,000 — 96,000 units A.D.S. on the 90th, 35th, and 36th day respectively. The last was diagnosed at another hospital and received 50,000 units A.D.S. on the 14th day.

Duration of Diphtheritic Skin Lesions

The treated cases averaged 38 days, the untreated 75. But the untreated were those with polyneuritis, and with the more extensive lesions as we have seen. The figures therefore mean little.

On the average lesions healed 18 days after serum therapy. It is the general impression that serum helps the ulcers to heal, presumably by neutralising local toxin, but I am not sure the point is proved.

Of those with polyneuritis, ulcers were still active in 5, present with negative swabs in 3, had just healed in 4, and had healed 2 — 4 weeks previously in 5.

Summary and Conclusions

1. Cutaneous diphtheria is a menace, being responsible for our only diphtheritic deaths, and for 40% of our cases of polyneuritis.

2. It is a menace chiefly because it is overlooked.

3. It is about as easy or as difficult to diagnose clinically as faucial diphtheria; routine swabs of indolent ulcers are therefore advisable. The diphtheritic ulcer is punched out and angular; its base is covered with a dirty slough.

4. Extensive or multiple lesions greatly increase the danger.

5. If treated within the first 10 days with 48,000 units A.D.S. complications are most unlikely. Serum should be given however, no matter how late the diagnosis, if ulcers are still present.

B. CIRCULATORY COLLAPSE

It has always seemed strange that measures in common use for the treatment of surgical shock are not employed in toxic circulatory collapse. The foot of the bed may be raised, and oxygen may be administered, but if any infusion is given it is usually glucose saline, and this may be restricted to dehydrated patients. The mechanism of toxic collapse depends upon a critical increase of the effective vascular capacity, beyond the limits of the blood volume, whether the vasomotor centre, the sympathetic nerves and nerve endings, or the vessels themselves be at fault. The fall in blood pressure which results, induces anoxæmia which further damages the vascular bed, so that the capillaries become more permeable, and plasma passes from the blood stream into the tissue spaces. This is the ordinary vicious circle of shock. Until we have some drug which will effectively reduce the vascular reservoir, it would seem reasonable to increase the blood volume by infusion of blood or plasma.

An opportunity to try plasma in a case of toxic shock presented itself on October 26th last year, when a case of m.t. malaria with extremely heavy parasitisation, collapsed at 07.45 hrs. He had been admitted the previous evening on the fifth day of his disease, and had had two injections of quinine, gr. 10, one intravenously, one intramuscularly. His B.P. had been 115/75, and judging by his tongue and skin, he was not dehydrated. When examined at about 08.00 hrs. on the morning of the 26th, he was pale, pulseless, and unconscious. The foot of the bed was raised, and he was given oxygen. He was observed for an hour during which there was no change, and he looked as if he were going to die. Plasma was commenced at 09.00 hrs., and continued until 18.00 hrs. in the evening, the patient receiving 3 pints in 9 hours. The effect seemed to be dramatic. The pulse returned within the hour, and by 2 o'clock his blood pressure was 85/60, and by 6 o'clock it was 95/60 and he appeared out of danger. Consciousness returned with the pulse. The following morning he looked and felt well; B.P. 110/80.

This was encouraging, and I determined to use plasma more freely in toxic circulatory failure. I wondered whether it should be tried in cases of diphtheria with peripheral circulatory failure. This presented a more difficult problem because one would like some assurance that the heart was relatively sound; that the collapse was in fact entirely peripheral. The opportunity arose on November 18th last year, when a patient with diphtheria developed circulatory failure on the 20th day of his disease. He had received 64,000 units A.D.S. on the second day, and 96,000 on the third day. His pulse first showed signs of weakening on the fourteenth day, when his B.P. dropped to 85/70. During the next 4 days it varied between this and 100/80. The patient looked and felt perfectly well. An electrocardiogram showed depression of the RS-T segment in all leads. The heart, however, was not enlarged; there was no gallop, no rhythm change, and no evidence of heart failure. I thought the e.c.g. changes were due to anoxia, for they resembled the pattern following large hæmorrhage, C.O. poisoning, and vasomotor collapse; and a similar picture is often recorded during an attack of angina pectoris. By the twentieth day the B.P. was difficult to record, and the pulse only just palpable at the wrist. The systolic pressure was about 80, but it was impossible to measure the diastolic. Plasma was started cautiously at a speed of 30 drops per minute. After 3 hours there was obvious improvement, the pulse was easily palpable, and the B.P. had risen to 95/70 where it stayed during the rest of the evening. The following morning, when on his third bottle of plasma, he had a rigor, and the infusion was stopped. With the rigors, which were mild, the pulse became weak again, and the B.P. dropped to 85/60, and remained so for rest of the day. The following morning, however, it had risen to 110/90, and after this it never fell below 100. Recovery was uneventful. The e.c.g. gradually returned to normal, and no signs of cardiac trouble occurred. Polyneuritis followed later.

The rigor was unfortunate, and makes interpretation difficult. The immediate effects however were encouraging.

C. THE EFFECTS OF EXERCISE ON THE COURSE OF DIPHTHERITIC POLYNEURITIS

As there has been some difference of opinion amongst physicians in the C.M.F. concerning the effect of exercise upon the course of diphtheritic polyneuritis and as it is a point which might have some bearing on the course and treatment of the condition, an attempt was made to investigate the problem.

Method

The method consisted of comparing the course of the disease in each leg, one of which was exercised and the other rested. An Ergometer was arranged so that full plantar flexion lifted a 10 lb. weight about 4 inches. Repeated movement of this kind, about 25 times a minute, would induce fatigue in

about 10 mins. If there was any difference between the two legs the worse was selected for effort. The exercise was carried out for about 10 mins. every hour, for 8 — 10 hours a day, and was continued for 2—10 weeks.

Results

Observations were made on six patients. In the first three, effort was started when the disease had reached the peak of its severity and it was continued until recovery was complete. The behaviour was the same in each case, details of one of which were given. Power, sensation and tendon jerks recovered symmetrically. It was concluded that effort, sufficient to cause fatigue, had no effect on the course of the disease when it was begun after polyneuritis had reached its maximum severity.

In the next three cases, effort was commenced either before there was any evidence of polyneuritis at all or when the disease was in its early stages. In one case power, sensation and tendon jerks diminished and recovered symmetrically: in the other two, power and sensation behaved as in the first case, but the tendon jerks were diminished and lost a little earlier in the exercised leg, but they recovered earlier. It was considered that even when effort sufficient to cause fatigue was commenced before the onset of polyneuritis it did not materially influence the natural course of the disease. Details of one of these cases were given in full.

Conclusion

It follows that there can be no object in treating these cases by means of rest if they are able to get about without embarrassment, once the period of cardio-vascular complications is passed. It is held that if there are no symptoms or signs of cardio-vascular toxæmia by the end of the second month there is no further danger.

It would appear that if exercise or fatigue plays any part in the development of diphtheritic polyneuritis it must do so in the stage of active circulating toxin.

DIPHTHERIA

by

Major A.C. DORNHORST, RAMC

The employment of a standard regime of treatment in a variable disease implies an inability to assess the significance of the individual variations, and so invites periodic review in the light of further experience.

It is my purpose to review the management of diphtheria in soldiers, and to recommend the view that a substantial number of patients can, with advantage, be handled more confidently than is at present usual.

Restriction of Activity not Proportionate to Usual Clinical Indications

Diphtheria patients are in general restricted in their activity to a degree which would be considered absurd in the treatment of a patient of equivalent degree of "unwell-ness" due to any other condition. The aim, of course, is the avoidance of various complications.

Rest and the Incidence of Neuritis

I know of no satisfactory evidence as to the effect of prolonged rest in the post-acute phase on the incidence of neuritic complications. I am satisfied that the recovery of the milder neuritides is not materially delayed by ambulant treatment, and so am inclined to doubt the efficiency of rest as a prophylactic.

Dissociation of C.V.S. and C.N.S. Sequalæ

It is often assumed that a patient who has some neuritic sequelæ must necessarily have significant cardiac damage. I suggest that the evidence shows that this inference is not justified. Thus it was common in the M.E. and early in C.M.F. to find cases presenting an established peripheral neuritis. Such patients usually gave a history of being treated in field units for tonsillitis or desert sores. Frequently they returned to their units after a few days and continued on full duty for several weeks until the onset of tingling in the hands and heaviness of the legs compelled them to go sick. The complete absence of cardio-vascular disorder in these patients, treated as they had been in so unorthodox a manner is a finding surprising in itself and equally surprising in that it has aroused little or no comment.

Not all cases Cardiologically "A Risk"

The cause of this dissociation cannot here be discussed, but consideration of cases as mentioned above indicates that even in virulent untreated diphtheria, the heart is not always significantly affected.

A fortiori, we should expect that among adequately treated cases the proportion of these good risk cases would be greatly increased.

Types of C.V.S. Complications

Cardiovascular complications may be summarised as follows:—

(1) Early "Output deficiency."
(2) Congestive heart failure.
(3) Minor cardiopathies uncommon and transient.
(4) Remote effects — e.g. fibrillation. Denied by many.
(5) Late cardiac collapse.

Nos. 1 and 2 present no diagnostic or prognostic difficulties. No. 3 is certainly uncommon. There is no doubt that the most disturbing conception is that of late cardiac collapse.

Late Cardiac Collapse

It appears to be assumed that any patient who has had diphtheria, however mild, and however adequately treated, is liable for several weeks to drop dead without warning. It is the fear of such an event and not of late heart failure as properly understood that is allowed to dominate treatment.

The first thing to be said about this catastrophe is that it must be very rare, at any rate in adults. I have been unable to obtain a single first hand account of its occurrence in a military patient. I hope that members of this Conference will supply me with some examples. I will be interested if any example quoted fulfils the following criteria:— previously healthy adult, treated early and with good response to treatment, and without signs of circulatory upset in the first or second week.

Frequent Mildness of Diphtheria in Soldiers

Now with improving diagnosis and earlier administration of serum, the majority of soldier patients do fulfill these conditions, and if this bogey can be banished with regard to this important group, there would follow a considerable saving of time and a decrease in invalidism.

Bad Effects of Over Caution

For the bad effects of over-cautiousness are not limited to the wastage of hospital beds and the strain on nursing effort, though these can prove embarrassing during an epidemic. There is a feeling of uncertainty when the patient gets up and this may lead to the interpretation of the normal effects of prolonged recumbency as indications of cardiac damage. The feeling of uncertainty pursues the patient to Con. Depot where the period spent is often excessive.

Over Diagnosis of Cardiac Damage

Last year I was struck by the variation in the frequency of cardio-vascular sequelæ claimed by different observers. I was also struck by the differing frequencies with which patients, transferred as convalescents from various hospitals, complained of psychogenic cardio-vascular symptoms.

Causes of P.N. Reactions

It is not surprising that the diphtheria patient should develop these symptoms. He is regarded as more ill than he feels. Some fellow patient is sure to give a colourful account of the dangers, real or imagined. Nurses are not always innocent of attempting to frighten their more boisterous patients into quiescence by threats of sudden death.

His long period of recumbence will ensure that his reflex vascular postural responses are impaired. His M.O. may display uncertainty by frequent auscultation of the heart and may confirm his worst fears by ordering him back to bed.

Prevention

These symptoms are of course easily prevented, if, and only if, the Medical Officer is himself free from anxiety.

Continuity of Treatment

All will agree that the patient who is admitted direct to a holding unit is much easier to assess and causes less uncertainty than one who passed through several other units. The majority of cases will, however, always have to be moved during treatment. The proper evacuation policy is debatable.

Recording of Notes

Since most cases will have to be handled in their later stages by M.Os. who have not seen their acute stage, full notes are essential and some standard system of recording is desirable.

Suspicious Cases

Anti-toxin must be given on suspicion, and as diphtheria awareness increases the number of non-diphtheritic cases which receive serum will increase. I do not think that the giving of serum commits one inevitably to the diagnosis of clinical diphtheria, but the exactness of the diagnosis in a patient who is sent down the line of evacuation is extremely difficult unless the notes are unusually full.

Summary

(1) Diphtheria shows all variations from a very mild to a very severe disease. Logical treatment will take account of these variations.

(2) The answer to the diphtheria mortality and morbidity lies in the early recognition of suspicious cases, and in the early and adequate administration of serum.

(3) The importance of accurate observation and recording of notes during the acute stage is stressed.

(4) The positive diagnosis of normal heart must be made in all cases as soon as possible, and always before discharge to Convalescent Depot. Convalescence thereafter should not differ from that after other diseases.

USE OF PENICILLIN IN THE CARRIER STAGE OF FAUCIAL DIPHTHERIA

(Interim Report of its use in a group of 47 cases)

by

Major A.W. BAGNALL, RCAMC

and

Lt. A. F. BAIN, RCAMC

(Paper read by Major A. W. Bagnall, RCAMC)

In recent months there have been quite a few sporadic cases of diphtheria in the Canadian Corps in Italy. The bulk of these cases have been treated in the later stages of their disease at No. 14 Canadian General Hospital and, at present, there are some 175 patients on the Diphtheria Ward. Because of our geographical position at the base of the ambulance evacuation sector for Canadian Corps, these cases are not seen by us until they have been sick for about three weeks. Our problems then are mainly with the complications and only in retrospect with the acute or early phase of diphtheria, which is treated in forward units. This interim report deals with the use of parenteral penicillin in a group of 47 cases in an attempt to eradicate virulent diphtheria organisms from the faucial region when still present after the third week of the disease.

Methods: A uniform technique was employed from the start for the investigation of these cases of diphtheria. No doubtful organism has been included as C. diphtheriæ. One of us (A.W.B.) took all the cultures and supervised the clinical aspect of the problem. The other (A.F.B.) performed all the bacteriological investigation. Great care was exercised in taking the cultures to reach every irregularity in the faucial contour. No time was lost in planting the cultures, once taken, on tellurite agar. Suspicious colonies were transferred to Loeffler's Slopes for clarification of morphology and from the Loeffler's into sugars. Where there was any room for doubt, intradermal virulence tests were performed on guinea pigs using a control.

In 76 (62%) of the first 123 cases of diphtheria admitted this winter, C. diphtheriæ was found in throat cultures after the third week of the disease. A few of these were primarily nasal diphtheria, the rest were faucial. Intramuscular penicillin was employed in 47 of these 76 cases with a persistent positive culture in an attempt to reduce the disposal and housing problem which these " quasi-carriers " created. All 47 strains were quite sensitive to penicillin in vitro. The appearance of the tonsils was noted on the chart at the time of admission to our hospital and this initial clinical assessment is the one used for correlation with the persistence or recurrence of positive cultures. A bad pair of tonsils is thus defined as being scarred and irregular with deep clefts or stuffed crypts, whatever the actual size of the tonsils. The course of penicillin was begun in the fourth week of the disease in some, in the seventh week in others, but on the average during the sixth week. The first group of 22 cases (Group " A ") received 15,000 units of pencillin I.M. every three hours for five days, a total of 600,000 units. In all cases the throat culture became negative on or before the fourth day of therapy. It was soon found, however, that the effect of penicillin in some cases of this group was only transient. C. diphtheria being cultured from the throat in a few cases as soon as two days after completion of the course. A second Group (Group " B ") of cases therefore received 25,000 units of penicillin I.M. every three hours for six days, a total of 1,200,000 units. The following Tables summarize the results obtained as well as significant clinical details:

TABLE I.

Relation of Persistent Positive Throat Cultures to State of Tonsils.

	Tonsils Bad	Tonsils Good	Total Number
OF 123 CASES			
Number with Cultures Positive after 3 weeks .	51	25	76 (62%)
" " " not " " " "	17	30	47 (38%)
Total, Series of 123 Cases .	68	55	123
GROUP "A"			
600,000 units Penicillin:			
Between 35th and 40th day (average) "Failures"	13	1	14 (64%)
" " " " " "Successes"	3	5	8 (36%)
Group "A" Total . .	16	6	22
GROUP "B"			
1,200,000 units Penicillin:			
Between 35th and 40th day (average) "Failures"	6	1	7 (28%)
" " " " " "Successes"	9	9	18 (72%)
Group "B" Total . .	15	10	25

The cases for Penicillin therapy were selected from among the first 123 cases admitted to No. 14 Cdn. Gen. Hospital this winter. Positive throat cultures were obtained in the fourth week of the disease or later in 76 (62%) of these cases. The incidence of bad tonsils was high (65%) in this persistent positive group and low (35%) in the group in whom negative cultures were consistently obtained before the fourth week of the disease.

In Group " A " (22 cases given 600,000 units of Penicillin I.M. during the sixth week of disease on an average, because of persistence of positive throat culture up to that time) 13 of the 14 " failures " had bad tonsils. Five of the eight " successes " had good tonsils.

In Group " B " (25 cases given 1,200,000 units of Penicillin I.M. during the sixth week of disease on an average, because of persistence of positive throat culture up to that time) 6 of the 7 " failures " had bad tonsils. Nine of the eighteen " successes " had good tonsils.

TABLE II.

Time of recurrence of Positive Culture after Penicillin.

Weeks after Course completed	1st	2nd	3rd	4th	5th	6th	7th	8th
Group "A" — 14 Cases recurred	2	3	1	4	1	2	0	1
Group "B" — 7 Cases recurred	4	2	0	1	0	0	0	0

Cultures were taken two days after completion of the course of Penicillin and at least twice a week thereafter. All cases were followed for at least a month and then discharged if still negative and otherwise fit. Of the 14 cases in Group "A" in which a positive throat culture was again found after Penicillin, only five were discovered in the first two weeks and ten within the month. One patient managed to keep the organisms hidden for two months and would probably have been included in the "successful result though bad tonsils" group if he had not developed peripheral neuritis requiring prolonged stay in hospital. Six of the seven "failures" in Group "B" were discovered within two weeks but the other cases in this group have as yet not been followed longer than one month and several for less than three weeks.

TABLE III.

Tonsils removed in 7 of the "Failures" in Group "A"

Positive Culture of removed tonsils — 7; negative — 0
Average day of Disease removed — 82nd; variation — 54 — 108
Average day after Penicillin finished — 39th; variation — 20 — 68

The tonsils were removed in seven of the cases in which a positive throat culture was again obtained after completion of the smaller course of Penicillin. On an average, the tonsillectomy was three months from the onset of the disease and six weeks after the Penicillin. Virulent C. diphtheriæ were obtained in cultures from the depths of the tonsils in all cases. One case (Tpr. S.) was most instructive because none of the eight throat cultures taken in the five weeks intervening between Penicillin and tonsillectomy had been positive, yet the tonsils yielded a heavy growth of virulent C. diphtheriæ.

TABLE IV.

Positive Culture PERSISTING after 3rd week of Disease — No Penicillin.

20 Cases	Tonsils Bad	Tonsils Good	Total Number
Becoming negative after 24th to 47th day of Disease	11	5	16
Still not negative after 60-68th day of Disease —	3	0	3
Not negative until after tonsillectomy (47th day)	1	0	1
Total . .	15	5	20

TABLE V.

Recurrence of Positive Culture after 3 consecutive negative cultures. No Penicillin. Total of 11 cases, nasal cultures negative.

	Tonsils Bad	Tonsils Good	Total Number
With clinical exacerbation — 5 cases	4	1	5
Without clinical exacerbation — 6 cases.	4	2	6
After 3 consecutive negative cultures — 7 cases.			
After 4 consecutive negative cultures — 4 cases	Total — 11 cases		

Of the whole group of 123 cases of diphtheria, the cases included in Tables IV and V complete the total of 76 cases in which positive throat cultures were obtained later than the third week of the disease. In Table IV the 20 cases were consistently positive for three or more weeks and were not treated with Penicillin, whereas in Table V, three to six negative "clearance" swabs were obtained in succession before one or more late positive throat cultures cropped up.

The cases in Table IV may be used as a control group for those treated with Penicillin. Fifteen had bad tonsils yet the throat culture in sixteen of the twenty become negative during the fifth to seventh week and remained so. Had these patients received I.M. Penicillin, success might well have been attributed to its use.

The cases in Table V are interesting as a parallel to those in which the use of Penicillin resulted in temporary suppression of a positive throat culture. C. diphtheriæ seemed to have disappeared yet between the 30th and 44th days of the disease (in most cases), a positive culture of virulent C. diphtheriæ was again obtained. In five cases, the clinical picture of a mild attack of diphtheria preceded the return of the positive throat culture. The other six cases were discovered by accident in an attempt to find out how reliable three consecutive negative cultures were as a guide for release from isolation. Two of the five cases with a clinical exacerbation were subsequently treated with Penicillin and are also included in Group "B". One of these two cases again recurred with a positive throat culture two days after Penicillin.

Penicillin sensitivity tests were done on all strains before the administration of Penicillin and repeated in the 21 strains recurrent after Penicillin. We have yet to find a strain of C. diphtheriæ that is not sensitive to Penicillin.

Virulence tests have been done on 15 of the 21 strains recurrent after Penicillin. To our surprise 3 of the 15 were not virulent. One had been tested before Penicillin and was known to be virulent then. One was from a patient still confined to bed with peripheral neuritis. The third had not been tested previous to Penicillin but it was in all ways the same as the strain isolated during the acute phase from a membrane on the tonsil. The significance of the possible change of virulence in these three cases is difficult to assess.

Discussion

In considering these results of Penicillin therapy on the whole, one cannot become enthusiastic about the 26 cases out of 47 in which success was apparently achieved—for one reason, that many failures did not become apparent for weeks. Residual organisms left after Penicillin may lurk deep in the crypts of the tonsil, slowly multiplying, until, like a submarine, the surface and the culture again becomes positive. Nasal cultures were negative in all cases of recurrence except for the two cases in which the nose culture was known to be positive initially.

In several cases, one has been able to predict the return of a positive throat culture by observing increasing activity in the tonsillar crypts so that the tonsils assumed the appearance of a low-grade follicular tonsillitis. In three cases, at least, the patient

complained of a sore throat at this time. When a culture was taken with a wire loop from the depths of tonsils removed at operation, as was done in 7 cases in Group "A", virulent organisms were isolated. The situation then would appear to resemble closely the case of chemotherapy in bacterial endocarditis. There seems to be some barrier in the structure of the tonsil which prevents access of Penicillin or of leucocytes to the diphtheria organism in the same way that the masses of platelets in the superficial layers of a valvular vegetation diminish the effectiveness of sulphonamides or Penicillin on the streptococci in the deeper layers. In each case, the body fluid that one cultures becomes negative during, and for a variable period of time after, chemotherapy. Removal of the tonsils offers a much more reliable means of ending the infection in most cases and is certainly not the camouflaging manoeuvre that Penicillin therapy is.

On the other hand, Penicillin may well be of some value in diphtheria. In severe cases of diphtheria in the acute stage, it could be used as an adjunct to antitoxin, although it will certainly not replace antitoxin. A trial of Penicillin in the earliest stages of diphtheria with a total dosage of a million units, is at present being conducted at No. 1 and No. 14 Cdn. Gen. Hospital but it is still too early to warrant any statement of its value. A fairly extensive trial of I.M. Penicillin, as well as local Penicillin, under well-controlled conditions, in nasal carriers would seem advisable. Caution should be exercised, however, in releasing the patient following therapy because two of our three nasal carrier cases recurred on the 21st and 26th days after Penicillin.

Summary and Conclusion

An attempt has been made to assess the value of parenteral Penicillin in eradicating the faucial carrier state in convalescent diphtheria patients. Our results in a series of 47 cases suggest that failures may be expected in a considerable proportion of cases even with a fairly large total dosage of Penicillin, despite the fact that all initial, as well as recurrent, strains were quite sensitive to Penicillin.

The long delay which has been shown in many cases before return of a (virulent) organism on throat culture following the use of Penicillin might well create a dangerous illusion of success if cases were released after three consecutive negative cultures in the usual manner. One hiding place of persistent and recurrent strains was shown to be the depths of the tonsil. It is suggested, therefore, that in dealing with the faucial carrier state, the use of parenteral Penicillin be reserved for those cases in which removal of the tonsils has failed or is not advisable. Further clinical investigation is in progress, however, at Nos. 1 and 14 Canadian General Hospitals to assess the value of Penicillin in the acute phase of the disease. It is hoped that its powers to suppress the growth of surface organisms may lead to more rapid reduction of the local intense inflammatory reaction in a fresh case of diphtheria when used in conjunction with early and large doses of antitoxin. In addition, it is possible that if the superficial early diphtheritic infection is dealt with rapidly, there will be fewer cases in which the organisms will have the opportunity to invade in force the depths of the tonsils to set up the convalescent carrier state.

INFECTIOUS POLYNEURITIS

by

Major JOSEPH W. JOHNSON, JR., MC

Infectious polyneuritis is one name applied to a disease characterized by widespread motor and sensory signs and symptoms indicating involvement of spinal and cranial nerves. First emphasized in 1916 by Guillain and Barré is the concurrence of an elevation of spinal fluid protein without an associated increase in cells. This " dissociation of the cerebrospinal fluid " or " albuminocytologic dissociation " is a finding heavily leaned upon in differential diagnosis. Since the etiology is unknown and recognition of a varied and varying clinical picture has led to application of a variety of terms to the same syndrome, the spinal fluid findings have, perhaps not remarkably, received this emphasis.

The inadequacies of description and the difficulties of choosing a satisfactory name for a syndrome of protein manifestations, diffuse and varying anatomical compromise, and unknown etiology, are well illustrated by listing some of the terms which have been applied to the larger symptom complex. Thus, infectious polyneuritis, acute polyneuritis, acute febrile polyneuritis, acute polyneuritis with facial diplegia, radiculoneuritis, motoneuritis, neuronitis, myeloradiculitis, acute infective meningomyeloradiculitis, encephalomyeloradiculitis, acute ascending paralysis, Landry's Paralysis, and Guillain-Barré's Syndrome have all served various investigators and reporters. Further, this impressive battery of polysyllabics has not been considered adequate to the occasion and recourse has been had to the parenthetical title somewhat reminiscent of an earlier literary era and exemplified by " Acute Infectious Polyneuritis " (Guillain-Barré Syndrome), " Visceral Lesions in Infectious Polyneuritis (Infectious Neuronitis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome, Landry's Paralysis) and Guillain-Barré's Disease (Encephalo-Myelo-Radiculitis) ". Perhaps the happiest phrase is that of Honeyman: " Pathological Study of a Group of Cases Sometimes Referred to as Polyneuritis ".

Such titles suggest not only a considerable amount of latitude in terminology, and hence difficulty in communication, but some lack of agreement as to a clinical picture. It seems fair to assume, then, that the syndrome or syndromes under survey are not sharply defined. In view of the considerable study

devoted to the problem by well qualified and equipped investigators, it is not unreasonable also to assume that the subject should not be considered as a disease entity but rather as a group of cases having in common certain features, clarification of some of which, even in a restricted experience, is worth attempting.

For the purpose of this study the material was organized as follows:—

Infectious Polyneuritis

1. Statement of Purpose and Authority.
2. Statement of the Problem.
3. Methods:
   i. Collection of Material.
   ii. Presentation of Material.
4. Limitations.
5. Clinical Material.
6. Discussion.
   i. Differential Diagnosis of the basis of history and findings.
   ii. Differential Diagnosis on the basis of anatomical selection with certain considerations as to the nomenclature in the reporting of these cases.
   iii. Differential Diagnosis on the basis of etiology with further considerations as to nomenclature.
   iv. General.
7. Summary.
8. Conclusions.
9. Bibliography.
10. Appendix.

The complete report has been forwarded to the Office of the Surgeon and only matters bearing upon etiology and the summary and conclusion will be presented at this time.

The subject is pursued, then, by considering certain etiological factors. It is pursued, however, with the recognition that the evaluation of an agent's role in the etiology of a disease process must be measured against the susceptibility of the tissue concerned and the state of its natural defence at the time the factor considered causative enters the equation. Though little may be known about tissue susceptibility or tissue defences, an awareness of the soil upon which the seed is sown is an implied consideration in evaluating the seed and its product. The remarks which follow concern a number of agents or situations which singly or jointly may precipitate an illness recognized as belonging to this " group of cases sometimes referred to as polyneuritis ".

Certain agents which cannot be considered infectious are associated with the peripheral neuropathies. Some of these are alcohol, lead, arsenic, triorthocresyl phosphate and the sulphonamides. Other agents, somewhat closer to the concept of an " infectious " factor, are the neurotropic toxins elaborated by several organisms such as diphtheria, botulinus and some of the dysentery group. Perhaps the viruses, if any can be implicated, and, of course, they have, would come closest to the etiological concept implied by the term " Infectious Polyneuritis ".

However, certain of the influences to which nervous tissue responds are hardly to be considered agents in the present state of our knowledge, but rather metabolic situations embodying the total organism and its environment. Coincident debilitating, febrile, or hyperkinetic illness, the utilization as well as the availability of food are offered as examples of processes or situations rather than agents which influence the tissues of the nervous system. Little is known about the combined effect of these influences, but certain mutual relationships are pertinent, less, too readily, the much indicted virus, ubiquitous in etiological concepts at present, be seized upon as agent.

The nutritional factor in the maintenance of the functional integrity of nervous tissue has long been studied and the deficiency states may be associated with a variety of nervous system manifestations. It has been impossible to obtain significant dietary data on this group of patients. In those studied by the present reporter it could only be stated that the patients were either on B rations, which are considered adequate, or only briefly on C and K rations, which are said to be adequate but are very frequently not eaten as a complete ration under field conditions. Only three of the cases reported were attributed to deficiency states and in none is history or findings available. In four other cases a state of nutritional deficiency was postulated, when, having been shot down over Roumania, with only inadequate diet available, the neurotoxin of diphtheria was added to the dietary influences impinging upon the tissues of the nervous system. However, as pointed out by Captain Harshman in his presentation of these and other similar cases, the fliers had been on a POW status for only four or five weeks prior to the onset of diphtheria, and though the diet was scanty, consisting chiefly of bread and bean or cabbage soup, it included also lamb stew " which contained everything but the wool ". Spinal fluid examinations were not done in this group of cases.

In two patients to the nutritional deficiency the only other recognized factor added was alcohol, a very moot agent indeed. Both of these patients had been on grossly inadequate diets for a matter of months, in addition to consuming large amounts of alcohol. Case 20 was associated with an " albuminocytologic dissociation " with three spinal fluid examinations showing respectively 98, 103 and 54 mgms. per cent. of protein. Case 44 was reported as showing " increased globulin " on two examinations, protein determinations not being reported.

To what extent fever with its associated metabolic changes may be considered a significant factor is difficult to evaluate in the material at hand, but fever combined with sulphonamides an agent very frequently present in the prodromal histories of this group of cases, has led to some recent and pertinent observations by Garvey, Jones and Warren. In an article under the title " Polyradiculoneuritis (Guillain-Barré Syndrome) Following the Use of Sulphonilamide and Fever Therapy " they report six cases. Case 1 of theirs, for example, had been given 38 grams of sulphonilamide in early April and fever therapy in late June with onset of neurological symptoms two weeks later; a spinal fluid protein of 170 mgms. per cent. with four cells was noted on 16 August, 140 mgms. per cent. on 10 September and 45 mgms. per cent. on 21 November, cells being " normal " on each of the latter occasions. Their six cases are quite similar, are associated with a latent period and with a CSF protein increase as high as 240 mgms. per cent. They refer to a similar case reported by Orun-

steen and Furst and to cases where fever alone produced the syndrome, concluding that it is the result of activation of a virus.

In Blankenhorn's article on "Multiple Peripheral Neuritis Occurring with Sulphonamide Therapy" there is only the statement that there were no "cerebrospinal fluid changes referable to neuritis alone" —apparently not enough to postulate "the activation of a virus" or to warrant more specific comment. In the one case in the present series, which seems perhaps attributable to sulphonamide therapy, no protein determinations are available.

Neither fever nor sulphonamide therapy, nor a combination of both, is frequently followed by symptoms of polyneuritis, nor for that matter are "respiratory infections" or "sore throats". Yet throughout the experience in the theatre, and certainly throughout the literature, emphasis is placed upon these prodromal findings. It is perhaps because they are so very common and so rarely complicated by polyneuritis and yet, paradoxically, so frequently herald such an illness that the concept of another agent persists in such phrases as "due to activation of a virus" or "of suspected virus etiology".

A virus etiology was given initial impetus by Wilson, who, during the last war, thought he was able to culture an organism, believed to be a virus, from the spinal cords of cases described by Bradford and Bashford and with it produce the disease in monkeys. This agent, however, has never been confirmed, nor animal transmission accomplished, in spite of many efforts. Further, Arkwright (1919) disproved the postulated agent by showing the globoid bodies which Wilson demonstrated to be contaminants and Wilson in a note appended to Arkwright's paper retracted his previous claim. Though polyneuritis has been described as following diseases of known virus origin, for example mumps, it has yet to be shown that the virus rather than the systemic illness gives rise to the nervous tissue response. Case 79 of this series followed a virus pneumonia. There seems to exist at present really very little to substantiate a virus etiology, though it has not been disproved and its fascination apparently remains, perhaps to the loss of other investigative possibilities.

Penta, in commenting upon the failure to demonstrate a virus or bacterial etiology for this group of illnesses, postulates an allergic mechanism, reporting also (1944) that "The Naples Polyclinic has never encountered so many cases of polyneuritis as in the past several months". He refers to a child who developed "polyradiculoneuritis between the 8th and 14th day after vaccination" and to similar clinical and histopathological characteristics, occurring not only in the roots but in the central nervous system, following serum administration. Porta presents a case of diphtheritic polyneuritis, complicated by a monoplegic, mononeuritic involvement of right arm, particularly involving the superior rami of the brachial plexus, which complication he attributes to serum therapy, following diphtheria anti-toxin. In commenting upon 13 cases of "unusual peripheral neuropathy" reported in the theatre bulletin, Weinstein and Gersten report that "clinically the aspects of the disease resembled the type of nerve involvement rarely seen in serum disease. Four patients developed symptoms within 20 days after toxoid or vaccine injection." However, "the normal spinal fluid finding ruled out a Guillain-Barré type of radiculoneuritis". Two cases in the present series were associated with transient arthralgias and four cases were associated with a transient cutaneous reaction at onset.

In recent American literature there are not only repeated failures to demonstrate a virus or effect animal transmission, but there is accumulating evidence that a toxin or toxins may be responsible. Though Honeyman was unable to demonstrate any neuropathological changes in the four cases he studied at autopsy and refers to botulism and mussel poisoning as examples of fatal toxic action on the nervous system which fail to leave microscopic evidence of the process, Sabin and Aring, studying the viscera and the peripheral and central nervous system in infectious polyneuritis, express the belief that "infectious polyneuritis is caused by toxin or toxins with affinities for the peripheral nerves and the viscera and elaborated by the micro-organisms responsible for the infection of the respiratory tract which usually precedes the onset of nervous symptoms."

Before turning to the further consideration of those agents responsible for respiratory infections which precede "the onset of nervous symptoms" and which loom so large in this theatre's experience, attention is directed to the experience of the German army in the Russian theatre. Wilke (1943) reports that during the battles on the Eastern Front numerous examples of polyneuritis were observed which resembled so-called "idiopathic inflammatory polyneuritis", exhibiting predominantly motor and sensory disturbances. Interestingly enough "the true neuritic nature of these complaints were overlooked and frequently the symptoms were attributed to neurosis"—among the Herrenvolk. The protein content of the CSF was increased to between 300 and 500 mgms. per cent. and most of the patients gave a previous history of specific infection with Flexner or Shigo-Kruse bacilli. Prognosis depended upon the healing of the dysenteric lesion and improvement in the general condition, but recovery was usually rapid. In Wilke's cases all degrees of nerve involvement were encountered, but the paralysis "affected chiefly the proximal muscles" from which he postulates "the condition was a proximal nerve paresis" (?) and so "differed from the well-known type of degenerative-toxic polyneuritis with distal paresis".

Of the agents responsible for upper respiratory infections followed by symptoms and signs of nervous tissue injury, the only one recognized in the material gathered has been the Corynebacterium diphtheriæ, and the remainder of the discussion of etiology will be devoted to the experience encountered in this theatre regarding it.

The problem of diphtheria, and particularly of its neurological complications, is made more difficult by a feeling that "our knowledge of diphtheria is most satisfactory in that we know the cause of the disease and its mode of transportation, we are able to check its spread and possess specific preventatives, a precise measure of susceptibility and a curative agency of great potency". Thereafter diagnosis seems somewhat anticlimatic; yet "diphtheria often comes on insidiously, the sore throat may be plastered with false membrane without attracting attention and sometimes the first inkling of an attack of diphtheria is the onset of post-diphtheritic paralysis". The problem of diagnosis in turn is complicated in this theatre by the impression that because a large proportion of American pre-school children,

notably in urban areas, have received inoculation, the probability of diphtheria infection is less likely when sore throat is encountered in an American soldier (e.g., less likely than acute tonsillitis, but particularly less likely than in the British soldier). The question is justifiably raised, however, as to "whether the brilliant results of prophylactic inoculation in North America owe their superiority to those obtained in Europe, to more comprehensive adoption and better execution, or to the absence of epidemic gravis diphtheria in the former area".

This variation among the Corynebacteria, coupled with the frequency of carrier states, the difficulty of completing adequate bacteriological studies, particularly virulence tests, under the exigencies of military conditions, lend weight to dissenting opinion when diphtheria is offered in the differential consideration of cutaneous, membranous or epidemic illness. It is always to be stressed that diagnosis by inference of etiology is hazardous, and yet early clinical decision is imperative lest therapy be delayed.

The recognition of diphtheritic complications when diphtheria has not been recognized may or may not be difficult, since complications may arise weeks after the acute illness and "typical" diphtheritic march through the nervous system may not occur. As long as proof of agent, however, remains isolation of the organisms by way of a scientific genuflection to Koch's postulates, a certain group of complications must be reported as of unknown etiology.

Turning, then, to this group of cases of nervous system disease associated with albumino-cytologic dissociation and unknown etiology, it seemed pertinent to investigate the occurrence of albumino-cytologic dissociation following recognized and treated diphtheria, and associated with similar syndromes unrecognized and untreated, for the observation of these spinal fluid alterations, rather than any sharply defined evidence of anatomical compromise or course of illness has, certainly in the experience of this theatre, led to the diagnosis of Guillain-Barré Syndrome. It is generally recognized that some elevation of spinal fluid, usually referred to as "moderate", may occur in post diphtheritic paralysis. However, in the French, Italian and German literature referred to by Fornara, considerable more emphasis has been placed on spinal fluid alterations in postdiphtheritic paralysis than in any of the American literature available.

Fornara tends to confirm the existence of central nervous system lesions following diphtheria, mentions the appearance of mild meningeal reactions and refers also to the work of others who describe clinical symptoms which must be attributed to lesions higher than the peripheral nervous system, mentioning especially the observation of nuclear lesions in cranial nerves and of anterior horn cell lesions occurring with ordinary peripheral nerve lesions. He reports from other writers several cases of post-diphtheritic pseudotabes, primarily a peripheral neuritis, associated with increased spinal fluid protein and includes a report published in 1915 by Chaufford and Lecomte; this followed diphtheria in a man of 42 who in addition to the more usual laryngeal and accommodation palsies presented a facial paralysis and a trigeminal neuralgia associated with an elevation of spinal fluid protein and a lymphocytosis of 30/mm3. Mazeron reported in 1920 two cases, one of postdiphtheritic paraplegia with 5 cells and a total protein of 240 mgms. per cent. and the other of palatal paralysis with 25 cells and a protein of 75 mgms. per cent. Fornara also refers to the work of Regan appearing in the Archives of Pediatrics and in the American Journal of Diseases of Children in 1918, 1923, and 1927. Reference is made to six cases in which 10 lumbar punctures were performed with the finding of an elevated protein in only one and a second series of 16 cases (six localized and ten generalized) with 28 lumbar punctures done. Globulin was definitely increased in only four and slightly increased in two.

Of the three scattergrams (Figures 1, 2, and 3) included in this paper, two bear directly and one indirectly upon this problem. Figure 1 relates as closely as possible spinal fluid protein determinations to time when nervous tissue injury first becomes evident. A single dot represents one determination where only one determination was done. Where successive determinations were done the findings in each case are joined by a line indicating the alteration of spinal fluid protein content on successive examinations in that particular case. It does not relate them to prodromata. Figure 2, however, relates these findings to the onset of sore throat, whether recognized and treated as diphtheria, or simply recorded as a prodromal observation which may or may not be interpreted as unrecognized and untreated diphtheria. Figure 3 relates spinal fluid protein observations to the interval elapsing in recognized and treated diphtheria. Because of interest in the considered role of diphtheria, both Figures 2 and 3 include also 17 spinal fluid protein determinations done early in 16 cases of diphtheria which so far had shown no evidence of nervous system disease. I am indebted to Lt.-Col. Hughes of the 225th Station Hospital, to Major Buchanan of the 300th General Hospital, to Major Golz of the 182nd Station Hospital and particularly to Major Price of the 17th General Hospital for these determinations of spinal fluid proteins in early and in convalescent cases of diphtheria under their care. Superimposition of the successive findings in any one case recorded in Figures 2 and 3 upon the findings recorded in Figure 1 will relate the sore throat and/or diphtheria to the onset of neurological signs and symptoms.

Tap, in a discussion of the postdiphtheritic nerve paralysis and the probable time of occurrence lists: (1) palatal paralysis: 10th day or later, (2) "ciliary paralysis": 3rd week or after, (3) facial paralysis: 3rd week or after, (4) oculomotor paralysis: during or after 3rd week, (5) pharyngeal paralysis: 3rd or 4th week, (6) laryngeal paralysis: 3rd to 5th week, (7) paralysis or paresis: 5th to 6th week, (8) paralysis of diaphragm: 5th to 6th week. Review of the 16 cases which are used in the construction of Figure 3 and, with some reservations, the additional 19 cases which have afforded data for the construction of Figure 2 will indicate that there is very considerable variation in the prodromal time factor. This might well be anticipated on recalling that symptomatic faucial and nasal diphtheria may or may not become symptomatic, and that symptomatic diphtheria either faucial or cutaneous may be promptly or belatedly recognized.

Because of this prodromal time factor which varies from days to several weeks a significant

dichotomy of approach has developed, one made particularly evident by the time factor in military evacuations and which seems substantiated by the experience in this theatre. It is offered as one factor contributing to the confusion which surrounds the problem and may be briefly stated. In terms of this theatre's experience it frequently happens that when a case of diphtheria is complicated by nervous system disease and the patient is under the care of a pediatrician or an internist, a spinal fluid examination rarely is done and it has happened that further neurological complications are not anticipated. On the other hand if the patient, some weeks after his initial illness, comes under the care of a neurologist, the history of significant prodromal sore throat may not be obtained or, because of the spinal fluid findings be considered insignificant. Gordon Holmes in discussing the differential considerations relative to acute febrile polyneuritis, though offering differential considerations for alcoholic, lead, arsenic and beri-beri neuropathies, suggests only that the recent occurrence of diphtheria "should in the first place be excluded". Guillain concludes "the evaluation of diphtheritic paralysis with the history of antecedent pseudomembranous sore throat, paralysis of the palate and disorders of accommodation, are entirely different" from the syndrome bearing his name, though he acknowledges post-diphtheritic albuminocytologic dissociation with protein content as high as 1200 mgms. per cent.

Relative to the preceding remarks are the following observations:

(1) Cases 51, 88, 115 and 117 developed palatal paralysis before discharge to duty shortly thereafter. Spinal fluid examinations were not done. Palatal paralysis developed very shortly (1-10 days) after discharge in cases 5, 14, 40, and 26.

(2) Two cases, with recent histories of diphtheria were diagnosed as Guillain-Barré Syndrome.

(3) Two cases, without a history of sore throat, but with finding of "paralysis of the palate and disorders of accommodation", were diagnosed as Guillain-Barré's Syndrome.

(4) Of 16 cases with a history of recently treated diphtheria, 13 had difficulties of deglutition and in 6 were recorded visual disturbances.

(5) Of 19 cases with recent sore throat, not diagnosed as diphtheria, 10 were diagnosed as Guillain-Barré Syndrome, 15 had difficulties of deglutition and in 2 were recorded visual disturbances.

To separate from the clinical material certain cases to emphasize a specific interpretation of the data is hardly in keeping with the presentation of material "unweighted by any factor other than accessibility". It will be recalled, however, that to Figures 2 and 3 were added 17 spinal fluid determinations done in 16 cases of neurologically uncomplicated convalescent diphtheria thereby adding to the construction of these two scattergrams a selected factor. Two of these cases, developed subsequent neurological disease, one, quite typical, with palatal, visual, facial, and peripheral findings and the other, numbness, muscle aches, and reflex alteration in one lower extremity without the palatal and accommodation paralysis which are considered typical. Of these sixteen cases one had two spinal fluid examinations. He had been admitted to the hospital on 16 August, a diagnosis of diphtheria established and antitoxin promptly administered. On 27 August spinal fluid examination revealed 4 cells, a protein of 80 mgms. per cent. and a positive globulin. On 3 September the examination was repeated and revealed 1 cell, a protein of 71 mgms. per cent. and positive globulin. It is interesting that this man was hospitalized from 1 May to 14 May and discharged with a diagnosis of tonsillitis, acute, ulcerative, mod. sv., right, due to Vincent's organism. Two weeks later he presented himself for consultation because of numbness in the radial distribution of the right hand for which no cause was found, and he was dismissed without spinal fluid examination but with the customary exhibition of thiamin.

One other case is referred to specifically because it epitomizes in many ways the difficulties encountered when the corynebacterium diphtheriæ cannot be isolated. Case 34 presenting paralysis of accommodation, palatal paralysis, marked sensory, motor and reflex evidence of peripheral neuropathy, and death in respiratory failure after ECG evidence of toxic myocarditis; findings which almost necessitate a diagnosis of postdiphtheritic polyneuritis. He had had for about six weeks multiple slow healing cutaneus lesions which the skin consultant, in retrospect, considers may have harboured virulent diphtheria, and for which he had been given large amounts of sulphonamides and penicillin. Cultures failed to reveal a significant organism either pre- or post-mortem.

General

Osler's description (1892) perhaps begins the critical study of the group of cases and is followed by that of Holmes (1917). During the last war Bradford, Bashford and Wilson (1918), Casamajor (1919) and Kennedy (1919) were particularly interested in it, and the literature since, which is extensive, refers to these earlier works with reference always to the papers of Guillain, Barré and Strohl (1916) and passing comment upon Landry's much earlier (1859) and probably invalidated description.

During the present war Fitzgerald and Wood (1944) and Stevens and Harris (1944) have reported cases in the United States Naval Medical Bulletin.

In addition to Harshman's study of 14 postdiphtheritic paralyses occurring in 21 cases of diphtheria developing in American fliers in a Roumanian POW Camp, Norris, *et al.*, report 18 cases of diphtheria occurring aboard a U.S. Naval Hospital Ship in whom 13 developed some form of postdiphtheritic paralysis, one with fatal results. The majority were not suspected of diphtheria until the paralysis had set in. In the Bulletin of the U.S. Army Medical Department (1944) Fleck reports an outbreak of diphtheria among German POWs. He calls attention to the trends in the recent literature on diphtheria which indicate an increasing incidence of the disease in adults and a clinical course not generally considered characteristic. In discussing complications, only 3 of the 7 cases showing cardiac involvement had had membranous sore throat. Of the 5 postdiphtheritic paralyses only one had been recognized and given antitoxin. The four other patients had not been previously diagnosed as diphtheria but gave a definite history of sore throat six to eight weeks before the onset of neurologic symptoms and one of these had been treated with sulphonamides. All five patients had "eye complaints

one month to six weeks after the original illness followed in sequence by dysphagia and regurgitation of fluids, paresthesias in fingers and toes, and finally muscular weakness most marked in the lower extremities". In none of these cases, nor those occurring aboard the hospital ship, nor among the fliers shot down over Roumania were spinal fluid examinations reported.

Fleck feels that diphtheria had not been diagnosed in the initial outbreak of diphtheria because "the clinical picture was that of follicular tonsillitis". He concludes that less than one-third of the patients properly diagnosed presented typical membranous sore throats and that the epidemic he studied represented the aftermath of diphtheria endemicity encountered by German troops in various parts of Europe and the middle East.

During the preparation of this report every effort was made to discuss the difficulties encountered with the diagnostic problem of diphtheria in this theatre. It can only be offered as an impression that there are significant variations in professional estimations of its frequency, its manifestations and the efficacy of treatment. Difficulties seem also to have been encountered in the isolation and identification of the organism. The period of hospitalization and search for potential complications have varied in different installations. Comment has been made on occasional extremely virulent organisms but so far as could be ascertained in this corrolary aspect of the present study, the gravis form has not been a significant bacteriological implicant.

The role of nutritional deficiency as a predisposing influence, suggested perhaps by Harshman's study and by the prevalence of the disease during the past year in Naples reported by Penta, cannot be evaluated. The Report of Malnutrition During Convalescence prepared by the National Research Council indicates that reports from hospitals receiving the wounded from practically every theatre confirm the prevalence of malnutrition as shown by moderate to severe weight loss. No serum albumin determinations were done in the series reported in this study.

Returning to the problem as it has been manifested in this theatre, certain results of this group of illnesses are offered. Of the 119 cases studied, 7 per cent. died and 50 per cent. were returned to the Zone of the Interior. Twenty-five per cent. were retained in this theatre, 15 per cent. being reclassified and of the 10 per cent. returned to duty, most were in rear echelon duties. The incidence of subsequent hospitalization in this group is not known. The disposition was not available in the remaining 18 per cent. The period of hospitalization varied for many reasons, but hospitalization in the theatre as brief as 3 weeks and as long as 7 months are recorded. The average period of hospitalization is estimated as about 2 months, but with hospitalization for prodromal illness may be significantly more.

From the few follow-up reports from the Zone of the Interior it is apparent that hospitalization may be prolonged there. The only patient who has reported Disability Adjustment by the Veteran's Bureau was given 100 per cent. disability for one year. This patient was ambulatory during his period of two hospitalizations in this theatre which with intervening period of relative disability on duty, amounted to two and one half months.

Summary

One hundred and nineteen cases considered as belonging to a group of ill-defined conditions of the nervous system have been collected and studied. Similar cases have for many years been studied and the results presented under many and various designations. A few of these such as acute infectious polyneuritis, infectious myeloradiculitis, and Guillain-Barré's Disease will serve to identify the group. The cases selected have been so on the basis of accessibility in an active theatre of war.

The study is organized to include a statement of the problem, a description of the methods utilized and of their limitations. The 119 cases are presented in brief summary and there follows a discussion. This is organized to include differential considerations which have arisen on the basis of history and finding, differential consideration relative to etiology.

In 51 of the 119 cases the term "due to Guillain-Barré's Disease," or the parenthetical (Guillain-Barré's Syndrome) were used to modify a diagnosis stated in other words, or the diagnosis "Guillain-Barré's Disease" was made. An effort has been made to establish the meaning of this term in theatre experience and nosological consideration have been presented.

In 98 of the cases there have been performed 280 spinal fluid examinations and records have been available to indicate the quantitative spinal fluid protein determinations in 240 examinations in 78 of these patients.

A scattergram relates single and consecutive CSF protein determinations to the onset of recognized nervous system disease in 70 of these cases. A second scattergram relates spinal fluid protein determinations to the prodromal symptom of sore throat in 35 cases. A third scattergram similarly relates these findings to the onset of clinically recognized and treated diphtheria in 16 cases.

A report is made of dispositions and an estimation of disability is offered.

Mention is made of the historical development of the problem and to such contemporary military medical literature as has been available. Conclusions follow.

An appendix includes autopsy protocols deemed pertinent and summary of certain cases in more detail for more critical reference on controversial matters.

Conclusions

1. The term Guillain-Barré Syndrome has been used in this theatre as a synonym for albuminocytologic dissociation and in general its usage has borne no other relation to a syndrome described by Guillain and his co-workers.

2. Emphasis on the finding of an elevated spinal fluid protein has lead on occasion to the misinterpretation of the total clinical picture. There may be marked variation of spinal fluid protein during a period of time and if diagnostic weight is to be attached to spinal fluid findings successive examinations of the spinal fluid should be done.

3. Many influences bear upon the tissues of the nervous system and nervous tissue may be damaged by several agents. Fever and nutritional deficiency are two of the influences which may have played significant precipitating roles in the development of the illnesses studied.

4. Of the several agents, the only one that has been recognized in this study has been the neurotoxin of diphtheria though sulphonamides have very frequently been circulating in various concentrations in the blood stream. The combined effect of influences and agents, of mutual and of individual significance are not understood.

5. In the experience of this theatre the diagnosis of diphtheria has not always been easy and the recognition of post-diphtheritic neurological complication when diphtheria has not been recognized may be difficult. At times it has not been considered because of the finding of an albumino-cytologic dissociation of the cerebro-spinal fluid.

6. It has long been reported that a very high spinal fluid protein may exist with post-diphtheritic polyneuritis and that central as well as peripheral nervous tissue may be damaged by this neurotoxin, but this knowledge has not been in general dissemination in this theatre.

7. The immunological techniques of the laboratory merit further utilization in evaluating the role of diphtheria in this group of paralyses for the isolation of the organism is rarely possible and because of the carrier states may bear no relation to a particular case of paralysis under investigation. It seems likely that such techniques applied to the bacterial toxins bear greater promise in this group of cases than if applied to the field of viruses.

8. This group of cases should be reported under terms which are primarily anatomical and modified as deemed pertinent according, for example, to agent and associated findings, lest an eponym mask epidemiologically significant disease in the figures reported to the surgeon.

9. The patients studied under this group of illnesses bear a very poor military prognosis. It has proven impossible from the data available to estimate the incidence of the related illnesses. It is not considered great.

10. The implications of a diphtheria epidemic occurring in American troops serving on European soil may be grave and merit more adequate investigation.

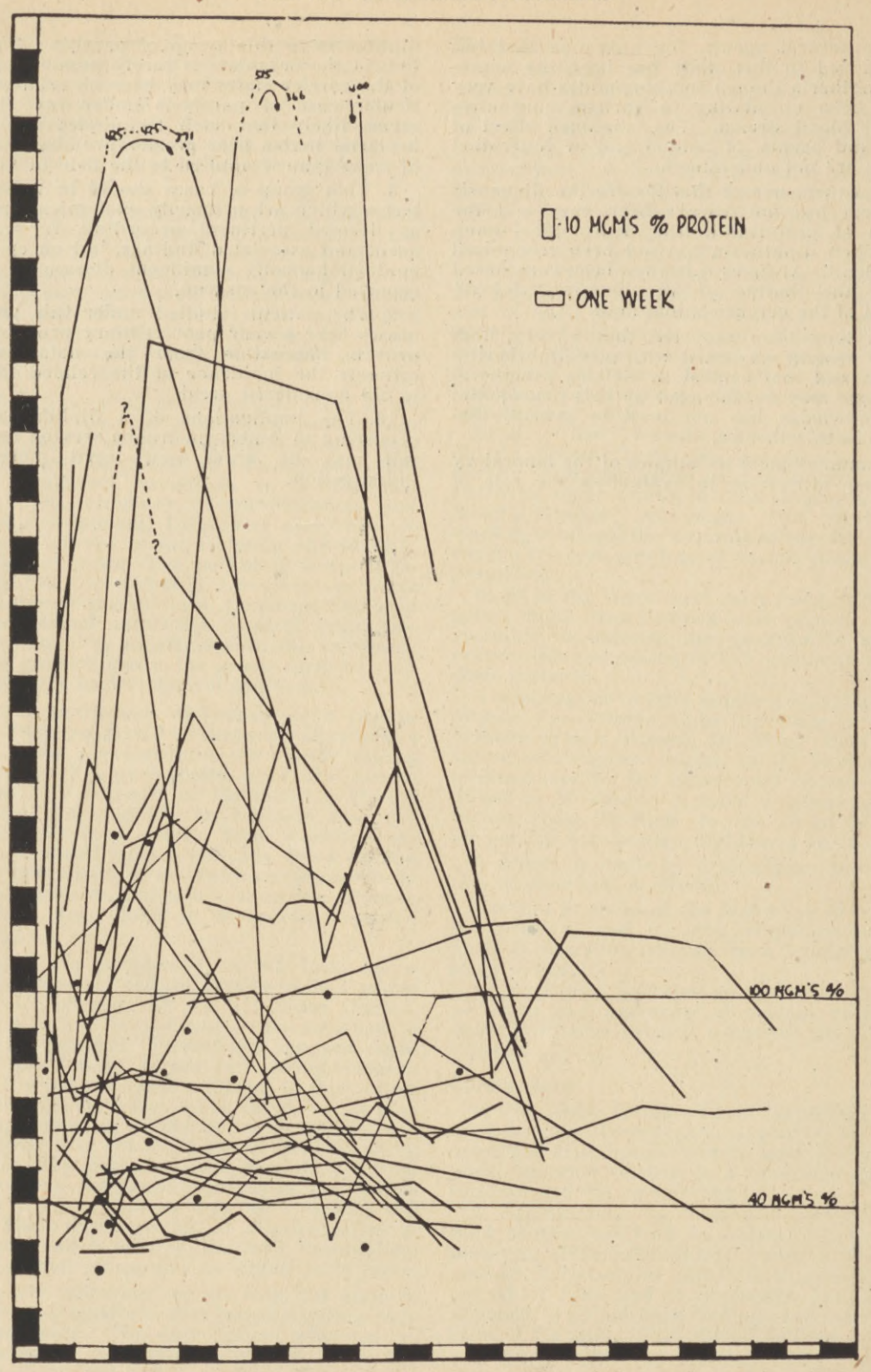


FIGURE 1.

Is based on 217 spinal fluid protein determinations on 70 cases. These are cases numbered 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 18, 20, 21, 25, 29, 30, 31, 33, 34, 36, 39, 40, 41, 42, 43, 46, 48, 51, 52, 54, 56, 57, 58, 61, 62, 66, 67, 69, 72, 73, 74, 77, 78, 81, 82, 83, 84, 85, 86, 87, 88, 90, 91, 92, 94, 96, 97, 98, 100, 102, 106, 107, 111, 112, 113, 115, 117, 118, and 119.

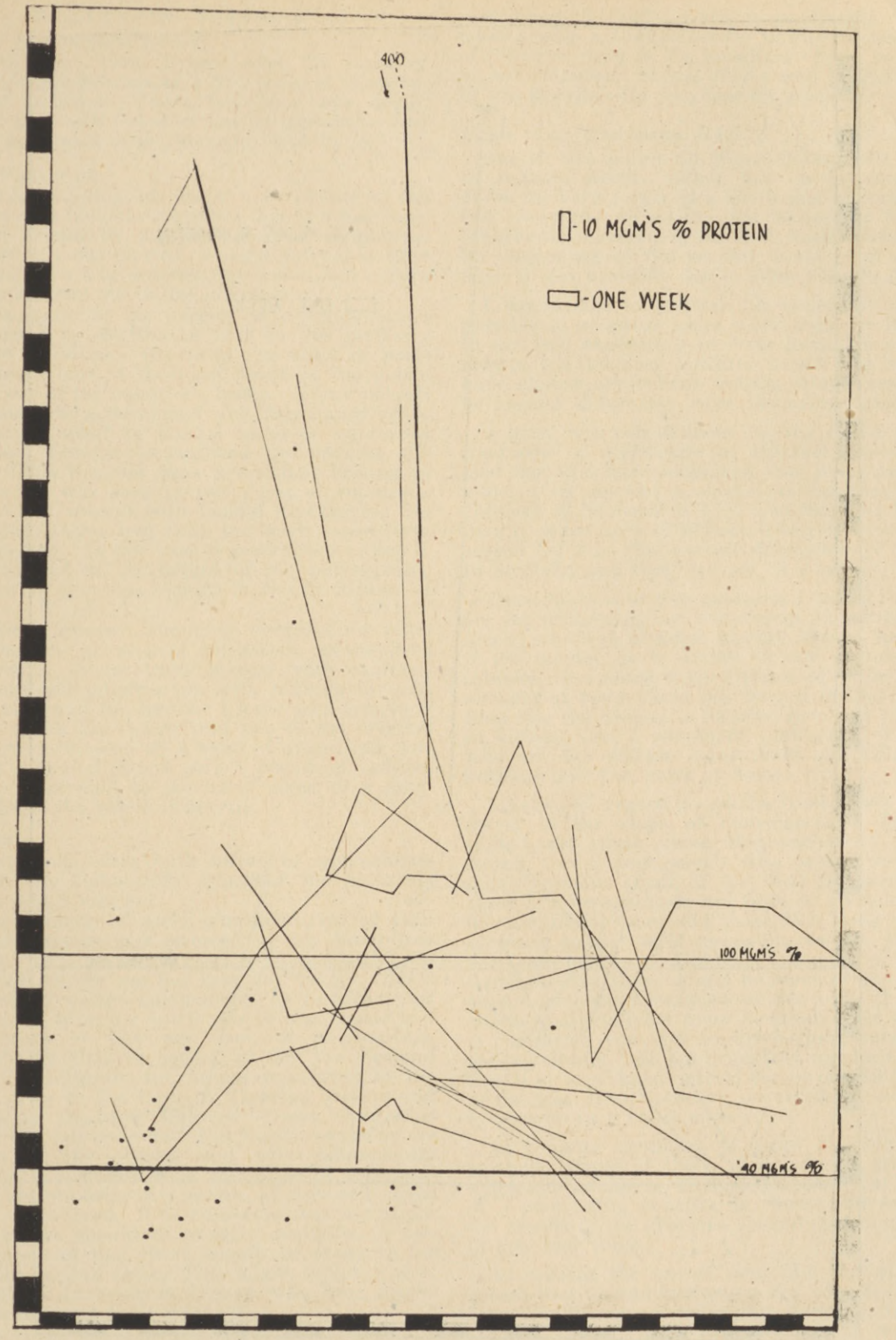


FIGURE 2.

Is based on 85 spinal fluid protein determinations in 35 cases. These are cases numbered 5, 6, 9, 10, 12, 14, 21, 25, 30, 31, 40, 51, 54, 62, 66, 67, 72, 73, 74, 77, 83, 85, 87, 88, 91, 92, 94, 97, 100, 106, 107, 111, 115, 117, and 118.

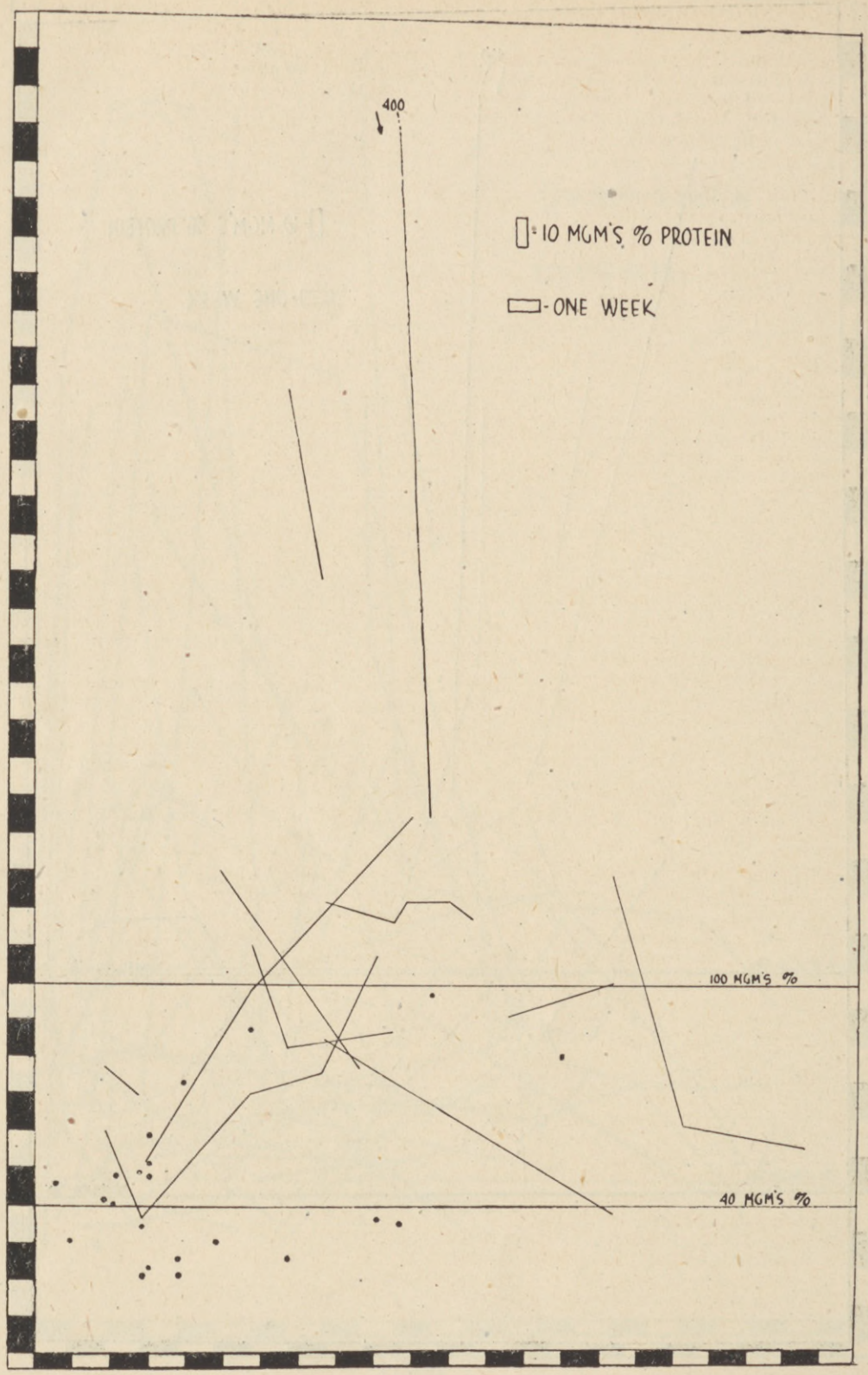


FIGURE 3.

Is based on 35 spinal fluid protein determinations in 16 cases. These are cases numbered 9, 12, 14, 25, 30, 51, 62, 66, 67, 73, 77, 92, 97, 111, 115, and 117.

DISCUSSION—Diphtheria

Lt.-Col. J. E. Caughey, NZMC

Since October, 1940, I have seen 25 cases of diphtheritic polyneuritis at 2 N.Z. General Hospital, a 600-bed hospital. There has been one death. Fifteen of the cases followed faucial diphtheria and ten were associated with cutaneous diphtheria.

Clinical Features.

Nasal regurgitation of fluids may occur in the early days of a faucial diphtheria due to a mechanical defect caused by the swelling and membrane. This clears in a day or two. Palatal palsy may then develop due to a true polyneuritic lesion and occurs 3 to 6 weeks after the initial infection.

The specificity of the paresis of accommodation was recorded by Walshe in 1918 in the quarterly Journal of Medicine. He noted the onset of polyneuritis at the site of the local lesion in the palate or at the site of the cutaneous lesion. There paresis of accommodation developed and this appeared to be a specific affect in faucial nasal or cutaneous diphtheria. Finally, generalised polyneuritis developed. This has not been a constant finding in our cases. It was seen in two cases of cutaneous lesions and in several with faucial diphtheria. No case of hemiplegia was seen but such cases have been described. In one case a generalised epileptic attack occurred at the height of the polyneuritis. There was no previous history or family history of epilepsy.

Peripheral lesions: The only evidence of polyneuritis may be an area of anæsthesia surrounding a skin lesion. A case may present with evidence of a generalised polyneuritis with nothing to indicate the nature of the lesion. I have seen two such cases in which the nature and site of the original infection was revealed by a band of anæsthesia surrounding a healed desert sore. The deep reflexes may be exaggerated in the early stage of a polyneuritis when the palate is paretic.

Treatment:

We have had cases with advanced polyneuritis in which the Laboratory reported the infecting organism was a virulent.

The importance of early administration of anti-diphtheritic serum was stressed by Sir Humphrey Rolleston. In a series of cases who received anti-diphtheritic serum on the first day of the illness 3 per cent. developed polyneuritis. A further series who received it on the fourth day of the disease had an incidence of 26.9 per cent. of polyneuritis. During the El Alamein period, in the New Zealand Division, anti-diphtheritic serum was given in the forward areas in the Casualty Clearing Station and in the Main Dressing Stations. Cases were seen who had had adequate anti-diphtheritic serum on the first day of the disease and who subsequently developed polyneuritis. The possibility of deterioration of anti-diphtheritic serum in forward areas must be considered. It is advisable that anti-diphtheritic serum should be readily available in forward areas and that there should be facilities for the proper care of same. This might be taken over by the Blood Transfusion Groups, who have means of refrigeration at their disposal.

I have used Penicillin both parentally and locally as well as large doses of anti-diphtheritic serum, (80,000—120,000), in extensive cutaneous diphtheria and in severe faucial diphtheria.

If Major Bagnall's work is applicable in cases treated with anti-diphtheritic serum the persistence of infection deep in the tonsillary crypts and in unhealed cutaneous lesions might well be the solution of the diphtheritic polyneuritis problem.

Major Scott Thompson, RAMC

One or two points on Major Dornhorst's remarks as regards deaths rather late in the disease in children. Very rarely is a death due to cardiac failure. Normally all deaths due to cardiac failure in diphtheria occurred in the first week; sometimes at the beginning of the second week. If it occurred later, it was probably due to other complications.

I would like to endorse his statement that it is possible to prognose cases when they are first seen. In my own experience in fever hospitals you could always tell whether patients would live or die. I have almost never been wrong. Milder cases could be treated differently from the severe cases.

A point was raised about the big advances in the treatment of diphtheria in different places. I was glad that this was recognised. One point mentioned, which I am not sure is correct, is that deaths among children in Scotland is 10% and that this is higher than in other parts of Britain. There is a very simple reason for this. The correct diagnoses are recorded in Scotland and they are not in England.

There are one or two questions I would like to ask on the occurrence of diphtheria in adults in the Army, which is of great interest. Has it been noted if the disease as it occurs in our soldiers affects soldiers who come from villages or cities? At the moment at home there has been a feeling for some time that the disease is handled better in cities than in villages and I wondered perhaps if the people who get the disease come from our villages and perhaps outlying parts at home.

Finally, in regard to swabs from cases of diphtheria in the stage of convalescence. Perhaps I should not speak about this because I have too strong views, and people who have strong views should remain silent. I feel that the swabbing of cases in convalescence has little or no value except in exceptional cases and those have been described as being people with unhealthy tonsils yielding a very rich culture of diphtheritic bacilli; it is understandable that these should be incarcerated until the bacilli have been reduced or removed. If you discharge patients from fever hospitals after treatment is completed you will be discharging carriers into the population. I do not think this will be a problem, it will be a problem only to the physician in charge of the case. If an epidemic occurred, he would have to answer in a court of law.

As regards swabbing of cases of diphtheria. I certainly doubt if there is any value attached to wholesale swabbing. It is well known that a chance of a man being negative is almost independent of the results of the previous swabbing. I doubt if it is of any real value.

As regards the use of penicillin. I was not surprised that its administration did not affect carriers for penicillin is not antiseptic. Even although diphtheritic bacilli were prevented from multiplying over a period of 3 to 5 days they would not be killed off and would still be present later and I doubt if the method could be expected to be effective.

Lt.-Col. G. S. Hall, Adviser in Neurology, AFHQ

Briefly two points—one is that a recent history of blood stained nasal discharge in middle aged persons should not necessarily lead to the diagnosis of diphtheria polyneuritis until the possibility of carcinoma has been excluded. The further point is, if I have understood Lt.-Col. Paul Wood and Major Dornhorst aright, that the onset of polyneuritic symptoms and signs, do not call for any extra care in the convalescence of these patients, I must say that I am in profound disagreement. I think it is a very dangerous procedure and I would welcome other neurological views on this point.

Air Commodore R. N. Ironside, RAF Medical Services

One of the misfortunes of service medicine is the time which elapses between wars, during which a new race of doctors appear who have had no opportunity of studying lessons learned in the last war.

F. M. R. Walshe, serving with the British Army overseas did classical work on diphtheritic polyneuritis, published in the Quarterly Journal of Medicine in 1918-19. He described 30 cases of desert sore with polyneuritis and deduced: (i) that palatal paralysis did not occur except in faucial diphtheria, (ii) that paralysis of accommodation (second or third week) was *specific* whatever the site of infection, (iii) the general paralysis came on in the sixth week or later. One case with a perineal sore had sphincter paralysis and symptoms indistinguishable from those of a cord lesion involving S.2-5. The few cases of serum neuritis I have seen have all affected the brachial plexus.

The decision to give serum in late cases with cutaneous sores depends on whether toxin is still being absorbed. Rest in bed should be maintained so long as there is cardiac involvement. It is, however, sometimes impossible to predict sudden collapse and death.

Lt.-Col. C. B. Prowse, RAMC

I also would like to speak in favour of conservatism in the treatment of diphtheria cases, and in support of that I can say that during the period of time in North Africa when we were getting cases from other hospitals in Italy, the percentage of those who had neuritis was very high, and during the recent time when we have only had diphtheria cases from the immediate locality we have been treating them from the start in the same place. We treat them on routine convalescent lines, and we have had no cases up to date of polyneuritis, and it seems a pointer that this evacuation and all this rapid moving about which takes place when cases are moved long distances disturbs them and makes them likely to get complications. With regard to the use of penicillin we have had a number of cases 7 in all, very resistant carriers, which have remained with virulent organisms for periods varying from 2½ to 4½ months.. Eventually I consulted the pathologist to see what effect we could make on them with penicillin. We agreed that the usual methods of administration would not be of much value in view of the fact that the infection was a surface one and not likely to be reached through the blood stream. We therefore concocted some lozenges which we made out of gelatine 80% and incorporated penicillin in these in a dosage of 1000 units per lozenge. We eventually managed to produce lozenges which were sufficiently resistant to the heavy suckers to last for 25 minutes. The gentlemen concerned were to suck them all day for three days, and after a two day period without any lozenges they were swabbed again. They all became positive again. They were all cases of tonsillar sepsis. The reason why I did not seriously consider tonsillectomy was on the advice of the ear, nose and throat surgeon who took rather a poor view of the results to be obtained from tonsillectomy, but I have little doubt that could be done now. I should add that all these cases were sensitive to penicillin.

Capt A. L. Wyman, RAMC

I was very much interested in the opening remarks of the last speaker because working in a C.C.S., one great problem is to decide when and under what circumstances to evacuate our cases. I have always been brought up in the doctrine of absolute rest in the case of diphtheria. I must say I was very often worried and greatly perturbed about the evacuation of these cases of diphtheria which I knew had to be kept at complete rest. I often had to send away after starting them off on treatment patients who must have had an uncomfortable ambulance journey lasting several hours and often might only then end up on one stage of the journey. This necessitated considerable movement of the patient and prevented him from having absolute rest and I often wondered what happened to these cases, and feared some day a rocket would come back. The follow up card system is not entirely satisfactory and since very few of these cards ever return one is left in ignorance. I was very interested to hear from the last speaker that the cases which had to travel had developed a higher percentage of polyneuritis than those taken from the immediate vicinity. I would also like to ask whether cardiac complications are more common in these people. The other point I would like to ask about is the question of a throat swab in the initial phase of the illness. We could only take a direct swab and personally I have never relied on it and treated cases purely on clinical grounds. In a General Hospital in the Middle East a couple of years ago one was surprised to find in most of the throats which apparently had a diphtheritic membrane that in these cases most of the swabs came back negative, and in other cases which were only suspicious they came back positive. There seems to be a direct connection between the membrane and the swab and I would like to hear further views on this. Finally I would like to say I was very pleased to see this divergence of opinion expressed at the conference because I must say I am relieved to find that I am not alone in wandering along in the morass of uncertainty.

Lt.-Col. G. M. J. Slot, RAMC

I would like to say in my opinion that diphtheria in its clinical aspects is not the same in any one soldier. I agree with many of the opinions expressed by Lt.-Col. Hutchinson but there are many important differences.

As regards cases which die suddenly of which Major Dornhorst has spoken, we have had about 200 diphtheria cases here and probably 250 or so in the Middle East, and I have never seen one die suddenly. I have had three cases in Europe on which I had post-mortems. They all had suprarenal hæmorrages and the collapse was associated with it. It is difficult to see how any prolonged period of rest in bed is likely to affect that issue. As regards cutaneous

diphtheria of which we saw a great deal in Iraq I must say I found it difficult to distinguish between diphtheritic and non-diphtheritic conditions, although in one case here and there you can say it is possibly diphtheria I confess I still find it almost impossible by clinical means alone to differentiate between them. Nearly always there was secondary infection. I agree with a good deal of what Major Dornhorst has said. I have seen a good many of the cases which he described. I think it is reasonable to divide our cases into groups. Those obviously toxic from the start and those non-toxic from the start, and mild cases with early diagnosis. It is perfectly clear that they behave in different ways. The mild respond very rapidly if they are kept quiet in bed. They are very soon up and around in any case and so I do not reasonably feel a great deal is achieved that way. We can divide cases into three groups. The serious, non-serious and the intermediate. The first series should be kept in bed for a long period of time. On the intermediate group I play for safety and keep them in for three or four weeks followed by a period of convalescence. Loss of man-power in diphtheria cases means a lot of valuable time wasted. In Major Bagnall's paper there may be a very valuable explanation of the development of polyneuritis later in the disease, for if diphtheria organisms remain at the end of 21 days it may well be that the polyneuritis is caused by the toxin produced at that stage. When that is so it does not seem that any prolonged rest in bed does anything to stop that. I do not feel we need take too dismal a view of these cases. The number of severe cardiac changes in cases of diphtheria are relatively small and I am reminded of a statement made by Major-General Sir Henry Tidy that if a doctor is going to take the responsibility for treating the disease he must realise that he may make occasional mistakes. The number of mistakes one can make, and we are dealing in quite large numbers, are certainly not greater than in comparative surgical conditions.

Lt.-Col. A. L. Agranat, SAMC

I would like to make three brief points. The first is in connection with what Lt.-Col. Wood said on the use of plasma. One has got to be very careful in this condition of vascular failure, not to do anything to prejudice the patient. It is rather unfortunate that in our hospital recently we had two deaths as a result of that. In a number of cases one finds that reactions occur and I think there is a certain amount of risk in the use of plasma, that is in its administration. The second question concerns persistent diphtheria. I have had 27 beds recently blocked on account of this. One wonders whether we might ask the authorities if under circumstances of that kind where cases have been in bed for three or four weeks, they might be evacuated down the line.

The last point is the question of immunising the army. This question might be considered by the authorities.

Major G. A. G. Peterkin

I want to speak about skin diphtheria. Lt.-Col. Paul Wood has mentioned the case that shook us to the core at 103 General Hospital in 1943. This man, who was the rufus type with red hair and freckles, was admitted from a convoy with practically healed desert sores of the hands. Had I known then what I know now, I should have treated him for skin diphtheria.

From the cases I have seen during the past 2 years, I believe that cutaneous diphtheria can take many different forms:—

1. It may be a secondary infection on any septic skin condition such as scabies, impetigo, and seborrhoeic dermatitis.

2. It may take the form of the typical K.L.B. ulcer, i.e., a sudden intense brawny induration, with adenitis, and followed by reduction of the swelling and the appearance of the typical ulcer slough.

3. It may commence as a bullous dermatosis, leading to circular ulcers.

4. It may appear, usually after slight trauma, as a superficial ulcer with clean cut edges and coral red bases, no slough, shaped in angular forms, e.g., diamond pattern.

5. It may look like a gaping pea-pod, with undermined edges, particularly over the knuckles and the dorsa of the feet, and lastly:

6. May come as deep penetrating ulcers, in the webs of the fingers or toes, perhaps in association with a fungus infection.

I feel strongly that serum should be given on clinical diagnosis, and that one should not rely too greatly on the results of bacteriological examination.

Lt.-Col. Lee Lander, RAMC

I would like to suggest that polyneuritis is not caused by multiple travelling.

One other thing I should like to own up to. I am one of the people who had a cardiac death, not of the type described by Major Dornhorst, but a real cardiac failure which occurred about the fifth week.

Lt.-Col. James B. McLester, MC

I would like to sound a note of warning regarding the use of morphine to control restlessness in diphtheria. I agree with Col. Hutchison that morphine can be extremely effective in controlling restlessness in diphtheritic patients, but it is essential to remember that it must be used in small doses. Something like a quarter or even a tenth of the usual doses can be used effectively without danger.

The second point is regarding management of cases of diphtheria as to when to give extra pillows to the patient to increase rest. In my own experience I find that the pulse rate is by far the most important individual guide. A few years ago I had the privilege of carrying an electrocardial examination of the heart in a diphtheritic patient and comparing the result with the other clinical investigations and my conclusion was that the electrocardiagram provided evidence which was far too sensitive. Again I found that the observation of the pulse rate over a period of a week or so was the most useful guide or criterion. Finally I should like to fire a small broadside at the experimental work of Lt.-Col. Paul Wood. I have no doubt the control method used is the best that could be devised, at the same time I very much doubt if you exercise the right leg whether you can regard the left leg as a perfect control. I am no physiologist but it would appear to me that one is dependant upon a comparison between the effects of exercise on the one side and lack of exercise on the other. In these circumstances, the changes which occur in the body are shared throughout all the tissues.

Lt.-Col. K. Shirley Smith, RAMC

Two suggestions have been made in this discussion which I think are dangerous. The first is that you can gauge from the severity of the infection the risk of cardiac disease and death. I have seen quite troublesome cardiac disorders develop in a patient who had the most trivial throat infection. The second suggestion is that you can gauge from the degree of cardiovascular damage in a particular case whether or not there is serious cardiac failure or whether or not there is a risk of death. I think that where a patient shows any abnormality whatever he should be regarded as possibly having serious cardiac disease and at risk of death. I would like to ally myself with those who advocate a period of rest whether the illness be slight or severe.

Lt.-Col. ? , RAMC. (It is regretted that the speaker's name was not recorded: Ed.)

I would like to mention one treatment we have been using in our hospital, but before I do so, I would like to congratulate Major Bagnall on the work he has been doing and also say that he has had severer cases than ours. We have had since coming to Italy some 60 cases of diphtheria and 11 of these we have considered as chronic carriers. We have used a method of treatment which was mentioned in the British Medical Journal in 1940 or 1941, that is sulphonamide in snuff which is made up and given to the patient at 4-hourly intervals by mouth for a week, equivalent to what can cover a dime or sixpence and the patient is made to snuff that up each nostril. This we carried on for 7 days and of these 11 cases we have had only one proved to be positive after that treatment. He had a positive throat and we evacuated him for tonsillectomy.

Col. Perrin Long, MC

Here are a few details about the incidence of diphtheria in children and adults over the past 20 years. To begin with the incidence of diphtheria in the American forces is about 1/10th of that in the British Forces. I think one can attribute that difference to three factors. First, that during the past 25 years one of the chief public health programmes in the United States has been the immunisation of a number of school children. Secondly, more Americans have their tonsils out than almost any other race, and if you don't have tonsils you show a comparatively lower rate of infection with diphtheria. Then the third factor is the dilution of our troops with individuals from the Southern States. As you know as you approach the equator the rate and percentage of negative persons increases and on the equator diphtheria is a disease almost unknown. According to statistics, Santos, Brazil, over a 5-year period, had only two cases of diphtheria. In San Paulo, 100 miles west on the same latitude, but higher by 3500 feet and with a temperate climate, they had 700 cases.

In respect of the treatment of diphtheria I have always been an advocate of a single large dose. I don't believe if you give a single large dose, it will be necessary to give secondary doses.

About 40 years ago Madison worked out just how long diphtheria anti-toxin stays in the blood. He has shown very definitely that if you give an intramuscular dose you maintain a high titre of anti-toxin in the blood decreasing slowly for a period of 21 days after which none is detectable. I believe in giving a large dose absolutely invariably in moderate or severe cases.

It has always been our policy in Baltimore to take tonsils out of diphtheria carriers. We have found there on an average 2/3rds of all the school children at one time had a positive culture of Diphtheria bacilli. Still we have very little diphtheria in Baltimore.

Regarding cardiac failure, I would like to point out that I always prefer to have a syringe full of adrenalin 1cc kept at the bedside for at least an hour after administration of serum. We try to keep our patients quiet. We don't keep them absolutely quiet. As soon as your back is turned they get up and wander around and you can't keep them quiet, and that is about the best you can do. I don't believe in these reports of where on one culture the organism is virulent and on the next non-virulent.

On carriers I would always take tonsils out. One doctor wanted to wait six weeks after seeing a sore throat before he took the tonsils out. Now I think you could cut that down. I would not hesitate to take tonsils out in three weeks. We give sulphonamides for a day before and three days afterwards. I think it is rather important to consider giving a prophylactic dose of anti-toxin serum. At 3 weeks the blood is relatively free from anti-toxin and I have seen numerous cases of diphtheria in the slough following tonsillectomy. Penicillin has some effect in the carrier state. There is no question about that. Major Bagnall has pointed out why we do that with varying degrees of success.

One thing I would like to stress and that is that in cold weather if you turn these carriers loose and send them up front where they are living in close quarters in houses you are going to have a large secondary attack rate of diphtheria.

Brigadier E. R. Boland

I find myself in the position of the villain of the piece. The treatment which I advocate is said to be responsible for loss of man-power. I admit that. I am accused of wasting serum. I admit that too. I am quite prepared to believe that if one treated a case of diphtheria as a case of tonsillitis with a mousy smell and just gave serum and discharged it in a few days one might get away with it in 60 per cent, in 70 per cent, or even in 90 per cent of the cases, but I am quite sure if you did such a thing you would help to kill many of the remainder. Deaths which occur in diphtheria occur in one of three stages. The first stage is during the first few days and these cases I agree are usually easy to diagnose. These are cases in which with early diagnosis and adequate treatment it is comparatively easy to prevent death. The second stage is somewhere about the third week. Probably the majority of deaths in this theatre are at sometime after this phase. The third is in the later stages where the cases of sudden death usually occur. Major Dornhorst has said that he has always hoped to meet a man who had actually seen one of these cases. I am one of these men! I am quite prepared to agree that a great number of cases of diphtheria are overtreated. One could no doubt discharge a number of patients after about a fortnight to three weeks but the difficulty is to recognise which are the cases that should be kept and which should not. I

don't agree at all with Major Scott-Thomson when he says you can easily foresee the future course of a case of diphtheria. There is a file of reports on this table which shows I am not alone in this difficulty. Many of these cases which have died have appeared to be perfectly straightforward in the early days, many comparatively mild, others were obviously ill from the start, and therefore we keep them all for treatment, which although it causes a waste of man power, does prevent death, which is the complication of diphtheria in which I am most interested.

I would like to hear from Brigadier Bedford if an early series of electrocardiograms might give one a line on the prognosis of these cases and might enable one to get the more rational line of treatment which Major Dornhorst and myself are so anxious to see. In war one has occasionally to square one's medical principles with the exigencies of the situation, but there is a limit. Whether I am right in advocating in the treatment of these cases long periods of rest and long periods of hospitalisation, I do not know but I do know that every death from diphtheria means a death in this theatre which was unnecessary and might have been avoided, and if the patient has a long period of rest it does at least ensure close observation and the detection of the earlier signs of circulatory failure before it is too late.

Regarding one pillow. It may not matter tuppence if there are 1, 2, 3, or 4 pillows. The main thing is to keep the patient quiet and it is easier to keep a patient quiet with one pillow than with several but a good sister could keep him quiet with half a dozen. If as a result of the patient being kept at rest, he develops a cardiac neurosis, the fault is probably bad treatment on the part of the sister or the medical officer who is responsible for it.

Dr. Banks, M.D., F.R.C.P., UNRRA

I have been most interested in the account of diphtheria in the Middle East and in this theatre. I find most of the points I had intended to bring up have been dealt with by my friend Perrin Long. I would like to say something about the treatment of diphtheria by anti-toxin. It must be most confusing to hear today that we should give repeated doses of anti-toxin because all the talk of the last 20 years has been in the direction of estimating what is required by thorough examination of the patient and then giving the dose required. About 1943 there was some confirmation of Mathieson's work on the absorption of anti-toxin. He gave what was regarded as quite a small dose; 10,000 units by 4 different methods, subcutaneous, intramuscular, oral and intravenous. By the intravenous route you get a large amount of anti-toxin circulating at once. He gave 13 units per cc. By intramuscular injection with 7 units per cc., it took nearly 36 hours to reach that dose. The intravenous route is far more preferable to intramuscular. I would advocate giving intravenously, as I have done for many years now, the whole dose in all cases of severe diphtheria, and not intramuscularly at all. The reason for that appears to be that a form of anti-toxin is still present in the blood in proportion of one half to two thirds, after three days. After a week of the 10,000 unit dose, between 1 and 2 units per cc. of serum could be recovered which is far above the majority of cases of natural immunity from diphtheria, so that previously that man would neutralise any small amount of toxin which might be absorbed after a number of days when the membrane is breaking up. One dose of anti-toxin is the best thing in theory and also in practice. If you make a mistake in your assessment of the first dose you must start afresh and give the large dose as if you had given none at all.

The second point I want to raise is the question of the suspicious case that is given serum and never really diagnosed. Our method for many years has been not to rush and give serum right away in the suspicious case. There is no great hurry for anti-toxin. We would do a Schick test on admission and see the case again in 3 to 6 hours. If it was still regarded as suspicious we gave anti-toxin. The Schick test having got that start will register truly and you will get a Schick test positive or negative in spite of the administration of intramuscular anti-toxin. The third point—I would like to enter the lists on the question raised by Major Dornhorst. I think he was very bold for doing it and going against expert teaching. I would support him with reservations. I think he mentioned four criteria: a previously healthy adult, treated early and with a good response to treatment, and without signs of cardio-vascular upset in the first two weeks. Given these conditions that is quite a different thing from the cutaneous case. I think there is a case for a limited period of rest and period of disability. I will not say more. It is so much bound up with experience and judgment. The next point was the old query that diphtheria is a disease of the young person. But the theory as we know it is that diphtheria in children and young adults does not leave any trouble behind.

Regarding the question of plasma transfusion. I was very interested but I would like to sound a note of warning. I do not think there is any great place for it. A case mentioned was a patient who showed first signs of cardiac deficiency on the 14th day. The nearer you get to the 16th day of the disease before the cardio-vascular symptoms come on, the more likely is the patient to recover. The 16th day I would regard as the crisis. If it comes on on the 14th day he has a good chance. But in the very severe cases which develop early, I should think it is very likely you will not get very good results from plasma.

Lt.-Col. R. C. Dickson, RCAMC

At our hospital we follow very rigidly the conservative school. We have had no difficulty with cardiac neurosis. We have had some cases and they fall into two different groups. The first group presented evidence of neurotic stress all their lives with mild symptoms of effort syndrome prior to diphtheria. The second very interesting group occurred among fairly stable individuals who happened to be present in the ward where a sudden death occurred. They were very difficult to reassure.

Brigadier Evan Bedford, Consulting Physician Middle East Forces:

It is extremely difficult to say a great deal about deaths in diphtheria. Few of us have seen many cases, and very few from the beginning. In a large number of these cases therefore we are to some extent going on the observations of others. There is no doubt whatever that in the early stages of diphtheria the striking phenomena one encounters are due to circulatory and suprarenal failure, and one

must assume that the heart is not involved. My own impression from examination of a number of diphtheritic hearts is that the damage is done early. There is both circulatory and cardiac failure. As in coronary thrombosis, one to some extent masks the other. We should regard these people for all practical purposes as suffering from severe lesions of the heart. It is of course fairly well known that diphtheria is not a cause we can recognise of chronic heart disease. These cases have been followed up by many different people in all parts of the world and we are all agreed that you cannot trace chronic heart disease to diphtheria.

I do feel in diphtheria you are well justified in giving what may be regarded as a safe measure of rest. There is no profit in seeing how early you can get the patient up. If he is in a diphtheria ward I strongly urge you not to try and experiment too much to shorten the course of illness. The difficulty of deciding when to allow a coronary thrombosis to get up is perfectly similar. I have seen a coronary thrombosis who has never been to bed at all, but that does not seem very wise even if you do "get away with it".

Another question arises. One often sees a convalescent diphtheria complaining of his heart and of short windedness and one naturally has to be very careful. There is a period after which we can almost ignore such conditions. I should place it at 3 months. After 3 months if the man is fairly well you can ignore minor cardiac symptoms. In regard to the question of pillows this is largely a matter of discipline and common-sense.

Summing-up by Opening Speakers

Lt.-Col. J. H. Hutchison, RAMC

Most points have been replied to by the last speaker. There are just one or two things. Major Dornhorst raises the question of evacuation. That is a very difficult matter for people working in forward areas. I have never evacuated a patient suffering from diphtheria at any stage of his illness except three cases of severe polyneuritis who went home.

In the last 4½ months in my hospital—a 600 bedder—we had about 170 cases of diphtheria. It was possible to hold all these 170 cases. It is not as great an administrative difficulty as is sometimes suggested.

I have some figures which might be interesting regarding Indian troops. It is well known they have some inherent immunity. In the Middle East they did Schick tests on British soldiers which gave 27 per cent positive findings. They did Schick tests on 900 Sepoys with 1.1 per cent. positives.

Lt.-Col. Paul Wood, RAMC

I should like to make it clear, sir, I also hold my patients in bed for a month or two.

Brigadier Evan Bedford, Consulting Physician, Middle East Forces

Do you think three months is a safe period beyond which cardiac complications need not be expected?

Lt.-Col. Paul Wood, RAMC

I should say so.

Major F. C. Dornhorst, RAMC

I have nothing further to add.

Friday, 2nd February, 1945

AFTERNOON SESSION

Subject:

Neuropsychiatric Problems in Italy

(The Problem of the Inadequate Personality)

and

Medical Uses of Penicillin

Presiding:

Brigadier T. C. Hunt, Consulting Physician

Persia & Iraq Force

and

Brigadier E. R. Boland, Consulting Physician

Allied Force Headquarters

THE PROBLEM OF THE INADEQUATE PERSONALITY

by

Lt.-Col. J. D. W. PEARCE, RAMC

Brigadier Boland and Gentlemen,

I propose, with your indulgence, to give a brief outline of the present psychiatric organisation in Italy. This is based on a system of three levels. The first level is at Corps. At Corps H.Q. there is a Corps Psychiatrist; his functions will be described later by Major Hunter. Each Corps in the line has a Corps Psychiatric team attached to an F.D.S., Field Ambulance or C.C.S. as far forward as possible on the main line of evacuation. The staff comprises a psychiatrist, a G.D.M.O., six M.N.Os and the ancillary clerical staff. It is equipped with 100 stretchers. All cases labelled "Exhaustion" are admitted to the C.P.T. A psychiatrist is attached to Rear H.Q., 8th Army, working with the A.A.G.

The second level is just behind Army, viz, 7 Base Psychiatric Centre, usually known as the Advanced Psychiatric Centre. This ordinarily contains some 400 patients.

Linked with the first and second levels is the Advanced Re-allocation Centre. Recovered cases remaining in A category are sent there for three weeks' intensive advanced training and field exercises prior to return to their field force units. The name is misleading as neither re-allocation nor down-grading is carried out.

The C.P.Ts. retain cases requiring only some 4 days' treatment and evacuate all others to 7 B.P.C.; 7 B.P.C. retains those requiring only 14 to 21 days' treatment and evacuates all others to the third level.

The third level comprises 6 and 8 Base Psychiatric Centres located in the Base Zone. Long term cases are treated here. Others are evacuated to the U.K. or Delta. Linked with the second and third levels there is the Re-allocation Centre (All Arms) to which men whose category requires to be lowered are transferred, put through personnel selection and psychiatric filters, and posted to suitable employment.

A psychiatrist is a member of 52 W.O.S.B., where potential officer material is screened. There is strictly limited out-patient consultative service, the shortage of psychiatrists at present preventing its further development.

In an Army at war the first duty of every officer is to the Army. The Army psychiatrist places the interest of the Army above that of his patient, as indeed do all other officers of our Corps. It is necessary never to lose sight of this orientation.

In 1888 Koch described a condition which he named constitutional psychopathic inferiority. Though this label has fallen into disuetude it is useful in that it tells us that the condition is constitutional in origin and is a psychopathy the essence of which is an inferior quality of person. Such persons are nevertheless at least of normal general intelligence. The inferior quality may apply to various facets of the personality but it is constant and constantly present. Kraepdin elaborated this concept, describing many varieties simply according to the principal overt feature. Examples of these are the aggressive, the querulous, mendacious, timid, eccentric and passive. An important fact, as reported by Healy, in America, is that these conditions are readily identifiable in later childhood and adolescence, and my own experience in civil practice has fully confirmed this.

The nomenclature applied to these conditions has undergone various vicissitudes, and, as I frankly admit it to be none too satisfactory, I would suggest that, if you agree, Sir, the subject of psychiatric nomenclature should be avoided in the discussion. Henderson calls them "Psychopathic States," which is a simple and non-controversial name.

If it is agreed that these observations are accurate —and on that there can be no shadow of doubt—it follows that these individuals are no more personally responsible for their state than the colour blind person for his colour blindness. Quite early in the war the Oxford University Press published a small book entitled "Our Towns," a social survey of the state of affairs revealed by the evacuation of London. This book, which stirred so many thinking readers out of their complacency, disclosed the inescapable fact that there is a lowest 10% of the population consisting of mental defectives and psychopaths. Similar surveys of other cities have produced comparable figures.

It is convenient to divide the psychopathic states into three main groups, viz., the predominantly creative the predominantly aggressive and the predominantly inadequate or passive. The last group is our main concern this afternoon, but if you will bear with me for a moment or two longer I shall make some comments on the other groups. All three groups have certain features in common, viz., these individuals all seem to be incapable of adequate social integration; they are unable to develop any persistent consistent social aim; and many appear to have little ability for abstract thinking.

The predominantly creative are a small group. We all know the prima donna type of individual who, if successful in finding a field wherein his genius may flower and attain fruition, makes an outstanding contribution to society, but who otherwise is a misfit in the community and a liability to society. In the Army such persons are exceptionally difficult to employ usefully. A study of the life histories of many famous people reveals with remarkable frequency trends aproximating closely to what we understand as emotional instability, psychosexual immaturity, and, at the least, frank eccentricity. It has been my lot to deal with more than one such person during my Army service.

The predominantly aggressive are persons whose way of life is characterised by seriously violent conduct, usually episodic in occurrence. Their detailed life history shows that all along they have been like this, impulsive, wayward and undependable. Many are alcoholics, but I hasten to reassure you that the temporary state of alcoholism which often characterises the intervals between the sessions of a conference such as this does not necessarily indicate a

predominantly aggressive psychopathic personality. Others are epileptics or perverts. They have little place in an Army, and they do not make good commandos. Efforts to employ them in the Army have met with but little success. Fortunately they are not a very large group.

The predominantly inadequate or passive is quite the largest group and constitutes a formidable manpower problem. These are men who are not actually ill, but have always reacted inadequately to the demands of life, and who are frightened and ineffective in action. Most of them are placid, suggestible, submissive, lacking in initiative, always taking the line of least resistance, expecting others to look after them and their troubles, or really looking to Mother to kiss the painful place well. Some are cold, detached, apathetic and entirely self-centered. All of them lack foresight, judgment and ordinary prudence; and they seem unable to profit from experience. Some are petty delinquents, and get along by lying and swindling. Many become chronic sick room attendants, lapsing into invalidism. They are to be found among those who succeed in having a sixth fractional test meal at a sixth hospital, or in displaying their feet to a series of medical officers and orthopædic surgeons. Certainly many, but by no means all, find their way eventually to the Army psychiatrist. Be that as it may, most of this group are quite honest and are merely inadequately and inferiorly endowed men. It is well to remember the old adage that one cannot make a silk purse out of a sow's ear. Each case must be viewed dispassionately, though always with the compassion which every physician has for every patient. As Henderson says, this group constitutes a challenge to preventive medicine.

Most true psychoneurotics are persons who command our respect. Their illness is the result of severe emotional stress, external as in battle, or of internal origin as in obsessional self-criticism. Some psychoneurotics are inadequate personalities with a super-added psychoneurosis. Many patients referred to the psychiatrist as psychoneurotic have no psychoneurosis but are inadequate personalities in a state of self-pitying hypochondriasis. Prognosis and disposal depend essentially on the quality of the personality.

How does the inadequate behave and what is his efficiency in the Army? If with a field force unit they are frightened and ineffective in action. They often disappear at the onset of an action to reappear afterwards. They display remarkable compassion in their eagerness to assist a wounded man to the R.A.P. or further. With commendable vigour they dig deep slit-trenches wherein they remain until the battle is over. Some of them spend years in the Infantry without firing a shot. Shellfire makes them panic. The problem of cowardice may be referred to in passing. A coward is a man who can control his fear but will not. The true anxiety state is where the man does his best to control his fear but cannot. Between these two extremes is a range of mixed cases very difficult of assessment.

If at L of C or Base their officers complain bitterly of their inadequacy and uselessness. In point of fact they are a constant nuisance to everyone, just as they have always been in civil life.

Their disposal is an administrative nuisance to the psychiatrist as they are neither really nor remedially ill. I would suggest for your consideration that the disposal of these men is primarily an A and not an M responsibility.

In conclusion may I formulate some questions, to some of which I shall suggest answers.

1. Do these men earn their Army pay? I think definitely not.
2. Are they militarily worthwhile? In my opinion, no.
3. Are there any as yet untried methods of utilising them in the Army to the Army's advantage? Remember, this problem has now been exercising the wits of the Army for some five and a half years.
4. What disposal is best for the man's personal interest? My reply is unquestionably retention in the Army under discipline and control; but the Army is not a colony for psychopaths.
5. What disposal is best for his family's interest? Obviously retention in the Army.
6. Do his associates regard his evacuation as "getting away with it"? Only rarely so. The majority of men forward feel hostile to any authority which saddles them with such associates whom they know to be unable to "take it."
7. What disposal is in the best interest of the Army? I leave that to the discussion.

THE WORK OF A CORPS PSYCHIATRIST ON THE ITALIAN FRONT

by

Major H. D. HUNTER, RAMC

Early Development

When a psychiatrist was attached to each of the three British Corps invading Italy in September, 1943, no one was quite sure what their functions would ultimately be. Not altogether unwisely, they were sent into the field to build up the job for themselves.

The writer landed with 10 Corps at Salerno towards the end of September, carrying on his back a minimum of personal kit and 1000 tablets of phenobarb gr i.

His first task was to check the trans-mediterranean flow of minor psychiatric casualties evacuated from battle, many of whom were then arriving in North Africa practically symptom free. Necessity gave birth to improvisation, and in face of many obstacles a forward psychiatric centre was opened at C.C.S. level, accommodating first 20 then 50 patients, precariously staffed by one or two borrowed nursing orderlies and a number of enthusiastic convalescents.

At this period the average stay of a patient in the centre could not be more than four days, owing to the inflow pressure caused by the bitter fighting on and north of the Volturno. None the less, the number sent out of Italy was reduced to under 10% (including psychotics). Some 30% were returned to their original units and the remainder were found other employment locally by a somewhat rough-and-ready selection procedure.

The organisation at this stage owed much to the work of Palmer, in Tripoli, though there were some differences in treatment.

Out-patients had to be seen and court-martial cases reported on; minor administrative wars had to be waged over questions of personnel, transport, tentage and equipment. But all the time, in the background, loomed the greater problems: how to check the flow of patients at the source, how to create a wider understanding of the causes and mechanisms of psychiatric breakdown, how to come to grips with the basic factors which influence a man's capacity and will to fight; in fact the whole positive side of a Corps psychiatrist's job.

Contact With Fighting Troops

As more psychiatrists arrived in Italy working conditions improved. Time was then found to visit infantry and other units in the line, and to stay with some of them for a few days. These contacts with combatant officers and men profoundly influenced the outlook of the writer on all problems of military psychiatry, and indeed continue to do so.

The Army psychiatrist must first know the Army. Only when he has established his norms can he adequately assess the deviations from them. Moreover, the present environment of the patient is the Army at war, and neither his past nor his future can be relevantly considered except in relation to this. Mentally he is indeed in a new world, with standards and values of its own.

Group Loyalties

One must understand the framework of group loyalties in which the soldier works and fights, which holds him to his task or lets him go, and outside of which he is a lesser and more self-centred man than ever he is within it. To consider the individual soldier as an isolate, entirely detached from the group, is to pave the way both for erroneous theories and for unwise decisions. Every fighting service evolves a structure of group loyalties peculiar to itself, conditioned by the nature of its task. These differences make it dangerous to apply automatically conclusions reached by the psychiatrists of any one service to either of the others.

We must beware, too, of the tendency to argue from the abnormal to the normal, from the sick man to the healthy. It is the essence of modern doctrine that physical medicine should be based on psychiatry. Psychiatry should keep its roots deeply bedded in the rich earth of the healthy human mind.

Mental Health

The charter of the duties of a Corps psychiatrist issued by the War Office in February, 1944, specified, among others, the following functions:—

(a) To advise on all matters pertaining to mental health.
(b) To advise on the psychiatric aspects of morale, discipline and training, and by lectures and informal discussions with officers (staff, regimental and medical), assist in the promotion of mental health and preventive psychiatry.
(c) To visit Medical units and Regimental Aid Posts and advise on the management of psychiatric and psychosomatic problems.
(d) To keep himself informed of changing psychiatric problems during training and fighting periods with a view to the development of the mental toughness essential in fighting troops.

When, later on, the Corps psychiatrist was relieved of direct responsibility for routine clinical work and placed on the establishment of Corps Headquarters, it became possible to develop more and more this prophylactic side.

Health may be defined as the capacity of an organism to function efficiently within its established environment. From the Army's point of view a soldier is mentally in perfect health when his mind, undisturbed by unresolved emotional conflicts or by irrelevant external stress (*e.g.*, domestic disharmony), is concentrated on the job in hand, with a positive determination to see it through, contributing all he can to the success of the enterprise. Such a man has achieved perfect adjustment to his new environment, the Army at war, and is thus able to function as a fighting soldier with complete efficiency. His limited inherent capacity to withstand stress is free to meet whatever blows the enemy can hurl against him.

Adjustment of the usual peaceable citizen to life in a fighting army is not always easily achieved. Anything tending to disturb this adjustment will correspondingly tend to disturb his mental health by creating emotional stresses which impede his efficiency. Morale, defined by Dicks as "A conviction of personal power, competence and worth, animating a group in relation to the task in hand," is the corrolary of mental health in the armed forces: it is the final expression of group integration and purpose.

Personal Adjustment and Unit Morale

The factors which on one hand promote, and on the other disrupt, the personal adjustment of the individual and the morale of the group within the army are almost innumerable, and might well form the subject of a separate paper.

The former include, in the individual, a good personality, free from much internal stress; a well-socialized outlook, not overvaluing the self and ready to endure hardship for the sake of others, a consciously held purpose in relation to the war, and a knowledge that he is valued by the group. In the war, good leadership, centering on an inspiring C.O. who becomes in time a true "Father-figure," intelligently directed training leading to clearly foreseen ends, sound motivation and a knowledge, widespread among the men, of the unit's task in relation to neighbouring formations, a feeling on the part of the men, fostered by efficient organisation and good welfare, that their officers are concerned for their well-being.

Factors which influence individual adaption adversely include home worries, separation from the group (through sickness, change of unit, etc.), wounding, unduly long service overseas, especially

where these occur in a personality torn by deep internal stresses, poorly socialized or inadequately equipped to meet the changing demands of life in any sphere. Adverse effects on unit morale accrue from battle-weariness, uncertainty fed by lack of knowledge, unfulfilled promises or false rumours, long continual idleness, poor organization and leadership.

Many more examples could be cited. It is part of the Corps psychiatrist's job to point out to higher authorities factors adversely affecting mental health and morale in the Army and to persuade them to do whatever may be possible to minimize or remove them.

Visits To Units

Visits to combatant units are made for the dual purpose of gathering and distributing information. The psychiatrist's first contact is with the R.M.O. but when the opportunity is favourable he welcomes the chance of meeting the C.O. and other officers. If the incidence of psychiatric casualties is lower than the average he will be interested to find out why this is so. If it is high he will seek possible explanations. These may lie in the exceptional conditions encountered, the loss of trusted officers and N.C.O.s, or an unduly long period of continuous action; it must never be assumed that the cause lies in the unit unless there is good evidence for this.

The R.M.O. may have problems to bring up. The question "When should a man be evacuated?" is a perennial one, with many aspects. The fate and progress of men returned to unit from Psychiatric Centre is of interest, and in the long run may have a direct influence on disposal policy. Queries may arise regarding the use of drugs. But the commonest question of all, on the lips of both medical and combatant officers, begins, "What would you do with a man like this. . . ."

Discussion on more general problems relating to the minds of men at war tends to arise spontaneously in the relative leisure of the evening hours. For this reason, one overnight visit is worth three at midday. Provided the psychiatrist brings his own rations and is willing to dig his own slit trench, a visit paid while the unit is in the line is rarely unwelcome, and may indeed be apreciated more than one when the unit is at rest.

Lectures and Conferences

Conferences are held from time to time with the officers of, *e.g.*, a resting brigade. The Corps psychiatrist may open with a lecture, which in the first instance usually deals with management of potential psychiatric battle casualties or various types. In general, there is a tendency to discard the weaker, inadequate man too early, and to delay resting the good soldier who is on the verge of breakdown until it is too late. Only with the co-operation of the Company and Platoon Commander (or their equivalents in other arms) can these tendencies be corrected.

The discussions aroused at these conferences are often very lively, and the psychiatrist usually goes away feeling that he has learned as much as he has imparted.

General Problems

Psychiatric advice may be sought or spontaneously offered on a great variety of special problems with which the Army is faced. Of these, compassionate postings, absence without leave, venereal disease, the optimum use of rest periods, rehabilitation training, and post-hostilities planning are examples. There are indeed few problems which have not some psychological aspect.

Though the Corps psychiatrist is responsible to D.D.M.S. Corps, his work involves constant liaison with the Adjutant-General's Branch and its Education, Welfare and Legal Sub-Branches.

Conclusions

The Corps psychiatrist, in addition to supervising the management of psychiatric casualties, has many other functions, designed to reduce the incidence of breakdown and to maintain the morale and efficiency of the troops. His usefulness varies directly with his own capacity to adapt, his willingness to learn, his ability to get on with combatant officers and men and to offer technical advice under the guise of "plain, ordinary common-sense" and the extent to which he can identify himself with the basic aims of an Army at war.

While making full use of his professional training he must keep both feet firmly planted in the real situation, which is the Army as he finds it. He must indeed feel himself to be genuinely part of that Army and not an outsider, looking on.

In matters military the soldier is always right, because, in the highest grades at least, his professional knowledge and skill are second to none. It is the job of the Army psychiatrist to interpret for him attitudes and trends of thought which may affect the morale and fighting efficiency of his men.

Acknowledgements

Grateful acknowledgements are proffered to Lt.-Col. S. A. Mackeith, RAMC, Adviser in Psychiatry, AFHQ, for continual help and encouragement, to Brig. E. M. Townsend, RAMC, DDMS, 10 Corps and his predecessor Col. (Late Brig.) W. R. Croker, RAMC, the C.O.s and officers of 92 (Br) GH and 14 CCS for invaluable help in the difficult early days, and finally not least to Lt.-Gen. Sir Richard L. McCreery, K.C.B., etc., late GOC 10th Corps, for his constructive understanding of the problems discussed in this paper.

GASTRO-INTESTINAL DISORDERS OF PSYCHOGENIC ORIGIN

by

Major JAMES A. HALSTED, MC

Between October, 1944, and January, 1945, an attempt was made to diagnose, evaluate fitness and effect disposition within the Army area, of soldiers with gastro-intestinal disorders, particularly those with chronic complaints. This was undertaken at an Army Clearing Station which was designated a gastro-intestinal centre for Fifth Army troops. Our object has been to sort out those patients with functional disorders and to discharge them from medical channels as early as possible, either to duty or to limited service. Experience at General Hospitals has shown that over three-fourths of patients with chronic gastric complaints have no organic disease, the majority suffering from psychoneurosis. It is a well-known fact that the longer patients with neurosis remain in hospitals the less effective they become for further duty, and the more fixed the neurosis becomes, particularly if the patient is treated from an organic view-point. This report will be concerned with the problem of chronic epigastric distress largely from the view-point of psychoneurosis, as this is the main core of the problem.

Gastro-intestinal disorders form the single largest group in psychosomatic disability among soldiers. By psychosomatic disability is meant an illness in which physical symptoms are the prominent feature in the clinical picture, in which the patient complains primarily of physical rather than mental discomfort, but wherein the cause is emotional disturbance and not organic disease. Among American troops in this war psychogenic gastro-intestinal disorders probably constitute about a third to a half of all psychosomatic disability. In the last war cardio-respiratory manifestations of neurosis were more common than gastro-intestinal and more common than they are in this war. The reasons for this are not clear.

Because psychosomatic illness is a neurotic illness it should be treated as such. Inasmuch as it simulates organic disease the general medical officer will be the first to see these patients, rather than the psychiatrist. Although the treatment and management is a psychiatric problem the first essential is the making of a correct diagnosis and this requires the teamwork of both internist and psychiatrist. However in the majority of cases the general medical officer with experienced clinical judgment will be able to make reasonably accurate diagnosis if he possesses an understanding of the psychodynamics involved. If we are to salvage a significant number for combat duty diagnosis and disposition should be made in the Army area with as little hospitalization as possible.

Psychodynamics

In psychosomatic illness physiological changes are set up in an organ by autonomic nerve impulses generated as a result of emotional conflict. Wolf and Wolff (1) have repeatedly demonstrated these changes in the stomach of a man with a gastric fistula whom they studied with great care over a long period of time. During various states of emotional tension marked changes occurred in gastric motility, secretion and vascularity. Reddening and engorgement of the mucous membrane were noted, often producing the appearance of gastritis as seen by gastroscopy.

A psychogenic gastric disorder is not a true conversion hysteria as it is sometimes considered, but a disorder accompanying anxiety. It is the peripheral manifestation of neurosis, as the anxiety is the mental manifestation. Unlike true conversion hysteria it does not solve anxiety although the patient's fixation on the physical aspect may minimize it. Anxiety is aways present though it may not be immediately apparent to the physician, nor to the patient, because of the prominence of the physical symptoms. If it is possible to remove the physical symptoms by psychotherapy, free anxiety becomes more severe.

It should be kept in mind that psychogenic symptomatology represents a flight into illness and the longer the patient is studied and treated as an individual who may have a physical illness, the less willing he will be to tolerate his symptoms, to remain on duty in spite of them. This is particularly true of patients evacuated to base hospitals. Why is this so? First, he has been removed from the rigours of front line existence and allowed to relax into the comforts of "civilized" life, facing no responsibility. Quite naturally he does not wish to return to the former existence. Second, he has been removed from his unit to which he has had ties of loyalty. To the average American soldier this is one of the strongest motivations for fighting. The longer he is away from his unit the more likely he is to lose this motivation. Third, the sense of guilt over failure usually possessed by the soldier with a pure anxiety state does not exist to the same degree in a patient whose anxiety is overshadowed by physical symptoms, especially if it is treated as a physical illness. He feels justified in leaving his job because he believes himself to be physically ill. The symptoms provide an automatic solution to the two basic conflicts of self-preservation and self-respect. Thus patients say, with monotonous uniformity: "I want to go back and do my part, but my stomach won't let me". If the medical officer focuses on the stomach and treats the symptoms, without recognizing or dealing with the neurosis which causes them, the patient cannot be blamed for really believing that his stomach will not let him go back—because neurotic stomach symptoms in soldiers rarely disappear as a result of medicinal treatment or rest.

If the flight into illness is arrested through early diagnosis and disposition from medical channels, not only is the neurosis checked but there results a saving in manpower and unnecessary hospitalization. In the case of soldiers with gastric complaints a correct diagnosis may be made after a few days' clinical observation in most cases.

Diagnosis

Let us consider the diagnostic problem which confronts us in a patient complaining of chronic epigastric distress. The cause may be first, organic

stomach disease—which in soldiers is practically limited to peptic ulcer; second, a reflex mechanism from disease in other organs than the stomach, such as hepatitis, cholecystitis, appendiceal disease, amœbiasis, intestinal parasites, or pathology in the urinary tract; third, systemic disease such as tuberculosis, nephritis, etc.; fourth, psychoneurosis. Inasmuch as the problem in the vast majority of cases consists in differentiating between peptic ulcer and psychoneurosis this will be the chief concern of this report, the assumption being made that the other causes mentioned have been excluded by appropriate examination.

In differentiating between psychogenic and organic gastro-intestinal disease, a painstaking and accurate history is all important. It is of far greater value than laboratory examinations, and, in my opinion, than of X-ray studies, although these are necessary in a certain number of cases. Too often the history is limited to the presenting episode when a complete past history would make the diagnosis clear. It should be inclusive and accurate as regards symptoms, particularly a past history of poor digestion with the circumstances surrounding its onset and exacerbations. It should include what has been called a psychosomatic history. In this one obtains a brief survey of the patient's life, his family relationships, his education, martial relationships, work record, etc. This is necessary in evaluating the patient's personality. Of great significance is the military history. Length of service, length of time overseas, amount of combat and the relationship of symptoms to each of these episodes may provide important clues. Evaluation of the degree of anxiety displayed in combat and whether this is more than the normal battle reaction is important to establish.

Symptoms beginning before Army service and without real remissions are more likely to be functional than organic. On the other hand symptoms of brief duration should make one more alert for organic disease. Symptoms of vague and varied nature, not characteristic of any organic disease are usually psychogenic. However, to make a diagnosis of psychogenic gastric disorder there must be positive evidence of neurosis. The psychiatrist's opinion is necessary unless the internist is competent to judge that it is present, as is often true in obvious cases. It is not a diagnosis of exclusion.

The response to treatment is an important guide in diagnosis. Patients with psychogenic symptoms rarely respond symptomatically to medicinal or dietary treatment, or to rest. Patients with organic disease, on the other hand, usually do. The symptoms of peptic ulcer nearly aways abate in a few days if the patient is given frequent feedings and alkalis.

On the basis of statistics one can be sure that a chronic gastro-intestinal complaint in a soldier is considerably more likely than not to be functional. At the 6th General Hospital, in Rome, 140 patients were studied during the summer and autumn. In only 20% could organic disease be demonstrated. There were 10 patients with peptic ulcer. At another General Hospital during the same period 191 patients were studied. Of these, 24% had organic disease, among them 19 patients with peptic ulcer. At the Fifth Army Gastro-intestinal Centre there were 167 patients with chronic or obscure complaints. Seventeen per cent. had organic disease of which there were 12 patients whose clinical and X-ray findings were sufficiently suggestive of peptic ulcer to warrant evacuation to the Base for more complete study. Thus the incidence of peptic ulcer in each of these three groups of patients was about the same, namely 8%-10%.

Clinical Aspects

1. *Psychoneurosis (Psychogenic disorders of the stomach)*

The majority of patients with a psychogenic disorder have had symptoms for several years. Seventy-two per cent. of a group of 100 consecutive patients studied in Casablanca had symptoms prior to entry to the Army. However, in a forward area there are greater numbers with symptoms of briefer duration, although even in acute anxiety states with predominant gastric manifestations which occur in combat past history reveals stomach trouble in the majority. Characteristically there is little or no remission. Often the symptoms have never been severe until entry to the Army, and at each episode involving entry into a less stable or more dangerous environment there has been an exacerbation. Frequently patients are hospitalized at these times, but little improvement is admitted and the patient often says, "They didn't tell me what was wrong", or "They said it was a nervous stomach but I am sure it is those C rations".

The symptoms are varied. Usually the patient complains of epigastric distress, a burning feeling, or heartburn while eating or immediately afterward. It rarely comes on after an interval. He usually has a good appetite, wants to eat but feels full after a few mouthfuls. Soda sometimes relieves the distress, food rarely does. Vomiting is very common, but on close questioning it usually consists of regurgitation of a few mouthfuls. Altered bowel habits are uncommon.

Very commonly the patient has other symptoms, such as insomnia, pains in the chest, headache, etc. Invariably these patients feel tired, particularly in the morning, as in most psychoneuroses.

Free anxiety may be severe, mild or absent. If the patients are seen in a forward area during a combat period, the majority are quite aware of being very nervous, have battle dreams, are apprehensive and tense. This state is rarely as severe as seen in patients evacuated to the Army Psychiatric Centre for an acute anxiety state incurred in battle.

A large group of patients with little or no free anxiety have only the gastric symptoms which have been described. The neurosis is "fixed" on the stomach. The patients frequently have had lifelong food idiosyncrasies. Although they are convinced that diet is of paramount importance in the etiology of symptoms, that their difficulties are only due to C rations, they rarely feel any better when given a bland diet in the hospital. What they unconsciously or consciously want is relief from unpleasant duty and usually if a decision has been made to send them home or reclassify them they complain very much less. However, relief from duty does not result in cure. The mechanism is much deeper and more complicated than mere reaction to an unpleasant situation.

Because there is little apparent anxiety in this group of patients they are often considered to have organic disease such as chronic gastritis or peptic

ulcer. It is the group most commonly evacuated to the Base for further study. However, careful evaluation of symptoms, psychiatric examination, and if necessary, a therapeutic trial on a soft diet, with alkalis, for a few days is sufficient to establish the diagnosis with reasonable assurance of its being correct in all but a few doubtful cases.

Psychodynamically this group is essentially the same as those who have an obvious anxiety neurosis with gastric manifestations of brief duration. The pathways between the emotional conflict and the stomach dysfunction are much more devious and often exceedingly complicated. The patient may have an obsessional fixation on the stomach. Because of the different clinical features, with special diagnostic problems involved, it is advisable to use a different name for this group. We have called them psychogenic dyspepsia.

The personality pattern of patients with psychogenic dyspepsia is quite uniform. They are outwardly submissive, and unaggressive. They show abnormal concern over the stomach and magnify symptoms, with obvious desire to impress the medical officer with the gravity of their distress. A characteristic feature is the resistance of the patient to acceptance of the explanation that symptoms are of psychogenic etiology. Often they say, "Yes, I know I am nervous but my stomach makes me that way". Understanding the psychodynamics makes it easy to see why patients wish to be considered organically ill and why it is strongly to their interest to believe it themselves.

2. *Peptic Ulcer*

The clinical features of peptic ulcer should be well understood in order to differentiate it from psychogenic dyspepsia. The symptoms may not be typical of ulcer, namely dull, gnawing epigastric pain occurring two hours after a meal and relieved by food, but almost invariably there are certain distinctive features. Perhaps the most important is that if symptoms have existed for several years there are remissions of a few months during which the patient can eat what he likes without discomfort. Peptic ulcer is a chronic, recurrent disease. The patient is often awakened at night by pain which rarely occurs in psychogenic dyspepsia. Vomiting is not a common symptom of ulcer as we have seen it in soldiers. The patient does not have a full feeling after a few mouthfuls of food like the dyspeptic patient, but has a good appetite and eats a full meal.

The patient's personality is almost the opposite of the patient with a functional gastric disorder. He is aggressive and independent, a good soldier, often a leader, restless and ambitious. He often asks to be returned to duty and means it. He has not visited sick call readily at the first sign of distress as the patient with psychogenic dyspepsia is apt to do. He tells a "straight" story, and it is easy to obtain a clear-cut history from him. He rarely has other symptoms and does not magnify his distress to the medical officer.

It is believed that peptic ulcer and psychogenic dyspepsia can be differentiated on the basis of history in over 80% of the cases. This belief is based on experience in studying over 200 patients with peptic ulcer and over 300 patients with psychogenic disorders at a General Hospital where they were X-rayed and studied thoroughly from all angles. The correlation between clinical and X-ray diagnosis was close, very few patients with neurosis showing an ulcer deformity.

It is the policy at the Army gastro-intestinal centre to X-ray only those patients in whom there is some doubt as to the diagnosis, such as patients in whom incidence of neurosis is not clear cut, or whose symptoms have some characteristics of peptic ulcer. It is not ideal, from the civilian medical viewpoint but it is justifiable because the value of early disposition from medical channels of the 90% of patients who do not have ulcer outweighs the occasional error one may make, particularly as such an error is not a serious one from the patient's viewpoint.

3. *Chronic Gastritis*

In patients with chronic epigastritic distress the diagnosis of chronic gastritis is often made. This is a disease which can be diagnosed accurately only by gastroscopy. The incidence of gastritis, the etiology and pathogenesis are poorly understood. A certain number of patients diagnosed as psychogenic dyspepsia may have gastritis. In connection with this, however, it should be kept in mind that Wolf and Wolff demonstrated transitory changes indistinguishable from gastritis in the gastric mucosa of their subject with a gastric fistula under states of emotional tension. Furthermore, the interpretation of mild gastroscopic changes is difficult. Changes in the gastric mucosa characteristic of chronic gastritis have been found in a small percentage of normal individuals without gastric symptoms. (2)

It is believed that if a patient with positive evidence of psychoneurosis has chronic non-ulcer dyspepsia it is important not to call it gastritis in the absence of undoubted gastroscopic evidence because it will more readily fix the symptoms and make it more difficult to salvage the soldier. We know that a neurosis may cause epigastric distress but we do not have exact knowledge about gastritis.

Treatment of Psychogenic Gastro-intestinal Disturbances

In civilian practice treatment of functional gastro-intestinal disorders by sedatives and diet often results in temporary symptomatic relief. In the Army, particularly in the combat zone, such measures rarely provide any relief because it is so much to the patient's interest unconsciously to remain ill. In both civilian and Army medicine psychotherapy is the only means whereby a cure might be effected. Among soldiers the results are extremly disappointing as might be expected because these neuroses are deep-seated and complex in most cases. Furthermore, the patient is better off with stomach symptoms than with the anxiety which would ensue were they removed. However, in a negative sense, perhaps, it is therapy to limit the neurotic's possibilities for escape. Certainly it has been shown that the longer he is cared for in a hospital the worse he becomes. Through firm and prompt management, with discharge from the hospital as soon as the diagnosis is made, and provided the patient is not physically depleted as is occasionally the case, he often does make a temporary improvement, useful combat service resulting in many cases returned to duty.

Disposition

The decision as to whether a patient with a psychogenic stomach disorder is to be returned to

duty, reclassified for limited service or sent to the United States, is almost entirely a psychiatric problem based on the severity of the neurosis.

When the 6th General Hospital was in Casablanca patients arrived from the combat zone after several weeks of hospitalization. Sixty-two per cent. were sent to the United States and almost none to combat duty. When it had moved to Rome and received patients a few days after they were evacuated from the front 55% were returned to full duty, the remainder being placed on limited service. The time spent in hospitals, replacement centres and in transit was about five weeks for those returned to duty. At the Fifth Army Gastro-intestinal Centre 76% were returned to duty, 17% reclassified for limited service in the Army area and 7% sent to Base Hospitals. These patients were received the same day they left their units. The average duration of hospitalization from the day they were evacuated to the date of discharge was 7 days.

An attempt is being made to determine the effectiveness of soldiers with psychogenic gastric disorders returned to duty. Reports from company commanders of 50 patients, received 5 to 8 weeks after discharge from the hospital, stated that 34 of them or 68% were regarded as average or superior soldiers. The remainder were ineffective or had been rehospitalized. A follow-up study of a larger group by means of personal interviews with the soldiers' squad leaders is in progress. By these means it is to be hoped that more efficient criteria for disposition may be established.

When it is decided that a patient is to be returned to duty an attempt is made to give him insight into the nature of his symptoms but this is rarely effective. About all that can be done is to tell him that he does not have organic disease, that he must live with his symptoms, that others are doing it and he also can. It is important that the patient be made to feel the medical officer knows he has real distress and is not "goldbricking," that he be treated as a man with a mild illness which, though handicapping, is not disabling. It is important to be firm and never should one tell the patient to "go back and try it," as the patient will then assume that his own serious doubts as to his ability to carry on are shared by the physician, and is likely to report to sick call immediately on return in an attempt to be re-evacuated.

Conclusion

It is believed that disposition from medical channels of soldiers with psychosomatic disorders as early as possible is of marked military benefit in saving manpower for greater effectiveness by checking neurotic tendencies, and in reducing hospitalization time. This has been done in the Army area, with success, in the case of gastro-intestinal disorders.

Extension of facilities for evaluation and disposition of all types of psychosomatic disorders within the Army area is in progress, the personnel consisting of two internists, a psychiatrist, an orthopædic surgeon, and a rœntgenologist, with adequate medical personnel as ward officers.

References

(1) Wolf, S. and Wolff, H. G.; Human Gastric Function, Oxford University Press, 1943.
(2) Fitzgibbon, J. H. and Long, G. B.; A Gastroscopic Study of Healthy Individuals: Preliminary Report, Gastroenterology, 1:67, 1943.

DISCUSSION—The Problem of the Inadequate Personality

Lt.-Col. F. R. Hanson, MC

I don't feel that I could add much to the subject of the discussion. I would like to make a few comments on Major Halsted's paper. One is the problem of handling these cases. It is a problem for the internist and the psychiatrist, but I do not feel that they should claim that the problem is all theirs. Another point is, I should like to ask Major Halsted as to what his criteria are in asking the psychiatrist to see a patient. How does he decide which patient wants seeing and which doesn't?

Lt.-Col. A. M. Doyle, RCAMC

Regarding the difficult type of individual mentioned by Col. Pearce as a psychopathic, we have one or two methods of dealing with this which have proved successful. We have employment companies previously called pioneer companies. We have three such companies, two forward and one at the base. These forward companies have been able to build bridges under shell fire. They have also been found very useful as attachments in medical installations. I have found in my travels recently some of my former patients employed as medical orderlies. Our real criterion should be, is the man of any use as a fighting soldier. That is the only thing of any value and the sooner we settle that the better. It has been a very great pleasure to listen to these papers this week and to observe the psychological attitudes throughout the discussion. I was particularly interested in the various attitudes expressed at yesterday morning's discussion and I would like to say I found that there was a wide divergence on what a physician could do to an individual. I found it was their opinion that a chance remark mentioning amœbiasis or some other such condition could greatly influence the patient's personality and create a neurotic individual. That has not been my experience, and if it is true, it should be easy to reverse the process. If an individual develops neurosis you may rest assured he was neurotic in the years before he came in the Army. It is true that many patients are leaving hospital without any clear idea as to just what is the matter with them, and I think we have been lax in the responsibility of making sure that they quite understand what is the matter with them. The more one talks to a man the more one realizes you have a neurotic personality on your hands.

Capt. Weinstein, MC

I want to emphasise the fact that the man who is hospitalized without having any obvious physical disability feels a strong sense of guilt about this, especially if he is surrounded by other patients with various bodily lesions. It is important to bear this in mind, as an essential part of the treatment is to expose and deal with this crippling sense of guilt.

Lt.-Col. G. S. Hall, RAMC

Regarding Col. Pearce's paper. I think he described a coward as a man who can control his fear but won't. I rather feel it should be CANNOT rather than WILL NOT. The other point is in connection with inadequate personality. How far does he feel that the absence of religious background plays a part in this. I have a feeling it is quite important.

Lt.-Col. W. A. Loewenthal, SAMC

Col. Pearce's paper was extremely illuminating and I would like to ask him one or two questions

which arise perhaps because it was too illuminating. I agree with Col. Pearce—one of our chief problems is the border line cases, those whose personalities can be adequate with the right leadership.

Arising out of the question of a psychiatrist attached to a hospital, I am lucky enough to have a psychiatrist attached to my division. He is very useful and saves us a lot of headaches. He does a lot of work and deals with a lot of inadequate personalities. I cannot help feeling if the psychiatrist were not there a large proportion would not arrive at the hospital. The times when you have the psychiatrist are the times when you have the psychiatric patients. When he returns from leave the cases roll up. I am not trying to be funny even if I am succeeding, but when the back door is open there is going to be a rush. I have a feeling it is the border-line case who makes for the back door. I have no arguments to bring forward re the inadequate personality. We don't want him, and the unit doesn't want him. In connection with the borderline case I want to know what percentage they constitute who would remain on duty if the back door were kept closed.

Commander Lane, RN

Surely the medical services at home are very much to blame for allowing such men as have been described by Col. Pearce to come into the Army and to be sent overseas. The Navy has special labour camps for its persistently anti-social personnel, and these have been very successful.

Major H. A. C. Mason, RAMC

There is some danger in grasping at the conception of the "psychopath" too easily, as the deeper the investigation the more acquired traits tend to be discovered, and to my mind the problem of the inadequate personality is most difficult in the borderland where the passive psychopath and the mild neurotic merge into the normal—by civil standards. Nevertheless, broadly speaking it is reasonable that just as intelligence can be demonstrated to be distributed on a curve comprising a large mass of averages, and tailing off at each end to the sub- and super-normals, so the capacity for aggression is similarly distributed, and in war it is the sub-normal aggressives who largely figure as our inadequate personalities—they are with us in their thousands. Out of my last 100 battle casualties at Anzio 25% were in this category; of my last 100 base cases in Rome 37%—showing the selective distribution. Out of 49 deserters seen at a Divisional Cage during the attack on the Gothic Line, 28 (57%) were in this group—not real neurotics but driftwood. It is only natural that under stress this type snaps first. It is a question how far punishment pays dividends. Again, the introduction of shooting for the criminal as opposed to the neurotic way of escape to some extent equalises the danger before and behind a man and may put your problem further off but it does not remove it. Battle exhaustion, or war neurosis, though true neurotic cases are seen, is much more a pre-neurotic stage of mental escape by any means, not yet stylised and elaborated. Hence the importance of catching the patient at the early stage.

My feeling is that there must be two definite levels in treatment, the forward level where the necessity of giving battle is never considered past—the man is there for a rest and a talk, and the good man will rebound. Here is the level where pressure may judiciously be applied. At your rear level, in the main it is better to cut your losses. Pressure may drive a man to keep his symptoms through feelings of guilt, shame or aggression. The physician's duty is to reconcile, not to sneer, and in my experience scrimshankers are rare.

Summing-up by Opening Speakers

Lt.-Col. J. D. W. Pearce, RAMC

I have rather a formidable list of questions to answer. The question of Canadian special employment companies was raised. I understand that this is under consideration in this theatre for British troops at the present time, but one must remember that in the Canadian Corps one is dealing entirely with volunteers. Our Army is essentially a conscripted army. In Canada at the pre-selection boards the rate of rejection is very much higher than ours. Re the question, are these men any use as fighting soldiers, we do not think many of them are. If my information is correct, the Canadian Army is essentially a field force and does not carry L. of C. or base troops.

In reply to Col. Hall's question about the coward, what I said was that the coward has got the ability to control his fear but is not willing to do so. At the other extreme there is the man who wants to control his fear, is doing his best, but just cannot control it. In between there is a whole range of cases, and the judgment of a Solomon is necessary in the in-betweens. Regarding the absence of a religious background, I don't want to involve myself in a prolonged discussion, and I will speak to Col. Hall later. Absence of religious background is so common-place—certainly not less than 50% of the Army—that I don't think it matters much in these inadequates. In reply to Col. Loewenthal, who says that where there is no psychiatrist available no cases are referred and who asks where they go, I would reply to this by asking him what happens to routine surgical cases where there is no surgeon. I can tell him where he will find the psychiatrist cases: let him visit any depot. Major Hunter mentioned in his paper that the inadequate tends to be evacuated too soon. I quite agree that good leadership can carry borderline inadequates for a considerable time. To the suggestion that when the back door is open there is a rush, Major Hunter has already given the reply in his paper when he said what his first task was at Salerno.

Our Naval colleague raises the question of selection of personnel, and of course there has been during the past two and a half years an excellent personnel selection set-up in the British Army which has done much to lessen these problems in the later call-ups. The Army has its labour companies, but these have been far from an unqualified success. As Major Hunter has said, the same standards are not applicable to the different fighting services.

The *sine qua non* is that these inadequates be recognised and identified as they form a very large group about whose proper place and function in society, military or civil, there is need for much careful thought.

Major H. D. Hunter, RAMC

I have nothing further to add.

Major J. Halsted, MC

Closing remarks were unfortunately not audible: Ed.

MEDICAL USES OF PENICILLIN

by

Lt.-Col. J. K. SLATER, RAMC

Introduction

It seems best in opening this discussion to recall briefly a few important facts about the arrival of Penicillin, in order, so to say, to clear the air and set the matter in its true perspective. The history of this preparation is so freshly in the minds of everybody, that it is unnecessary to weary you with detail, but it is essential to separate facts from theories, early hopes from tried experience, and above all to try and visualise what role this new therapeutic weapon is destined to play in the future, as well as to determine how we with our present excellent opportunities can contribute towards placing it on an accurate basis. In this respect a comparison between the Sulpha group and Penicillin is helpful. Both rank as chemotherapeutic agents, as arsenic and quinine have done for so long, each is bacteriostatic and not bacteriocidal, accident, followed by much patient research has been conspicuous in their evolution and development as a therapeutic measure. These then are similarities, but it is not difficult to find contrasts and of these the fact which concerns us most as practising clinicians is that the advent of the Sulphonamides occurred in peace time whereas Penicillin came into use in the midst of a great war. Let us look for a moment at what this has meant. Sulphonamides came in with a rush and in next to no time the market was flooded with a wide profusion of proprietary names. By 1939 the one chemical formula had fifty or more synonyms in Britain and abroad, conversely the word Prontosil stood for four different formulæ. Worse still the lay Press had created in the public at large a constant questioning and even criticisms of physicians in regard to using, more often not using, these new drugs. Extravagant claims were made for one preparation after another. This rushed and sketchily controlled competition was not without its tragedies. The profession were only rescued from this intolerable situation by the war, when we learnt at last to call each drug in the series by its chemical name and apportion to each its sphere of usefulness along more strictly bacteriological lines, instead of as a panacea for all ailments, much as in days gone past had been regarded sour milk and ultra-violet light in the flush of their passing success. This, then, very briefly was the situation when the new drug Penicillin was first rumoured. But what a very different story can be told about its development. It has been under the strictest control from the first, even now has no alternative name and has, and is, experiencing the unsurpassed advantage of collective and selected observations on chosen groups of clinical material the greatest proportion of which falls within a limited age group. As physicians we might be pardoned for feeling a little envious of the early monopoly allowed to the surgeons, justified as it was in the circumstances, but I for one sensed advantages in this, having been trained by one of the old school whose therapeutic teaching is summed up in the couplet by Clough: "Be not the first by whom the new is tried, nor yet the last to turn the old aside"! Moreover, a trick of chance had given me an early experience in a purely medical case. An isolated study no doubt, but since it was a failure, it prevented my enthusiasm from getting out of hand and instead renewed in me a wholesome respect for dice that were loaded. It occurred in the summer of 1942 when I happened to be working at the Cambridge Hospital, Aldershot. A young man aged 25, the only child of a high ranking Briton and not himself in the Army, was seen by me. He was known to have a Mitral Stenosis, but fairly compensated and able to be at work until some days before my visit when he had become breathless and fevered, with praecordial pain and palpitation. He looked seriously ill and a provisional diagnosis of Bacterial Endocarditis was made. From a blood culture Streptococcus Viridens was grown. Much pressure was put on me "to do something." So with considerable diffidence I telephoned Professor Florey and described the case. He informed me that he had barely enough Penicillin in the whole country to treat five cases, and most of this was already in use. Most gallantly, however, he asked me to submit the culture which would be tested for Penicillin sensitivity. This was done with results which were promising if not altogether satisfactory. After the lapse of some 10 days, the patient, whose condition had slowly deteriorated, was started on treatment. This was given by both I.M. and I.V. routes at different times until the enormous quantity of over 3 million "Oxford" Units had been exhibited. There were moments when hope was considerably stirred, but eventually death stole the prize. Early lessons are remembered longest. This one emphasised clearly several outstanding facts; (1) The importance of a bacteriological diagnosis, over-riding any clinical pigeon hole; (2) The supreme care with which data and facts were being observed and collected; (3) That the method was not infallible; (4) That even large doses if unsuccessful were at least not harmful in themselves. Following this, almost a year passed, during which one heard in common with most, the increasing promise of wonderful things to come, when at last the initial technical problems of production and control had been mastered. Then in May, 1943, when in Sousse, North Africa, Professor Florey came and stayed in our mess, complete with staff and supplies alleged to be worth some fabulous sum. He remained for over a month in all and during this time one observed some very interesting things, not the least of which was to appreciate the extreme need for a scrupulously careful technique in handling and administration, if the best results were to be obtained, due to the twin factor of instability and the great liability to deterioration in the presence of so wide a variety of common matters ranging from fresh air, through numerous acids and alkalis to every usual form of antiseptic. In fact unless every handler from the fungus onward to the muscle or vein of the patient played his part with unassailable conscientiousness the treatment was doomed to fail before it had

started. The cases thus treated were a series of septic skulls, uncomplicated flesh wounds and a few joints. The results are well known, but I make no apology for referring to the matter, since the principles then laid down exist as seriously to-day when we are in the happy position, thanks in large part to the generosity of the United States Government through their Army Medical Advisers, of being able to utilise the benefits so carefully evaluated, in the treatment of what are purely medical conditions. These, after all, are the maladies which in the future will hold the spotlight. The onus will fall increasingly on Physicians to ensure that no vestige of quackery creeps in: that the highly scientific standard of control is maintained which can only be accomplished on our part by an altruism which deplores the rushing into print with ill-considered and misleading papers describing inadequate numbers of cases, or worst of all, only one case.

Selection of Cases for Treatment

In the past 3 years this can be divided into several phases. At first it was solely in the hands of those privileged to conduct research and experiment. Later it became available in limited quantity for selected types of wounded. Later still as amounts increased it is being employed by an ever-increasing circle of Army Physicians. Finally and quite recently the needy public in Britain are being served through the aegis of teaching hospitals. Throughout this widening scope the basic principles have been passed on from one group to another. At this stage with the fundamentals so well understood our contribution can only be concerned with detail. From the clinical angle it is now accepted as proven that Penicillin has certain definite characteristics, which may be summed up briefly under different headings: (1) It acts on the great majority of pus producing organisms, i.e., Staphylococci, Streptococci, Pneumococci, Gonococci, Meningococci, the organisms of Gas Gangrene, Diphtheria, Tetanus, Anthrax and Actinomyces. More recently it is known that the Spirochaetum Pallidum is also sensitive, but it has little or no effect on organisms which are more prone to invade the gastro-intestinal tract, such as coliform, typhoid and dysentery organisms, nor does it have any effect on the tubercle baccilus or any virus infection; (2) It is bacteriostatic and not bacteriocidal. Watch must, therefore, be kept on the behaviour of the white cells; (3) It is not toxic, therefore extremely large doses may be given for an indefinite period without any fear of ill effects; (4) It is destroyed by acid and alkali, in fact by anything other than a neutral Ph., therefore it cannot be given by mouth or by rectum. Many other chemical substances such as alcohol and heavy metals will destroy it, so that it is futile to prescribe it in conjunction with any antiseptic. Soap and water are as good a way as any of cleansing a part preparatory to application. Lastly, heat and certain bacteria found in the air destroy it. Preparations, therefore, must be treated aseptically, stored in a refrigerator and only uncovered momentarily when in use; (5) It is rapidly excreted by the kidneys. This means that frequent administration must be carried out in order to ensure the continuous presence of the drug; (6) Its action is not inhibited by normal tissue fluids or pus, but of course these may prevent its access to the affected part. No clinician is entitled to prescribe Penicillin who is not prepared to abide by the rules which these characteristics impose. They are clear and irrefutable. Research is undoubtedly proceeding, chiefly under the guidance of the M.R.C. Nothing is more futile than to attempt treatment of disseminated Sclerosis, acute Nephritis or any of the many virus infections, all of which it should be well known by now are quite uninfluenced. We must beware and recognise clearly the limitations of our brief, which even pruned of all the traps and side issues is important enough, since it must concern itself with detail. The cases to-day should be self-selected for treatment, but, and this is the point, there is a good deal of variation in both the methods of administration and the dosage employed. We are well advised to focus attention on this aspect of things. If the same amount of Penicillin is twice as effective by one route as by another the mere convenience of the less effective route seems hardly a sufficient reason for employing it. This was brought to my notice quite early in two cases of anærobic liver abscess which happened to be in Hospital at the same time, each was started on 15000 Units I.M. 3 hourly, and received in this way 360000 Units, but with no apparent improvement, a further similar quantity was given by I.V. drip, after which both cases were remarkably better, one indeed was cured, the other relapsed after about a week and was drained surgically, B. Welchii being demonstrated, but one wondered if this man had been given a drip from the start how he might have fared. A recent case of staphylococcal septicæmia illustrates the question of dosage. This patient was admitted acutely ill with a history of recent furunculosis; while investigations were proceeding he had a profuse hæmaturia and the diagnosis was in doubt until a positive culture was obtained, after which he received by I.V. drip 240000 units in 24 hours, but succumbed without rallying in the least. Post-mortem revealed a small peri-nephric abscess which had invaded the left kidney. Should a much larger dose have been given? If so, how much and should treatment have been started before investigation, the diagnosis based on the known history of furunculosis? To the first question I think the answer is yes, and the amount in so desperate a case probably a Mega unit. To the second question my answer is no, since there were alternative diagnoses including at least one surgical one and Penicillin is not a Panacea. Sometimes our disappointments are culpable, as witness a case of only last month. This man also had a history of boils and was admitted with pain below the left costal margin. Everything including X-ray and the blood picture pointed to a commencing sub-phrenic abscess. Penicillin was decided on and instructions given for 120000 units I.M. in each 24 hours at first for 3 days and later this was extended to 5 days. Control was made through the blood picture and at the end of the time he was decidedly better, free from pain and with no abdominal resistance. In 8 days he had completely relapsed and the surgeon removed 5 ozs of pus by rib resection, from this, Staphylococcus Aureus was grown on culture in spite of the fact that a direct film showed very degenerated cocci. Checking detail I discovered quite by accident that an unfamiliar staff had thought that sleep was the great restorer and an extra dollop could be given in the morning. There is no doubt that had I prescribed 3 hourly injections night and day to a total of 120000 units in 24 hours that patient would have been saved an operation. To-day medical cases for whom Peni-

cillin is a necessity require it urgently and continuously. Intermittent therapy is unsatisfactory in the absence of a simple method for use at the bedside of estimating blood concentration. Elaborate micro-titrations are of little use to the clinician, the method must be so foolproof that only a few drops of blood are required. Obviously the effect on the lesion will vary greatly between a concentration of 0.12 units per ccm and one of 0.5 units per ccm, and yet in a recent paper by Fleming and Others (Lancet 11 Nov, '44) those figures represent the best levels found after a single I.M. injection but the essential point was that the high level was found in about 6 minutes and only maintained for about 10 minutes, after which there was a fairly rapid falling off until at the end of 3 hours little or no Penicillin could be detected. The comparative readings for a single I.V. injection were appreciably worse. Therefore we must accept the fact that the practice of periodic injection was at best a compromise between the patient's needs and the shortage of supply, as indeed were many of the numerous claims of success with minimum dosage. It is also an established fact that a blood culture may become negative and yet leave a local focus of infection as a reservoir. Thus nothing short of a continuous concentration at the optimum not minimum level will suffice. How is this to be achieved? Two methods only are available—the continuous I.V. drip and the continuous I.M. drip. The former is unwise in cases with a full blood volume, unless as is often possible in Septicæmia a previous venesection is undertaken to remove 15-30 ounces. The continuous I.M. drip is the one of choice, and there is a large field here for perfecting apparatus for the purpose. McAdam, Duguid and Challinor describe a "Eudrip" in the Lancet, 9th September, 1944, which has the advantage of greatly reducing the volume of solutions, thus preventing the water-logging of the leg. This apparatus with modifications will soon be available but in the meantime improvisation is reasonably simple. One small point about giving either I.M. injection or a continuous drip is the need for an orderly procedure, using the Right Thigh, Left Buttock, Left Thigh and Right Buttock in rotation. Muscular people much prefer the thigh to the buttock for obvious reasons. Considerable attention has been drawn to the pain of intra-muscular injections, but in my experience this is an exaggeration, and can in most instances be got over by varying the site as suggested, however I have had a few cases in whom the pain has been severe and in these a few drops of Percaine solution and an injection given very slowly without after rubbing were all that was necessary.

It is a well-known fact that Penicillin given either I.V. or I.M. does not penetrate well into serous cavities such as the pleura and the theca, but luckily when these regions are alone infected it is a simple matter to instill the solution directly. This requires to be done not less often than once in 24 hours and may have to continue for many days or even weeks as in empyema. Such treatment must in no instance be regarded as superceding established surgical practice, but solely as an adjunct to it.

In cerebro-spinal meningitis the results with sulphathiazole have been so satisfactory that Penicillin should seldom be required; in fact in two cases of this disease I have reversed the usual sequence and after giving intrathecal Penicillin for 3 days have then changed over to the older drug with definitely more dramatic results. There are some who advocate the combination of the local instillation with the usual intramuscular course. To my mind this is quite unnecessary unless there is reason to suppose a generalised infection.

A chance occurs from time to time to make a suitably controlled comparison between one line of treatment and another. One such example came my way a few months ago. On the same day within a few hours of each other there arrived two severe cases of Erysipelas of the face, both almost equally extensive and neither having had any previous treatment. One patient announced that a year previously he had been found to be sulphonamide sensitive and warned to mention this fact. This patient was given over five days a total of 480000 units of Penicillin, at first by 3 hourly and later by 6 hourly I.M. injections. The other man was given over a corresponding period a total of 35 G. Sulphapyridine. Improvement ran a neck and neck course to complete recovery: the one was slightly sore the other slightly sick, otherwise they were very satisfied with their treatment. The only thing the experiment lacked was a third case who might have been given no treatment at all.

No attempt has been made in this paper to be other than discursive. It seemed better to make such an approach in the time available. The discussion to follow will fill in the many gaps.

Lastly we must not lose sight of the fact that in a few years or less the wiles and caprices of Penicillin will be commonplace. We will then be probing something else. It is that which makes clinical medicine so beautifully expectant and so delightfully tolerable.

"And meet the time as it seeks us".

Summary

1. A comparison is made between the advent of the sulphonamide drugs in peace time and the strict war time evaluation of Penicillin.

2. The principle characteristics as appertaining to clinical medicine are discussed.

3. The rules for selecting cases for treatment are described.

4. The merits of different methods of exhibition are debated.

5. Emphasis is laid on the necessity for ensuring a continuous and uniform concentration throughout a course of treatment.

MEDICAL USES OF PENICILLIN

by

Lt.-Col. R. W. D. TURNER, RAMC

These remarks refer to a study of case sheets submitted by hospitals in 3 District together with our own experience in 92 Br. General Hospital, and is therefore limited.

The principle indication for using Penicillin in Medical Divisions has been on skin patients, and this subject is being dealt with by OC No. 2 Dermatological Wing, Major Peterkin. As regards such cases occurring in the general wards, I would only state that boils clear up very well, but the resistence of the patients seems to be unaffected in that they tend to relapse just as quickly.

It seems to me that the difficulties of assessment of Penicillin are considerable. In the first instance, there have been too few examples of each condition. Next, the follow-up, and this applies particularly to skin cases, is not always adequate. Many patients who are seriously ill have been put on Penicillin and also one of the Sulphonamide group of drugs simultaneously, so that the part played by each is impossible to assess.

In some cases Penicillin was started too late, and in others when they were likely to be on the turn for the better anyway. Perhaps the most important point is that there has been a tendency when response has been satisfactory to stop Penicillin too soon, so that a relapse has set in.

In most medical conditions such as septicæmia, pneumonia and meningitis, in which Penicillin is indicated, it would probably be wisest to give an initial course of one million units always.

Penicillin has proved of no value in the treatment of Undulant fever.

There is no convincing evidence that it is of any value in virus conditions of the C.N.S. It was used on a number of cases of poliomyelitis in Sicily by Lt.-Col. Ackerman, both intrathecally and intramuscularly, and our experience has been similar. In a few cases Penicillin was given early, but diagnosis was subsequently changed, intrathecal Penicillin was quickly followed by severe headache, increase in neck rigidity and meningeal signs, and a repeat Lumbar puncture showed an abnormal C.S.F., although the fluid removed before the introduction of Penicillin was quite normal. This irritating effect of Penicillin when given intrathecally was temporary and would not be any contra-indication were there any evidence that Penicillin really did any good in these virus infections.

In Typhoid fever it has not been of value except possibly to treat a complicating pneumonia, but in the only instance of this of which I am aware the chest cleared up, but the patient died of toxæmia.

Amœbic Hepatitis normally responds well to Emetine, but if this fails owing to an abscess being present, for example, the Penicillin will fail too, unless adequate drainage is established. However, it may help to prevent secondary infection, and reports on its local and general use as regards this will be welcome.

Penicillin is certainly of value in preventing secondary infection in the treatment of hæmothorax or tuberculous empyema.

In delayed resolution of pneumonia, usually after some form of chemotherapy, Penicillin does not seem to have accelerated resolution.

It appeared to abort the development of a perinephric abscess in one case. However, it should be remembered that this sometimes resolves by itself, especially with the help of chemotherapy.

In two cases of dermatitis following treatment with arsenic Penicillin was a great help in controlling secondary infection, and presumably also did the syphilus good. However, in the third case the dermatitis was unaffected.

Penicillin has proved strikingly valuable in G.C. arthritis, lymphogranuloma, and, of course, septicæmia and meningitis.

There is some evidence that local application to the nose and nasal sinuses helps to prevent secondary infection following a cold. A fair number of our staff have tried this.

It is possible that Penicillin may be of value in Diphtheria in the early days, but, of course, it can have no effect on the toxæmia. No information is available on this point as far as I am aware. We are at present using it as a local application for Vincent's Angina.

The only other case of special note is one reported by Lt.-Col. Ackerman, of acute lynphatic leukæmia, in which the white count was reduced from just under 900,000 to just under 9,000 coincidentally with parenteral administration of Penicillin, and at the same time the granular cells increased by 48% relatively, indicating that the reduction in the white count was not in the nature of an agranulocytosis. The patient died, but the aplastic termination was not due to overcrowding but to the failure of the hæmopoetic system. It was noteworthy that sepsis was practically absent.

It will be interesting to know whether it is of value in rheumatic fever and rheumatoid arthritis.

PENICILLIN IN DERMATOLOGY

by

Major G. A. G. PETERKIN, RAMC

So far little has been published concerning the treatment of skin diseases by Penicillin, and I cannot remember any papers on the subject except two —one by Roxburgh in the *B.M.J.* and the other by Johnson in the Archives of Dermatology. I have been unable to find any publication of the results of parental Penicillin in cutaneous conditions. Thanks to the kindness of those in charge of the supplies of Penicillin in this Command, I have been able to treat several hundred cases with local Penicillin and about 130 intramuscularly.

This talk will be a summary of my own (and no doubt prejudiced) views, plus what information I have garnered from friends using the drug at home and from American colleagues here and in the States. I must also thank Lt.-Col. Turner, my Officer i/c Division and Penicillin Controller for 3 District, for giving me access to the results of Penicillin treatment in other hospitals; the latter, however, I have not employed in this paper.

I have divided the subject into three main groups:—

1. Penicillin as a Local Application.
2. Intramuscular Penicillin.
3. Reactions to and Complications of Penicillin Therapy.

1. Penicillin as a Local Application.

First, it must be remembered that the optimum results will be achieved if certain well-known facts are borne in mind. (*a*) Metals tend to inhibit the action of the drug, *i.e.* the Sod. Penicillin should not be mixed with such drugs as, say, mercury or zinc oxide; should not be kept in metal containers; should be applied with a wooden spatula rather than a metal applicator. (*b*) Contamination with the hands, etc., should be avoided as much as possible. (*c*) The drug should be used as an aqueous solution or as a water-miscible cream. (*d*) It tends to deteriorate in heat, and therefore should be kept in as cool a place as possible. Thanks to the D.D.P., Col. Montgomery, who sent me the information, I know now that Garrod has conducted some experiments in vitro which tend to show that the cream loses its potency very gradually in a cool place, and that even at the end of 100 days there is still some activity. (*e*) Finally, it will naturally only produce healing in infections due to a Pencillin-sensitive strain.

In Dermatology, Penicillin should obviously not be applied as the powder, as this contains Sulphathiazole. It can be used as a wet dressing, a spray or a cream.

The wet dressings are useful in certain cases such as ulcers, but tend to be more wasteful than the cream. The spray I have little experience of but it appears to be useful in cases of superficial infection, and is convenient to use. The cream is the preparation most generally used for the skin. At first it was thought that the Penicillin must be made up in 30% Lanette Wax in water as it was considered it might deteriorate in other bases, but I have used the ordinary Lanette Wax Cream containing Paraff: Moll: or Adeps Benz: for months and have found it just as, if not more, effective. Garrod has shown that a cream made up in Lannette Wax soft paraffin and water keeps its potency almost as well as the simple cream, which has little penetration and tends to form a solid wax mould over the lesions.

I do not know how many cases have been treated during the year 1944 in this Command with local Penicillin, and out of the cases I have treated I have selected a consecutive series of 200 outpatients and admissions treated with 250 units per gram or c.c. for the purpose of analysis, though an adequate follow through has not been possible in all cases.

Dermatitis	Healed	Improved	Improved but relapsed	I S G	No follow up	Worse	Total
Infectious Eczemat	1	4	3	1	—	1	10
Seborrhœic	21	11	4	4	11	4	55
Sulphonamide Light	4	2	3	3	—	2	14
Contact (various)	4	3	1	2	—	1	11
Impetigo	11	1	—	—	4	—	16
Ecthyma	7	2	1	2	1	—	13
Staphylococcal Folliculitis	3	1	—	—	—	—	4
Furunculosis	5	1	—	2	1	—	25
Sycosis	7	8	9	—	1	—	25
Acne Vulgaris	1	5	—	1	—	—	7
Chronic Ulcer	2	4	—	3	—	—	9
Tinea (Sec Infect)	10	6	3	3	—	1	23
Pompholyx (Septic)	—	1	—	—	—	—	1
Acne Necrotica	—	1	—	—	—	—	1
						Total	200

Thus of 200 cases treated, 81 (40.5%) were healed; 47 (23.5%) were improved; 24 (12%) improved but relapsed; 21 (10.5%) uninfluenced; and 9 (4.5%) were made worse; in 18 the progress could not be followed for various reasons. Myself, I regard these results for some reason as presenting too roseate a picture and feel that a more prolonged follow-up would reveal relapses in many of the cases such as Sycosis and Furunculosis before many months have passed. As much, if not more depends on the soil rather than the weed, and many of these skins seemed to be an ideal culture medium for the omnipresent hordes of septic bacteria.

Certain results appear evident, however — (1) The cream is effective at least temporarily in conditions caused by a Penicillin-sensitive organism. (2) It gives good results in most cases of Impetiginised Seborrhœc Dermatitis; Staphylococcal Folliculitis; and Ecthyma. (3) The results in Impetigo are as good as but no better than those obtained by other means. (4) Temporary improvement is obtained in Sycosis Barbæ and Pustular Acne, and gives X-ray therapy a better chance to produce a permanent cure. (5) 4.5% developed a Contact Dermatitis to either Sod: Penicillin or the cream.

2. Intramuscular Penicillin.

Here again it is essential to consider certain points before ordering the injection of the drug:— (1) It should be employed in disease caused chiefly

by organisms sensitive to the drug. (2) Other organisms such as Bacillus Pyocyaneus will tend to flourish profusely on the devitalised skin. (3) No immunity against future infection is conferred by a course of Penicillin (this is well shown in coloured troops in whom primary Syphilis is not uncommon after the original infection has been cured by the usual dosage). (4) It cannot be expected to cleanse the skin even of Penicillin-sensitive bacteria, as the blood supply is meagre to some cutaneous structures in neurological cases. Therefore local treatment is absolutely essential in conjunction with the injections.

In dermatological cases a thorough follow-up is perhaps more essential than in medical or surgical cases, as in these the effect can often be assessed in a short time. In military spheres however with a changing population progress notes are usually difficult to obtain, and one feels a gentle melancholy at the thought of the hundreds of Forms ME 39 — Follow up Case Card — which have passed away "ere half their span in this dark world and wide," perhaps still reposing coyly in a 3118 or consigned via the basket, paper, waste, to the uttermost darkness.

Therefore, please expect no complete follow-up over 1, 2 and 3 month periods, but rather think that the results quoted are designed to give a broad general impression rather than a statement of cold, hard accurate facts.

TABLE OF CASES TREATED PARENTERALLY BY PENICILLIN

Dermatitis	Healed	Improved	Healed but Relapsed	I.S.Q.	Worse	No Follow up	Total
Arsenical	3	1	—	—	1	—	5
Seborrhœic	3	8	3	4	1	—	19
Sulphonamide Light	5	6	—	—	—	—	11
Contact (Sulph)	1	1	—	—	—	—	2
Infectious Eczematoid	5	5	2	7	—	—	19
Ecthyma	4	2	1	—	—	—	7
Staphylococcal Folliculitis	1	1	—	—	—	—	2
Furunculosis	35	3	6	1	—	—	45
Sycosis	1	—	2	—	—	—	3
Tinea (Septic)	—	1	—	—	—	—	1
Erythema Multiforme	1	—	1	—	—	—	2
Psoriasis	—	—	1	2	—	—	3
Tropical Lichenoid Eruption	—	—	—	2	—	—	2
Diphtheroid Ulcer	1	—	—	—	—	—	1

49.1% were healed and may still be well; 23% improved; 13.1% healed but relapsed; 13.1% remained uninfluenced; and 1.64% became worse while under the treatment.

Furunculosis

It will be gathered from this table that out of 122 cases, 45 were Furunculosis. These were all patients who had their boils for some time ranging from 3 to 18 months, and it will be seen that of the 45, only 35 have kept well so far, and may yet relapse. The immediate results were gratifying, and the boils disappeared with a rapidity exceeding the response to any other treatment. At first, it was my practice to give 500,000 units, but it was found that this was often not nearly enough in a chronic case, and often 1,000,000 were required. It was suggested by one of my assistants, Captain J. Rogers, that these cases might do well with a vaccine used just at the close of the course of injections, as theoretically this should be an ideal time for a vaccine. This plan has now been adopted, and a stock vaccine is now given intradermally twice a week to these men. So far the results seem to be promising, but it is too early to be dogmatic. It should also be remembered that the skin should be disinfected as thoroughly as possible without traumatising it by such things as Pot: Permang: baths, and local applications such as Penicillin Cream 70% Spirit or Ichthyol Soaks such as Sod: Sulph are strongly contraindicated.

Dermatitis.

It is well to remember that the name dermatitis by itself merely means "inflammation of the skin," and is practically meaningless unless qualified by some adjective such as "Contact" or "Infective." Thus the five types of Dermatitis mentioned are all different, and must be dealt with separately.

1. *Arsenical Dermatitis.* — 5 cases treated. The first two cases were given Penicillin because they were dangerously ill with a crusted weeping exfoliative Dermatitis, and had signs of early Bronchopneumonia. The result of the drug in the first two cases was really dramatic—in 5 days the skin was dry and scaly, the temperature had fallen to normal, their chests were clear, and they felt very much better. They made a quick recovery. In the next case of severe exfoliative due to arsenic, the result was not nearly so impressive, as the skin, after the course, was still oozing though improved, though the temperature had settled and the patient's general condition was much better.

The last 2 were cases of chronic Arsenical Dermatitis who were given the drug chiefly for their Syphilis, i.e., 2,400,000 units. In one the Dermatitis, of a follicular nature, cleared well; in the other, a Keratotic Psoriasi-form type, affecting the palms and elbows the plaques spread steadily during the treatment, and eventually after reaching twice their size gradually peeled off.

2. *Seborrhœic Dermatitis.* — Parenteral Penicillin was used only in the severe and chronic cases with crusted weeping red heads, and usually lesions on the ears, axillæ, groins, etc. They also received local treatment at the same time. The results of the drug were disappointing, as only 3 healed of 19 cases treated, and 4 were either I.S.Q. or worse. There appears to be no indication for Penicillin in these patients.

3. *Sulphonamide Light Dermatitis.* — It may seem extraordinary that a condition which is in part a combination of a Contact Dermatitis and a Drug Rash should be treated in this series. But a predominant part is played in the etiology by a Penicillin-sensitive strain of Staphs: which appear to love this photosensitived skin. 11 cases were treated, 5 were cured, and 6 improved. The results were dramatic, and it seemed that if the men were given 500,000 units as soon as the crusting of the exposed areas appeared that they were able to tolerate light extremely well when healed, I feel that this condition is a strong indication for the drug.

4. *Sulphonamide Contact Dermatitis.* — 2 cases only were treated, both because they were so grossly infected. One was cured, but the other only improved as the skin had become eczematised.

5. *Infectious Eczematoid Dermatitis.* — Of the 19 cases treated, 5 were cured, and 5 much improved. Here again, the result depended entirely on how far the condition had progressed. If the disease had altered from an infectious process to an eczematous one, i.e., if the skin cells had become sensitised to the bacterial infection, no improvement could be expected.

MISCELLANEOUS.

1. *Ecthyma and Staphylococcal Folliculitis.* — Either healed or improved greatly with the injections, but local therapy was essential as well.

2. *Sycosis Barbæ.* — One patient was apparently cured, but his further progress has not been followed and I think a relapse is likely, as all the others recurred after healing well.

3. *Tinea (septic).* — This patient had a gross secondary infection which was rapidly cured. The ringworm infection was unaffected.

4. *Erythema Multiforme.* — Two cases were treated; both cleared satisfactorily, but one soon relapsed and the other could not be followed up.

5. *Psoriasis.* — Three cases were treated experimentally, partly to see if the psychological effect played a part in healing of other conditions. Two showed absolutely no difference; the third, whose Psoriasis erupted after a tonsillitis, improved for a short time and then relapsed.

6. *Diphtheroid Ulcers.* — No K.L.B. ulcers were treated, but three ulcers of the Diphtheroid type, the most chronic and recalcitrant known, were given 1,000,000 units, with benificial results.

3. REACTIONS TO AND COMPLICATIONS OF PENICILLIN THERAPY

A. Local—Contact Dermatitis.

1. Due to the Lanette Wax, or the oily base.

2. Due to the Penicillin itself: a. erythematous type.
b. weeping type.

3. Due to Penicillin powder—usually due to the Sulphathiazole, but may be a polysensitivity.

B. *General.* — As a rule, there was little reaction to the injections. Occasionally there was some pain at the site and a slight urticaria-like reaction. This reaction was seen only with some brands; the Commercial Solvents product never gave any unpleasant reactions.

In a few cases, a generalised mild urticaria was produced, and twice I have seen true anaphylaxis—somewhat like an atopic dermatitis, but with swelling of the face.

C. *B. Pyocyanous infection.* — A few patients whether treated by the cream or by injections developed a bullous dermatitis, which was due to infection with B. Pyocyaneus. This looked in some cases like a Pemphigus Foliaceus, but it responded rapidly to treatment with 1% Gentian Violet.

Follow-up of 50 I.M. Cases (mostly Furunculosis):

Cured	15 =	30%
Improved	6 =	12%
Healed but relapsed	8 =	16%
I.S.Q.	3 =	6%
Worse	0 =	0%
No answer	18 =	36%
	50 =	100%

Summary

1. Two series of cases are described—the first, 200 consecutive cases treated with the local application of Penicillin Cream or solution (250 units per grm. or cc.); the second, 122 patients treated parenterally with a dosage ranging from 500,000 to 2,400,000 units.

2. With local treatment, encouraging results were obtained in Impetiginised Seborrhœic Dermatitis, Staphylococcal Folliculitis, and Ecthyma, while Impetigo usually cleared rapidly. The effect in Sycosis Barbæ was disappointing—rapid improvement followed by relapse; in Pustular Acne, the staphylococcal infection was held in check, enabling other treatments to cure it.

3. Parenterally, the drug is strongly indicated in severe Arsenical Dermatitis in a dosage of 2,400,000 units; in severe Sulphonamide Light Dermatitis, early infectious eczematoid Dermatitis, and bad cases of Ecthyma (500,000—1,000,000 units).

4. Furunculosis cleared rapidly, but tended to recur unless a stock vaccine was used when the course was stopped.

5. The results of the injections were disappointing in Sycosis Barbæ, chronic Infectious Eczematoid Dermatitis, and chronic Seborrhœic Dermatitis.

6. The cream will retain its potency over a long period if kept in a cool place and can be made up with Paraff. Moll. or Adeps. Benz. Contact Dermatitis is liable to occur in a certain number of cases (4.5%)—either due to the Penicillin itself or to the base.

7. It is important to remember that local treatment is essential in all cases treated intramuscularly.

DISCUSSION—Medical Uses of Penicillin

Surg. Lt.-Comdr. R. P. K. Coe, RNVR

I was interested to hear the previous speaker's remarks on the ineffectiveness of penicillin in the treatment of Undulant Fever. In Malta this disease is now seen only rarely amongst British service personnel since the practice of selling goat's milk at the barrack gates has been suppressed. The disease is, however, fairly common amongst the civil population and amongst Maltese naval ratings and army ranks.

Having tried penicillin in a few cases without effect I tried to obtain literature on any experimental work of Penicillin on the Brucella group of organisms and I was lucky enough to meet with some success.

Walter Kocholaty in work carried out at the Schools of Medicine and Veterinary Science, University of Pennsylvania, has found that Penicillin grown under slightly different conditions from those usually employed with small amounts of Manganese in the Czapek-Dox medium will produce a substance which is bacteriostatic to the Brucella group of organisms to a marked degree.

This substance he has called Penatin and it is possible that it is the same substance as Notatin and Penicillin B of other writers.

If laboratory tests are confirmed by clinical trials this substance offers a real hope in the treatment of Undulant Fever.

So far I have been unable to find out whether Penatin is being produced on a commercial scale or

is available through private sources and I should welcome any help from anybody present on this subject.

CONCLUDING SPEECHES

Brigadier E. R. Boland

I am sure that this Assembly would wish me to express my gratitude to Professor Giuseppe Caronia, Rector of the University of Rome and to Professor Domenico Marotta and Professor Massimo Pantaleoni, of the Instituto Superiore di Sanita, for having put this excellent hall at our disposal. A very great number of people in Rome and elsewhere have contributed to the success of this meeting and many have worked as hard to get you here as Major W. McLeod is doing to get you away again.

Colonel T. D. Inch, of Rome Area Allied Command, has done a great deal in Rome to oil the wheels of this conference.

In your name I should like to thank the Commanding Officers of the hospitals which have extended hospitality to delegates from all over the country and also Lt.-Col. J. H. L. Easton and his colleagues, Sgt. Bain and Pte. Rimner, who have sat through the whole of the conference taking assiduous notes. They are taking these notes because it is hoped that it may be possible to get these proceedings published. This possibility depends on whether we can get official sanction for the publication of what will be rather a large volume and whether we get commentaries in promptly. It will only be published if we can get the volume out quickly. I am still waiting for the proceedings of the Cairo conferences of 1941 and 1942 so that there are ominous precedents.

Lastly I would like to express the thanks of this conference to Lt.-Col. G. Kauntze and his helper, Staff-Sergeant Benson, who have done an immense amount of work in organising the arrangements in Rome for this conference and the entertainments in connection with it. They have worked very hard for a great number of weeks. Finally you would like to thank my own helper, Sergeant Wade who has done all the work of organisation at Headquarters.

Brigadier R. A. Hepple, Deputy Director of Medical Services, A.F.H.Q.

As you know the Director of Medical Services was expected here this afternoon and I have come up in his place for the end of the conference and to explain why he has not been able to come. He has been in the Middle East and to Greece and was hoping to reach Rome from there yesterday but unfortunately the weather has prevented flying and he has not yet been able to return.

He has taken the greatest possible interest in the conference and I know that he is very sorry to have been unable to attend. For myself I know from the little sample I have had this afternoon and from the reports that have filtered through to us at Headquarters that this show has been a magnificent success. I shall be able to tell him what a great time you have all had.

Brigadier E. R. Boland

General Stayer opened this conference, and he has been a most indefatigable attender. I now call on General Stayer to close the conference.

Closing of conference by Major-General M. C. Stayer, Surgeon, MTOUSA.

Brigadier Boland, Gentlemen,

I want to take this opportunity on behalf of my colleagues of the medical profession in the United States Army to thank you for the privilege of attending this very fine meeting. I am sure all of us have been stimulated to do greater things. These papers and discussions are the finest I have ever heard at any military or civil meeting. Everybody seemed to want to attend and the seats have always been filled. Although we are military people, we are just the same kind of people. We all have problems, and many of them are not solved. I am sure we will go home to our stations greatly stimulated to solve some of these problems always present with the medical profession.

I wish you a safe journey to your stations.

PSS A 4274 IM Books 3-45

SUPPLEMENT TO

Proceedings of the Conference

OF

Army Physicians

Central Mediterranean Forces

Held at the

INSTITUTE SUPERIORE DI SANITA

VIALE REGINA MARGUERITA, ROME

29th January to 3rd February, 1945

SUPPLEMENT TO

CONFERENCE
OF ARMY PHYSICIANS

Central Mediterranean Forces

ROME 1945

Foreword

The contribution of Colonel Marion H. Barker to the session of the Conference of Army Physicians of the Central Mediterranean Force arrived too late for publication with the proceedings and in order to make the record complete it is now circulated separately.

E. R. Boland,
Brigadier,
Consulting Physician,
AFHQ.

REMARKS ON HEPATITIS IN THE AMERICAN FORCES IN MTOUSA

by

Colonel MARION H. BARKER, United States Army Medical Corps

It is a pleasure indeed to hear and take part in this symposium on infectious hepatitis. I have had the good fortune to visit certain British, New Zealand, and Indian installations in this theater, where the excellent results of therapy and reconditioning of cases of infectious hepatitis have been obtained, as reported here this afternoon.

We have profited from the veteran experiences of the British and New Zealand forces early in Africa. The U.S. Armed Forces in North Africa first encountered this disease late in July, 1943. Two probably important events preceded the outbreak. First, the capture of large numbers of German and Italian prisoners in Tunisia, whose sick and wounded included a substantial per cent of jaundiced cases. Second, there was a prolonged diarrhœa of six to eight weeks' duration among the units which then came down with a high attack rate of jaundice. In these instances, flies and water were suspected.

The importance of this disease was further forced upon our attention when, during the Italian invasion and during the advance from Paestum toward Naples, many became ill with hepatitis and had to be hospitalized. Among those who had had the disease weeks earlier, it recurred during this period of advance and they, likewise, had to be relieved of duty. The problems raised by the larger numbers of troops involved and the increased load on available medical facilities resulted in the organization of the study for the recognition of hepatitis with or without jaundice, together with the search for the best possible forms of treatment that might return the largest numbers to duty in the shortest period of time. Because of the prolonged nature of many cases, and because others were at times unable to remain in active campaign after return to duty, additional studies were initiated to try to establish adequate measures of recovery and physical fitness which would insure return to combat status.

It was not long before it became evident that most cases were falling into certain general groups which were roughly classified into (1) hepatitis acute with jaundice, (2) hepatitis acute without jaundice, (3) hepatitis chronic (prolonged) with or without jaundice. This rough classification has been a helpful basis for the discussion and disposition of patients in the various hospital echelons.

Source of Patients.—The chief source of patients has been from the combat infantry. Mechanized, headquarters, and artillery units have a much smaller incidence, while base section and hospital personnel have had a very low incidence of infectious hepatitis. Such experience attracted our attention to the various conditions of the men in active combat, and attempts were made to contrast these with features that seemed to lead to security from the disease among those living under more favorable conditions.

The onset of the disease has been varied. Approximately 40 per cent have had the chills, fever and aching which might be confused with the onset of an upper respiratory infection — pneumonia, malaria or sandfly fever. An equal per cent have begun primarily with reference to gastro-intestinal tract. The remainder have presented symptoms of hives, head colds with herpes, arthralgia, severe headaches, neurocirculatory æsthenia, or other psychosomatic manifestations. A few soldiers became jaundiced without any previous symptoms being mentioned. By and large, the greater group present combinations of any or all of the above which present one of the most interesting and difficult problems of diagnosis for the battalion surgeon.

Aside from jaundice, the physical examination of infectious hepatitis is not striking, but a few points of abnormality are very important, particularly in those cases where jaundice has not yet or never does appear. Most common early finding is that of a painless enlargement of the lymph nodes, particularly those of the right side of the posterior triangle low in the neck, also of the axillary and right epitrochlear nodes. The sentinel node of the deep posterior cervical chain often heralds the appearance of jaundice by 7 to 14 days and is best found by rotating the head sharply to the left, then passing the finger gently along the posterior border of the sterno-cleido-mastoid muscle where the soft, almond sized body may be easily moved about. Presumably this may be related to the glands in the mesentery, and from the dome of the liver. With, or soon after the appearance of jaundice, these nodes rapidly reduce in size and become small and shotty. The most common physical finding is that of an enlarged and tender liver. The liver may descend from 1 to 4 inches during which time the patient may feel a sharp, intermittent sticking pain in the right upper quadrant.

Since the liver margin is hard to palpate, its true size may be found only by dipping the finger tips or by direct percussion in the right upper quadrant or epigastrium. Such enlargement usually precedes jaundice by 3 to 14 days. Early in the pre-icteric and early icteric stage of the disease, the spleen is enlarged in approximately 20 per cent of the cases. Since the clinical picture and the course of infectious hepatitis has been so clearly presented in Lt-Col R. C. Dickson's paper, I shall briefly cover some of the laboratory observations which have been carried on in our American Army Hospitals in this theater.

The most helpful tests early in the disease have been those of finding of bilirubin and urobilinogen in the urine. The cephalin-cholesterol precipitation test has become strongly positive 3 to 10 days prior to the appearance of icterus and it has remained strongly positive until about the time that the blood bilirubin may begin to decrease. This observation has been most helpful to us in certain of the cases that have not become jaundice.

Simultaneously with the positive cephalin-cholesterol test, serum phosphatase has increased from the normal of 1.5-4.0 units to 5-14 units but some cases will show regularly positive cephalin flocculation or phosphatase tests which are very helpful in the non-icteric or in prolonged cases where a doubtful recovery obtains. The same is true of the sharp

increase of the serum globulin. The normal serum globulin level of 1.5 to 2 grams per 100 cc. blood may increase to as much as 5 grams per 100 cc., thus raising the total serum protein to 9 or 10 grams per cent. This sharp increase in serum globulin without reduction of the serum albumin fraction is in sharp contrast to jaundice of chronic liver disease.

Later, in the convalescent period, the blood bilirubin, serum phosphatase, serum globulin and cephalin-cholesterol flocculation tests are usually normal. However, the persistence of one or more of these abormal findings usually has indicated that complete recovery has not been obtained and that an additional period of hospitalization may be desirable.

Perhaps the most informative of all the liver function tests that we have used is that of bromsulfalein excretion. Five milligrams per kilogram of this dye has been given intravenously and samples have been drawn 45 minutes later. Our experience indicates that the normal soldier will excrete all, or at least 97 per cent of the dye within the first 45 minutes. Certainly all of the dye should be excreted at the end of the hour. Bromsulfalein retention of 10 or more per cent may be encountered 10 days to 2 weeks prior to appearance of icterus and in the non-icteric cases it persists far into convalescence, so that it may serve as an important diagnostic aid in the pre-icteric stage and in the non-icteric cases as a means of differential diagnosis. So rarely has any soldier having 8 or more per cent retention of dye 2 weeks after acute hepatitis, been able to remain in combat duty, that the bromsulfalein excretion test has served as a valuable aid in determination of disposition to duty.

Additional liver function tests consisting of hippuric acid excretion, blood amylase, glucose and galactose tolerance have not given sufficient information to justify their general usage. Prothrombin time has been only slightly altered early in the disease, but it has real value in fulminating liver necrosis where its downward trend indicates the gravity of the situation suggesting frequent fresh whole blood transfusions and large doses of vitamin K.

The treatment of hepatitis has undergone revision during the past two years, in that the commonly prescribed high carbohydrate, low fat diet has been supplanted by one that is high in protein and low in rancid fat. Because of the nature of the usual hospital ration, the conventional high carbohydrate—low fat diet results in a caloric intake of 2000 or less calories per day. This was due, in part, to the customary exclusion of fat, which took with it practically all of the available protein because of the types of meat ordinarily available. Special nutritional studies indicated that combat soldiers were in great need of additional protein for liver repair and rehabilitation. As a result, the Surgeon, Quartermaster and Consultant in Medicine, MTOUSA, were able to make available powdered skim milk and certain lean cuts of beef for a special hepatitis study. The results of this observation clearly demonstrated that the course of hepatitis and the period of convalescence were both shortened, resulting in a sharp increase in the percentage of men returning to combat duty and in a shorter period of time.

Briefly, this diet consists of protein 225, fat 50, carbohydrates 400. The high protein content has been made available by giving 200 grams of powdered skim milk in solution daily to each patient, along with two servings of lean, fresh beef. It has been found that whenever adequate protein substance, notably fresh meat, has been made available, the American soldier will readily eat large quantities of carbohydrates. Formerly, it was difficult to get them to ingest rice, beans, potatoes or macaroni in sufficient quantities to raise the carbohydrate much over 350 grams per day. With the availability of adequate protein substance, which is low in fat, the carbohydrate intake promptly increased to 450-500 grams per day. This caloric intake results in weight gains of ½ to 2 pounds per week, as contrasted to the common weight loss while taking the conventional high carbohydrate, low fat diet originally employed. Fresh eggs and fresh butter are tolerated without ill effect. The vitamin adjuncts have not been shown to be of value but certain experimental evidence suggests polyvitamin therapy. During the early hours of the disease, when nausea and vomiting are encountered, the judicious use of intravenous glucose has been helpful and is recommended. However, the giving of intravenous saline has often resulted in the enlargement of the liver with an aggravation of jaundice, so that the giving of intravenous saline is discouraged.

More benefit has been obtained, in my opinion, by the early administration of 3-4 units of plasma (250 cc. units) during the first 24 hours of hospitalization. The rapid disappearence of all symptoms and sharp improvement of the patient's feeling of well-being with return of appetite suggests a somewhat specific effect which is hard to explain on the basis of protein, mineral or methionine content. Knowledge of benefit from certain globulin or antibody content of pooled plasma remains to be demonstrated. Our present plan for forward echelon therapy consists of the infusion of plasma to those that are nauseated and vomiting. Ordinarily, powdered skim milk solution (50 grams in a glass of water) is tolerated and retained at a very early period, so that additional available foods will secure the patient's nutrition at an early period. It is important to note that skim milk contains 3½ per cent of methionine so that if such amino acid is necessary for the maintenance and repair of the liver cell, the above program will give the patient not less than 7 grams per day. Certainly it may be said that the dietary program now in effect has resulted in general physical improvement so that the hepatitis patients are entering the reconditioning center in excellent physical condition.

Reconditioning: Reconditioning, under the direction of the ward surgeon, has been of recent development with us. Early patients were allowed to go to duty when they appeared to be free of icterus and claimed to feel well. A number of such cases relapsed or were otherwise found unfit for duty when they became ambulatory so that a special study was made of problems of reconditioning. The results of that study indicated that a patient might well be allowed out of bed after the blood bilirubin has been normal for not less than a week. An additional 5 days of ambulant ward activity seemed to be sufficient to permit their going on to light exercise. A specially instructed non-commissioned officer was put in charge of group thus rehabilitated, who then put them through gradually increasing marches, hikes, callisthenics and games until by the 10th day it was shown that they were able to meet minimum requirements for combat duty. These minimum

requirements were a 5-mile hike, some of which is done at double time, two periods of 20 minutes each which include jolting exercises, such as side-straddle hop and liver jolting games such as volley or basket ball. If the reconditioning non-com noted any member of his group to be lagging or otherwise unable to carry out this program, his ward surgeon would conduct physical and liver function studies for evidence of relapse of the disease. If recovery was thus demonstrated to be incomplete, a return to bed rest for another 10-20 days usually results in complete recovery.

This, in our experience, has been a most important measure to establish physical fitness for combat duty. All cases of latent hepatitis or those with continued or doubtful degrees of activity of the disease are thus more clearly evidenced by increase of symptoms, enlargement and tenderness of liver, and an aggravation of the liver function tests, notably an increased retention of the bromsulfalein dye.

Although our results are not as good as some reported here this afternoon, I am happy to state that we have been able to return 92 per cent of our cases of hepatitis to combat duty in 52 days. This 52-day period includes the 10-day reconditioning period and approximately 4 days of necessary transfer and administrative requirements. The remaining cases have been prolonged or recurrent problems which may be assigned to light duty. Less than 3 per cent have been returned to the United States for further care because of chronicity or delayed recovery.

Hepatitis without jaundice has been a controversial point among some officers. However, the history of physical findings, liver function studies and liver biopsy specimens indicate that hepatitis may and does exist without the patient ever becoming jaundiced. This apparently is due to the disease being milder in degree so that the blood bilirubin does not remain high enough over a sufficiently long period of time for the tissues to become saturated, causing the icteric appearance. Our experience reveals the cases to be identical to those with jaundice, but the course and laboratory findings suggest that it is a milder form in every way excepting for debility or relapse.

During the epidemic periods, the ratio of cases of hepatitis with jaundice to those without is high, whereas in the other seasons they may be equal in number. In combat troops, where physical effort aggravates the process, instances of jaundice are higher than among rear echelon troops, where the soldier may be able to take it somewhat easier when he does not feel up to par. Recognition of the disease in the pre-icteric stage results in a reduction of demonstrable icterus by 40 per cent.

The relation of icteric and non-icteric cases was shown in the hepatitis following a yellow fever vaccine given in the United States, where all men receiving similar lots at the same time were shown to have the disease without jaundice 2½ times the number that actually became icteric. Although it is difficult and less important to pick up all non-icteric cases of hepatitis in the field, much evidence has been accumulated to show that a similar mild form may be experienced where jaundice never appears. Doubtful cases will develop symptoms, enlargement and tenderness of the liver, together with aggravation of bromsulfalein retention or elevation of the blood bilirubin if subjected to the exercise tolerance program.

The term "chronic hepatitis" has been applied to those cases that have failed to recover within a period of 4 to 6 months because they are given to prolonged symptoms, physical findings, abnormal liver and function tests. They are unable to tolerate the graduated exercise test and they may suffer relapses to such an extent either in hospital or after return to light duty that jaundice may appear the second or third time. These cases may arise from soldiers whose first attack was either with or without jaundice. Studies indicate that the greatest number of the chronic and relapsing patients are derived from those cases which were never recognized or hospitalized in the initial episode. Others arise from those privileged or essential soldiers permitted to remain on duty or because of being discharged to duty before true recovery had been established. Intercurrent infections, particularly malaria, or severe or chronic enteritis and at times severe trauma have caused relapses among those patients previously having infectious hepatitis. Such patients have not done well and approximately 75 per cent have had to return to the United States for further care because of the evacuation policy.

A palpable liver without tenderness may be a normal physical finding or it may follow malaria or other unknown conditions. Generally, liver function tests are quite normal and such a finding is anatomical and not a contra-indication to full duty. Men with hepatomegaly and mixed symptoms, but without abnormal liver function studies and with a normal graduated exercise test, have been returned to duty without the diagnosis of active hepatitis.

A palpable liver with symptoms of abdominal distress, right upper quadrant aching and indigestion which show an aggravation of symptoms, size of liver and liver function tests have been regarded as having an active or chronic hepatitis and they have been given the advantage of the treatment by absolute rest and diet. It is gratifying that this latter group has done very well and has been returned to duty in more than 50 per cent of the instances. It is important to realize that an enlarged liver should not preclude the proper evaluation with the return of the soldier to his organization, but it is our experience that if one has a chronic hepatitis, it is better to recognize it as soon as possible and institute adequate therapy.

Biopsy specimens obtained by the peritoneoscope from soldiers during the pre-icteric, icteric, convalescent and reconditioning periods have been very helpful in the concurrent evaluation of symptoms, physical findings and liver function studies discussed. Likewise, the liver biopsy specimens taken from patients with chronic active hepatitis, as well as those with hepatomegaly have been selected as a guide to our interpretation of symptoms, laboratory findings and for therapy. These will be reported at a later date. I hasten to add that a recent visit with Professors McMichael and Dible in London has encouraged us in this manner and I am happy to refer you to their publication with which we are in accord.

Studies in transmission of disease, as suggested by Van Rooyan, and supported by McCullum, Paul, Stokes, Oliphant and their co-workers have caused us to collect specimens of blood, fæces, urine, duodenal contents, mosquitoes and other possible vectors to be sent to the United States for human volunteer studies. Certain outbreaks among our various organizations strongly suggest that the disease may be transmitted by water, food or other means similar to that of typhoid fever.

Transfusions of blood, plasma, or other hypodermic injections may well explain a number of sporadic cases. Therefore, until the true etiology of the disease is understood, every sanitary measure for the control of food, water and hypodermic instruments should be exercised.

A circular letter by the Surgeon, MTOUSA, setting forth the cardinal features of the symptoms, signs, laboratory findings, clinical course and prognosis of cases of infectious hepatitis has served to facilitate their early recognition, treatment, rehabilitation and disposition.

PSS A 4808 1M250 7-45

Printed by Printing and Stationery Services, C.M.F.