[Kolb - page 36]

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DIVISION OF MENTAL HYGIENE

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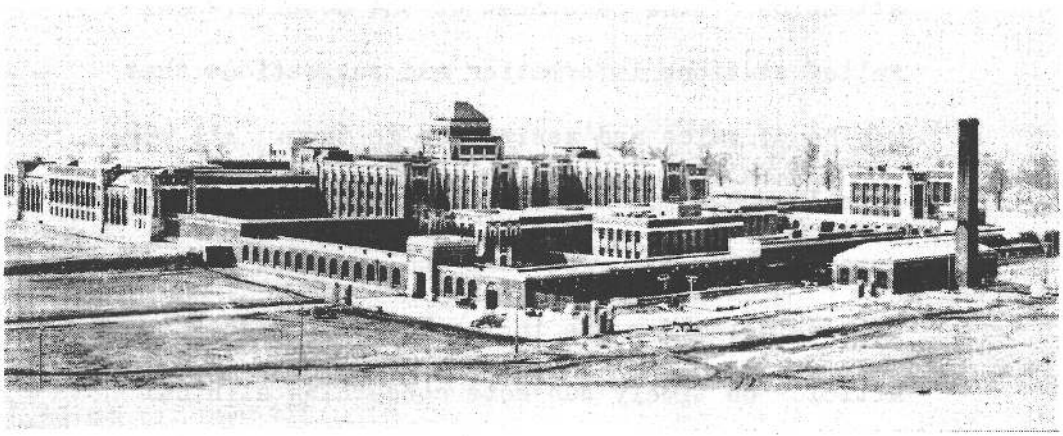


U. S. PUBLIC HEALTH SERVICE HOSPITAL, LEXINGTON. KY.

ISSUED FOR THE INFORMATION OF THE PERSONNEL OF THE
PUBLIC HEALTH SERVICE ENGAGED IN HOSPITAL AND RELIEF ACTIVITIES

TREASURY DEPARTMENT

WASHINGTON

The HOSPITAL NEWS is issued especially for the information of all personnel of the Public Health Service engaged in hospital and clinical work. It is hoped by this means to bring to the attention of the personnel of the hospitals and relief stations information and suggestions that may be of value and assistance to them. All personnel engaged in hospital and clinical work are urged to submit suggestions and articles that may be considered for use in the HOSPITAL NEWS. Articles on timely subjects concerning clinical research, case histories, practices, and observations, and reports on improvements in methods and new devices are solicited.

The HOSPITAL NEWS will be the basic subject for discussion at the staff meeting following its receipt at a station.

C O N T E N T S

HOSPITAL NEWS

VOL. 3 DECEMBER 1, 1936 NO. 23

SYMPOSIUM ON DRUG ADDICTION

United States Public Health Service Hospital, Lexington, Kentucky
October 14, 1936
W.L.Treadway, Assistant Surgeon General, U.S.Public Health Service, Chairman.

INTRODUCTORY REMARKS

By William Charles White, M.D., Chairman, Committee on Drug Addiction of the National Research Council

In January 1929 the National Research Council was entrusted with a sum of money for the study of drug addiction. After nearly fifty consultations with various individuals it was decided that the best use of this money would be to make a study of the physiological action in animals and man of the various structural chemical modifications that could be made in the morphine molecule and a study of the physiological action of compounds that could be made synthetically from the phenanthrene nucleus, attempting the approach step by step to the morphine molecule which is the major substance responsible for drug addictibn in man. One object was to find non-addicting drugs to replace the addicting drugs, while another object was to understand the physiology of the addicting drugs.

We were fortunate in finding at the head of what later became the Division of Mental Hygiene of the Public Health Service Dr. Treadway, who was made a member of our Committee, and through whom and the Surgeon General of the Public Health Service we have been able to draw into sympathy and coordination the several divisions of the Government that are concerned with the problem of drug addiction. These divisions, for those who do not know, are from the State Department, Treasury Department--U. S. Public Health Service and Bureau of Narcotics, and the Department of Justice--Bureau of Prisons.

Our first task after setting up the Committee and agreeing on the plan of work was to find a man who would undertake the chemical side of it. It was strange to find that there was practically no work being done in this field in the United States; but, luckily, through Professor Noyes, of the University of Illinois, we were mostly taken up by my trying to dodge the buckets of cold water Dr. Small poured over me. Eventually he showed some enthusiasm and said that our first task must be to bring our present knowledge of alkaloids of opium up to date so that we would have a base line from which to start. I was so impressed with Dr. Small that we arranged for him to begin immediately on this task. He finished this job two years later and Dr. Treadway arranged for the work to be published as one of the Supplements to the Public Health Reports. This book has become the world's standard book on chemistry of opium alkaloids and has been translated already into Japanese and

requests for translation into other languages are pending. Laymen, however, tell me that for them it is one of the best soporifics they have found, because they do not understand a word of it.

The next step was the organization of a chemical unit, and this was accomplished at the University of Virginia under Dr. Small, with the greatest sympathy and help from President Newcomb and Professor Benton, head of the Department of Chemistry. Dr. Small's difficulties were very great, for he found that there were no chemists in the United States engaged in the synthesis of the compounds he wished to make. But with the help of Mr. Brockett, of the Research Council, and the Department of Labor we were able to bring to Dr. Small's laboratory Dr. Mosettig, Dr. Burger, and Dr. van de Kamp. These workers have been with Dr. Small since the beginning of the study, and the University of Virginia has given them professorial rank. For the analytical part of the chemical study Dr. Small was able to use graduates from our own universities. Since the start of this work at Virginia Dr. Small has been able to place some seven or eight men in the industries in a field which was not provided for by any other university in the United States. Industry in the form of the great manufacturing houses in this field has been interested in the work from the beginning. Their chemists pay frequent visits to Dr. Small's laboratory, and they have provided fellowships under the direction of Dr. Small, with no restrictions attached to them. These fellowships are given through the National Research Council. The

firms that have provided them are Merck & Co., Mallinckrodt's, and Squibb's.

After the chemical unit had been organized, the Committee was ready to form a pharmacological unit for the testing of the substances prepared by the chemists. We were fortunate to have on our Committee Prof. Edmunds, of the University of Michigan, who was able to secure for us, to be in charge of the work, Prof. Nathan B. Eddy, who had always been interested in this line of study and who has conducted it with singular ability. The University of Michigan also provided Dr. Eddy with professorial rank. Both the Universities of Virginia and Michigan are to be commended for the excellent spirit of cooperation which they have displayed and they will be rewarded by the knowledge that the work that has emanated from their institutions in this particular field has revolutionized the literature of the world on the subject. A book bringing the pharmacological knowledge up to date, as was done in the case of the chemical knowledge, is about ready for publication by the Public Health Service. This has been written by Dr. Eddy and Dr. Krueger.

It naturally followed that, subsequent to the chemical analysis and synthesis and the testing of these substances in animals, those that gave indications of being valuable for man would have to be tried out clinically. Here again Dr. Treadway, with his wide knowledge, was the guide and director. Practically all studies in drug addiction heretofore had been done in general hospitals, where it is quite impossible to exercise the necessary control over the patients,

who can come and go at will and are at liberty to have guests who provide them with narcotics which they hide in places known only to themselves. Furthermore, in general hospitals it was impossible to provide adequate controls. About this time the Federal Government began its work at the Leavenworth Penitentiary Annex with studies on criminal drug addicts which eventually developed into this wonderful unit at Lexington. Here the patients are the wards of the Government and are committed for not less than a year and a day. Under the direction of Dr. Treadway and Dr. Kolb, the latter a life-long student of narcotics, an expert clinical and laboratory staff has been assembled and the whole problem of clinical study with reference to those who have already become addicted is centered here.

But there is another phase of the problem; that is the phase which has to do with those who, by virtue of disease such as cancer or tuberculosis, may become addicted and most likely will. The Public Health Service, through its association with the State health departments, was able to enlist the facilities provided by the Massachusetts Department of Public Health for a study of this phase. This is because Massachusetts has one of the most advanced programs of public health.

In this outline I have tried to give a picture of a unified effort on the part of a number of organizations which include parts of our Federal Government, a semi-governmental agency such as the National Research Council, a voluntary organization such as the Rockefeller Foundation, which provides the funds, industry repre-

sented by the manufacturing firms contributing fellowships, educational institutions, which have the responsibility of providing our youth with jobs and our industry with employees, and a State Department of Public Health which cooperates with the Federal Government, all banded together for the attempted solution of a serious problem affecting the people of our country. My part is to give you this broad picture of organization and effort on the part of already constituted agencies.

The plan of study itself, that is, starting with the chemical study, proceeding with tests on animals to determine the physiological reactions produced by the substances, and finally to make clinical tests on man, is in line with the best modern thought recently defined by Sir Frederick Gowland Hopkins, Nobel Prize winner, in his address before the Harvard Tercentenary in which he says: "The approach to a knowledge of the function of the whole can often only be made by analysis and study of the functions of its parts."

COMMENT

By Stuart J. Fuller, Assistant Chief of the Division of Far Eastern Affairs of the Department of State (American representative on the Opium Advisory Committee of the League of Nations)

When you were told that somebody from the State Department was going to speak to you, you probably anticipated a long and rambling

speech from a layman who does not know anything about the subject of tonight's discussion. I admit that my knowledge of the subject is limited, but you will be glad to know that I am a believer in the wheelwright's proverb, "the longer the spoke the greater the tire." This work which Dr. White has described for you in outline has been conducted in a quiet, earnest way, without any ballyhoo. Very little is known about it in this country. I venture to say that more is known about it abroad than throughout the United States. You will doubtless be proud to know that the eyes of the world are on the job which has just been described to you as being done here.

In the first place, there is the Committee on Drug Addiction. The first time that was mentioned in Geneva a keen interest was taken in it at once. That Committee, through Dr. Small, produced what is the authority in the world today on the alkaloids of opium --a treatise which filled a gap that was obvious. I am told-- I don't know, because I am not a scientist--but I am told by scientists that, in filling that gap, Dr. Small and the Committee earned the gratitude of the scientific world. As Dr. White said, this book is being translated into many languages; it is already widely quoted and referred to. The book is too deep for me to understand, but it a great help to me. When I am asked questions, I can get the book down, look at the index, find the page about the subject in question, and let the inquiring scientist figure it out himself.

The institution where we are meeting tonight is the first institution of its kind in the world. It is regarded throughout the world by people who are interested in drug addiction as the biggest step forward that has yet been made toward meeting the drug-addiction problem. It is regarded with admiration and with interest.

I know the extent of this interest because I go twice a year to the meetings of the Opium Advisory Committee, at which many of those interested in this problem participate. The meeting place of that Committee is the principal center in the world where those who are interested in preventing and curing the abuse of narcotic drugs meet together. From the time it was announced that we were going to put up an institution of this kind, I have been bombarded in the meetings of Opium Advisory Committee with questions in regard to details of every sort connected with this institution. Before leaving for sessions of the Committee, I always ask Dr. Treadway to give me a statement with regard to this hospital, and this I present to the Committee. That statement is listened to, questions are asked in regard to it, and I am always asked to say something more about it the next time I come over. The Committee realizes what an opportunity this institution affords for study of the drug addiction problem--clinical study, and for devising methods for cure of addiction. The world looks to this institution. It is realized that the staff of this institution is made up of men who are interested in the work, capable men, men whose publications command

the attention of the scientific world. The world is looking to Lexington--to Kentucky--for a valuable contribution to the solution of this problem.

I was allotted two minutes and I think that I have used up my time. There is a great deal more that I should like to say, but I will trespass no longer. Perhaps some time you will have another conference at which you may care to have described the set-up of the existing international organization to prevent the abuse of narcotic drugs. I consider it a privilege to have been accorded the opportunity of attending this meeting and hope that similar privilege will be accorded in the future.

I. GENERAL OUTLINE OF RESEARCH ON THE NATURE OF DRUG ADDICTION IN MAN

By E. G. Williams, Passed Assistant Surgeon, U. S. Public Health Service

The object of investigative work at this hospital is the establishment of facts upon which a more rational treatment of drug addiction, including preventive measures, may be based. The fundamental nature of the condition is unknown. The phenomena of tolerance and dependence indicate the presence of a mechanism, the function of which enables the organism to adapt itself readily to morphine, but which is incapable of reversible function.

An intensive study of physico-chemical, psychological, and

psychiatric changes resulting from single therapeutic doses of morphine, from repeated doses of morphine, during stabilized addiction, and during the post-addiction state will be undertaken as soon as we complete the assembling and calibrating of certain apparatus, and establish norms. During periods of investigation the subjects will be housed on the sixth floor of the hospital unit, which is being fitted up in the most attractive manner possible. From the standpoint of physical and mental comfort, they will be by far the best cared for patients in this institution.

Artificially one may speak of three divisions of this work:

1. Metabolic studies;
2. Psychological studies; and
3. Psychiatric studies

Metabolic Studies

Without going into the more academic elaboration of the statement that metabolism is the sum total of chemical changes going on in the organism, or a discussion of the genesis of our views, suffice it to say that we feel that various studies in metabolism offer the greatest promise of establishing fundamental facts and factors concerned with the nature and treatment of drug addiction from the somatic standpoint. For the purpose of presentation we may divide this portion of the study into

(a) Activity;
(b) Food and excreta studies;

(c) Gaseous exchange;
(d) Water balance;
(e) Carbohydrate studies; and
(f) Blood cytology and concentration

(a) Activity.--It is common observation that there is decreased general bodily activity following a dose of morphine, and that one of the early signs of withdrawal is restlessness. Does the organism become tolerant to this effect? And if so, to what extent? Further, since we are using 24-hour respiration periods, it is desirable to know roughly how much activity was indulged in during that period. In order to investigate these phenomena we have placed the respiration chamber on the floor of a platform scales, the head of which was modified for our purpose. Movements of the platform are amplified in the head, whence they are led off to a moving paper kymograph and recorded.

(b) Food and excreta studies.--The caloric value and its distribution as to fat, protein, and carbohydrate, as well as its water content, will be determined for all food and drink that is taken by each subject throughout the entire period of the investigation. All excreta except that from the skin and lungs will be collected, weighed, and evaporated in connection with water balance studies. Urinary nitrogen, sulphur, phosphorous, creatin, creatinin, etc., will be determined in order to ascertain the amount and degree of protein utilization.

(c) Gaseous exchange will be studied for periods of 24 hours by means of a respiration chamger and for shorter periods by the

Rein gasometabilograph. The room will be held at a constant temperature to within $\frac{3}{4}^{\circ}$F. and a constant humidity to within $\frac{1}{2}$ of 1 percent the year round. Thus our results will be comparable from season to season and from year to year. Effluent gases will be analyzed by means of the Carpenter modification of the Haldane apparatus, which is accurate to 0.001 of 1 percent. The interior of the chamber is painted a light blue-green, which is a pleasing and restful color, diminishing the sensation of being "cooped up." There is a bed with an air mattress, a chair, a table, reading matter, writing material, a radio, food and drink, and drugs if necessary. There is a telephone for communication. The food and drugs are kept in locked compartments which can be opened one at a time only by electrical release of the lock by the observer on the outside. Excreta will be collected in air-tight containers and later analyzed.

Obviously, a study of this kind, extending over a period of 24 hours, is subject to certain definite limitations, such as the immediate and progressively changing alterations, if any, of respiratory function. Recently the Hellige Company, of Germany, has marketed an apparatus devised by Professor Rein, of Göttingen, which measures and records photographically, rate, rhythm, and volume of respiration along with the percentage of oxygen and carbon dioxide in a continuous manner. By use of this apparatus we will be able to follow respiratory function, mechanical and chemical, for any period up to 8 hours.

(d) Water balance.--As one of the most striking signs of withdrawal is an upset in water balance, it follows that one would expect some alteration in the water economy of the organism during addiction. Our objective in studying water balance, or, better, water metabolism, is to establish whether or not this is the case and, if so, in what manner it takes place. We shall determine, by collecting and weighing the moisture in the air as it comes out of the chamber, the amount of water given off by the individual while in the chamber and check this figure by actual weighings of the man on an analytical balance having a capacity of 100 kg and a sensitivity of 0.1 g. The rate of insensible perspiration for short periods under varying conditions will also be studied by means of this balance. In addition to the above, we are devising a water tolerance test, i.e., a procedure which will tell us how and how well the body can handle an assignment of water under varying conditions.

(e) Carbohydrate studies.--There is definite evidence that in the addict there is a derangement of the carbohydrate metabolizing mechanism. We shall study this mechanism in relation to the various phases of addiction in the following manner: Blood sugar, blood concentration, inorganic phosphorous, blood lactic acid, and pH determinations will be made before, and half-hourly after the administration of given amounts of glucose. This, with the more indirect methods of studying respiratory quotient and excreta

analysis, will give us a fairly complete picture of the carbohydrate metabolism of our patients.

(f) Blood cytology and concentration will be followed as completely as time and personnel will allow.

Withdrawal, or the period of more or less acute illness which follows cessation of administration of narcotic drugs to addicts, presents certain features which preclude the use of the chamber method of investigation. We shall, however, study this phase very completely, covering the following and other points.

Blood cell volume;
Sedimentation rate;
Sp.gr. of blood and plasma gravimetrically and by the falling drop method of Barbour;
Water content of blood and plasma;
Oxygen content of blood and plasma;
Protein content and N.P.N. of plasma;
Glucose and inorganic phosphorous of blood;
Basal metabolic rate;
Caloric exchange, etc.

In order better to understand some of the aspects of withdrawal phenomena, we shall compare with addicts undergoing withdrawal (who voluntarily abstain from food and water) the effects of comparable food and water fast on normal individuals, on addicts during maintained addiction, and on persons who have been addicted but who are at the time apparently normal.

Dr. Miller, the senior dental officer at this station, is planning two studies which will possibly prove to be of interest far beyond, as well as in, the field of dentistry. It has long been observed that addicts as a class have poor teeth. Further,

it is thought that their dental condition is worse than can be explained on the basis of neglect. One of the proposed studies is a statistical analysis of the dental condition of large numbers of addicts and an equally large or larger number of sociologically comparable non-addicts; the other proposes to investigate whether or not dental abnormalities can be produced in experimental animals by the administration of morphine.

I will mention some of the things that are on our program for the near future: Lipid metabolism is most definitely enmeshed in the protein phenomena of drug addiction; this entails a study of phosphorous, which in turn entails a study of calcium. Our next major attack is, therefore, likely to be a study of this triad. The field of hormone physiology is at present bursting all bounds of imagination and continuity. In a few years it undoubtedly will have come down to earth to such a degree that we may proceed on stepping stones of solid rock and investigate the relationship of endocrinology to our problem. Another question which is most important and about which practically nothing is known is the fate of the morphine molecule in the animal organism.

Psychological Studies

The psychological studies that will be conducted as an integral part of our research may be briefly stated as follows: Two major objectives are considered: First is the effect, if any, of morphine on the reaction to certain standard situations, and second

is the effect, if any, of morphine on certain physiological reactions or responses to psychological stimuli. The specific measures selected for the first part of this program will cover a wide range of general psychological processes, with special emphasis on affection and on those correlated with emotive behavior. Preference, of course, is given to those measures which can be scored objectively. The second part of this program will be studied by means of the Darrow Photopolygraph, an apparatus which records on a single film the rate and amplitude of respiration, relative blood-pressure changes and pulse rate, tremor of both hands, amplitude and duration of skin reflex changes, and changes in apparent skin resistance, together with a registration of the time of the stimulus, time of response, and one-second time intervals. Reactions to sensory stimuli, indifferent and disturbing ideational stimuli, fatigue, and difficult mental work will be studied by this method.

Psychiatric Studies

All of our patients will be studied by Dr. Kolb as to personality changes and by Dr. Vogel as to suggestibility. It is anticipated that Dr. Felix will study cerebral potential phenomena and their alterations, if any, resulting from the use and abuse of morphine. For this purpose he will use an apparatus called the electroencephalograph, which amplifies and records changes of electrical potential--action currents--within the brain much as the electrocardiograph amplifies and records action currents of the

heart. This is the most direct way possible of studying neuro-psychiatric phenomena and carries with it the tremendous advantage of objectivity. By means of this apparatus a relatively simple and easily interpretable method of studying conditioned reflexes is at hand. We feel that a study of the ease with which man can be conditioned and deconditioned while using narcotic drugs and while abstaining is likely to shed valuable light on the fundamental nature of addiction and especially on the relapse to the use of such drugs. By this means we shall study also (1) the effects of emotional stress which may have a definite bearing on etiology as well as after treatment of addiction, (2) altered perception of stimuli in relation to the adjustment of the psycholobiological unit to the use of drugs, and then later to the non-use of them, (3) the nature of the function of the so-called vital centers in the medulla and any alteration of function produced by morphine, (4) the sleep pattern of the addicted versus the non-addicted individual, and (5) phenomena of hallucinations in connection with morphine action.

If I have not made it clear, may I now state that any divisions made in this presentation are almost purely artificial and are made for the purpose of clarity. The entire program outlined is a single coordinated study conceived by Dr. Treadway and more specifically by Dr. Himmelsbach, and worked out by those of us here at this hospital. The most important advantage of this over any other

possible approach is that we will have physiological, biochemical, pharmacological, psychological, and psychiatric information collected on the same individuals, at the same time, and under the same conditions, each group of data to be analyzed in light of all other data.

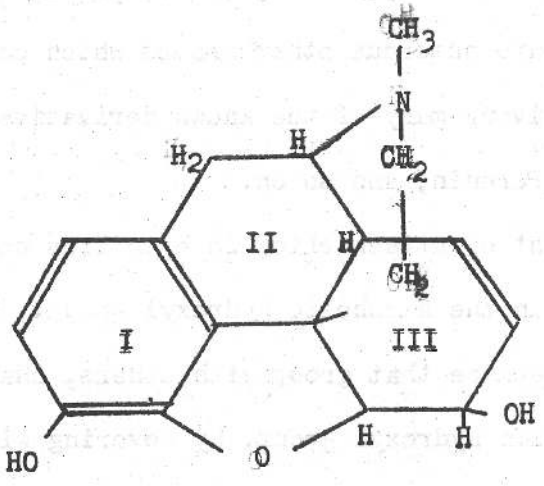
II. CHEMICO-PHARMACOLOGICAL STUDIES OF MORPHINE AND ALLIED DRUGS

A. CHEMICAL STUDIES IN NEW NARCOTICS

By Lyndon F. Small, Consultant in Alkaloid Chemistry, U. S. Public Health Service, University of Virginia

I shall try to explain as briefly as possible, in view of the complexity of the subject, the lines of approach we have made in the study of drugs which may serve as substitutes for morphine without the disadvantageous actions which are exhibited by that drug and which are so well known to you. Faced with this problem, the chemist did just what any of you would have done--he sat down and thought about it for a long time. Morphine, as you know, is an alkaloid produced by the poppy plant; and if you take a sample of it and analyze it for the constituent elements by methods probably familiar to most of you, you will find that it has the formula $C_{17}H_{19}NO_3.H_2O$. Now, due to the extraordinary ability of carbon to group itself in chains and in rings in space, there can exist a great number of substances containing these relative proportions of carbon, hydrogen, oxygen, and nitrogen. Fortunately we were able to avail ourselves of the research of hundreds of chemists, extending over the past

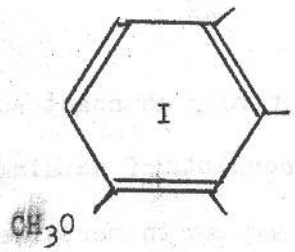
century, and we know the structural formula of morphine to be that of a hexahydrogenated phenanthrene oxide, carrying a nitrogen-containing ring and two hydroxyl groups. This is of the greatest importance to us, because the logical approach to the problem seemed to be, first, to determine what in the morphine molecule is responsible for its physiological effect, and then, if possible, to determine what structural feature is concerned with habituation to the drug. If we represent the spacial relationship of these atoms, we are forced to resort to a device of the chemist in which the corners of these rings represent carbon atoms, usually carrying hydrogen; and on that basis morphine assumes the following structural formula: Three rings grouped together containing only carbon and hydrogen, a fourth ring containing oxygen, and a fifth ring containing nitrogen.



MORPHINE

Ring I is, as we say, aromatic, that is, unsaturated, in a particular way, and it carries a hydroxyl group which is acidic in character, like the hydroxyl group in phenol. Morphine also contains a hydroxyl group which is nearly neutral in nature like that in alcohol. That, in brief is the way in which a chemist represents the molecule of morphine. If we pick out the salient features which are to the chemist obviously open to attack, the first of them will be the phenolic hydroxyl, which has properties similar to those which we know from the chemistry of dozens of representatives of the phenols, cresols, and other such substances. This phenolic hydroxyl is subject to change in a variety of ways. One of the simplest is covering it through some reaction in which the acidic hydrogen atom is eliminated; namely, by substituting a methyl group in place of hydrogen; and by this simple change, morphine is converted to codeine. There are numerous other groups which can be placed in this position, giving many of the known derivatives of morphine, such as Dionin, Peronin, and so on.

Another point of attack which is open lies on the other side of the molecule in the alcoholic hydroxyl group. By various methods we are able to replace that group with others, changing it just as we did the phenolic hydroxyl group, by covering with a methyl group, or eliminating it entirely, that is, replacing it by hydrogen. Similarly, there is another vulnerable point in the molecule--the unsaturated linkage. As you know, a double bond, as it is called,

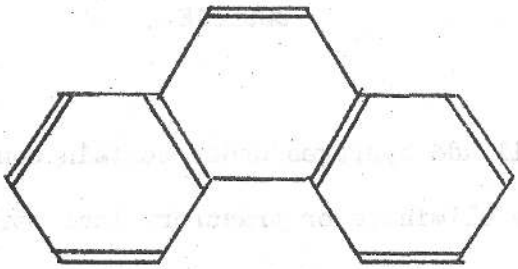


CODEINE

of this type will add hydrogen under certain conditions, and by this reaction we eliminate or transform that structural feature, adding two hydrogen atoms. Still another method of attack lies in breaking the nitrogen-containing ring, giving us a derivative of the codeine molecule, in which we have only four rings. Similarly, if we wish, by certain reactions we can open the oxygen-containing ring and are now down to three rings. By following in the animal each one of these changes as they are carried out successively, we can arrive at the physiological result of covering one group, replacing the other group, of opening rings, and see how these changes affect the various characteristic actions of morphine in the animal body.

You will notice in the morphine molecule the characteristic picture presented by these three rings. The logical thing, having gone through all these transformations and found the physiological functions of each of these, in themselves, simple groups, is to pick out something more fundamental; namely, What is the influence of these three rings? We have in coal tar, the source of so many

medicaments and dyes, a relatively abundant substance called phenanthrene; and phenanthrene consists of nothing but those three rings, arranged in the same way as in morphine.



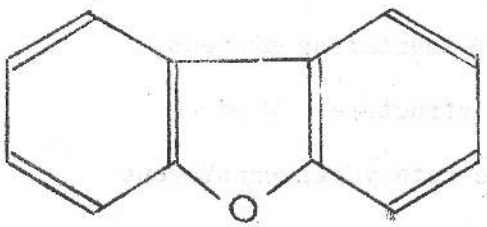
PHENANTHRENE

Phenanthrene can be converted chemically into derivatives carrying the various groups present in morphine, so that having started from morphine and successively split off one group after another, opened one ring after another, and followed the physiological result of these changes, we can now start with phenanthrene and add groups to see what the physiological effect of substituting these groups in the three-ring system will be. This phase of the chemical studies has been carried out under the able direction of Dr. Erich Mosettig. We have been able, for example, to introduce, chiefly in two positions, such groups as the hydroxl and the amino, which are present in morphine, and with hydroxyl groups on both ends of the molecule we approach a little nearer to the morphine structure; and finally, with the introduction of cyclic amino groups, we build up to more complicated substances which may be expected more nearly to resemble morphine in their physiological effect. You will notice

that in morphine one of the carbon rings is what we call aromatic; that is, has three doubly-linked carbons in a special arrangement, whereas the other rings are more or less saturated with hydrogen. So the next logical step is to reduce the phenanthrene nucleus, thus coming closer to the morphine type of structure. When we succeed in substituting into the asymmetric octahydrophenanthrene nucleus both alcoholic and phenolic hydroxyl groups, and a tertiary, perhaps ring-linked, nitrogen atom, we shall have a molecule which rather well approximates in its functional groups the morphine molecule. We can't say that it will be identical--we wouldn't want it identical, because then it would be morphine; but we want to come by steps as close as we can and follow the changes in action in the animal body.

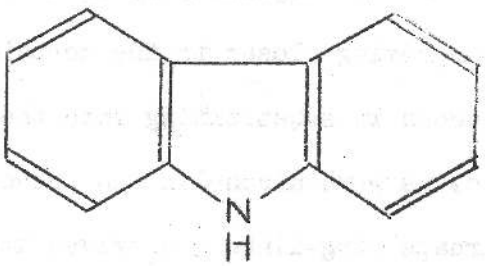
The three rings of phenanthrene are not the only ones of interest in the molecule, and we have another substance in coal tar which embodies two carbon rings and one oxygen-containing ring, namely, dibenzofuran. This substance can likewise be obtained from coal tar in practically any amount we want, and into this nucleus we introduce groups comparable to those put into the phenanthrene nucleus. A third coal tar product which is very interesting has in place of the oxygen atom of dibenzofuran a nitrogen atom. This compound, called carbazole, can be changed by putting in hydroxyl groups, amino groups, and so on, again building toward the type of structure which we know to be present in morphine and

which is so physiologically active in animals and in man.



DIBENZOFURAN

CARBAZOLE



This summary, necessarily, can not by any means embrace the variety of compounds which we have investigated in an attempt to find out what in morphine is responsible for the analgesic and other effects; but it shows briefly the line of reasoning that we follow, and in many cases we begin to feel that we have been justified by the results which have been obtained by the pharmacologist.

B. PHARMACOLOGICAL STUDIES

By Nathan B. Eddy, Consultant Biologist in Alkaloids, University of Michigan

In the complex organization that Dr. White described to you, the men working with me and I have been assigned to the task of evaluating the substances made in Dr. Small's laboratory by himself and his associates in terms of action in the body; and then, if it seems desirable, to make recommendations as to the possibilities of the clinical usefulness of any of these substances.

The general hypothesis of the work is very easily stated. Dr. Small has told you something of the complex chemistry of morphine and its derivatives. You yourselves know that the action of morphine in the body is equally complex; that it does a great number of things, some useful, some undesirable. For instance, it has an effect on respiration, it relieves pain, it produces sleep, it sometimes causes vomiting, it affects the gastro-intestinal tract, and it leads to tolerance and addiction. We know to start with that if we modify morphine chemically, we ought to modify its action in the body. What we would like to know is this: If we modify morphine chemically and modify its action in the body, do we modify all of its actions in the body, either in the same direction or to the same extent? If we do we are wasting time, because if we do, then we reduce equally the useful pain-relieving power of morphine and its undesirable properties. Or, let us put it the other way around: If chemical modification of morphine affects all properties of morphine alike, then a change which reduces the dangerous addicting property would at the same time reduce the useful pain-relieving property of the drug, and the resulting substance would be of no value. So, what we are concerned with--the hypothesis on which we are working--is this: Do chemical changes, or the chemical changes which can be effected starting with these known chemical substances (morphine, codeine, etc.), modify all of the actions of morphine in the same way, quantitatively and qualitatively? In order to answer

that question, we have proceeded in the manner which I shall now explain.

There is no other animal which presents the whole picture of the effect of morphine as we see it in man. Certain species are suitable for demonstration of the hypnotic power of morphine; other species are especially suitable for determining the pain-relieving power; others for determining the effect on the gastro-intestinal tract, etc. Now from previous and our own experience, what we have done is to select species which exhibit each of the actions of morphine in the most suitable fashion and then to work out a method for that species for determining or evaluating that particular action in as nearly a quantitative way as possible. Furthermore, we have to use species that we can handle unanesthetized, because we don't want the result affected by administration of other agents such as anesthetics; we want the changes to be due solely to the substance administered--morphine or a morphine derivative.

Just for example, we use the cat to determine the pain-relieving power of morphine; and you may, perhaps, be interested in the method we employ in this connection. Quite some years ago, faced with the task of determining whether or not certain hypnotics had any pain-relieving power, I played around in an attempt to get some quantitative measure of pain-relieving power; that is, analgesic action. Practically all of the methods at that time, and most of them now, depend for their answer on complete suppression of any

response to pain. That didn't seem to us quite good enough; what we wanted was something that would tell us when the responsiveness of an animal to pain was reduced--that is, partially removed but not completely suppressed. I discovered, more or less by accident, what I already knew in one sense, that if you pinch the cat's tail the cat responds by crying and getting away or going after you with its claws. Then I discovered that the same cat responded in the same way at different times during the same day, or different days, to the same amount of pinching of the tail. And the elaboration of that fact has furnished a very satisfactory method for determining the pain-relieving power of a great many substances.

What we actually do is this: We have a device which various individuals have called my "tail squeezer." It is a device which consists of two plates, one of them being fixed in position--just a flat metal plate--and another plate above it capable of being moved up and down in a vertical plane. Above the upper plate is a stiff spiral spring, and on top of that is a crank, so that we can compress the spiral spring and, therefore, exert pressure on the upper plate. The cat's tail is put between the plates and the crank is used to compress the spring, bringing the upper plate down on the animal's tail and against the lower plate. When we have applied the proper amount of pressure the cat hollers or tries to get away. It doesn't take much experience to know when the cat feels the pressure. This reaction is uniform in the same cat as

long as the cat remains normal. Now if we give the cat a substance like morphine, it may go crazy--it may run around in its cage, have hallucinations, and show other signs of excitement. But in spite of that fact the response to pain is reduced. After a small dose of morphine is given to a cat that would have previously responded to the application of 4 or 5 pounds of pressure on the tip of its tail, it doesn't respond until a pressure of as much as 50 pounds is applied to its tail. There is no question that the responsiveness of the animal to pain has been reduced.

Similarly, a quantitative method has been worked out for determining the effect of morphine on the respiratory system, the rabbit being used for this purpose, for the rabbit is especially susceptible to the respiratory effect of morphine. Again, the dog is used for measuring the effect on the gastro-intestinal tract. In this case the dog is operated on, with the production of an intestinal fistula. After the fistula has healed and the animal has completely recovered and has been trained to lie quietly on a table without restraint, a balloon, or sausage-shaped rubber sack, is inserted into the fistula and through this the movements of the intestine are recorded.

I might have mentioned that we have to select carefully and train our rabbits, too. One doesn't usually think of rabbits as being susceptible to training, but at least some of them are. The rabbit's respiratory activity is very susceptible to outside in-

fluences--noise, temperature changes, even wind currents--so that the rooms where the experiments are being conducted and the adjoining corridors have to be carefully guarded, and cautions in regard to noise strictly enforced.

Still other species are used for other types of action. For sleep-promoting power we have a very simple method in which rats are employed; the mouse for determining toxicity; and the rat, dog, and monkey come into use for the study of tolerance and addiction. In each instance we have worked out as nearly as we could a quantitative method for determining a specific action of morphine. The result is that, having determined the activity of morphine in each of these respects, we can do the same with any one of its derivatives and from the sum-total of the knowledge thus obtained determine whether or not all morphine-like actions have been modified and whether or not they have all been modified in the same direction and to the same extent.

Without going into details, I can tell you right now that the hypothesis has been supported. It is possible to modify morphine chemically in such a way that some actions are increased while others are just as definitely decreased. Just a few instances will illustrate for you what happens when certain changes are made.

Dr. Small drew attention to the two hydroxyls of morphine as points of attack for chemical modification, for example, by substitution of a methyl group for the hydrogen of the hydroxyl. If

such substitution is made on the phenolic hydroxyl, most of the actions of morphine are reduced approximately ten-fold. This same change, however, increases some effects, most notably the effect on the spinal cord, leading to convulsant action. On the other hand, if the methyl substitution is made on the other, the alcoholic, hydroxyl, the pain-relieving power and especially the effect on respiration are increased about ten-fold. Methylation of the phenolic hydroxyl of morphine produces codeine; methylation of the alcoholic hydroxyl produces heterocodeine. The analgesic effectiveness of the latter is about 100 times greater than that of the former. Many other substances derived from morphine by other types of chemical change have been studied, and each chemical modification has effected its own characteristic change in the action of the new substance in the body. No change, however, has affected uniformly every morphine-like action.

Turning now to phenanthrene and those compounds which have been built up from it, phenanthrene itself is an almost inert substance pharmacologically, but the addition to it even of such simple groups as OH or NH_2 or COOH causes the resulting compound to begin to exhibit both analgesic and hypnotic power. Increasing the complexity of the added groups increases the effectiveness of the phenanthrene derivative, and in some instances the addition of an alkylamine side-chain causes the appearance of other morphine-like actions. But if, instead of using phenanthrene itself as the base, derivatives are made by additions to a partially

hydrogenated nucleus, one more nearly resembling the phenanthrene nucleus of morphine, the activity of such derivatives is very greatly enhanced.

When dibenzofuran is used as the starting point and a parallel series of derivatives is built up, using the same substituents as were previously attached to phenanthrene, the analgesic effect of these dibenzofuran compounds is greater than that of the corresponding phenanthrene series. Unfortunately, however, the dibenzofuran derivatives exhibit increased toxicity and other undesirable side actions.

One of the most interesting and perhaps the most promising group of substances is that derived from carbazole. These compounds have shown relatively great analgesic and depressant effects and appear to be very low in toxicity. The members of this series that have been studied have been very poorly soluble and so far unsuitable for clinical trial; but if the chemical difficulties in this field can be overcome, it is possible that sufficiently active and useful substances may be obtained.

Finally let me repeat our hypothesis of unequal modification of morphine actions--increase in some and decrease in others--by chemical modification has been substantiated and, furthermore, some of the useful morphine-like actions have been demonstrated in comparatively simple derivatives of phenanthrene and other simple bases.

C. CLINICAL STUDIES

By C. K. Himmelsbach, Passed Assistant Surgeon, U. S. Public Health Service, U. S. Public Health Service Hospital, Lexington, Ky.

The new drugs which appear most promising, from the pharmacologic point of view, are selected for clinical study. The object of the clinical studies is to determine whether these new drugs possess addiction liability.

The detection of the presence of addiction liability in these new drugs is accomplished by the use of a method based upon the only true criterion of addiction (dependence), that is, the constant appearance of a characteristic syndrome of abstinence phenomena subsequent to abrupt and complete withdrawal of drugs capable of maintaining dependence. The abstinence syndrome is composed of numerous objective and subjective phenomena. From the investigative point of view, only the objective manifestations need be considered. A careful study of the objective manifestations of abstinence led me to group them in the manner shown in table 1. Numerical values were assigned to the four degrees of intensity shown in this classification.

Table 1

Objective Abstinence Phenomena			
Mild	Moderate	Marked	Severe
+	+ +	+ + +	+ + + +
Yawning	Anorexia	Hyperpnea	Emesis
Lacrimation	Mydriasis	Fever	Diarrhea
Rhinorrhea	Tremor	Restlessness	Weight Loss
Sneezing	Goose-flesh	Insomnia	(5 lb.-24 hrs.)
Diaphoresis		Elevated B.P.	

It will be seen that several of these manifestations are accurately measurable. It has been found that the extent of their respective deviations from addiction levels during abstinence are consistent with the severity of the composite abstinence syndrome. The usual extent of deviation per degree of total abstinence intensity of the measurable signs is shown in table 2.

Table 2

Evaluation of Abstinence
Measurable Signs

Signs	Moderate	Marked	Severe
Caloric intake Decrease, %	-20 to -40	-41 to -55	over -55
Weight Loss, %	-3 to -4.5	-4.6 to -6	over -6
Fever °C. Increase	+0.3 to 0.45	+0.46 to 0.6	over +0.6
Hyperpnoea Av.per.min.increase	+3. to 4.5	+4.6 to 6.5	over 6.5
Basal metabolic rate, %	+10. to 20	+21 to 30	over 30
Blood Pressure mm Hg Increase	+5. to 10	+11 to 15	over 15
Blood Sugar mg Increase	+10 to 20	+21 to 30	over 30

The assignment of numerical values to the composite abstinence syndrome and to several of its component parts permits graphic illustration of the major sequences of events which occur following withdrawal of addictive drugs from individuals who have acquired physical dependence upon them. The curves shown in figure 1 illustrate the mean changes which occurred following abrupt and complete withdrawal of morphine from a group of 10 control cases.

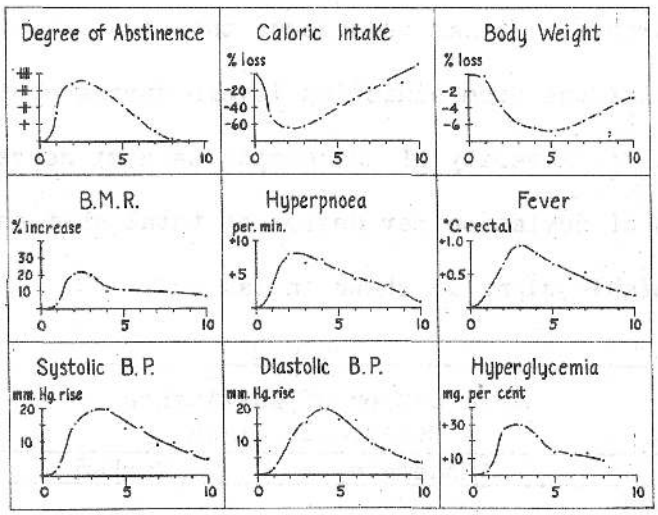


Figure 1

It is by use of these criteria that the presence of addiction liability in the new morphine derivatives is determined. The use of this system of abstinence evaluation provides an accurate and thoroughly objective method for detecting the presence and determining the extent of physical dependence. It also provides an excellent means for determining the efficacy of withdrawal therapy.

The validity of the method developed for testing these new drugs depends upon the contention that a drug which will maintain preformed addiction is capable of producing addiction, that is, that the terms "addiction liability" and "dependence satiation" are synonomous. The use of this method obviates the necessity for attempting to produce addiction through the chronic use of these new drugs, a method to which would attach several obvious disadvantages.

Since this substitution method requires clinical material in whom dependence is already present, it is first necessary to demonstrate the presence of dependence prior to the initiation of study. We have found that only about 20% of addicts who present themselves here for treatment while still using narcotic drugs have acquired physical dependence of sufficient intensity to be of any value for study purposes. Our routine method of selection is to withhold opiates from all cases for 30 hours. If abstinence of + + to + + + + intensity is exhibited during the latter part of this period, the patient is given the choice of becoming a study subject or of taking our routine codeine reduction treatment.

Study subjects are then stabilized on morphine (the minimum daily requirement for the prevention of abstinence) for about one week. Then the drug to be investigated is substituted for morphine in doses calculated to be equally effective. After proper dose adjustment, both as to amount and duration of effect, the administration of the new drug is continued for about one week. It is then withdrawn and observations for evidence of abstinence are continued for 10 days. During this period certain therapeutic measures which have been shown to be without demonstrable effect on the abstinence syndrome, but which do offer temporary subjective relief, are administered.

In this manner the presence of addiction liability in the following drugs has been demonstrated:

1. Isocodeine
2. Pseudocodeine
3. Codeine
4. Dilaudid
5. Desomorphine
6. Dihydroisocodeine
7. Dihydroheterocodeine
8. alpha-isomorphine
9. Dihydro-alpha-isomorphine
10. Dihydrodiacteylmorphine

The series is too small at present to permit inferences as to possible relations of chemical structure and addiction liability. From the pharmacologic standpoint, however, it does seem that the compounds of higher potency, more rapid onset of action, and briefer duration of action are more rapidly and powerfully addictive than compounds of lesser potency, slower onset of action, and greater duration of action.

III. THE TREATMENT OF OPIATE ADDICTION, WITH SPECIAL REFERENCE TO WITHDRAWAL THERAPY

By Lawrence Kolb, Medical Director, U. S. Public Health Service, in charge U. S. Public Health Service Hospital, Lexington, Ky.

The treatment of drug addiction is a subject which has vexed physicians more or less ever since it became apparent that the continued taking of opium was harmful and to be avoided or cured if possible. Addiction has obviously been prevalent ever since opium was discovered more than two thousand years ago, but it excited no great interest in medical literature until the early part of

the last century. Apparently it was no great problem in western countries before that time, or, if addiction was prevalent to any great extent, it was ignored as being harmless or at least not so harmful as to require the attention of governmental authorities or to give serious concern to physicians. We know, however, through the medium of lay literature that certain famous people took opium to excess, and addiction is occasionally mentioned in medical literature of remote periods. During the past hundred years there has been an increasing interest in the subject on the part of both governments and the medical profession, and much has been written about the nature of drug addiction and about cures. The invention of the hypodermic syringe and the discovery of opium alkaloids increased the seriousness of the problem in western countries especially, and for this reason increasing attention has been focused on the subject.

A very large proportion of the literature has been devoted to a discussion of withdrawal therapy. Books have been written that are devoted almost exclusively to this alone. Withdrawal therapy is, however, comparatively unimportant. If it occupied as large a place in the drug addiction problem as some authors apparently assume, the problem could be quickly solved.

So-called cures are notoriously followed by relapses. The important thing, then, is to prevent relapses and to so order the handling of narcotics as to prevent innocent or especially suscept-

ible people from becoming addicted. The latter is largely a function of governmental authorities, and much progress in prevention has been made by these authorities during the past forty years. Prevention is also a function of physicians who, with increased knowledge of disease and the danger of addiction, do not prescribe opiates so freely as they did in the past.

Psychopathic characters and persons in general whose personalities deviate from the normal are especially susceptible to opiate addiction and to relapse after cures. The most important phase of treatment for them is not the physical withdrawal of opium, but a reorientation of their personalities so that they do not again feel the necessity for seeking relief from the stresses of life by resorting to opiates. The rebuilding of personality can not be accomplished within a few weeks, and in many cases cannot be accomplished at all; but it is not our intention to discuss this phase of the treatment today. The withdrawal of opium from addicts has attracted a great deal more attention and many physicians seem to consider it more important. We shall, therefore, attempt to cover briefly the history of withdrawal therapy and present some lessons we have learned.

Theories of the nature of opium addiction, about which practically nothing is known, have been built around withdrawal symptoms, and on the basis of these theories some treatments that are claimed to be specific have been advanced. Before proceeding to discuss some of the well-known treatments a few remarks about withdrawal

treatment in general will serve to orient us in evaluating the various methods. It is well known that anyone addicted to opium suffers from certain symptoms when the opium is withdrawn. Treatments are designed to reduce or eliminate this suffering and also to obliterate permanently the craving for opiates. Claims about the latter are made, however, only by persons who have had very little experience in the handling of drug addicts.

The withdrawal of opium is one of the simplest procedures in medicine. This, together with the fact that addicts vary greatly in their reaction to withdrawal, explains in part why so many treatments have been and still are being invented for this condition. Another reason is that so many addicts who have very little habit or who have been deprived of their favorite opiate for several days and are, therefore, almost over the withdrawal period when they present themselves for treatment are treated by physicians who have not taken these factors into account and who consequently attribute the mild withdrawal symptoms to the special treatment that they happen to be giving. Some of these physicians have seen patients suffer intensely under withdrawal. Others, who have advocated certain specific treatments and have proved their value to their own satisfaction on a few cases, never saw an addict before but have read vivid tales of the suffering incident to withdrawal.

About 20 percent of any large group of relapsing addicts will truthfully tell you that they have had many treatments and that some

time during their addiction careers they have, without any assistance from physicians, "kicked" the habit at home, showing, of course, that the process is rather simple. Addicts who have strong habits and even those who are mildly addicted react very differently to withdrawal treatment. Some will suffer uncomplainingly; others, especially certain temperamental individuals or individuals whose desire for treatment is not strong, will whine and complain bitterly as soon as they begin to feel restless or otherwise uncomfortable. Some who vomit, are very restless, and have mild twitchings or other symptoms showing that they are going through severe withdrawal, will tell you that they are doing very well; others, who have scarcely any objective symptoms of discomfort, will complain bitterly especially if they feel there is a chance that the physician in attendance will will give them morphine or give them more than he has been prescribing.

The objective method of evaluating withdrawal symptoms devised by Dr. Himmelsbach eliminates errors of evaluating treatment to which a superficial observation of such patients would lead. We have found by careful observation of patients admitted with habits that only about 20 percent of them have severe enough habits, based on objective symptoms, to justify their use in making observations on the relative merits of various methods of treatment.

Treatment falls into three main groups--abrupt withdrawal, rapid withdrawal, and slow withdrawal. Practically all of the so-

called specific treatments have been grafted on the abrupt withdrawal or rapid withdrawal methods. The slow withdrawal method was practically in universal use up until about 45 years ago. By this method, patients were withdrawn over a period of a month or two, or even longer, by gradually reducing the amount of opiate that they had been taking. It was the treatment of choice when addicts were treated mainly at home, and it often resulted in complete cure. It is stated that, by this method, addicts were taken off drugs with very little suffering. Objections to the treatment are that it unnecessarily prolongs the suffering, even though this is mild, and that the patient is likely to change his mind before the treatment is concluded. Many patients treated by this method deliberately cheated; in other words, they deceived their physician by getting a supply of the drug surreptitiously. At the present time, when most addicts are unstable, treatment at home by this method is almost certainly doomed to failure and, what is more important, it is likely to be used by insincere addicts merely to get morphine from physicians when their illegal source of supply fails. The slow withdrawal method outside of institutions is now frowned upon by physicians as well as by the authorities. In sanitaria this method is still used to a certain extent, not because the physician in charge thinks it is the best method, but because in many cases it is the only method that the patient will stand for. It often fails even in sanitaria. We have had patients come here after a month or so of unsuccessful

treatment by this method in sanitaria, in some cases the transfer being advised by the superintendent. Such patients are, of course, practically always unstable and are usually insincere, having been driven to seek treatment by the urging of friends or threats of officials.

The first rapid withdrawal treatment that received any great attention was the "hyoscine treatment." This was advanced in 1901 at first by Lott and later by Petty. By this method patients are made delirious during the withdrawal period by the use of hyoscine given hypodermically every few hours. Purging was also used in the original Petty method. After the hyoscine had been discontinued and the patient had come out of his delirium, he was over the worst of the withdrawal symptoms but remained more or less weak and shaky for several days. The advantage of this treatment seemed to be that it made the patient so irresponsible that he could be restrained and kept under treatment during a rapid withdrawal period. It was claimed that the hyoscine treatment had some specific effect in detoxitizing the patient and obliterating the craving for opium, but more careful study has shown that it increases the suffering of the withdrawal period and leaves the patient at the end of it with an indefinite craving which he is likely to satisfy by returning to opiates as soon as the opportunity offers itself. The treatment is also dangerous to life. I know of one institution where out of 130 patients treated by this method six died under treatment.

It was thought by Petty that the essential pathology of narcotic addiction was a toxemia, the toxins being of drug, auto, and intestinal origin. This aparently was the reason why he considered purgation essential in the treatment. There is, however, no reason to believe that any form of toxemia is responsible for withdrawal symptoms. It is well known that morphine is rapidly eliminated from the body. It all disappears between the third and fourth days. The symptoms of withdrawal in any event are due not to the morphine in the body but to the withholding of it. Another important consideration is that due to the relaxation resulting from the withdrawal of morphine there is usually a diarrhea which is at times severe. Purgation only tends to accentuate this condition and to devitalize the patient. Petty gave strychnine as part of his treatment, and other authors have advocated the use of strychnine apparently on the basis of observations that strychnine cured their patients. Treatment by strychnine is just as illogical as treatment by purgation. The patient in withdrawal is hypersensitive to all sorts of stimuli. They are restless, apprehensive, and usually are purging. Strychnine is preeminently a drug which increases the acuteness of perceptions and also, by stimulating peristalsis, aids in evacuating the bowels. The withdrawal symptoms are, therefore, increased by this drug, and the fact that patients in withdrawal can be thought by the attending physician to be benefited by it illustrates how many important factors are overlooked in evaluating the merits of different

methods of treatment.

A variant of the hyoscine treatment is the Towne-Lambert treatment. This and the hyoscine treatments were for years the favorite methods of withdrawal. In this treatment the drug is rapidly withdrawn while the patient is given a mixture of belladonna, hyoscyamus, and xanthoxylum, along with extreme purgation. The belladonna mixture was first described in 1900 by Dr. Albright, of Philadelphia, and later incorporated into the Towne-Lambert treatment. The belladonna is gradually increased until the patient gets under the influence of this drug, and every 10 hours the patient is given 5 compound cathartic pills along with 5 grains of blue mass. Salines are given in between and castor oil at the end of the purgation period, which usually comes at the close of the third day. Other drugs such as oxgall, phenacetin, caffein, pyramidon, salicylates, sodium nitrate, sodium bromide, codeine, and chloral are also advocated as part of the treatment, depending upon the symptoms. It was claimed that this treatment obliterated the craving for narcotics. It became very popular and it has been given to thousands of patients. Some years ago I interviewed several hundred patients who had gone through with the Towne-Lambert treatment, and most of them expressed a horror of it. I also personally gave it to 50 patients and finally became convinced that it not only increased the suffering of the patients but was positively dangerous. The advantages of this treatment, if any, are that in sanitaria the patient is so disabled by it

that he is likely to stay until the morphine is withdrawn. The psychotherapeutic value of giving some form of medication every few hours is, of course, not to be overlooked.

The advent of biochemistry and immunology into medicine led to the invention of a number of treatments based on a supposed disturbance of the chemistry or metabolism of the body tissue and so we have--

Autohaemotherapy (injection of blood previously withdrawn from the patient);
Autogenous serum therapy (injection of serum from an artificially-produced blister);
Narcosan treatment (injection of vegetable lipoids);
Sodium rhodanate treatment (based on the theory that the nervous tissue has been agglomerated by morphine and sodium rhodanate peptizes it);
Lipoid therapy (based on feeding or injection of lipoids to correct a so-called lipoid disturbance of the nervous tissue. The Narcosan treatment was also concerned with lipoid metabolism);
Rossium treatment (based on an anaphylactic theory of drug addiction); and
Insulin treatment.

All of these treatments are useless; most of them are harmful; some of them have been described as being absolutely specific for opium addiction.

The errors into which observers may fall and to which all of the advocaters of these specific treatments have fallen is illustrated by the history of Narcosan. This preparation was invented by a chemist who claimed experimental proof of certain lipoid disturbances that were corrected by Narcosan, said to be a solution of lipoids together with non-specific proteins and water-solution vitamins. A

glowing account of the virtues of this treatment was given by two prominent New York physicians after it had been tried on 366 patients in a New York institution. From their report it seemed that the treatment problem had finally been solved. Narcosan was said not only to relieve the distresses of withdrawal, but it created some situation whereby patients undergoing this treatment developed a positive distaste for narcotics so that morphine or heroin given to such patients brought about distressing symptoms and even collapse. The Narcosan treatment, it was said, was self-protecting against the patient's indulging in narcotics on the sly. The article in question created interest in this treatment all over the world, but many physicians were skeptical. Finally, a committee of prominent physicians, known as the Mayor's Committee, was formed in New York to study the drug addiction problem. This Committee, with Dr. Alexander Lambert acting as Chairman, investigated various methods of treatment, including Narcosan. A group of controls was used so that the patients receiving Narcosan and the accompanying control were in complete ignorance of the nature of the treatment employed; in fact, thought the same treatment was given each. The Committee (1) found that the Narcosan treatment was not only not beneficial but that it increased all the distressing symptoms of withdrawal and was positively dangerous to life. It also found that the treatment was not self-protective against the patient's indulging in narcotics on the sly.

The New York Committee tried out treatments with belladonna and

hyoscine in the same way and got the same results; in other words, patients receiving these treatments suffered a great deal more than those who received abrupt withdrawal, the so-called "cold-turkey" treatment.

The autohaemotherapy was tried out by A. G. Biggam (2), in Egypt, who found that it had no effect on withdrawal symptoms and did not have any tendency to prevent patients from relapsing as had been claimed by certain observers. In this treatment, blood was obtained from a superficial vein and injected deep into a muscle of the gluteal region. Injections of from 2 to 60 cc were made daily for about seven days. Biggam also investigated the autoserotherapy of Modinos, the so-called blister treatment. In this treatment a blister is made on the body and after 12 to 14 hours the serum from this blister is withdrawn in amounts of from 5 to 20 cc and injected immediately under the skin. Two other injections are made at intervals of 4 days. Modinos claimed that withdrawal symptoms were slight and that the patients so treated have no desire to return to the drug after discharge from the hospital. Biggam, however, treated some of Modinos' patients who had relapsed. He tried this treatment on 40 cases, using controls who were treated at the same time by the application of blisters and injections, not of serum but of a normal saline. The only effect that Biggam noticed from the blister treatment was that the blister caused considerable discomfort. There was no effect on the withdrawal symptoms.

Lipoids have been given by injections and also by feeding, with varying results reported by different observers. One Chinese observer feeds lipoids and gives his patients all the opium they want. He claims that they soon develop a distaste for opium and stop its use. We are not inclined to try this form of treatment, especially in view of the fact that an American observer found that Narcosan developed a distaste for morphine and heroin.

The insulin treatment has also been reported upon with varying results. In this treatment from 20 to 80 units of insulin are given daily, and it is claimed that this drug eliminates or prevents signs of abstinence by reestablishing equilibrium in the vegetative system that has been disturbed by the withdrawal of morphine. Dr. Himmelsbach, of this institution, found that insulin had no effect on patients treated here.

The latest specific therapy that I have any knowledge of is the Rossium treatment, based on an anaphylactic theory of drug addiction. The anaphylactic theory is not new, but the inventor of the Rossium treatment added some refinements to it, most of which are obviously errors. Because of the advertisement given this treatment, it was decided to try it out here, and Dr. Himmelsbach has run a carefully-controlled series of experiments that will be reported upon later. He has found that Rossium is of no value in the treatment of drug addiction.

Morphine withdrawal has been treated by hypnotism and by a conditioned reflex treatment. Using the latter treatment, one author thinks that he conditioned his patient by massaging the dorsal surface of the forearm for one minute after each injection. In a month's time he was able to substitute the morphine by physiological hypodermics. The injections were discontinued entirely in six weeks. The patient was said to grow sensitive to the needle. Another patient was conditioned by means of a tuning fork held close to the ear during the gradual withdrawal of morphine. These two cases obviously had nothing of value except a withdrawal treatment and the report is cited only to show how easy it is to be mislead about the effects of any given treatment.

The abrupt withdrawal, so-called "cold turkey" treatment, has been used extensively in prisons. It was, however, advocated by some observers as being the treatment of choice as long as 50 years ago. This treatment works very well in prisons where patients can be controlled. In young and healthy individuals the worst of the withdrawal symptoms are over within about five days and in about ten days such patients begin to gain weight. There is less suffering and decidedly less danger with this form of treatment than with some of the so-called specific treatments for which great claims have been made. The abrupt withdrawal treatment is not without danger in patients who are feeble from age or debilitated by disease, but the danger is decidedly less than with the hyoscine or belladonna treatments. I visited a prison some years ago where

2,400 patients had been treated by abrupt withdrawal, and only two of them had been given any morphine whatever. Each of these got one-quarter grain to avoid what appeared to be an impending collapse. There were no deaths.

There is no justification for giving the abrupt withdrawal treatment to patients with strong habits, as such patients suffer intensely and an occasional dose of morphine will take the edge off this suffering, thus avoiding possible collapse and also putting the patient in a better frame of mind. The extensive use of the abrupt withdrawal method in prisons seems to have been brought about partly by the too prevalent notion that the addict is a good-for-nothing criminal who deserves nothing but punishment, and partly through the idea (that even some physicians have) that the giving of morphine to an addict, even in treatment, is a sin. From the psychological point of view this attitude is entirely wrong, and the physician who approaches his patients with it will, of course, not see the necessity for attempting a reorientation of their personality so that they are fortified against a return to the use of narcotics. Nevertheless, the use of the abrupt withdrawal treatment in prisons in preference to the so-called specific treatments has doubtless saved a number of lives, and this method, if used along with some supportive treatment and a sympathetic attitude on the part of the physician, is the method of choice in prisoners who do not have strong habits.

The method of choice in prisons may not be applicable to sani-

taria or hospitals. The sanitarium physician must temporize with his patient somewhat in order to get him to accept treatment at all. Many patients come to these institutions dreading the treatment, and they would leave if an abrupt withdrawal should be attempted.

The New York Committee tried out a number of hypnotics, sedatives, and analgesics and found that none of them gave any obvious advantage over abrupt withdrawal and some of them made the patients worse. This Committee tried out two rapid withdrawal treatments with morphine and one with morphine and codeine. In a 7-day withdrawal the patient, after being stabilized on a certain amount of morphine, had one-seventh of this amount withdrawn each day for 7 days. In a 14-day withdrawal the patient, after being stabilized, had one-fourteenth of the amount withdrawn each day. In both of these treatments the results were decidedly superior to any of the specific or drug treatments that were tried and were also superior to the abrupt withdrawal method in that suffering was less intense, although the prolongation of the treatment caused some trouble in that patients would ask for more morphine than they were receiving.

The Committee also tried a codeine-morphine withdrawal in which the morphine was rapidly reduced in four days while codeine was given in 5-grain doses three times per day alternating with injections of morphine. On the fifth day after the morphine had been withdrawn, 5-grain doses of codeine were given every four hours. The dose was then gradually decreased until on the seventh and last day of the

treatment only a total of 6 grains were given. This treatment gave results between the 7- and 14-day withdrawal treatments.

Some years ago I found that rapid withdrawal in from 5 to 7 days, during which time the patient would only get from 2 to 3 grains of morphine, gave better results than other treatments.

Our method of treatment at the Lexington Hospital varies according to indications. Many patients come in who, for reasons already given, do not have very strong habits. These are usually abruptly withdrawn and given only supportive treatment, and most of them suffer very little. Aged patients, or patients suffering with strong habits, are rapidly withdrawn either with morphine in small doses, or codeine, or both. The idea is quickly to get them off the opiate they have been using by a method that guards against collapse and prevents excessive suffering. They are also given certain supportives, such as a warm bath of 5 or 10 minutes' duration three times a day, 2 drams of paraldehyde in order to produce sleep at night, and for those who do not eat well 1,000 cc of 10 percent glucose, which may be given three times a day. We have found that these glucose infusions tend to relieve the subjective symptoms for several hours. Salicylates and sodium bicarbonate may also be given according to indications. The results have been very good. There have, of course, been a number of patients abruptly withdrawn as a part of our research studies.

Patients from whom morphine is withdrawn rapidly gain weight

beginning about the 10th day. They also quickly regain full body vigor and feel well, but we have observed that old men who have had the habit for years take a much longer time to recuperate than young men. Some of the old men lie around without any "pep" and complain more or less for a month or two before they regain normal physical and mental vigor.

Many tuberculous patients have become addicted through the giving of opiates for cough. Our experience indicates that this is never justified unless the patient has such an advanced disease that death is certain. Our tuberculous patients all gain weight after the drug is taken away, and they do not cough any more than when they are receiving it. An example of the effect of morphine addiction and its withdrawal on tuberculous patients is that of an old man, a doctor, who came here with moderately advanced tuberculosis and drug addiction. He was rather feeble for the first two months after the drug had been withdrawn, but then began to gain weight and vigor, and on discharge, after 7 months, he had gained 50 pounds.

In conclusion, I may say that nothing is known about the fundamental mechanism of drug addiction, and that all withdrawal treatments based on theories of the mechanism have been failures.

Any treatment that has as a part of it the withdrawal of the opiate will effect physical cure of the addiction.

A large proportion of the treatments that have been advanced cause more suffering and more danger to the life of the patient

than abrupt withdrawal.

The treatment of choice, based on present knowledge, is rapid withdrawal, in 14 days or less, supplemented by certain supportive measures.

References

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