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Report of the Scientific Researches on the Venereal Diseases

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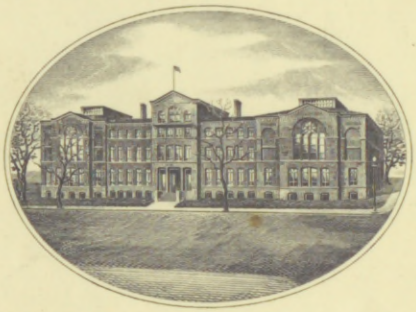

WASHINGTON, D.C.

Report of the

Scientific Researches

on the

Venereal Diseases

Published by the American Social Hygiene Association by agreement with the United States Interdepartmental Social Hygiene Board

370 Seventh Avenue New York, N. Y.

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PREFATORY NOTE

This report has been edited with the object of stating as concisely and directly as possible the results of the Scientific Researches concerning venereal diseases that were financed and directed by the U. S. Interdepartmental Social Hygiene Board during the years 1918, 1919, 1920 and 1921. After this time, the American Social Hygiene Association made grants to some of the investigators in order to enable them to complete the studies which were well advanced and for which funds were available.

These results have an immediate clinical interest and should prove of practical value to the busy practitioner of medicine, whose attention is hereby respectfully called to them.

EDWARD L. KEYES, M.D.

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PART I.

REPORT ON THE RESULTS ACHIEVED UNDER THE SCIENTIFIC RESEARCH FUND OF THE U. S. INTERDEPARTMENTAL SOCIAL HYGIENE BOARD

The United States Interdepartmental Social Hygiene Board was authorized by act of Congress on July 6, 1918, to consist of the Secretaries of War, Navy, and the Treasury (or their representatives), and the Surgeon Generals of the Army, the Navy, and the Public Health Service. The functions of the Board included "medical measures for the prevention, treatment, and control of venereal diseases; protective social measures primarily directed to the problem of safeguarding the Army and Navy; scientific research for the discovery of better medical methods for the prevention and treatment of the venereal diseases; and educational measures for the discovery or development of better educational methods in the prevention of venereal diseases, or for psychological or sociological research related thereto."

This report is concerned with "the scientific research for the discovery of better medical methods for the prevention and treatment of the venereal diseases."

PRELIMINARY OBSERVATIONS—The story of the national war emergency that awakened the people of the United States to the grave national menace from venereal disease, the impairment in military efficiency resulting therefrom, and the necessity of attacking this menace at its source in the civilian population, may be found in the Congressional Record (notably in the report of the Sub-committee of the Senate on Military Affairs for June 18, 1918) and in the Reports of the Interdepartmental Social Hygiene Board for 1920, 1921, 1922. It suffices to note here that the summary of scientific research concerning the venereal diseases detailed in the following pages amply supports the statement (in the report for 1922) that "there can be no question as to the success of the interrelated medical, social, scientific, and educational activities that have been instituted by this board pursuant to congressional authorization and direction. . . . The program of medical research stimulated by the United States Interdepartmental Social Hygiene Board has stimulated a much larger degree of scientific interest in these diseases than ever before. The investigation of venereal diseases has been made respectable. Several hundred scientific men and women have been led to devote their technical skill and their medical knowledge to the problems of treatment and prevention. Twenty-five of the best equipped of our scientific institutions have concerned themselves with these researches. These activities will not terminate with the withdrawal of governmental support even though there will be an immediate reduction in research activities."

THE DIVISION OF SCIENTIFIC RESEARCH—The special division for scientific research of the Board was organized as follows:

FUNCTIONS

1. Select colleges, universities, other institutions with adequate technical equipment, personnel, experience in research.
2. Sift, judge, and estimate value of researches proposed.
3. Apply rules and regulations of Board as required by law.
4. Determine sums to be expended on approved researches.
5. Approve budgets and authorize revisions.
6. Follow up disbursements and determine value of research work done.
7. Prepare reports, technical data, memoranda, and bulletins.

PERSONNEL

A. Division Staff—

Chief of Division, Executive Secretary
Supervising Assistant 1
Stenographer 1

Note:—General services furnished this division by—
Executive office.
Business office.
Division of Records, Information, and Planning.
Personnel Section.

In January, 1919, the Board adopted the following rules and regulations to cover appropriations for scientific research as follows:

1. Appropriations from this fund will be made only to universities, colleges, or other suitable institutions that give satisfactory evidence of possessing a staff of scientific experts and an equipment of scientific apparatus, supplies, and resources that will guarantee that the researches undertaken will be carried out under approved scientific conditions and in conformity with scientific methods.
2. Appropriations for this fund for scientific research will be made only for definite investigations that are described by the proposers in sufficient detail to satisfy the Interdepartmental Social Hygiene Board that there is a justifiable expectation that these researches "will discover more effective medical measures in the prevention and treatment of venereal diseases."
3. The universities, colleges, or other institutions proposing researches and asking for appropriations will furnish information on the following subjects:
   (a) Name of institution requesting appropriation.
   (b) Name, office, and address of official representative of this institution.
   (c) Title concisely descriptive of research proposed.
   (d) Laboratory in which research is to be carried out.
   (e) List of more important scientific publications from this laboratory.

(f) Name and concise statement of the scientific training of the laboratory chief or director or other individual responsible for the scientific policy of the laboratory.

(g) Laboratory staff, giving names, degrees, etc.

(h) Laboratory equipment and facilities, with a concise statement indicating scientific and working capacity of the laboratory, and coöperating laboratories, departments, and agencies.

(i) Description of research proposed; outline plan in sufficient detail to show clearly its scientific character and justify the expectation that it will discover "more effective medical measures in the prevention and treatment of venereal diseases." Include references to important scientific investigators, but may include salaries for technical assistants.

(j) Will this institution be able to carry on the research proposed if it receives no financial aid from the Interdepartmental Social Hygiene Board?

4. Universities, colleges, and other institutions asking for appropriations will furnish the Board with a budget made out on forms supplied by the Board and will make an accounting of their disbursements in conformity with the rules of the Comptroller of the Treasury of the United States Government.

The Division of Scientific Research distributed $100,000.00 (approximately) a year during the years 1919 and 1920, and during 1921 distributed $85,000.00 (this last on a 50-50 basis) for 40 scientific researches in 23 institutions. (See Appendix A.) Two of these researches were concerned with chancroid, 14 with gonorrhea, 23 with syphilis, and 4 with general problems relating to venereal disease.

COMMENT ON RESULTS ACHIEVED—As a preface to the detailed consideration of the researches endowed by the Interdepartmental Board it seems well to discuss several questions that naturally arise in connection with the profit to be expected from such endowment under other conditions. In other words, do the results of this experiment in government subvention of laboratory and clinical activities encourage the belief that such subvention might profitably be adopted by the government as one of its normal functions?

The actual results of the present experiment tempt one to answer in the affirmative. One might pick out almost (but not quite) at random a number of contributions on the list, any one of which might well be estimated as reimbursing the total governmental expenditure. Among those that will most immediately appeal to the practitioner of medicine may be mentioned the interpretation and reduction of the toxicity of arsphenamine, the great improvement in culture methods for the gonococcus and the bacillus of chancroid, and equally startling improvement in staining methods for spirochetes in tissue and in smears, the first clinical tests of tryparsamide and the support thereby of the organotropic as contrasted to the spirotoxic attack upon syphilis, the most thorough study that has yet been made of the diagnosis of

chronic gonorrhea in the female, and the series of studies at various institutions upon the clinical and pathological problems of hereditary, cerebrospinal and familial syphilis. And to these one must add the more elusive results, such as the impetus given to the study of the problems of venereal disease in institutions all over the country, and the final profit to be expected from many of the researches that have as yet shown only the prospects of ultimate application to practice.

In this connection two questions naturally arise. In how far has government support furthered the results we claim for it? And what further progress is immediately in sight?

As to the first question, there can be no doubt. The money required for these studies was not in sight. At some future date some among them would undoubtedly have seen the light; most of them would, to say the least, have been indefinitely delayed. But the question was asked at the close of each investigation whether further financial support could be made use of for immediate development of the problems at hand, and in a surprisingly large proportion of instances the reply given indicates that the immediate problems at hand have been disposed of, and that the head of the department sees no further development of his problem in sight.

This situation was, of course, not universal. Indeed, it should perhaps be insisted upon chiefly because it illustrates so admirably the honest spirit in which these investigations were conducted. But inasmuch as the best workers of the country were engaged in the work, it also suggests that a continuance of the fund, with the inevitable insistence of money—especially government money—to get itself spent, would have seen a deterioration in the product and a final degeneration of the whole mechanism into an official routine quite incompatible with free research. The scientific work of the Interdepartmental Board was conceived and executed in that spirit of idealism on the part of the government officials in charge which was calculated to meet the scientists on their own ground. That youthful idealism which the War inspired has gone, and gone with it is the probability of reproducing the circumstances necessary to the successful continuation of this work at the present time. The scientist, like the rest of us, must return to the humdrum of peace.

But to return to our topic; what shall be the evaluation of the scientific achievement? Time alone can answer that question. We shall not attempt an answer, but refer the curious to the following excerpts, summaries and quotations of original publications from which to draw their own conclusions.

PART II.
THE RESEARCHES SUMMARIZED

STRAINS OF GONOCOCCI—Ever since Torrey in 1907 published his conclusion that the gonococcus group embraces a heterogeneous collection of types or "strains," few serious efforts have been made to determine the serological unity or diversity of these and other strains, and such investigations as have been made have resulted in no fixed conclusions. Hermanies studied eighty-five strains and divided them into six serological groups, forty-one in group 1, thirty-six in group 2 (with four sub-types), and the rest scattering.

Torrey and Buckell[1] have resumed the study of gonococcus strains, using seventy-seven cultures obtained from the most diverse sources, anatomical (male urethra, female urethra, cervix, joint, blood, eye, and the vagina of infants) as well as geographical (England, France, Germany, Belgium, Egypt, Mexico, Panama, and various states of the United States). Their analysis by agglutinin absorption methods of the serological relationship among these strains indicates that they may *not* be distributed among a number of clear-cut immunological types.

"Although this investigation has not demonstrated the existence of distinct immunological types to each of which a considerable number of gonococcus strains might be referred, it was found feasible to classify our strains under the three general headings of (a) regular, (b) intermediate, and (c) irregular strains.

"Evidence is submitted which indicates the existence of a marked tendency to antigenic lability on the part of the gonococcus. We believe that instability of antigenic constitution is a general characteristic of the gonococcus group and that the strains exhibiting this tendency may not be segregated into one particular type, as suggested by Hermanies.

"Cross absorption experiments have indicated clearly that no definite serological distinction may be drawn between strains isolated from vulvovaginitis in children and those from gonorrheal infections in adults (as had been suggested by Louise Pearce).

"Among our regular strains, we have found certain ones which are highly generalized from the antigenic standpoint, and which appear to be representative of a large part of the gonococcus group.

"A marked degree of correspondence was noted between strain affinities as revealed by agglutinin absorption and complement fixation tests."

These observations are most important as emanating from the author of the well-known "Torrey strains." In 1907, Torrey was inclined to group his strains under three types of rather loose constitution, and this position has been confirmed by his present researches; but for practical purposes the great interest in his work attaches to his observation that in the fourteen years intervening between the two studies, five strains that had been apparently distinct serological entities in 1907 had, in 1921, become very closely related as regards their

antigenic constituents; i. e., the antigenic relation of strains is changeable (labile). The corrolary to this he also proves; viz., that there exists a type (or types) of gonococcus possessing generalized relationships and a wide range of antigenic properties fitting it peculiarly for vaccine and anti-serum, while other strains are peculiarly suited for preparing antigen for the complement fixation test.

Cook and Stafford[2] have also failed to type strains of gonococci "by means of the alexin fixation and agglutinin reactions or by means of the method of absorption of agglutinins."

GONOCOCCUS CULTURE—The difficulties that surround the culture of gonococci for diagnostic purposes are well known. These difficulties arise both during the transfer of specimens from the patient to the laboratory and during the isolation and cultivation of the microörganism.

Torrey and Buckell[3] have devised the following method whereby secretions containing gonococci may be preserved several hours "with a minimal risk of loss of viability on the part of the gonococci."

"One c.c. portions of a mixture of 2 parts of semisolid 'vitamin agar C' (see below) and 1 part of ascitic fluid are placed in narrow test tubes (6" x ½"). This mixture is semifluid in consistency. After the swab has been infected with the gonorrheal discharge it is placed in a tube containing this medium, care being taken that the swab becomes well moistened with it, and is left there. This tube is then placed under the clothing; preferably next to the skin. It is advisable, though not essential, to warm the medium slightly just before introducing the swab. On reaching the laboratory the tubes containing the swabs are placed at once in the incubator. The plates, which should be slightly warmed, may be seeded then or the tubes may be left there for three or four hours before this is done. Within this period the gonococci apparently do not die out at all; in fact, they begin to increase in numbers. The plating, however, should not be delayed so long that the contaminating bacteria have an opportunity to overgrow the gonococci. Even at room temperature gonococci in pus deposited on the surface of an ascitic semisolid agar tube and kept in a dimly lighted place have remained viable for a surprisingly long time." Gonococci in pus obtained from acute urethritis in the male have been found alive after 48 hours: after three days they had died.

"In seeding plates the swabs are applied to only about one-fourth of the surface area of the medium. The swab should be rolled so that all parts come in contact with the medium. With a platinum loop the other three-fourths of the plate surface are now seeded by streaking from the part to which the swab was applied. In that way a proper distribution of colonies is likely to be obtained on some part of the plate. Before a second plate is seeded the swab should be reintroduced into the tube containing inoculated semifluid ascitic agar, and so on for each plate."

The media employed for the isolation of the gonococcus by Torrey are the following:

A. (A modification of Thalmann's medium). Place 1250 gm. of fresh, chopped, fat-free veal and 2 liters of distilled water in a pot and bring slowly

to a boil, allowing it to simmer for 20 minutes, with occasional stirring. Strain through cotton flannel, cool and remove the fat. Place in a double boiler over a saturated brine bath and raise the temperature to about 60° C. Add 20 gm. of peptone (Difco), 40 c.c. normal, fresh urine, 10 gm. NaCl, 40 c.c. glycerole and 36 gm. flaked agar. Allow this to boil for 45 minutes and then adjust the reaction to pH 6.9, using 10 per cent sodium carbonate, and boil for 20 minutes longer. Remove from the brine bath; make up loss from evaporation to 2 liters with distilled water. Filter through canton flannel and tube in 10 c.c. amounts. Autoclave at about 12 lbs. pressure for 10 minutes.

In preparing the plates, 5 c.c. of ascitic fluid, free from bile, and 0.5 c.c. of a 1:3000 dilution of iodin-green (Grubler) are added to each tube of melted medium, just before pouring. The final reaction is generally about pH 7.2. It should not be more alkaline than this.

If to be used in slants, the amount of agar is increased to 40 gm.

B. (a modification of Huntoon's "hormone" medium). Five hundred gm. of fresh, chopped beef heart, free from fat, one whole egg and 1 liter of distilled water are placed in a double boiler over a free flame and the temperature maintained at 60° C., with constant stirring, for 5 minutes. Fifteen gm. of peptone (Difco) and 18 gm. of flaked agar are now added and the temperature raised until the mixture assumes a brownish color. The mixture is then made slightly alkaline to litmus, using a 10 per cent solution of sodium carbonate. It is next placed in a flask, or preferably a coffee pot, and heated to 100° C. in the Arnold steam sterilizer for 1 hour. The clot is then separated from the sides of the receptacle, and it is replaced in the sterilizer for another hour. It may be cleared by centrifuging or by straining through fine wire mesh and then through glass wool. A clear medium may often be obtained if the meat residue is deposited on the glass wool in a funnel and the fluid portion allowed to percolate through several times. Neither cloth, cotton nor any other material with absorptive properties should be used in clarifying the medium. After filtering the reaction is brought to pH 6.8. It is reheated and tubed in 10 c.c. amounts. It may be sterilized in the autoclave at 12 lbs. pressure for 10 minutes, but fractional sterilization at 100° C. flowing steam is preferable. In preparing the plates, 5 c.c. of ascitic fluid is added to each tube of melted medium, just before pouring.

Torrey employs the following modification of Medium B for carrying stock strains of gonococcus. It is semisolid and contains no ascitic or other serous fluid. This medium may be employed for primary gonococcus culture (for identification purposes) by the addition of about 1 c. c. of ascitic fluid per tube.

C. The ingredients are the following:

Distilled water	1000 c.c.
Fresh chopped beef heart	500 gm.
Peptone	10 gm.
NaCl.	5 gm.
One whole egg	

The same procedures are followed as in the preparation of Medium B, and the final reaction is adjusted to pH 6.8. The medium is tubed in about 7 c.c. amounts and sterilized in the Arnold sterilizer.

Cook and Stafford report that "gonococcus stock cultures grow satisfactorily for all routine work on testicular agar. Chocolate blood testicular agar was found to be a useful medium for increasing the vitality of a weakly growing culture." They do not give the precise method of preparing the media.

Erickson and Albert[4] prefer testicular blood agar with a reaction of pH 7.4—7.8 both for isolation and subsequent cultivation of the gonococcus. They give the following formula:

"Beef testicle from which all connective tissue has been removed is put through the meat grinder, weighed and, with twice its weight of distilled water added, is infused over night on ice. The following morning the mixture is heated in a double boiler to 50° C., allowed to stand for one hour and then brought to the boiling point. Let it stand for another hour to let the solid particles settle, after which the liquor is decanted off and used as the infusion for the preparation of culture media.

"For the preparation of testicular infusion agar, 2 per cent peptone, 0.5 per cent glucose, 0.2 to 0.3 per cent monobasic sodium phosphate and 2.5 per cent granular agar are added. This is heated over a flame and stirred constantly until the agar is dissolved. The medium is titrated with phenol-red as an indicator and the reaction adjusted to pH 7.4 to 7.8; if phenolphthalein is used as an indicator, it should be adjusted to a 0.6 reaction. The medium is tubed and autoclaved at 15 lbs. for 20 minutes. The titration is checked after sterilization. While the tubes are still liquid (just before the agar solidifies) human blood in the proportion of 0.5 to 2.5 is added. If human blood is not available, defibrinated rabbit's blood (1-2 per cent) may be substituted."

The conditions favoring maximal growth of the gonococcus have been studied by each of the three groups of observers.

Torrey and Buckell summarize their conclusions as follows:

"For the optional growth of the gonococcus the reaction of the medium should be set close to the point of absolute neutrality; between pH 6.8 and 7.4. The reaction range, however, compatible with growth on a semisolid medium containing a growth accessory factor was found to extend from pH 5.8 to 8.2.

"The relation of viability to reaction of the medium was studied. A slightly acid reaction was found, on the whole, more favorable than a slightly alkaline reaction. The remarkable retention of viability for one year was noted in reference to one strain seeded on a semisolid 'hormone' agar (Huntoon) with a primary reaction of pH 6.3.

"No better growth was obtained by the use of a medium containing a high concentration of amino acids than when prepared with the specified amount of peptone.

"The presence of glucose does not enhance the growth of the gonococcus.

"The growth stimulating principle in a medium prepared according to Huntoon's method was found to be slightly impaired by exposure in the autoclave to 120° C. for 5 minutes and seriously injured, but not entirely destroyed, after 30 minutes at that temperature.

"Abundant moisture in the air of the incubator is a prime requisite for the optimal growth of the gonococcus, especially on first isolation, but a reduced oxygen tension was not found to be advantageous.

"Fermentation tests constitute the most valuable single criterion for the differentiation of gonococci from other similar gram-negative diplococci. No one of 86 gonococcus strains tested split maltose, and all but one fermented glucose. None of the strains tested on levulose and galactose split these sugars. A sugar free, semisolid, ascitic agar medium, with bromthymol-blue as an indicator, has proved satisfactory as a base for fermentation tests. Differential readings may be made after 18 to 24 hours' incubation.

"A semisolid, sterilizable medium with a growth accessory factor (Huntoon formula) was found admirably adapted for carrying a large collection of gonococcus strains. Replantings have not been necessary oftener than once in three or four weeks.

"The plating mediums are described which have been found serviceable in the isolation of the gonococcus. One of these mediums is made in some degree selective by the incorporation of a dye, iodin-green. For the best results the reaction is of prime importance; the final ion concentration should be about 7.2."

Erickson and Albert summarize as follows:

"The absence of sodium chloride (from their testicular blood agar medium), the proper reaction (pH 7.4—7.8) and moisture content are especially important.

"Blood or blood serum mixed with the testicular agar or smeared on the surface of slanted tubes is necessary for the ready isolation of the gonococcus, but is not essential for the securing of growths of stock cultures.

"Fermentation tests made with solid mediums containing 0.5 per cent glucose and phenol-red as an indicator result in a significant primary acidity and secondary alkalinity.

"Reduced oxygen tension is of no practical value for either the isolation or subsequent cultivation of the gonococcus.

"Analine dyes of the violet and green colors tend to inhibit the growth of staphylococci more than that of gonococci from cases of mixed infection. Methyl-violet added to blood-testicular agar in a proportion of 1:200,000 to 500,000 appears to be of great value."

Cook and Stafford[2] state that "Environmental requirements of the organism included moisture of the atmosphere but not a reduced oxygen tension."

Swartz,[5] and Herrold,[6] on the other hand, have claimed some advantage from growing gonococci in an atmosphere the oxygen tension of which is reduced. But Erickson and Albert, after trying the methods of Swartz, Herrold, and others and failing to verify the advantages claimed for the reduction of oxygen tension, suggest that "it is probable that the more satisfactory results attained by certain investigators is due, not to a reduced oxygen tension, but to the presence of an increased amount of moisture due to the technic used to exclude air."

GONOCOCCUS COMPLEMENT FIXATION TEST—The studies of Torrey and Buckell[7] should introduce a new and much needed degree of accuracy in the complement fixation test for gonorrhea. Hitherto the word "strain" has had only the vaguest significance, and the multiplication of so-called strains has been quite blind and in large measure purposeless insofar as the preparation of a polyvalent antigen was concerned. But Torrey and Buckell have shown that their strains 34 and 41 are so generalized in their antigenic affinities, so nearly "supergenococci" in this respect, that they say "If a single antigen is employed for diagnostic tests, we would advise using either strain 34 or 41 alone, or perhaps in combination. It seems very questionable if better results would be obtained by combining a large number of regular and irregular strains in an attempt to produce a polyvalent antigen. In the first place, it is questionable if such an antigen covering all the possible variants could be prepared; and, in the second place, when a large number of strains each with more or less limited affinities and representative of an equal number of so-called types are combined in a single antigen, then the antigenic elements of each of these types becomes so diluted that, in the dosage permissible, the effectiveness of each type would be greatly curtailed. Perhaps the best procedure would be to use two separate antigens in each test; one prepared with one or two representative strains with generalized affinities and good combining qualities, and the other with selected irregular strains."

PRECIPITIN REACTION—Margaret F. Kelley[8] proves that the gonococcus precipitin reaction of Robinson and Meader is not applicable to the determination of the presence of gonococci. (Herrold obtained fairly accurate results with precipitin.)

INTRACUTANEOUS REACTION FOR GONORRHEA—Cook and Stafford[2] tested 11 persons proven or suspected of harboring gonococci and 18 controls by cutaneous injection of "gonococcin" and of "meningonoccin." In general the results were identical for the specific and the nonspecific vaccination both in the gonorrheal cases and in the controls. They conclude that the test is without value.

PROVOCATIVE VACCINATION—Herrold[9] failed to evoke a focal reaction in the gonorrheal urethra by the subcutaneous injection of gonococcus vaccines. The secretions were cultured 24 hours after the injection. Ten cases with negative culture before injection remained negative; seven positives remained positive; one positive before injection was negative thereafter.

(It has long ago been shown that a positive complement fixation test can not be evoked by vaccination unless the blood has recently been positive. Such an evocation therefore means that the patient has recently had gonorrhea.)

COMPARATIVE VALUE OF SMEARS, CULTURES AND COMPLEMENT FIXATION TEST IN THE DIAGNOSIS OF CHRONIC GONORRHEA—Herrold has tabulated the results of his study of 100 cases of gonorrhea *in the male* as follows:

Number of cases	Culture		Complement fixation				Positive smear	Duration of infection				Anterior urethritis	Pus cells in prostate or semen	
	—	+	0	± or +	++	+++ or ++++		2 to 6 mos.	6 to 12 mos.	Over 1 Year	Average mos.		Absent	Present
30	30	0	30	0	0	0	0	4	17	19	16	16	11	19
26	26	0	0	19	5	2	0	7	8	11	11	11	9	17
44	0	44	0	6	16	22	14	33	10	1	4	22	4	40

It is to be noted that he obtained positive smears only in those cases showing both positive culture and fixation; that all cases showing positive culture had also a positive fixation (though this reaction was vigorous only in half the cases); that the duration of the infection in this positive group averaged four months; that the milder degrees of fixation persisted long (sometimes as long as a year) after it was impossible to identify gonococci by smear or culture; that pus in the prostate or semen is not an evidence of infectiousness.

But the diagnosis of the presence of gonococci in the cervix or urethra of women is a much more complicated matter. Torrey, Wilson and Buckell state "that the results of this investigation tend to confirm the general impression that neither clinical observations alone, cultural tests, gram-stained smears nor fixation tests, as single methods of diagnosis, can be relied on as guides to diagnoses of actual infection with the gonococcus in cases of suspected gonorrhea in women."

"Considering first clinical observations, we find that 9 of our 29 culturally positive cases harbored the gonococcus in the cervix uteri without . . . symptoms definite enough to warrant a clinical diagnosis of gonorrhea. Also 7 other cases, diagnosed as doubtful gonorrhea, which were culturally negative, gave definitely positive complement fixation, and two of them also positive smears. Conversely, among 33 cases given a diagnosis of chronic gonorrhea, there were 5 cases in which the clinical diagnosis was supported neither by the cultural test nor by repeated fixations and smears. . . .

"By way of a general conclusion it may be stated that the smear, cultural and complement fixation methods of diagnosis in chronic gonorrhea in women have all proven useful, and that their relative values correspond to the order in which they are named, the last being the most valuable. Whenever possible, however, each test should be carried out, as it is shown that they tend to supplement each other."

MERCUROCHROME—Studies of mercurochrome have been published by White,[10] its inventor, and Young,[11] White and Swartz.[12] These publications encourage the use of mercurochrome in a great variety of infections, because of its singular combination of blandness, antisepsis, and deep penetration.

The authors state that it "has not proved to be vastly superior to all other drugs in acute gonorrhea, although certainly quite efficient. . . . In chronic infections of the urethra, prostate and vesicles its great value has been amply proven. . . . The results obtained in many cases of chronic cystitis are remarkable, long standing infections often clearing up in a few treatments. The coccus infections are more resistant to mercurochrome than the colon bacillus infections. . . . Mercurochrome is less irritating and produces less reaction in the renal pelvis than silver nitrate solution, while possessing about equal germicidal powers, but in some cases both drugs should be used alternately and sometimes silver is better. . . . Continued use has proven mercurochrome to be a most satisfactory dressing for venereal ulcerations and buboes. . . ." It is also recommended for general surgical use.

It is not to be expected that mercurochrome should prove so generally efficacious in other hands as it did in those of the first experimenters. It is now chiefly employed as an irrigation for bladders infected by the colon bacillus, in the absence of pyelitis.

URINARY ANTISEPSIS FOLLOWING THE ORAL ADMINISTRATION OF PROFLAVINE AND ACRIFLAVINE—Davis,[13-14] after pointing out that hexamthylenamin is the only satisfactory urinary antiseptic we possess, and that it has grave inconveniences, such as its irritating qualities, its ineffectiveness when the urine is alkaline, and its problematic value at the level of the urinary pelvis, shows that "proflavine and acriflavine, administered by mouth in 0.1 gram and even in 0.05 gram dosage, to normal individuals is secreted in the urine in sufficient concentration to render the latter an unfit culture medium for the colon bacillus and staphylococcus, *provided the urine is alkaline.* . . . This antiseptic action becomes evident about two hours after drug-administration, and persists for at least eight hours. . . . No claims are made for clinical results following the internal administration of these dyes. . . . Experimentally, however, the above results constitute a distinct step forward, in demonstrating the hitherto theoretical possibilities offered by the analin dyes."

SALIGENIN—Hart and Hirschfelder[15-16] were inspired by the relatively low toxicity of phenyl carbinols, the presence of carbinol groups in many of the most active natural alkaloids, and the interesting local anesthetic and anti-spasmodic properties possessed by phenyl carbinols and their esters, to experiment upon the mercurial compounds of this group as antiseptics. Much chemical ground has been covered, but no striking results applicable to venereal diseases obtained, except that Hirshfelder and Wynne[17] find that a 4 per cent solution of saligenin acts as efficiently as an anesthetic in the female urethra as does a 10 per cent solution of cocaine.

A SIMPLIFIED TISSUE STAIN FOR SPIROCHAETA PALLIDA—Warthin and Starry[18] in January, 1920, first described a method whereby the spirochaeta pallida could be demonstrated in ordinary tissue sections; a method whereby the old Levaditi method, requiring at least ten days for its performance, and the examination of hundreds of sections, the hunting for spirochetes becoming a "needle-in-the-haystack affair," was superseded. A year later they introduced a further modification of their method, simpler, more rapid, more certain. They describe this method as follows:

Warthin and Starry's Silver-Agar Method[19]

1. Tissues fixed in neutral formaldehyde.
2. Embed in paraffin.
3. Cut, and mount sections on cover-glasses with albumin fixative.
4. Remove paraffin (xylene, alcohol, water).
5. Rinse cover-glass with section in 2 per cent silver nitrate; cover wet section with another perfectly clean cover-glass, so that they are held together by capillary attraction; then place them carefully in a bottle of 2 per cent silver nitrate and place in incubator for from thirty minutes to one hour; then remove from the silver nitrate and separate cover-glass.
6. Place cover-glass with section in this reducing mixture:

2 per cent silver nitrate solution	3 c.c.
Warm glycerin	5 c.c.
Warm 10 per cent aqueous gelatin solution	5 c.c.
Warm 1.5 per cent agar suspension	5 c.c.
5 per cent aqueous hydroquinone solution	2 c.c.

7. After the section is reduced, remove and rinse in 5 per cent sodium thiosulphate (hyposulphite) solution.
8. Rinse in distilled water.
9. Absolute alcohol, xylene, balsam.

GENERAL CONSIDERATIONS.—Fixation should be complete to give the best results. Thin slices of tissue, 5 to 7 mm. thick, left in 4 per cent neutral formaldehyde (10 per cent formaldehyde solution) from one to three days give the best results. If tissue is put into alcohol before the formaldehyde fixation is complete, the results are less satisfactory. If the formaldehyde fixation is complete it is not necessary to wash the tissue in water before putting it into 96 per cent

alcohol. Some of our best results have been obtained in tissues kept many years in 4 per cent formaldehyde. The importance of fixing tissues as soon as removed from the body, or as soon as possible after death, must be emphasized again.

From 96 per cent alcohol the tissue is run through absolute alcohol, two changes of xylene and two of 52° C. paraffin. The sections should be cut about 5 microns thick for the best results, although from 8 to 12 microns give practical sections. As they are cut they are floated on warm distilled water that has recently been boiled to drive off the air. The under or shiny side of the section is placed on the water. When the sections have flattened out on the warm water they are caught upon the prepared cover-glasses, the water blotted off, and then dried over the flame, or in the drying oven. The cover-glasses should be No. 1 or thin No. 2, three-quarter inch squares, or larger if the size of the section requires. They must be perfectly clean, free of all dirt and grease. A minimum amount of albumin fixative should be spread evenly on the clean cover-glass, so that there will not be enough of it to become heavily stained. The prepared cover-glasses should be placed on a clean card-board, covered with clean paper and dried in the incubator for twelve hours before using. They should not be dried by passing through the flame. It is advisable, therefore, to keep a supply of such prepared cover-glasses on hand.

After the mounted paraffin sections have been dried on the cover-glasses, the paraffin is removed by heating over the flame and dropping into xylene, followed by absolute alcohol and then distilled water.

The silver impregnation should be carried out in the dark (dark bottles covered with black paper). Wide-mouthed bottles with tightly fitting corks should be used. The mounted cover-glass is taken from the distilled water, rinsed in 2 per cent silver nitrate solution, and then covered with another clean cover-glass also wet with the silver solution. The silver solution should always be freshly made, and should never be used after it is from 3 to 4 days old. During this time the same solution may be used over and over again, if kept uncontaminated and in the dark bottle. The bottle should contain enough of the silver solution so that when the cover-glasses are placed on edge against the side of the bottle, it will not completely cover them. The cover-glasses are held together by capillary attraction, and if placed against the side of the bottle wet and the silver solution then poured in so as not to cover them completely, they will be held upright also by capillary attraction, and will not slip apart. The bottle is then tightly corked and placed in the incubator for from thirty minutes to one hour. After impregnation, the cover-glasses are removed, separated, and the mounted section put into the reducing mixture section side up.

The reducing mixture consists of 3 c.c. of a 2 per cent silver nitrate solution, 5 c.c. of warm glycerin, 5 c.c. of a warm 10 per cent gelatin solution, and 5 c.c. of a 1.5 per cent warm agar suspension, to which mixture from 0.25 to 2 c.c. of a 5 per cent hydroquinone solution is added just before using. The warm glycerin and gelatin solutions and the silver nitrate are first thoroughly mixed, then the agar suspension is stirred in with a glass rod, and finally the hydroquinone, just before the sections are placed in the mixture. The agar suspension must be carefully made. One and five-tenths gm. of agar cut up into small bits is added to 100 c.c. of distilled water and carefully and slowly heated to the boiling point, being constantly stirred with a glass rod. When the agar has gone into fine suspension, the solution is poured into a bottle, which is corked

lightly and kept on top the paraffin oven. Should the agar become flaky and settle out, it must be brought to the boiling point again with constant stirring. It should be just thin enough to pour, and not too thin and watery. The glycerin and gelatin solutions can also be kept warm on top of the paraffin oven.

The amount of hydroquinone added to the reducing mixture varies somewhat with the tissue and the fixation. In general it is best to use as small an amount as possible so that the reduction is not too rapid. A slow reduction usually gives the best results; but if too slow, precipitates will form and the spirochetes will not be well stained. Usually from 0.5 to 1 c.c. gives the best results; but in some cases more may be required. After the hydroquinone has been added, the mixture is stirred vigorously for a short time. It is then poured into a staining dish, and the mounted section removed from the silver solution, the cover-glasses separated, and that holding the section immersed in the reducing mixture for a number of seconds until reduction is complete. The longer the section is in the reducing mixture, the darker it will be. When it becomes a light reddish brown it is removed and washed in a 5 per cent sodium thiosulphate solution, then rinsed in distilled water, dehydrated in absolute alcohol, cleared in pure xylene, and mounted in balsam. When the sections have been properly stained they will now be light reddish brown. If a deep brown or black, the tissue will be too deeply stained and the spirochetes not sufficiently contrasted. Usually the albumin fixative on the cover-glass about the section is stained somewhat, and this can be rubbed off with a clean cloth, care being taken not to touch the section with the cloth. The upper surface of the cover-glass should be similarly cleaned. The section, of course, should never be allowed to get dry after the paraffin has been removed.

The use of the second cover-glass during the impregnation in the silver solution seems to be an essential feature of the method. We have never been able to secure good results by leaving the sections uncovered during impregnation. The spirochetes will stain only very faintly or not at all, precipitates more readily occur, and the tissue elements are more deeply stained.

It is important that the alcohol used be pure, and contain no mercuric chloride, copper or other metal. Alcohol dehydrated over copper sulphate should not be used. The tissues are easily mordanted, and the differentiation of the spirochaeta made difficult or impossible.

All solutions should be made in distilled water; and all glass-ware must be clean. Acid fumes should be avoided.

Our experience has taught us that not all formaldehyde-fixed tissues react to the silver impregnation method in the same way. Controls show that, with the same solutions and same conditions otherwise, some tissues appear granular, some a bright yellow, and others brown or black, while others will not stain at all. We believe that these differences in staining reactions are in part due to slight differences in fixation, contamination of the formaldehyde, etc., giving rise to differences in the process of reduction. We have found that by changing the reaction of the tissue before staining, it is often possible in such cases to affect the tissue conditions to such an extent that good staining results can be obtained. The best results have been obtained by the use of a 1 per cent solution of uranium or copper nitrate, or a 0.5 per cent solution of ferric alum. This is accomplished by placing the sections, from water,

after the removal of the paraffin, in one of these solutions for several minutes, and then washing thoroughly in distilled water before putting them into the silver solution. These solutions do not act uniformly in all cases. Uranium nitrate usually gives the best results, as, after its use, the tissue elements do not stain so deeply, leaving the spirochetes better differentiated. Copper nitrate and ferric alum have given especially good results in isolated cases of poor formaldehyde fixation. If the tissues are well fixed in formaldehyde, it is not necessary to use any one of these reagents, and they should be tried only when the method proper does not yield good results.

Aside from the use of the second cover-glass to cover the section during the impregnation, the successful operation of the method depends on the reduction process. This can be controlled to a great degree by varying the amount of hydroquinone and also by the temperature. After a little experience in judging the color obtained by reduction there should be no trouble in obtaining sufficiently good stains for diagnostic purposes. With a little more skill obtained by practice, the most beautiful preparations can easily be obtained. Any failures or inconstant results are due to differences in the physical condition of the reducing mixture, or in the fixation of the tissue.

THE WARTHIN TISSUE-SPIROCHAETA STAIN APPLIED TO SMEARS—Warthin and Starry[20] have adapted the above stain for use with smears of secretions or other fluids containing spirochetes. They very justly observe that the darkfield and India ink methods are not wholly reliable in inexpert hands even for the diagnosis of genital lesions, and are often misleading even to the expert in the diagnosis of lesions about the mouth. They cite cases and depict spirochetes resembling the pallida and commonly found about the mouth, in support of their contention. They describe the method as follows:

Method for Silver-Impregnation of Spirochetes in Smears on Cover-Glasses:

1. Prepare smears on No. 1 cover-glasses.
2. Dry thoroughly in the air.
3. Place in absolute alcohol 3-5 minutes.
4. Wash in distilled water.

(If hydrogen peroxide is used to clear background, the smear is placed in concentrated hydrogen peroxide for 5-20 minutes, and then washed thoroughly in a distilled water.)

5. Rinse cover-glass with smear in 2 per cent silver nitrate. Cover the smear side with another perfectly clean cover-glass also rinsed in the silver nitrate solution. Place the adherent pair of cover-glasses carefully, so as not to separate them in a bottle of 2 per cent silver nitrate, and place in an incubator for 1-2 hours; then remove the cover-glasses from the silver nitrate solution and separate them.
6. Place the cover-glass with the smeared side up in the following mixture:

2 per cent silver nitrate solution	3 c.c.
Warm 10 per cent aqueous gelatin solution	5 c.c.
Warm glycerol	5 c.c.
Warm 1.5 per cent agar suspension	5 c.c.
5 per cent aqueous hydroquinone solution	2 c.c.

7. After the solution is reduced remove and rinse in 5 per cent sodium thiosulphate solution.
8. Rinse in distilled water.
9. Absolute alcohol, xylol, balsam.

Discussion of the Method.—Clean cover glasses are essential. The cover-glass smears are prepared in the usual way. It is important that they be thoroughly dried in the air before attempting to stain them. Long exposure to air does not affect the staining quality if they are protected from dust and dirt. Dried smears containing Leptospira icteroides stained readily after standing 4 weeks. After drying, the smears are placed in absolute alcohol for 3-5 minutes, and are then washed with 2 changes of distilled water. It is essential that no other method of fixation than drying in air followed by absolute alcohol be used.

The silver-impregnation is carried out in wide-mouthed dark bottles fitted with tightly fitting corks. The smear is taken from the distilled water, and rinsed in 2 per cent silver nitrate solution; the smeared side is then covered with another perfectly clean cover-glass also rinsed in the silver nitrate solution, so that the wet cover-glasses adhere. The silver nitrate solution should be fresh, not over 6-7 days old. During this time the silver nitrate solution can be used over and over if kept in the dark bottle and free from contamination. The adhering pair of cover-glasses are put into the bottle so that they stand on edge against the side of the bottle, and enough silver nitrate is poured into the bottle to come about half way up the cover-glasses. If round bottles are used a small meniscus is formed between the cover-glasses and the side of the bottle, thus holding them in place. It is a good routine measure always to place the smeared cover-glass next to the wall of the bottle, so that there will be no danger of getting the cover-glasses mixed and placing the wrong one in the reducing mixture.

The reducing mixture is prepared by mixing the silver nitrate solution, gelatin and glycerol in order. This mixture is thoroughly stirred, and the agar suspension stirred in last. The hydroquinone solution is added just before using. About 2 c.c. give the best results. If the reduction takes place too rapidly add less, if too slowly, add more. The agar suspension should be carefully made as follows: One and a half gm. of agar are broken up fine, and placed in 20-30 c.c. of distilled water, and allowed to soak for a few minutes until the agar is saturated with water. The excess is then poured off and the agar washed with several changes of distilled water; 100 c.c. of distilled water is then added; and it is carefully brought to the boiling point with constant stirring. When the agar has gone into fine suspension the mixture is poured into a clean bottle, corked and allowed to cool. As the agar thickens it is occasionally shaken, and when it begins to set it is thoroughly broken up by violent shaking. It is then placed on top of the paraffin oven, after which it will remain a thick heavy mixture just fluid enough barely to run. All of the solutions used should be made up in clean porcelain or glass ware, and not in metal containers.

The hydroquinone is added just before using. After it has been added the mixture is stirred vigorously for a short time, when it is poured into staining dishes, and the smears removed from the silver nitrate solution, the cover-glasses separated, and the one having the smear is immersed in the reducing mixture for a number of seconds (30 seconds to 2 minutes) until the reduction is complete. The smears turn a light brown; if very thin they may scarcely change

color. When reduced, the smears are removed and placed in a 5 per cent sodium thiosulphate solution for a few seconds. They are then rinsed in water, dehydrated in absolute alcohol, cleared in xylol and mounted in balsam. The longer the smears are in the reducing fluid the darker they are; it is, therefore, advisable to leave them in it until the reduction is nearly or wholly completed.

The use of the extra cover-glass in the silver solution seems to be essential. Good results are rarely obtained if the smear is left uncovered, as the serum and cellular elements of the smear take a deep brown stain and the spirochetes are usually indistinguishable.

It is essential that all the reagents used be chemically pure and free from all contamination. The alcohol must be pure; if it contains phenol, mercuric chlorides, etc., the smears are easily mordanted, and the staining of the spirochetes becomes difficult.

The spirochetes in the stained smears should appear black against a light background. In heavy smears with much serum or cell material we have found it of great advantage to use hydrogen peroxide to clear up the background. Between steps 4 and 5 of the method the cover-glass is placed in concentrated hydrogen peroxide for 5 to 20 minutes. It is then washed in two changes of distilled water before proceeding with the silver-impregnation in No. 5. In smears made from macerated liver we have found it possible to secure nearly colorless backgrounds for the spirochetes. The hydrogen peroxide must be pure and free from such impurities as barium chloride and other substances commonly found in commercial hydrogen peroxide. We have found that put up in pure form in slightly acidulated water, made by Parke, Davis and Co., to be satisfactory. With care the same solution can be used over and over for several weeks.

The spirochaeta are increased in apparent size by this method, particularly insofar as their thickness is concerned. The precipitation of silver is chiefly a surface reaction on the spirochaeta. There is apparently some difference between different forms of spirochetes with relation to the intensity of this precipitation. The spirochetes of syphilis, relapsing fever, mouth and smegma precipitate silver much more intensely than Spirochaeta icterohaemorrhagica and Leptospira icteroides, and the thickness of the first named group is increased proportionately, that of Spirochaeta obermeieri about three times. This magnification of the size of the organisms is of the greatest advantage in diagnostic work, as every morphologic detail of the organism is proportionately increased in size and intensity and differential morphological characteristics are accentuated. The number, size and character of the turns of the organisms are easily determined, more so than by any other method.

The stained smears are not always permanent. After 4-6 weeks some of them fade, while others have retained their original intensity for a year and longer. We have found this fading particularly marked in the case of Leptospira icteroides. When for purposes of record it is desirable to make permanent preparations we have found that the smears made according to our method can be stabilized and, so far as our present experience goes, made permanent by toning with gold chloride. We have found Perrin's[1] method very satisfactory. After the smears are stained they are washed in a solution of sodium hyposulphite, then with distilled water and then toned in the following solution:

[1] Arch. f. Dermat. u. Syphilis, 1920, 21, p. 354.

Ammonium sulphocyanide	6.25 gm.
Tartaric or citric acid	.50 gm.
Sodium chloride	1.25 gm.
Distilled water	2.50 c.c.
Solution of gold chloride (1:100)	6.25 c.c.

After a short time in this solution (5-15 minutes) the stain turns to a blue-black color. The smears are then washed in distilled water, dehydrated and cleared, and mounted in balsam.

We believe that our method of demonstrating spirochetes in cover-glass smears by silver-agar silver impregnation is the surest and safest diagnostic method yet devised. It should replace the use of the dark-field and the India-ink method in the diagnosis of syphilis. The morphologic details of Spirochaeta pallida and the mouth and smegma organisms so often mistaken for it by workers using the dark-field or India-ink method, are so accentuated that differential diagnosis is made much easier. The India-ink method is especially dangerous for inexperienced workers. If spirochetes are present in the smear they will be stained by our method if directions are followed. The method is not formidable as it may seem because of the full directions given. It is easily acquired by laboratory workers. Aside from the time required for silver-impregnation in the incubator, it is a relatively short method, and a large number of smears can be kept going in different bottles at the same time. For bacteriologists and laboratory workers engaged in spirochete studies this method is of the greatest advantage in recovering organisms from the organs of inoculated animals, or from the blood or urine. It lends itself particularly well to the laboratory study of Spirochaeta icterohaemorrhagica and Leptospira icteroides. Nevertheless, it is in its application to the clinical diagnosis of syphilis that it possesses its greatest value.

THE WARTHIN STAIN FOR SPINAL FLUID—Warthin, Wanstrom and Buffington[21] have adapted the above method to the demonstration of spirochaeta pallida in the spinal fluid by means of coagula obtained by the Altzheimer method, by the following technic:

1. Four parts of spinal fluid and eight parts of 96 per cent alcohol are centrifuged, at first at a low rate of speed for a long time, and then at a high rate of speed for a short time to pack the clot more firmly.

2. When a firm clot is obtained, the alcohol is poured off and replaced by 10 per cent neutral formaldehyde solution. Small clots are left in the formaldehyde solution for at least thirty hours; larger clots, for three days. In the formaldehyde solution the clot becomes firmer and can be handled with ease, as if it were a piece of tissue.

3. The clot is then run through the routine method of embedding in paraffin: through dehydration in absolute alcohol, a half hour in two changes of pure xylol, one-half hour in paraffin No. 1, and twelve hours in paraffin No. 2. A paraffin melting at 52° C. is used. Embedding and blocking are carried out in the usual way for tissues.

4. Sections of the embedded clot are cut at from 5 to 7 microns. As the sections are cut they are floated on warm, freshly boiled distilled water until perfectly flat and smooth. They are then caught up on cover-glasses on which a minimum amount of albumin fixative has previously been spread and dried in the incubator. No. 1 or thin No. 2 cover-glasses should be used.

5. The cover-glasses mounted with sections are now dried, and the paraffin removed from the sections by successive immersion in xylol, 96 per cent alcohol and distilled water.

6. From the distilled water the mounted cover-glass is placed in a concentrated hydrogen-peroxide solution for from ten to fifteen minutes. It is then thoroughly washed in distilled water.

7. The mounted cover-glass is then taken from the distilled water and rinsed in 2 per cent silver nitrate solution; the wet section is then covered with another perfectly clean cover-glass wet with the 2 per cent silver nitrate solution so that the two cover-glasses are held together by capillary attraction. The wet adherent cover-glasses are then placed on edge in a dark bottle, holding the cover-glasses against the side of the bottle so that they are held by capillary attraction while a 2 per cent solution of silver nitrate is poured into the bottle until the cover-glasses are nearly, but not quite, covered by the solution. The bottle is then tightly corked and placed in the incubator for one hour. The silver solution should always be freshly made; it should not be more than three days old.

8. After impregnation the cover-glasses are removed, separated and the mounted section placed section side up in the reducing fluid as follows:

2 per cent silver nitrate solution	3 c.c.
Warm glycerin	5 c.c.
Warm 10 per cent aqueous gelatin solution	5 c.c.
Warm 1.5 per cent agar suspension	5 c.c.
5 per cent aqueous hydroquinone solution	0.8-1.0 c.c.

The sections are reduced for from one to five minutes until the mixture becomes dark brown, when the background of the section is light tan or grayish tan. The reduction depends on the temperature and exposure to light, being slower in the dark at lower temperatures.

9. After reduction is complete, the sections are rinsed in 5 per cent sodium hyposulphite solution, and then in distilled water.

10. The sections are then dehydrated in absolute alcohol, cleared in xylol and mounted in balsam.

The spirochetes should appear black against a grayish tan background. Nothing else is black except the nuclei of the white cells and the red blood cells. These are brownish black, and not the gray-black of the spirochetes. There are no fibrillae of any nature in these clots that are stained black, so that there is no danger of confusion. In the sections prepared by the aluminum-cream method, clumps of thick black rods larger than bacilli occur, probably crystalline formations. Morphologically, these are easily distinguishable from spirochetes.

As a rule, the spinal fluid coagula yielded about ten to fifteen seven-micron sections. Six sections of each block were examined in a routine manner. If positive findings were made in these, no other sections were examined in that case. If the six routine sections proved negative, ten or more—all of the sections obtainable from the clot—were examined. The fact that the spirochetes were usually found in one or two sections and fairly close together may be explained by the action of the centrifuge. The spirochetes present in the spinal fluid are undoubtedly concentrated in the same portion of the coagulum.

More fragments of spirochetes were found than well-preserved ones, and the whole organisms showed twisting, entangled forms, straightening of coils, granu-

lar appearance and fragmentation as the result of the centrifugation. The staining reaction is, however, characteristic and the morphologic characters are usually sufficiently well preserved to permit identification. We accepted only well-preserved forms as positive. There is a marked tendency for the spirochetes to fragment into pieces of from two to three coils. Acquaintance with these fragmented forms leads us to believe that they are sufficiently characteristic to possess diagnostic value. There is nothing else in the spinal fluid coagula that will stain with the silver method or that resembles these fragments morphologically.

SPIROCHETURIA AND SYPHILITIC NEPHRITIS—Warthin[22] has applied the methods described above to the study of syphilitic nephritis and of the urine passed during the existence of this lesion. He finds that the organisms are excreted chiefly through the convoluted tubules, occasion degeneration of these, and are themselves mostly destroyed within these tubules. He concludes:

Spirocheturia appears to be a striking phenomenon of the entire group of spirochetal infections. The elimination of the spirochetes through the kidneys with the production of associated renal lesions appears to constitute a family characteristic insofar as the known types of the organisms have been studied thoroughly. It is best known in the case of infectious jaundice, and in this disease is a factor of considerable diagnostic value.

Syphilitic spirocheturia occurs in the stage of septicemic syphilis, in both the congenital and acquired infections. Spirochaeta pallida (as are Spirochaeta icterohaemorrhagica), may be excreted in enormous numbers through the convoluted tubules. During such excretion through the kidneys the spirochaeta of syphilis suffers greater destruction than does the icterogenic parasite, so that fewer spirochetes may reach the urine in syphilis than in infectious jaundice. The demonstration of the occurrence of syphilitic spirocheturia is, therefore, not likely to possess such diagnostic value as that of icterogenic spirocheturia.

It seems probable that spirocheturia is more likely to occur when the spirochetes in the blood stream are exposed to the action of antibodies or spirocheticidal drugs. Further, spirocheturia in any degree, both in the case of syphilis and infectious jaundice, appears to be associated with definite degenerative lesions of the epithelium of the convoluted tubules. Such lesions may make the tubules more pervious to the passage of the spirochetes.

NON-SYPHILITIC RABBIT SPIROCHETOSIS—In a profusely illustrated contribution, Warthin, Buffington and Wanstrom[23] disclose the results of "a more detailed study of the cuniculi disease than has yet been made." They note the discovery of non-syphilitic rabbit spirochetosis by Ross in 1912, and quote subsequent observers to the effect that the disease closely resembles rabbit syphilis, and its organism is indistinguishable from the pallida.

The material consisted of 18 rabbits inoculated from one source. Stains were made by the Warthin methods. They sum up their conclusions as follows:

The study of 18 rabbits infected with Spirochaeta cuniculi shows that the

spirochetosis produced by this organism is a superficial lesion, papillomatous or condylomatous in character, limited to the mucous membranes or skin, and spreading by continuity or contiguity or auto-inoculation, and transmissible by inoculation, contact, and coitus. The lesions are essentially epithelial and not vascular, limited to the epithelial surface and upper portion of the sub-epithelial tissues, with marked hyperplasia of the epithelium and papillary layer. A well-developed lesion is essentially a condyloma, and does not suggest a chancre histologically. No evidence of systemic infection was found. No lesions containing the spirochetes were found in any of the internal organs. The general health of the infected animals remained good except in the case of intercurrent infections. The Wassermann reaction was negative. No general immunity was developed. The local lesions, when protected from trauma or local irritation, showed a tendency to resolve and become slight scaly latent lesions, from which spirochetes could still be obtained in numbers by scarification, and which, through trauma, could be revivified into more active and extensive lesions.

From the lesions the spirochetes can be easily obtained by cover-glass smears of the surface, or by scarification. The organism is most easily and best demonstrated in cover-glass smears stained by the Warthin-Starry silver-agar method for cover-glass smears. In such preparations, its morphologic characteristics are more clearly seen than they can be in the dark-field or by other staining methods; and to one acquainted with both forms there should be no danger of confusing cuniculi with pallida. In sections of the tissue lesions, the spirochetes may also be easily stained by the Warthin-Starry silver-agar method, but they are less satisfactorily demonstrated in rabbit tissues than is pallida in human tissues. In the tissue, cuniculi lie in thickly crowded and entangled masses on and in the epithelium, and just below it. They are not found in numbers very deep in the tissue. Their localization is essentially an epithelial one, and not a vascular one. Their entrance into the blood stream is accidental and occasional. No generalized spirochetemia and spirochetosis occurs in this infection. No colonization of cuniculi in any of the internal organs was found. Because of the genital lesions, urine and semen are easily contaminated; but no evidence of any true spirocheturia is as yet forthcoming.

Cuniculi spirochetosis is, therefore, a local disease of epithelial surfaces, the clinical course and local and general pathology of which do not in any way resemble those of syphilis. It should not be called "rabbit syphilis," and the term paralues cuniculi should also be discarded. The spontaneous rabbit disease can be easily differentiated from pallida infections by its morphology, as shown in silver-agar cover-glass smears, and by the pathology of the lesions.

Nevertheless, it is disconcerting to find that there is a spirochaeta infection of rabbits, apparently widespread throughout the world, caused by a spirochaeta that resembles pallida sufficiently closely to make possible the occurrence of mistaken identifications of the one for the other, in the case of any worker who is not acquainted with the two organisms and their differential diagnosis. It is unfortunately true that the great mass of experimental work on the transmission of human syphilis to the rabbit has been carried out in such ignorance of the spontaneous rabbit disease, and the value of that work now becomes legitimately doubtful. It is extremely likely that mistakes have been made. Now that the knowledge of this primary rabbit spirochetosis has been obtained, the possibility of future error should disappear with intimate acquaintance with the cuniculi

organism. It will, however, be necessary to repeat much of the work in this new light, particularly that concerned with the production of rabbit syphilis from paretic brains and human semen, and the production of reinfection and superinfection, immunity and cure. Too many important deductions have been made from rabbit experimental work to admit of any doubt being allowed to remain as to their accuracy.

DIAGNOSIS AND CULTURE OF SPIROCHAETA—Rosenberger and Fanz[24] have published as one communication five distinct studies concerning the recognition of Spirochaeta pallida, its culture, and the effect of various dyes and physical agents suggested for its destruction, as follows:

IMPROVEMENT OF DARK-FIELD ILLUMINATION BY THE INTERPOSITION OF COLOR SCREENS—They have experimented with various screens and solutions in the effort to cut off the eye-fatiguing ultraviolet rays in the intense light of the dark field illumination. Their greatest success was attained by the use of the following:

(1) Acriflavine solution, 1-5000, in flat culture flasks (3½" wide and ½" deep). The only disadvantage in the use of this solution is that it deteriorates slightly and requires filtration after several weeks. "The intense scintillating, dazzling white light from the four hundred watt dark field lamp was so mellowed by the removal of chemic rays that the motile bodies of Treponema pallidum were readily seen in more detail and could be viewed and studied for very long periods of time without optical discomfort."

(2) The No. 8K2 Kodak filter. These filters are stable, but must be placed as far as possible from the source of light, for "due to the peculiarity in mounting with the balsam, they cannot be kept in the heat of the dark field lamp over a prolonged or unreasonable period of time."

(3) The No. 1 Beta-Naphtholdisulphonic Acid Kodak filter. This is inferior to (2), but inasmuch as it gives a white light, is better adapted for the examination of stained specimens.

ANALINE BLACK STAIN FOR CHANCRE SMEARS—

"There are observers who believe that the dark field illumination is the only and best method for recognizing the Treponema pallidum, but we believe that 'the analine black method, devised by Fanz,' is equally efficient." The technique is described as follows:

SOLUTION NO. 1 (ANALINE OIL WATER).—"Analine oil water is made by adding 1½ c.c. pure oil to 100 c.c. of water, shaking thoroughly and filtering."
SOLUTION NO. 2 (OXIDIZING REAGENT).—"The oxidizing reagent is made by adding 5 c.c. concentrated sulphuric acid and 15 grams of C.P. potassium bichromate to 375 c.c. of distilled water."

TECHNIC.—The serum is obtained, free from blood, and spread upon a slide in the usual manner. "Thinness of the preparation is the keynote to success. Fixation is then accomplished by gently heating the slides about six to eight inches above the flame of a Bunsen burner. Four to six slides will ensure a correct diagnosis. After fixation and drying, each of the slides should be covered with 10 drops of solution No. 1, while still slightly warm. Solution No. 1 is

allowed to 'soak in' to the suspected preparation for about two minutes; then Solution No. 2 is added in equal amount. This is allowed to remain for five or six minutes to oxidize the analine which the presumed organism has absorbed. During the action of the oxidizing solution the color changes steadily from orange to green, dark green, and then to metallic blue black, with the formation of a scum over the surface of the stain. Washing is the next step, and is accomplished by flushing the slide thoroughly and vigorously under a faucet of running water. After drying the slides thoroughly, immersion oil may be directly applied and the slides studied under the twelfth inch objective. The organism is seen on a delicate blue background containing precipitated granules of stain, varying in number according to the expertness of the technician and the thoroughness of the washing. The Treponema appears as a black, opaque structure displaying its specific morphology in detail. Allied organisms, particularly the Spirochaeta refringens, can be readily differentiated; blood corpuscles and epithelial cells are likewise stained an opaque black of varying intensity."

INTRAVITAM DAHLIA STAIN FOR SPIROCHAETA—Intravitam staining consists in drying the stain first on a perfectly cleaned slide and then adding a drop of chancre secretion, applying cover-glass and oil immersion. The Treponemata are first seen colorless and motile, then absorbing the color, and finally dead and stained. Dahlia was found to give the best results. "Slides were thinly coated with a one to two per cent (1-2 per cent) alcohol solution of the color, permitted to dry and stored for use. Suspensions of several strains of the organism were dropped on the area of stain, covered with a cover-glass and examined under the twelfth inch objective. The organism gradually absorbed the stain, being apparent in five minutes. After fifteen minutes had elapsed the organism was seen to exhibit clear definition and an utter lack of motility."

SPIROCHAETA CULTURE IN DEFIBRINATED BLOOD MEDIA IN PARTIAL VACUUM—

"The underlying principle of the various important methods of Treponema culture is to furnish a condition of partial anaerobiosis or diminished oxygen tension brought about by addition of tissue, either fresh or sterilized by heat, having the property to absorb oxygen gradually in small amount. On analyzing this principle it occurred to the writers that in all probability the reducing property of the tissue was due in part to the red blood cells therein contained."

Defibrinated blood or blood hydrocele agar (1½ per cent agar Jelly, two parts; hydrocele fluid, one part; to 10 c.c. of this add 1 c.c. of sterile defibrinated rabbit blood) is placed in sterile tubes 20 cm. long by 1½ cm. in diameter. The organism is next introduced by means of a special needle (12 bore; 27 cm. long) attached to a 10 c.c. syringe. The tube is softened and partially drawn out over a Bunsen burner, its contained air exhausted to as near a vacuum as possible by an air pump, the tube sealed and further reduction of the oxygen tension entrusted to the red cells of the medium.

The authors have found this technic successful and believe it a

valuable simplification of older methods. They have also devised an apparatus whereby several tubes may be handled at once, and the vacuum obtained by pump and corpuscles further increased by oxygen absorption through automatic mixture of pyrogallol with 25 per cent sodium hydroxide solution.

Effect of Radium and X-Ray Upon Cultures of Spirochaeta—The so-called "erythema" dose, whether of radium or of X-Ray, failed to inhibit growth or propagation of spirochaeta pallida.

Chemistry of Normal and Syphilitic Spinal Fluid—Egerer-Seham and Nixon[25] sum up their comparative studies in the chemistry of the blood and cerebrospinal fluid with the remark that "In the cerebrospinal fluid of syphilis no constant deviation from normal is encountered in sugar, creatinin or urea content, in acid base equilibrium, in specific gravity or in enzymatic activity." Their tables, giving the results recorded by various observers are worthy of reproduction.

Table No. 1 shows the per cent of sugar in normal spinal fluid as follows:

Author	*Per cent of sugar*	
Narwatzki	0.0555	
Cavazzani	0.0188	
Claud Bernard	0.0188	
Mastrezat	0.048-0.53	(20 cases)
Kopetzki	0.046	(8 cases; Benedict's method)
Hopkins	0.060-0.075	(Bang's method)
Jaksch	0.06-0.08	(20 cases)
Schloss and Schroeder	0.054-0.139	(Children; Lewis and Benedict)
Kraus and Corneille	0.055-0.110	(22 cases; above method)
Levinson	0.064-0.09	(5 cases)
Egerer-Seham and Nixon	0.045-0.095	(9 cases; above method)

"The creatinin value in normal spinal fluid varies from 0.45 to 2.20 mg. for 100 c.c. of spinal fluid."

Table No. 11 records the urea content of cerebrospinal fluid:

Date	*Author*	*Urea per 100 c.c.*
1896	Cavazzani	9.8 mg.
1896	Thiery	13.5 mg.
1904	Widal and Froin	0.015-0.025 per cent.
1906	Fraenkel	0.543 per cent Urea N.
1912	Mestrezat	0.06-1 per cent.
	Leopold and Bernhard	7.0-13.5 mg.
1914	Gumprecht	0.012 per cent in spinal fluid of cow
1916	Kahn	14-33.32 in 100 c.c. Urea N.
1916	Folin	6.25-20.75 Urea N.
1921	Egerer-Seham and Nixon	9.87 mg.

"Under normal conditions the carbon dioxide carrying capacity of the cerebrospinal fluid is somewhat lower than that of the blood, while in acidosis it is greater, in some instances at least. Whether or not this indicates the operation of a mechanism for the protection of the nervous system is not yet clear."

"The diastasic activity of cerebrospinal fluid is 21.9 per cent of that of the blood." Lipase was found only twice in 26 spinal fluids examined.

Table No. 26 records the specific gravity of spinal fluid:

Author	*Specific gravity*
Ch. Richet	1.006
Ch. Robin	1.005
Toison and Lenoble	1.007
Lassaigne	1.008
Marcet	1.006
Cheritier	1.002
Widal and Sicaire	1.004
Quinke	1.006-1.007
Egerer-Sehani and Nixon	1.0086

Nixon and Naito[26] have by their studies advanced our understanding of the nature of the Wassermann and colloidal gold reactions. They summarize their observations as follows:

"The globulin fraction in syphilitic serum contains the active substance in the Wassermann reaction. The filtrability of globulin in syphilitic serum by the ultrafilter was less than that in the normal serum."

"The lessened filtrability of the globulin in syphilitic serum they explain in part by the increased ease of absorption of the Wassermann positive globulin, possibly in part by an increase in size of this globulin, and its instability as compared with the normal globulin.

"Positive colloidal gold reactions are due to the presence of precipitating substances.

"Both precipitating and protecting substances are present in pathologic cerebrospinal fluid.

"Curves in Zones I, II, and III are due to varying amounts and proportions of the precipitating and protecting substances.

"Albumin and globulin may possess both precipitating and protecting power.

"Ultrafiltrates or syphilitic and non-syphilitic serums give curves that are more or less similar, but there tends to be a greater difference between the zones of reduction of the original and filtered serum in syphilitic than in normal cases.

"The protecting substance is decreased to a greater degree by ultrafiltration than the precipitating substance.

"Changes in the state of the protein modify precipitating and protecting powers.

"The salt solution used in the gold test partially neutralizes the protective action."

Diffusion of Fluids Introduced Into the Cerebrospinal Canal—Solomon, Thompson, and Pfeiffer[27] summarize our knowledge as to the formation and resorption of the cerebrospinal fluid as follows: "In conditions of normal health, cerebrospinal fluid is constantly being formed in the cerebral ventricles in considerable amounts. This fluid is absorbed in large part in the subarachnoid spaces, arriving there by a course through the acqueduct of Sylvius and the foramina of Luschka and Magendie." Thus, there is a flow of cerebrospinal fluid from cerebral ventricles toward the subarachnoid space, which flow is

rendered irregular by the proven influence of heart beat, respiration, etc. The principles governing the diffusion of solutions through the cerebrospinal fluid are not well understood; indeed the observations upon which those principles must be based are singularly at variance. Thus Schmorl reported that out of seven cases of paresis with the usual positive Wassermann reaction in the spinal fluid only one showed a positive Wassermann reaction in the fluid obtained from the ventricles. Cushing showed differences in the sugar content of spinal and ventricular fluid. Solomon found differences in the gold reaction. Dahlstrom and Wideroe confirmed the observation of Schmorl. Goldmann, Kramer and Horbatsky have each shown that certain injected dyes diffuse but slowly from the point of injection.

On the other hand Dandy and Blackfan showed that neutral phenolsulphonephthalein injected into the lateral ventricle appears in the lumbar spinal fluid in two to three minutes, and vice versa. It was in one case excreted by the kidneys as rapidly as though it had been injected intravenously. Weston failed to confirm these diffusion findings, but they have been confirmed by Dahlstrom and Wideroe, and by the authors of this monograph, who have carried the experiment one step further, and noted not only the diffusion of a dye, but also the diffusion of serum. They find a striking difference in results. The dye diffuses rapidly, the serum sinks toward the bottom of the cerebrospinal column, and if mixed with dye carries this with it. "Under ordinary conditions it is probable that there is not very much movement from one locus to another of the substances introduced into the cerebrospinal fluid. The movement of the introduced substances may depend either on the circulation of the cerebrospinal fluid or, what is more probable, on a diffusion of the substances due to osmotic and specific gravity effects. . . . We may, therefore, assume that when the blood serum is introduced into the subarachnoid space, it will tend to reach the lowest portion of the cerebrospinal fluid system by a slow diffusion process. On the contrary, there is no evidence to show that there is sufficient active circulation of the cerebrospinal fluid to displace the blood serum in a direction contrary to gravity. . . . It is to be assumed that a certain amount of the blood serum introduced intraspinally will make its way out into the general circulation from the spinal subarachnoid space. Under conditions in which intraspinal therapy is usually given for neurosyphilis and epidemic cerebrospinal meningitis, a large part of the subarachnoid space, surrounding the cerebral cortex and the greater part of the cerebral ventricular space, is at a higher level than the lumbar subarachnoid space. It is, therefore, to be assumed that the blood serum (injected) does not reach the ventricles or the cerebral cortex in any great amount, particularly as effort is usually made to introduce the serum into the spinal spaces under a comparatively low pressure. On the

other hand, serum introduced into the superior portion of the anterior horn of the lateral ventricle should tend to diffuse in the caudal direction because the superior portion of the anterior horn of the lateral ventricle is at a higher level than the lumbar subarachnoid space. In order to reach the base of the brain, the point of election for introduction of serum is the cisterna magna. For therapeutic purposes, blood serum should be introduced as near as possible to the area in which its effects are desired."

Effect of Treatment Upon the Lesions of Paresis—"In order to determine whether antisyphilitic treatment produces any effect on the paretic process," Solomon and Taft[28] instituted a study of brains from cases of general paresis that came to autopsy. There were 27 brains of treated patients and 15 brains of patients not treated since the onset of paresis. Inasmuch as the parenchymatous, vascular, and neuroglia changes characteristic of the lesion are organized no conclusions were drawn from the fact that these were unaffected. But the observations showed that the plasma cell infiltrate of the perivascular spaces, and the accompanying lymphocytosis were so often reduced in amount that from the observation of the tissue it was often possible to state that a certain case had received treatment. The pial inflammation was also influenced.

They further noted that the Wassermann reaction and cell count sometimes became negative during treatment, and that the cell count does not give a true indication of the amount or extent of cerebral meningitis.

They found that intraventricular injections of arsphenamized serum ordinarily produce no injurious effect upon the choroid plexus or ependymal lining of the ventricles, but note that the clinical benefit derived from this treatment was no more than might perhaps have been had without it.

Source of Cerebrospinal Fluid—Taft[29] noted in the course of his studies of paretic brains that the choroid plexus showed certain changes, not characteristic of paresis, but bearing upon the question of the method whereby the choroid produces the cerebrospinal fluid. He found a progressive fibrous change "beginning with general increase of connective tissue, followed by obliteration of capillaries, with formation of fibrous tufts, in which calcium salts are deposited, and final cystic conditions of the plexus. At this stage the capillaries have entirely disappeared, but the ependymal cells remain and are little changed morphologically." There is no lack of cerebrospinal fluid in paretic brains. Indeed the ventricles are often dilated. Yet with the disappearance of the choroid capillaries it is difficult to understand how this fluid is produced by filtration, as is commonly believed to be the case.

Coincidence of Lesions of the Cornu With Convulsions—Taft[30] has found confirmation of the relation of sclerosis of the cornu ammonis to convulsions in his study of paretic brains. Of the 50 cases studied histologically, 19 had a history of convulsions and all showed this sclerosis, the cells within the corpus dentatum being particularly affected. One other case showed sclerosis of the cornu, but the corpus dentatum was spared, and the history showed no convulsions.

Unreliability of Luetin Test—Alderson[31] notes that the luetin test is very generally depended upon in California as an important (and by some as an infallible) test of the presence of active syphilis. He himself found the original luetin, supplied by Noguchi, a useful agent. His results at that time confirmed the claims of Noguchi that luetin test is always positive in tertiary syphilis, usually positive in latent syphilis and usually positive in congenital syphilis. He quotes many confirmatory reports, but notes its ready deterioration and quotes Pusey: "It is only useful when one is using a supply of luetin which has been tried out and is of known reliability. As furnished commercially now with only sufficient suspension in a single supply for one or two tests, it is, I believe, unreliable."

He accordingly made a series of luetin tests upon 40 syphilitics and 7 non-syphilitics, using the freshest luetin available. He used three samples of luetin, and "there were so many luetin failures in our series of selected cases (63 negative, 21 positive, 3 doubtful) that were clinically and serologically positive that we fear that luetin purchased in the market here may be inert."

The Provoked Wassermann Reaction in Blood and in Spinal Fluid—Shepardson[32] has studied the provoked Wassermann reaction. Though reporting a provoked positive, i.e., a reversal from negative to positive, occurring after an interval of from two to fifteen days following the administration of arsphenamine (average dose 0.3 to 0.4 gm.), he calls attention to the report of Strickler, Munson, and Sidlock (J. A. M. A., 1448, lxxv, 1920), who obtained provoked Wassermann reactions in 16 out of 30 patients believed to be non-syphilitic, following injection of arsphenamine; and concludes that "we believe that an equally valuable and less time consuming procedure is to have the patient return for repeated Wassermanns (to be done by both the ice-box and water-bath methods) at varying intervals depending upon the clinical indications and history."

Solomon and Klauder[33] report six cases illustrating the reversal of Wassermann reaction from negative to positive in the spinal fluid during the course of treatment of late cerebrospinal syphilis. (They noted no instance of provoked blood Wassermann in this series.) The gold curve reacted sometimes in the direction taken by the Wassermann reaction, sometimes in the opposite direction. The Wassermann reaction was sometimes provoked by a series of intravenous

treatment, sometimes by intraspinal treatment. One of the patients was 36 years old and has recently had a fleeting hemiplegia and had been treated thereafter for syphilis, though he gave no history of the disease. He was admitted to the hospital suffering from headache, loss of memory, and an occasional slight speech defect. Mentally he seemed euphoric, but a searching examination, including spinal fluid examination, revealed no abnormalities other than slightly more active bicipital and patellar reflexes on the left side.

A provocative injection of arsphenamine was given. The blood Wassermann remained negative after twenty-four, forty-eight, and seventy-two hours; but later the spinal fluid became positive (with 1 c.c. and 0.8 c.c.) there were 53 cells per cu. millimeter; globulin present; albumin in excess; gold curve 244333000. The positive result of the provocative injection thus established the diagnosis.

Diagnosis of Hereditary Syphilis by the Wassermann Reaction—Jeans and Cooke[34] have studied the diagnosis of hereditary syphilis, and certain related items, such as the effect of treatment of the syphilitic mother in the prevention of hereditary syphilis. They studied the placenta grossly and microscopically and the Wasserman reaction of the umbilical cord blood of 2030 unselected infants. They then examined the blood of 389 of these infants after they had reached the second month of life, and concluded that the diagnosis of hereditary syphilis could be made in only 27 per cent from examination of the placenta, while from the Wassermann reaction of the cord blood 63 per cent could be diagnosed. They deduce an incidence of hereditary syphilis among the colored race in St. Louis of 15 per cent as against 1.8 per cent for the poorer whites, and less than 1 per cent for the well-to-do; a total incidence of hereditary syphilis for the city of 3 per cent.

They further observe that "syphilitic infants at birth have Wassermann reactions in the following proportion: 37 per cent negative, 18 per cent weakly positive and 45 per cent strongly positive. After the first few weeks or months all syphilitic children have strongly positive Wassermann reactions; yet syphilitic infants over two months of age fail to show clinical evidence of the disease at the first examination in 50 per cent of instances.

Non-syphilitic infants may give a weakly positive Wassermann reaction at birth which becomes negative later, but never give strongly positive reactions at birth or at any other time. All mothers of such non-syphilitic infants as give weakly positive Wassermann reactions have themselves reactions of equal or greater intensity than their infants. In these instances the fixing substances are probably transmitted from the mother to the infant without transmission of the infection."

In the older children with active hereditary untreated syphilis they also find the Wassermann reaction positive, except in the course of interstitial keratitis.

Such a doctrine is quite revolutionary. Accepted authorities on hereditary syphilis take a much more conservative stand on the merits of the Wassermann reaction as a diagnostic measure in hereditary syphilis, though as a rule according it more importance than for late acquired syphilis. There is seemingly a very human possibility of error in all Wassermann reactions.

THE NATURE OF SYPHILITIC IMMUNITY: SPIROCHETICIDAL PROPERTY OF SYPHILITIC IMMUNE SERUM: VIRULENCE OF SPIROCHAETA DURING IMMUNITY—The researches of Engman and Eberson[35-36] have convinced them that "latent infections connote a balance between the antibodies of the individual and the invading parasites. Thus the presence of spirochaeta pallida in the human or animal body at certain times need not imply disease, but rather a latent stage in which the spirochetes are able to survive in the immunized body."

Their observations have established the communicability of syphilis during latency, but have not shown the relative infectiousness of latent as compared to active syphilitics.

During latency they found no diminution of virulence of Spirochaeta (though they recognize that such may exist).

They observed spirocheticidal properties in the blood serum of latent syphilitics, of sufficient strength to protect rabbits when injected in combination with virulent strains of spirochaeta (control injections showed that non-syphilitic serum possessed no such protective properties).

This protective property was shared by sera obtained from syphilitics whose disease dated back from three to twenty-five years, some of whom had received treatment, while others had not; some of whom had positive Wassermann reactions, while others had not.

In the rabbit it was found that this spirocheticidal property of the serum developed in the course of six months to a year after infection, "In the rabbit, as in man, protective substances are found at a time when the infection has attained a relatively latent state. The presence of these substances in given sera apparently depends on the stage of infection. When definite latency has been established the serum appears to protect against experimental inoculation, whereas the serum from cases of early syphilis, or those in which true latency has not been attained is not spirocheticidal.

"Sera developed in rabbits by strains of spirochaeta pallida from latent sources manifested a wide range of protective properties, as shown by the inhibitive effect upon heterologous as well as homologous strains. Sera from latent cases behaved in a similar manner."

Chancre strains, on the contrary, did not protect from heterologous inoculation.

The treatment that renders the Wassermann reaction negative does not seem to diminish the protective spirocheticidal quality of the blood serum.

"By analogy with the trypanosome and spirillary diseases and the carrier state of certain well-known infections, syphilis offers immunity phenomena which tend to explain latency on the basis of a blood immunity which is progressively developed from a tissue immunity.

"The mechanism by which immunity develops in syphilis would seem to be an elaboration of antibodies commencing at the time when the initial lesion is present and continuing as a progressive extension of local immunity from one group of tissues to another until the immune substances are absorbed by the blood stream." Hence the relative innocuousness of the latent spirochaeta to its host, though its actual virulence may remain undiminished.

Though the protective value of serum immunity is thus of the greatest import to the syphilitic, and an instructive phenomenon in the laboratory, no practical application of this phenomenon to human therapy has been developed.

THE LATENT SYPHILITIC AS A CARRIER—Eberson and Engman[37] note thirty-eight previous attempts to infect rabbits by the injection of blood obtained from patients regarded as latent syphilitics with four positive results; but in each of these the syphilis may have been active at the time of injection.

Under the classification of latent syphilis were admitted patients with a positive Wassermann reaction and patients with visceral or cerebrospinal syphilis. Indeed they seem to have excluded only recently infected persons, those under active treatment and those who had recently shown lesions of the skin or mucous membranes. There were thus included fifteen per cent of 500 clinic cases.

Inoculations were made into rabbit's testicles of (1) defibrinated blood, (2) semen, (3) spinal fluid, (4) emulsion of (inguinal) nodes, (5) nasal washings, and (6) tonsils. The rabbits injected with tonsil emulsion promptly died of streptococcus septicemia. The results of the remaining injections are tabulated as follows:

Material	*Number injected*	*Positive inoculations*
Blood	73	0
Blood (incubated)	36	0
Spinal fluid	31	0
Nasal washings	24	0
Inguinal nodes	14	3
Semen	17	2
Testes (postmortem)	2	0

Infective material from inguinal nodes was obtained from one patient whose syphilis dated back at least eleven years, infective semen from one whose syphilis dated back thirteen years, the remaining "takes" were from patients whose syphilis was one year old.

"It appears from this investigation that the blood and other body fluids, excepting semen, are not infectious in latent syphilis, or if so, but rarely."

Syphilis a Systemic Disease Before Appearance of Chancre—Engman and Eberson[38] have corroborated the observation that the Spirochaeta pallida appears in the blood and lymph nodes within seven days of inoculation and 23 to 26 days prior to the appearance of any initial lesion, and that the organism may be recovered from the blood stream up to 26 days: thereafter it abides in the lymph nodes, whence it may be recovered long after it has disappeared from the chancre. Hence these observers stoutly oppose the excision of chancre, believing this lesion to be a protective reaction. They also call attention to the resistance to treatment of the spirochetes in lymphoid tissue; hence the need for prolonged specific intensive therapy of the disease.

Neurotropism Not Shown in Familial Neurosyphilis—The studies of familial neurosyphilis by Moore and Keidel and the discussion of one of these contributions when read before the Section on Medicine of the American Medical Association, shows that the question of the existence of a special neurotropic strain of spirochaeta, as suggested some years ago by Reasoner, is still unsettled. No clinic has yet been able to confirm by observation of the behavior of the disease in human beings the laboratory observations that suggested neurotropism in animals.

Diagnosis and Treatment of Early Asymptomatic Neurosyphilis—Keidel and Moore,[39-40-41] and Moore[42-43] independently, have attempted a classification of those cases of early syphilis that show changes in the cerebrospinal fluid productive of no symptoms, or only "manifested by mild symptoms or slight physical signs, not of themselves diagnostic of central nervous system damage. Patients in this group may complain of headache, neuralgic pains, insomnia, vertigo, or 'nervousness,' or may have no symptoms." The physical signs are "slight pupillary abnormalities (myosis, mydriasis, aniscoria, irregularity, or sluggish light reaction), and exaggeration, sluggishness or inequalities of the reflexes" not pathognomonic of syphilis.

"Such asymptomatic neurosyphilis constitutes the largest group of early neurosyphilis (76.6 per cent of 352 patients), and passes totally undiagnosed unless routine spinal puncture is resorted to. Early spinal puncture should be a routine part of the treatment of every case of syphilis, for thus only can the gravest lesions in the nervous system

be foreseen at a time when it is still possible by treatment to avert the development of such lesions."

Keidel and Moore perform spinal puncture after one or two routine courses of arsphenamine have been administered—not before this, for fear of exciting infection of the cerebrospinal fluid by spirochetes circulating in the blood.

For purposes of diagnosis and treatment they classify these asymptomatic neurosyphilitics into three groups based upon their spinal fluid changes, and corresponding to their response to various types of treatment, as follows:

Group I includes those patients whose spinal fluid shows a cell count of no more than 20 (usually less than 10), a slight increase in globulin (by Pandy's test), negative Wassermann reaction, and negative colloidal gold and mastic tests. Routine antisyphilitic treatment almost always suffices to clear up the signs and prevent the symptoms of such cases. The authors insist that the treatment of syphilis should be continuous and not intermittent. They begin with a course of eight doses of arsphenamine; then (beginning just before the last dose of the arsphenamine course) four weeks of inunctions; then three more courses of arsphenamine injections consisting of six injections in each course and with a lengthening interval (up to twelve weeks) so that the four courses cover a year of treatment, with intervals (of 26 weeks in all) during which inunctions are given. If the blood Wassermann was positive at the time treatment was begun, another course of arsphenamine is given after an interval of two months of inunctions. For cases showing the above type of cerebrospinal fluid changes no more than the above treatment is usually necessary to reduce the findings to normal.

Group II includes those patients whose cells are more than 10 and less than 100, usually less than 50; whose globulin content is on the whole greater than in group I; whose spinal fluid Wassermann reaction is either negative or mildly positive; whose colloidal gold test is of the "syphilitic" type (maximum in the third to the sixth tube; e. g., 1123332100 or 2445522100), whose mastic curve varies between the "syphilitic" and the "paretic."

Group III includes those cases whose cell count is high (50 to 200); whose globulin is high; whose spinal fluid Wassermann is positive in 0.2 c.c. or less; whose colloidal gold and mastic tests are usually paretic. Such cases are not controlled by the routine antisyphilitic treatment, even of such persistence and intensity as outlined above. They must be subjected to intraspinal treatment (or to some substitute for this.—Ed.).

Manifestly, therefore, intraspinal treatment should not be employed for cases that fall into Groups I and II until and unless they fail to respond to the usual antisyphilitic treatment; but should be employed in the treatment of cases that fall into Group III as early as possible, so as to avert the gravest forms of neurosyphilis.

The summary of Moore's paper contains several items of cardinal interest.

"1. It has been shown that early invasion of the central nervous system in syphilis is common, occurring in 16.4 per cent of a series of 352 patients with

primary or secondary syphilis. Of 94 early neurosyphilitics, 72 were asymptomatic, and were detected only by the routine application of spinal puncture.

"2. Early asymptomatic syphilis may be divided into three sub-groups on the basis of the spinal fluid findings and the response of the various groups to treatment.

"3. Invasion of the central nervous system probably occurs in the majority of all patients with syphilis and, unless the course of the disease is influenced from without (by treatment), this invasion takes place in most instances within the first year after infection. The ability of the invading organisms to produce clinical neurosyphilis probably depends on the defense mechanism of the individual patient. . . .

"4. Early asymptomatic neurosyphilis is more common in the white race than in negroes, but is equally frequent in men and women of either.

"5. Prolonged regular treatment influences favorably the incidence of early asymptomatic neurosyphilis. Irregular and lapsing treatment, on the other hand markedly increases its incidence.

"6. A study of this material from the standpoint of strains of Treponema pallidum furnishes no support to the theory of the existence of a neurotropic strain of the organism.

"7. . . . An appreciation of the (minor subjective and objective neurologic) signs, and of the significance of a persistent positive blood Wassermann reaction in treated patients, furnishes a clinical aid for the recognition of neurologic invasion.

"8. Spinal puncture is an indispensible routine procedure in the management of early syphilis. Unless it is employed many patients will be discharged as cured who are nevertheless candidates for clinical neurosyphilis. It should be performed as a routine after the first or second course of arsphenamine, and unless a lapse in treatment occurs, need not be repeated (if negative) until the end of treatment and the probation period.

"9. All three groups of asymptomatic neurosyphilis may be serologically and clinically "cured" by appropriate methods of treatment.

"10. Early asymptomatic neurosyphilis is the forerunner of clinical neurosyphilis. . . ."

THE INFLUENCE OF PREGNANCY ON SYPHILIS—The previously published work of Brown and Pearce (Am. J. of Syph., IV, 593) showing that in animals the course of syphilis is markedly affected by pregnancy has given the long awaited explanation of the clinical suppression of the disease in the pregnant woman. Moore[44] states that "A study of the pregnant woman, now in progress, has convinced us that the usual early manifestations of syphilis are markedly altered by the occurrence of pregnancy. A woman infected at or shortly after the time of conception usually does not develop a chancre or secondary syphilis. When infection takes place late in pregnancy, on the other hand, the usual course of events may follow, but is often much delayed."

He further shows that "In women with late syphilis (of more than one year's duration) the incidence of abnormal spinal fluids is

twice as high in a group of sterile women as in a group in which one or more pregnancies have occurred since infection.

"Multiparae seem to be less liable to late asymptomatic syphilis than primiparae.

"Pregnancy is one factor which may partially account for the comparative freedom of women from neurosyphilis."

TREATMENT OF SYPHILIS—TREATMENT OF NEUROSYPHILIS—Hoffman and Lyon[45] as a result of their study of the toleration of rabbits to arsphenamine injected intravenously find that visceral injury usually begins in the liver rather than in the kidney. Human syphilitics tolerate bi-weekly administration of neoarsphenamine in quantities paralleling the rabbit dosage without clinical hepatitis or nephritis. The bi-weekly dosage permits an increase in total tolerated dosage of 30 to 40 per cent more neoarsphenamine than by present methods. This schedule calls for 1.2 to 1.4 gm. neoarsphenamine weekly to individuals weighing more than 150 pounds. On account of the brief residence of the drug in the tissues it becomes apparent that the more frequent the administration of the drug and the greater the dosage, short of visceral damage, the nearer is the approach to the ideal treatment.

They also call attention to the observations of Merthens to the effect that 50 per cent of all persons have meninges impermeable to blood borne arsphenamine. Thus every other case requires some method of conveying the drug to the meninges.

They suggest the following plan of investigation as preliminary to the treatment of cerebrospinal syphilis:

1. Intravenous injection of arsphenamine or neoarsphenamine followed in 50 minutes by withdrawal of 40 c.c. of cerebrospinal fluid.

2. Test the cerebrospinal fluid for arsenic by Gutzeit's method. If arsenic is present intravenous therapy is presumably adequate for the case in question.

3. If arsenic cannot be detected, treat the patient (at another time) by the method of Corbus; injecting intravenously a pypertonic salt solution, and 6 hours later injecting intravenously neoarsphenamine. Fifty minutes later the cerebrospinal fluid is again tested for arsenic. If present the Corbus plan of treatment is pursued.

4. If arsenic is again absent, a second puncture an hour later may show arsenic.

5. If arsenic then fails to show, intraspinal therapy is required.

THE EFFECTIVENESS OF THE TREATMENT OF HEREDITARY SYPHILIS—White and Veeder[46] have investigated the social and clinical data in relation to 443 children (among 396 families) with hereditary syphilis, and also the effect of treatment upon the disease. They have attempted to evaluate the dividend to be expected in the form of economic physical result from the therapeutic attack upon hereditary

syphilis. They feel that their results are on the whole unsatisfactory, and believe that the only adequate attack upon hereditary syphilis is that upon the syphilitic mother.

Their conclusions are as follows:

"This study was undertaken with the purpose in view of determining whether or not the end-results of the intensive work with hereditary syphilis during the period 1912-1920 were of such a nature that future work along the same line is indicated or justified. During this period 443 patients with the disease were observed and followed with adequate hospital, clinic, and social service facilities available at all times. It is impossible to state the exact cost but when the time and salaries of physicians and social workers, equipment, drugs, etc., are considered we are justified in estimating it at many thousands of dollars.

"From the social standpoint we have found the group as a whole unsatisfactory and difficult to deal with. Lack of interest on the part of parents has led a large part of our material to discontinue treatment long before dismissal by the physician. While here and there families have been encountered who have coöperated most satisfactorily, their number is far overshadowed by the group of uncoöperative. Thus, out of 230 living patients in whom end-results are known, only 52 followed out a thorough course of treatment; while 95 were absolutely uncoöperative. A middle group of 83 cases continued treatment with a fair degree of regularity for a time, but dropped away before discharge. Allowing for the 78 deaths in the group there are still left 125 patients who for one reason or another were lost track of and a large per cent must be included with the group of "uncoöperative." In our experience, in spite of thorough and intensive follow-up work, only a third of the hereditary syphilitic patients were given the benefit of a satisfactory or fairly satisfactory course of treatment, and we question whether this figure can be improved under ordinary conditions.

"In discussing the results of medical treatment two viewpoints must be considered: first, the results of treatment in the individual case of hereditary syphilis; and secondly, the results of treatment for the group of 443 cases as a whole. So far as the individual case is concerned our results show that a given case has a fair chance of clinical and serological recovery or improvement; that such recovery or improvement may seemingly take place on little or practically no treatment, but that the chances for cure or improvement are very much better for a case thoroughly treated with arsenicals and mercury than for one poorly treated. The earlier the treatment is started the better the result. If the given case has either serological or clinical evidence of involvement of the central nervous system, the chances for recovery or improvement are poor. One is justified, therefore, in treating a case of hereditary syphilis thoroughly with the expectation that it will be benefited.

"As regards the group as a whole the results have been disappointing. The infant mortality rate is three times the rate for infants from all diseases. This is despite treatment and is seemingly dependent upon the extent to which the infant's nutrition and metabolic function have been impaired. Further, approximately one-third of the cases have had involvement of the central nervous system and as a group these have shown little improvement. Although active lesions in these cases have been checked, the residue of the infection leaves a child who as a rule belongs to the socially unfit. Considering the group of 308 cases whose

end-results are known we quote them briefly as follows: Cured or recovered, 67 or 22 per cent; improved, 108 or 35 per cent; unimproved, 55 or 17 per cent; died, 78 or 25 per cent. Thus we find that in our entire group, regardless of the amount of treatment received, 43 per cent were either unimproved or died. Despite the intensive work during this period only 22 per cent of our cases are known to have been cured or recovered.

"Certainly this cannot be considered a brilliant showing. While one is justified in urging thorough treatment in the individual case, our group results clearly show that from a social or group standpoint the treatment of hereditary syphilis in the infant or child leaves much to be desired. The problem is best attacked by reaching the syphilitic woman or mother before and during pregnancy. This is all the more apparent when one takes into consideration the fetal mortality. While by no means advocating the neglect of the syphilitic child, we feel that the results to be obtained are so poor as a whole that our efforts should be directed much more to the prenatal clinic than to the pediatric clinic."

THE EFFECT OF SYPHILIS ON THE FAMILIES OF SYPHILITICS SEEN IN THE LATE STAGES—PREVIOUS INVESTIGATIONS—Previous investigations either refer to syphilitics seen in the early stages or do not cover so large a group.

MATERIAL STUDIED—Families of 555 patients seen by H. C. and M. H. Solomon[47] at the Psychopathic Hospital with positive Wassermann reactions (only 236 of the mothers gave positive reactions).

RESULTS—1. Whether the disease shows itself as paresis, cerebrospinal syphilis or visceral syphilis without involvement of the central nervous system, the problems affecting the family are the same.

2. At least one-fifth of the families of syphilitics have one or more syphilitic members in addition to the original syphilitic parent.

3. Between one-third and one-fourth of the families of syphilitics have never given birth to a living child, while only one-tenth of normal families remain childless.

4. More than one-third of the syphilitic families have accidents to pregnancies; i.e., abortions, miscarriages or stillbirths (about twice the normal).

5. The birth rate in syphilitic families is 2.05 per family (as compared to a normal of 3.8 per family).

6. Two-thirds of these families show defects as to children (sterility, accidents to pregnancy and syphilitic children).

7. Between one in twelve and one in six of the children examined show syphilitic involvement.

REDUCTION OF TOXICITY AND INCREASE IN THERAPEUTIC EFFECTIVENESS OF ARSPHENAMINE—STUDY OF NEW ARSENICAL COMPOUNDS—The toxicity of arsphenamine has been searchingly studied during the last five years by many independent observers connected

with laboratories where arsphenamine was in process of manufacture. The result of these investigations has been to throw a good deal of light upon the chemical construction of the drug as well as upon its toxicity. Among those contributing are those which have been fostered by the Interdepartmental Board grants. At Harvard under the direction of Professor Reid Hunt,[48] Walter Christiansen[49] has published thirteen contributions upon a simplified method of producing relatively non-toxic arsphenamine, and concerning the toxicity of arsphenamine and its relations to the sulphur group. Professor Lewis in reviewing the work of Christiansen comments as follows:

"Christiansen states that relatively toxic or non-toxic products may be obtained from either of the three commercially feasible processes of manufacture of arsphenamine. The addition of so much as 5 per cent of such probable impurities as 4, 3, 5-HO (02N) 2-C6H2 AsO3H2, or a mixture of 2, 5-and 2, 3-HO (02N) C6H3AsO3H2 before reduction, caused but a slight variation in the toxicity of arsphenamine. Methods of forming the dihydrochloride from the base were not responsible for the variations, which Christiansen finally considers as dependent upon the conditions of reducing the parent 4, 3-HO (O2N)-C 6H4AsO3H2. He obtained products of low toxicity using hypophosphorous acid as a reducing agent. In subsequent articles Christiansen concludes that there is no direct relation between the total sulphur and the toxicity, and searchingly discusses toxic types in general. Hunt cites three distinct toxic types: (a) preparations the toxicity of which was due to the presence of amino-p-hydroxyphenylarsenous oxide (arsenoxide); (b) preparations the toxicity of which seemed to be due to the presence in the manufactured product of toxic substances other than arsenoxide; (c) those toxic on account of the presence of easily destroyable toxic principles.

Type (a) were not encountered commercially but were demonstrable in the laboratory. No toxic substance of type (b) was isolated but their occurrence is probable. Warming and in some cases standing at room temperature reduced the toxicity of type (c). Unique and unexplainable toxic types were also encountered."

Adams, Palmer[50] and Johnson[51] have exhaustively studied the chemistry of arsphenamine. To quote Lewis again "Adams and Palmer have compared the action of arsine and the substituted arsines with the corresponding nitrogen compounds. They were able to condense phenylarsine, the analogue of aniline, with aldehydes. Primary aromatic arsines react with aldehydes in three ways according to the conditions—i.e., R. AsH_2 + R CHO R As (CHOHR) 2; R AsH_2 + 4R CHO (R CHO AsR) 2 + 2R CH_2OH (Adams regards this product as a phenyl substituted heterocyclic ring of arsenic, carbon and oxygen); R AsH_2 + 2R CHO R — AS — R + R CH_2OH.

"Quick and Adams[52] have also exhaustively studied the preparation of aliphatic arsinic and arsinic acids, and aliphatic aromatic arsinic acids. These authors have improved upon Meyer's method of arsenating aliphatic compounds using alkyl bromides and chlorides instead

of the iodides and employing water as a solvent. Thus, the reducing effect of the liberated hydriodic acid on the arsonic acid is avoided on the one hand, and the formation of ether greatly lessened on the other. The arsinic acids are prepared from the arsonic acids by reduction with sulphur dioxide, in hydrochloric acid solution, to the alkyldiochlorarsines, which are then treated with sodium hydroxide and the alkyl halide."

Both of these groups of observers have made excursions into the building up of new compounds of arsenic and Professor Lewis[53] himself, in connection with Lowry and Bergein with Cheetham and Hamilton have built up and studied the therapeutic properties of new organic compounds of arsenic. Thus far, unfortunately, it is not known that any of these new drugs are calculated to surplant the older ones.

As a commentary upon the results of these investigations it has been concluded by one observer that "the field of organic arsenic has been fairly well investigated by Ehrlich and by American chemists. The arsphenamines have proven to be satisfactory spirocheticides, their principal weakness lying in their low degree of penetrability, rather than in their germicidal activity. Therefore it would appear that resources, invested in studies for improving the manner of conveying the arsphenamines to syphilitic tissues or binding them therein for long periods of time, promise more success than might be expected from synthesizing new arsenic compounds."

FLUMERIN—White, Hill, Moore, and Young[54] have developed and studied the therapeutic effects of this new drug for the treatment of syphilis. Their comment and conclusions are given in full.

The evaluation of the worth of any new drug in medicine, and particularly in the treatment of syphilis, is a difficult problem, which must be approached with the utmost caution. In this instance, it is fraught with special difficulties. It is obvious that flumerin cannot be compared with the arsphenamines. No strictly comparable studies with other mercurials, especially so far as rabbit syphilis is concerned, have been carried out. It is not permissible to conclude, because the single dose therapeutic ratio of this drug is the same as that of other mercurials, and because a quantity of flumerin from eight to twenty times greater than other mercurials can be safely employed, that the actual therapeutic activity of flumerin is, therefore, proportionally greater. Therapeutic activity depends on many other factors, chief among which may be mentioned the penetrability of a given drug, and its ultimate fate in the body. No comparisons are therefore attempted and it is given only as our clinical impression that flumerin is, from the standpoints of toxicity and therapeutic activity, superior to the soluble mercurial salts in general use by the intravenous route.

No attempts have as yet been made to employ the drug by the intramuscular route. For the present, and until adequate experimentation shall have demonstrated the limitation of toxicity, the factor of freedom from pain and the relative value of this route as compared to the intravenous route, we do not advise its use.

From the standpoint of the clinical results, it should be pointed out that, as yet, we have given only small doses of the drug. The results obtained in rabbit syphilis indicate the desirability of employing doses larger than 3 mg. per kilogram. The few instances in which we have recently administered 4 or 5 mg. per kilogram indicate that the effect of the drug on lesions and on the Wassermann reaction is enhanced. Attempts to increase the dosage must, however, be carried out cautiously and under adequate control. No attempt is made to suggest the ultimate place which this drug may attain in the treatment of syphilis. It is not available for general distribution, and, for the present at least, permission will not be granted for its commercial manufacture.

This paper deals with a new soluble mercurial drug of low toxicity and of remarkably non-irritating character when injected intravenously. The complete chemical name—hydroxymercurifluorscein—has been shortened to flumerin. This drug is effective in eradicating experimental syphilis in rabbits in doses which are well tolerated. Even in large doses, it causes little or no clinical injury to the kidneys of animals. In ninety-six human cases, definite proof of its value as an antisyphilitic drug has been given.

Doses containing from eight to twenty times the amount of mercury present in the therapeutic dose of other mercurial drugs commonly used intravenously have been given with impunity, and the maximum dose which may be employed serially in the human being has not yet been determined.

The therapeutic effect of the drug has been shown in primary, secondary and tertiary syphilis by the resolution of lesions and the reversal of positive blood Wassermann reactions. The number of cases treated is sufficient to demonstrate that this mercurial is of value, but is too small to permit the allocation of the drug to a definite place in the therapy of syphilis.

TRYPARSAMIDE—Lorenz, Loevenhart, Bleckwenn and Hodges[55] have reported with some enthusiasm on what may prove to be the greatest contribution to the therapy of syphilis since Ehrlich. They were given the opportunity by the Rockefeller Institute to experiment with tryparsamide on patients suffering from syphilis of the nervous system.

Tryparsamide is the sodium salt of N-Phenyl-glycineamid-p-arsonic acid, C_6H_4 ($NHCH_2$ CONH). AsO.OH.ONa) was first made by Jacobs and Heidelberger in 1915. "The biologic action of this substance has been studied experimentally by Brown and Pearce in normal animals and in animals infected with trypanosomes and with the spirochetes of relapsing fever and of syphilis. Tryparsamide has also been used in a comparatively small group of patients for the treatment of syphilis other than that of the central nervous system, first by Louise Pearce and later by Keidel and Moore; and at the time our investigation began it was about to be tested by Dr. Pearce in the treatment of human trypanosomiasis."

The work done by the observers had shown that doses as large as 5 gm. could usually be administered with safety, though its administration (even in smaller doses) may be followed by blindness, which our authors speak of as a transient amblyopia, but which has elsewhere proven permanent.

Indeed it should be said at the beginning that the observations thus far made unite in warning those who use the drug that it has the toxic effect.

The conclusions of Lorenz, Loevenhart, Bleckwenn, and Hodges have been confirmed and the general problem of the relation of tryparsamide to syphilis more intimately studied by Moore, Robinson and Keidel. The therapeutics of the new drug may be described as follows:

TOXICOLOGY—Tryparsamide, like other concentrated arsenicals, causes blindness if given in overdose. This blindness is "apparently a typical toxic amblyopia, due to retrobulbar neuritis, and quite similar to the effects of atoxyl." (Moore.) "When tryparsamide was used in 5 gram doses at weekly intervals, we found that after four or five such administrations approximately 40 per cent of our patients complained of dimness of vision. This condition was transient in all except two cases, and disappeared as soon as the drug was stopped. In the two cases in which the condition was persistent the patients were far advanced paretics who had had abnormal eyegrounds before treatment." (Lorenz). "Impairment of vision developed in Pearce's experience only in patients with moderately or markedly advanced trypanosomiasis of the central nervous system and not at all in the early stages of the disease. The phenomenon seemed to depend further on the size of the dose given, the upper limit of safety apparently ranging from 50 to 80 mg. per kilogram and on the spacing of the injections. An interval shorter than one week was especially likely to be followed by visual disturbance. The transient blurring of vision was usually mild in degree, though in four patients it was marked. On withdrawal of the drug there was always improvement, though in a few instances there was definite residual impairment of vision.

"Early in our own experience with syphilitic patients the same difficulty was encountered. Fourteen patients among about 150 treated have complained of dimness of vision during tryparasamide treatment. In ten of these the visual impairment was slight in degree and cleared up at once when the drug was stopped. In one a patient whose original lesion was syphilitic neuroretinitis, there was a slight permanent visual defect; while in three instances disturbance of vision was severe and there was a marked residuum. All of these fourteen patients had neurosyphilis, and in three there was preëxisting disease of the optic nerve. We have not seen an instance of amblyopia in early or late syphilis without involvement of the central nervous system. . . . Eleven neurosyphilitic patients, accepted for treatment on the basis of objectively normal eyes, have developed mild and transient amblyopia, often preceded for a few hours or days by the complaint of flashes or glimmering of light before the eyes, a phenomenon apparently dependent on irritation of the nerve or retina. This bore no particular relation to the dose employed. One instance occurred after four injections, the first of 0.5 gm., the rest of 1 gm. each. Several have developed after a few weekly injections of 2 gm., and in one of these there was permanent residual damage. In some of our mild cases we have found, as did Pearce in Africa, that it was possible to begin the drug again, after complete disappearance of the mild disturbance, and to reach the initial level of dosage without recrudescence of symptoms."

Comment on the above statements is all but superfluous. Personal report to the editor from two other sources amply confirms the fact that tryparsamide, as at present manufactured, may cause permanent blindness even when administered in small doses to patients showing no lesion of the eye or optic nerve that our methods of clinical examination can detect. Hence the accepted rules:

Tryparsamide should be administered only to patients whose eyes have been proven free from disease by skilled ophthalmological examination.

Patients taking the drug must be warned to report any flashes or glimmering before the eyes, and such report should be made the signal for stopping the administration of the drug, even though no objective signs of disease of the eye appear.

ADMINISTRATION—Tryparsamide is administered intravenously. "Our practice during the past year has been to dissolve 3 gm. of tryparsamide in 10 c.c. of sterile freshly distilled water, and to inject the total amount intravenously. This solution is given at intervals of one week and for periods of eight weeks." Nine intramuscular injections of salycylate of mercury are interspersed with the intravenous injections, followed by "a rest period of from five to eight weeks, when a similar course is repeated," and if necessary, a third. (Lorenz.)

"Treatment should be begun cautiously, the initial dose 1 gm., the second 2 gm., and the third and subsequent doses never more than 3 gm. At the slightest complaint of flashes of light or 'glimmering vision,' or of blurred or dim vision, the drug should be immediately discontinued." (Moore.)

The inconvenience following injection is reported to be negligible, far less than that which follows injection of arsphenamine.

TRYPARSAMIDE IN EARLY SYPHILIS—Moore treated eight cases, seven with early secondary syphilis, one with a seronegative chancre. From two to five injections were given without demonstrable effect upon the lesions, or disappearance of surface organisms.

TRYPARSAMIDE IN LATE SYPHILIS—Moore treated 24 patients with late syphilis, some with lesions, some with only a positive Wassermann reaction and obtained only the most negligible results. Then the cases were put upon the ordinary arsphenamine treatment and many of them immediately responded, showing the tryparsamide to be definitely inferior to the established forms of treatment.

TRYPASAMIDE IN EARLY NEUROSYPHILIS—Moore treated three cases. The symptoms of one case became worse, the spinal fluid picture of two other (asymptomatic) cases was improved, but one of these developed a secondary skin eruption while under the tryparsamide treatment. Hence "satisfactory results having been obtained with the arsphenamines, it seems inadvisable to substitute a weaker spirochetecidal agent."

TRYPARSAMIDE IN LATE NEUROSYPHILIS—The type of case experimented upon by Lorenz and his co-workers was wholly different from those treated by Moore and his co-workers. The former group treated institutionalized patients, the majority of whom had definite psychoses, and about half of whom were advanced general paralytics; moreover none of them had been treated for syphilis during the six months preceding the administration of tryparsamide. The latter group was made up of clinic patients, some of whom had had prolonged and recent antisyphilitic treatment. The Lorenz group treated 97 cases with a definite routine (described above) of tryparsamide and salicylate of mercury. The Moore

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group treated 40 cases of alternating courses of tryparsamide and inunctions of mercury, varying the dosage and the length of the course from time to time. Yet their results are in substantial agreement, as shown in the accompanying table (from Moore).

"In the whole group of patients there was only one in whom some improvement in the fluid did not occur as a result of tryparsamide therapy.

"From the clinical standpoint, ten patients were regarded as arrested, and seventeen as improved by previous treatment. These results were bettered by tryparsamide. Of eight previously untreated patients, five are regarded as arrested, two improved, and only one as unimproved. From the previously treated group, twenty-two are considered to be arrested, three improved, and four unimproved. Six of our patients have remained well for as long as three years following the institution of tryparsamide.

"With regard to the blood Wassermann reaction, a curious phenomenon is observed. In fourteen instances, the test was negative when tryparsamide was begun, and remained so. In eleven, it was positive at the start of treatment, but in only two of these was any change toward the negative phase apparent as the result of treatment. In four patients, the blood Wassermann reaction was negative when tryparsamide was started, and became completely positive during the course, even though in the same patients the spinal fluid was simultaneously changing toward negative. The same type of response was seen in patients with tertiary syphilis, as mentioned above.

"In this point only do our results differ from those of Lorenz and his associates. So far as clinical and cerebrospinal fluid results are concerned, the percentages are surprisingly close. The Wisconsin group, however, obtained a reduction or a reversal of the blood Wassermann reaction in 98.7 per cent of their cases, as compared with only 26.6 per cent in our material. The explanation for this variance is not clear to us. The only essential difference in treatment is that the Wisconsin workers employed a somewhat larger unit dose of tryparsamide plus mercuric salicylate in combination with it, while we used tryparsamide either alone or (in a few cases) in combination with an arsphenamine."

THE EFFECT OF TRYPARSAMIDE ON NUTRITION—"In common with others who have worked with this drug, we have been struck by the fact that some patients gained markedly in weight and the general physical condition improved. We have definite information available regarding the weight curves during a single course of tryparsamide (from four to eighteen doses) in fifty patients. In twelve there was no gain or loss; in nine, a slight loss in weight occurred during treatment (minimum 1 kg.; maximum 9 kg., the latter in a general aralytic whose clinical course was rapidly down-hill, average loss 3 kg.). Twenty-nine patients, however, gained in weight during their treatment, the average gain being 5 kg. In a few instances we have employed the drug solely for its tonic effect, sometimes with startling results. For example, a girl with congenital syphilis, age 24, weighed 41.8 kg. at the beginning and end of the first course of arsphenamine. During the subsequent four weeks she was given a weekly injection of 1 gm. of tryparsamide, with no other change in therapy, diet or mode of living. In these four weeks she gained 5.9 kg. (13 pounds) and has maintained this gain during the following year. In about half the cases of this type, a satisfactory gain in weight has followed the use of the drug; in the other half apparently similar

clinically, no gain has resulted. The question apparently hinges on factors with which we are as yet unfamiliar."

SUMMARY—"The place of tryparsamide in syphilotherapy has still to be defined. Our experience indicates its value in certain types of neurosyphilis, and together with the results of the Wisconsin workers, leads us to think it a more effective drug than any other now at our disposal. In other forms of syphilis, in which the nervous system is not involved, we have seen no evidence that the drug is of any value, except for its tonic effect in undernourished patients. It appears to be contraindicated in early syphilis because of its comparatively feeble spirocheticidal activity. In tertiary and latent syphilis, also, our experience leads us to believe that it is inferior to the arsphenamines, and that, if used at all in this stage of the disease, it should not replace the arsphenamines or mercury, but only supplement them. For the present, therefore, its use should, we think, be restricted to neurosyphilis, and, possibly, to cardiovascular syphilis. It is emphasized that the use of tryparsamide is to be avoided in all cases in which optic nerve impairment already exists, and it is recommended that during tryparsamide administration close attention be given to the fundus of the eye and the sight." (Moore et al.)

SYPHILIS OF THE INNOCENT—Under the above title Harry C. and Maida H. Solomon[56] have published a volume of 239 pages, the subtitle of which is "A Study of the Social Effects of Syphilis on the Family and the Community; with 152 illustrative cases." The volume is divided into chapters on "The Individual," "The Mate," "The Child," "The Family," "The Community," and covers the subject of the social aspects of syphilis in a full and judicial manner that has rarely been equalled. This is due to the method of approach, which is to quote all prominent authorities, giving their opinions as well as their statistics, and to reduce the authors' own comments to a minimum. The personal element is thus almost wholly eliminated and the reader is charmed from one page to another by the fascinating interplay of opposed opinion. Yet the whole is so judiciously edited that the volume might be entrusted to the hands of an uninformed person with less danger of ensuing harm than any such book we have read. The utmost limit of reticence is reached when the authors, after six pages of quotation of the "Opinion of Various Authorities on the Marriage of a Syphilitic," state merely that "it is evident that all these opinions allow a great lattitude in the interpretation of the term 'non-contagiousness.' It is also clear that the time element is brought in as a more important factor than a negative Wassermann reaction"—a wise conclusion, indeed, and a most temperate one, which they then proceed to illustrate by the case of a neurosyphilitic who married on the strength of a negative Wassermann reaction.

This volume is an admirable treatise on the social problems of syphilis. Though there is scarcely any strictly new and unpublished material between its covers, there is much to fascinate, much to inform even the expert.

DIAGNOSIS OF CHANCROID BY CULTURE—Teague and Deibert[57-58] have improved the culture of the Ducrey bacillus to such a degree that it can be used "with as much ease and almost as much certainty as the familiar culture of the diphtheria bacillus."

They submitted to culture the secretions from 274 sores of the male genitals, obtaining 140 cultures positive for Ducrey, and 134 negative. In the majority of cases the culture was taken the first time the patient entered the clinic, and without interrupting the routine treatment of the clinic. The authors estimate the accuracy of the method as "probably above 90 per cent," and cite a series of 32 cases examined at the United States Marine Hospital Clinic by Traynor with 22 positive and 10 negative results.

The medium employed is clotted blood; the technic as follows: "A rabbit is bled from the heart with a sterile 20 c.c. syringe and the blood is distributed in amounts slightly less than 1 c.c. in test tubes about 100 mm. long and 10 mm. in diameter. The blood is allowed to clot at room temperature, is then heated for five minutes at 55°C. and is either used at once or is kept in the ice box overnight and used on the following day. We found that instead of heating the clotted blood equally good results were obtained when the tubes were simply kept in the ice box for from three to five days before they were used."

Pieces of stiff iron wire, gauge 18, about 5½" long are bent upon themselves at one end for about ⅛". Ten or twelve of these wires are placed in a 6" test tube and are heated in the dry sterilizer. The patient is told to remove the dressing, if he has one, and a bit of the pus from the ulcer is picked up with the bent end of the sterile wire, the latter having first been rubbed gently over the base of the ulcer or its undermined edge. The pus is then transferred to a tube of clotted blood and is quickly distributed in the serum by passing the wire several times around the clot. A second tube is inoculated in the same way with a fresh wire. After from 20 to 24 hours' incubation at 37°C. the serum around the clot is thoroughly stirred with a platinum loop and then a smear is made and stained by Gram's method. Examination with the oil-immersion lens shows characteristic chains of small Gram-negative bacilli, sometimes apparently in pure culture, sometimes together with Gram-positive cocci or bacilli. If these characteristic chains are present it is stated that the culture is positive for Ducrey bacilli.

Positive cultures have been repeatedly obtained from lesions under treatment by argyrol, iodoform and other drugs. It was not found profitable either to use a larger number of tubes than two, or to cleanse the ulcer with salt solution. Human blood was not found as effective a culture medium as rabbit blood.

Cultures negative after 24 hours were reëxamined after 48 hours. Though a few late positives were thus obtained the authors advise that as routine the report should be made after the first examination at the end of 24 hours.

They give the following three characteristics of the Ducrey bacillus: (1) It is a small Gram-negative bacillus growing in characteristic long chains and tangles in clotted rabbit blood; (2) it forms on blood agar characteristic colonies

that readily glide over the surface of the medium; (3) it does not grow on any of the ordinary laboratory media with the exception of blood agar."

Secondary cultures may be carried on blood agar plates. The authors recognize that blood has been previously used for the culture of the bacillus of chancroid, but claim the first demonstration of the practicability of the method for routine diagnosis.

TREATMENT OF CHANCROID WITH MERCUROCHROME—Young, White, and Swartz[11] advise the use of "a starch paste containing 5 per cent of mercurochrome —220 by weight," the sore being dressed only once daily. "In all of the cases, the sores cleaned off in from one to four days, and presented a healthy healing surface." Thereafter, boric acid ointment and silver nitrate were applied to granulations. "Tables giving length of time required for complete healing are not included, as many of the patients left the clinic after the sore was partly healed."

In a later publication they quote Bowman as using 1 to 2 per cent pastes with excellent results, "all the sores immediately cleaning off and healing in from six to twenty days, without contraction of complications"; and themselves state that venereal ulcerations, when dressed with mercurochrome, "almost without exception . . . promptly become cleaner and the granulations healthy looking."

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3. "Cultural methods for the gonococcus," by J. C. Torrey and G. T. Buckell, Journal of Infectious Diseases, 31:125-47, August, 1922.

4. "Cultivation of the gonococcus," by Mary J. Erickson and Henry Albert, Journal of Infectious Diseases, 30:268-78, March, 1922.

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"Arsenated derivatives of siphenyldiketopyrrolidines. II," by C. W. Rodewald, I. A. Koten and Roger Adams, Journal of American Chemical Society.

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FINANCIAL DATA ON SCIENTIFIC RESEARCH FUND

State and institution.	Amount of appropriation.				Number of researches.	Scientists in charge.	Assisting professors, technicians, social workers, etc.
	1919	1920	1921, 50–50 appropriation				
			From Government.	From institution.			
California:							
Leland Stanford University	$7,200	$885	$1,200	$1,200	3	4	8
University of California	.....	3,875	.....	.....	1	1	2
Connecticut, Yale University	4,000	.....	.....	.....	2	2	4
Illinois:							
John McCormick Institute	.....	3,000	.....	.....	1	1	3
Northwestern University	.....	6,000	6,000	6,000	2	2	6
University of Illinois	.....	3,500	2,500	2,500	1	1	4
Indiana, The South Bend Clinic	.....	.....	6,800	6,800	2	2	5
Iowa, University of Iowa	.....	5,320	2,480	2,480	1	1	3
Maryland, Johns Hopkins University	19,050	19,050	9,000	9,000	6	6	13
Massachusetts:							
Harvard University	7,000	10,000	8,000	8,000	2	1	1
Boston Psychiatric Institute	.....	13,200	.....	.....	2	1	5
Michigan, University of Michigan	6,000	.....	.....	.....	1	1	4
Minnesota, University of Minnesota	8,250	9,000	.....	.....	3	4	5
Missouri:							
St. Louis University	3,000	4,000	1,500	1,500	1	1	2
Washington University	13,200	4,000	2,500	2,500	4	3	10
Nebraska, University of Nebraska	5,000	.....	5,000	5,000	2	1	5
New York:							
Columbia (College of Physicians and Surgeons)	.....	4,200	.....	.....	1	1	2
Cornell University	7,440	.....	.....	.....	1	1	2
New York University and Bellevue Hospital	.....	5,400	.....	.....	1	1	4
Union University, Albany Medical College	4,380	.....	.....	.....	2	3	6
Pennsylvania:							
Woman's Medical College	1,550	.....	.....	.....	1	2	4
Jefferson Medical College	2,500	.....	.....	.....	1	2	3
Wisconsin, University of Wisconsin	8,000	12,000	6,800	6,800	2	1	14
Total (14 States, 23 institutions)	96,570	103,430	.....	.....	43	44	115

NOTE.—The tabulated number of persons engaged in these researches refers to trained personnel, and does not include clerks, dieners, etc.

SUMMARY.

[Board began making appropriations for researches in March, 1919]

Number of researches started during fiscal year 1919	25
Number of researches started during fiscal year 1920	11
Number of old researches extended during fiscal year 1920	11
Number of new researches started during fiscal year 1921	4
Number of old researches extended during fiscal year 1921	11
Number of institutions represented in the 43 researches	23
Number of States represented	14
Number of scientists in direct charge of investigations	44
Number of trained assistants (professors, technicians, social workers)	115
Board's appropriations for scientific researches, 1919	$96,570
Board's appropriations for scientific researches, 1920	$103,430
Board's appropriations for scientific researches (50–50 plan), 1921	$85,000
Institutions' appropriations to match board's allotment, 1921	$85,000
Joint appropriation for scientific researches, 1921	$170,000
Number of researches completed	4
Number of reports published, 1921	20

LIST OF PUBLICATIONS CONCERNING THE RESEARCHES UNDER GRANT OF THE SCIENTIFIC FUND OF THE UNITED STATES INTER-DEPARTMENTAL SOCIAL HYGIENE BOARD

Boston Psychopathic Hospital

"A study of the economic status of forty-one paretic patients and their families," by Harry C. Solomon and Maida H. Solomon. Reprinted from Mental Hygiene, 5:556-65, July, 1921.

"The effects of syphilis on the families of syphilitics seen in the late stages," by H. C. Solomon, M. D., and M. H. Solomon, B. S., Social Hygiene, 6:469-86, October, 1920.

"The incidence of sclerosis of the cornu ammonis and convulsions in general paresis," by A. E. Taft. Reprinted from the Journal of Neurology and Psychopathology, 2:221-23, November, 1921.

University of California

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Columbia University, College of Physicians and Surgeons

"Some observations on the bacillus of Unna-Ducrey," by Oscar Teague and Olin Deibert, Journal of Medical Research, 43:61-75, January/March, 1922.

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Cornell University Medical College

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Harvard Medical School

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"Some factors relating to the toxic action of arsphenamine," by Reid Hunt, M. D. Reprint from the Journal of the American Medical Association, 76:854-59, March 26, 1921.

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"The hemolytic properties of arsphenamine and fifteen allied compounds," by G. P. Grabfield. Reprinted from the Journal of Pharmacology and Experimental Therapeutics, 19:343-52, June, 1922.

"The relation between the mode of synthesis and toxicity of arsphenamine and related compounds," by Walter G. Christiansen. From the Journal of the American Chemical Society, 43:2202-10, October, 1921.

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JOHNS HOPKINS UNIVERSITY

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"Studies on the the influence of pregnancy in syphilis. I. The course of syphilitic infection in pregnant women," by J. E. Moore, M. D. Johns Hopkins Hospital Bulletin, 34:89-99, March, 1923.

JOHN MCCORMICK INSTITUTE FOR INFECTIOUS DISEASES

"A simplified plate method of partial oxygen tension in the cultivation of the gonococcus," by Russel D. Herrold. Reprinted from the Journal of the American Medical Association, 74:1716-17, June 19, 1920.

"Determination of cure in gonorrheal infection of the male," by Russel D. Herrold, M. D. Reprinted from the Journal of the American Medical Association, 76:225-27, January 22, 1921.

LELAND STANFORD JUNIOR UNIVERSITY

"Rectal injection of massive doses of neo-arsphenamin," by Henry G. Mehrtens. Reprinted from the Journal of the American Medical Association, 76:574-76, February 26, 1921.

MASSACHUSETTS PSYCHIATRIC INSTITUTE

"Provocative reactions in the cerebrospinal fluid in neurosyphilis," by Harry C. Solomon. Reprinted from Archives of Dermatology and Syphilology, 2:679-91, December, 1920.

"The social worker's approach to the family of the syphilitic," by Maida Herman Solomon. Reprint from Hospital Social Service, 3:442-52, June, 1921.

UNIVERSITY OF MICHIGAN

"A study of rabbit spirochetosis," by Dr. A. S. Warthin, Dr. Ruth Wanstrom, Estella Buffington, Journal of Infectious Diseases, 32:315-32, May, 1923.

"A more rapid and improved method of demonstrating spirochetes in tissues," by A. Scott Warthin and Allen C. Starry. Reprint from the American Journal of Syphilis, 4:97-103, January, 1920.

"The cultivation of spirochaeta cuniculi," by Estella Buffington. (This work still in progress.)

"The demonstration of spirochaeta pallida in aortic lesions," by Dr. A. S. Warthin. (In process of publication.)

"Syphilis of the umbilical cord," by Dr. A. S. Warthin. (Will be published during the summer.)

"Occurrence and staining of leptospira icteroides in guinea-pigs inoculated experimentally, with a study of the lesions produced," by R. C. Wanstrom, Journal of Infectious Diseases, 34:110-16, February, 1924.

"Application of the Warthin-Starry silver-agar method to the demonstration of spirochaeta pallida in the spinal fluid by means of coagula obtained by the alzkeimer method," by A. S. Warthin, M. D., Ruth C. Wanstrom, M. D., and Estella Buffington, Archives of Dermatology and Syphilology, 8:461-68, October, 1923.

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"The excretion of spirochaeta pallida through the kidneys," by A. Scott Warthin. Reprinted from the Journal of Infectious Diseases, 30:569-91, June, 1922.

"The staining of spirochaetes in cover-glass smears by the silver-agar method," by A. S. Warthin and A. C. Starry. Reprinted from the Journal of Infectious Diseases, 30:592-600, June, 1922.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL

"Does the introduction of an ethoxy group into aromatic compounds increase their bactericidal action upon the pneumococcus and the gonococcus?" by A. D. Hirschfelder and L. J. Paukow, Society for Experimental Biology and Medicine, Proceedings, v. 19, p. 64-67, 1921/22.

"Comparative studies in the chemistry of blood and cerebrospinal fluid," by Greta Egerer-Seham and G. E. Nixon. Reprinted from the Archives of Internal Medicine, 28:561-85, November, 1921.

"Methods used in determining the electric conductivity of solutions," by J. F. McClendon. Reprinted from the Journal of Biological Chemistry, 43:317-22, September, 1920.

"The pharmacological action of some ethers and esters of saligenin," by A. D. Hirschfelder and H. H. Hensen, Society for Experimental Biology and Medicine, Proceedings, v. 19, p. 145-48, 1921/22.

"Mercury compounds of some phenol carbinols," by M. C. Hart and A. D. Hirschfelder. Reprinted from the Journal of the American Chemical Society, 43:2678-86, December, 1920.

"Saligenin as a local anesthetic for the female urethra," by A. D. Hirschfelder and H. M. N. Wynne. Reprinted from the Journal of the American Medical Association, 75:1770, December 25, 1920.

"Some derivatives of saligenin," by M. C. Hart and A. D. Hirschfelder. Reprinted from the Journal of the American Chemical Society, 43:1688-93, July, 1921.

"Studies of cerebrospinal fluid and blood of syphilitic and normal persons, with special reference to the immunity reactions and the colloidal gold test on the original and ultrafiltered fluids and serums," by C. E. Nixon, M. D., and Korchi Naito, M. D. Reprinted from Archives of Internal Medicine, 30:182-215, August, 1922.

UNIVERSITY OF NEBRASKA MEDICAL COLLEGE

"Further observations on acriflavine in gonorrhea," by Dr. Edwin Davis, Nebraska State Medical Journal, 5:19-23, January, 1920. (Problems under investigation.)

"Urinary antisepsis, a study of the antiseptic properties and the renal excretion of 204 anilin dyes," by Dr. Edwin G. Davis, American Journal of the Medical Sciences, 161:251-67, February, 1921.

"Urinary antisepsis—The secretion of antiseptic urine by man following the oral administration of proflavine and acriflavine—preliminary report," by Edwin G. Davis. Reprinted from Journal of Urology, 5:215-33, March, 1921.

UNIVERSITY OF NEVADA

"Cultivation of the gonococcus," by M. J. Erickson and Henry Albert, Journal of Infectious Diseases, 30:268-78, March, 1922.

NORTHWESTERN UNIVERSITY

"Arsenated benzophenone and its derivatives. II," by W. Lee Lewis and H. C. Cheetham Journal of the American Chemical Society, 45:510-15, February, 1923.

"Arsenated benzanilide and its derivatives," by W. Lee Lewis and C. S. Hamilton, Journal of the American Chemical Society, 45:757-62, March, 1923.

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"Some derivatives of phenoxarsin," by W. Lee Lewis, C. D. Lowry and F. H. Bergeim. Reprinted from the Journal of the American Chemical Society, 43:891-96, April, 1921.

"Recent developments in the organic chemistry of arsenic," by W. Lee Lewis, Industrial and Engineering Chemistry, 15:17-19, January, 1923.

"The preparation of phenylimido-phosgene, and the chlorination of formanilide," by R. S. Bly, G. A. Perkins and W. Lee Lewis, Journal of the American Chemical Society, 44:2896-2903, December, 1922.

"Some mercury derivatives of phenol ethers," by F. C. Whitmore and E. B. Middleton, Journal of the American Chemical Society, 45:1753-55, July, 1923.

"Reaction of alkali halides with mercury derivatives of phenol," by F. C. Whitmore and E. B. Middleton, Journal of the American Chemical Society, 43:619-24, March, 1921.

ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE

"Cultivation and isolation of the gonococci," by R. A. Kinsella, G. O. Broun and O. Garcia, Journal of Infectious Diseases, 32:1-7, January, 1923.

STANFORD UNIVERSITY MEDICAL SCHOOL

"Preliminary report on an investigation of the 'provocative Wassermann' controlled by the ice-box method," by Ruth T. Shepardson. Reprinted from the California State Journal of Medicine, 20:80-83, March, 1922.

"Value of tests with commercial luetin," by H. E. Alderson, M. D. Reprinted from the Archives of Dermatology and Syphilology, 5:592-600, May, 1922.

TULANE UNIVERSITY

"A method for the concentration of cells and bacteria in prostatic secretion," by Dr. Foster M. Johns, Journal of the American Medical Association, 80:463-64, February 17, 1923.

UNION UNIVERSITY MEDICAL SCHOOL

"Cholesterol and cholesterol esters in blood showing a positive Wassermann reaction," by A. Knudson, T. Ordway and H. Ferguson, Society for Experimental Biology and Medicine, Proceedings, v. 18, p. 229-30, 1920/21.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

"A biologic study of latency in syphilis: general considerations: latency—A biologic reaction," by Martin F. Engman, M. D., and Frederick Eberson. Reprinted from the Archives of Dermatology and Syphilology, 3:347-71, April, 1921.

"A study of the incidence of hereditary syphilis," by P. C. Jeans and J. V. Cooke. Reprinted from the American Journal of Diseases of Children, 22:402-11, October, 1921.

"The transmission of syphilis to the second generation," by J. V. Cooke and P. C. Jeans. Reprinted from the American Journal of Syphilis, 6:569-85, October, 1922. (Indirect result of the Social Hygiene Board grant.)

"Dissemination of spirochaeta pallida in experimental syphilis," by Frederick Eberson. Reprinted from Archives of Dermatology and Syphilology, 3:111-16, February, 1921.

"Immunity studies in experimental syphilis," by Frederick Eberson. Reprinted from Archives of Dermatology and Syphilology, 3:775-87, June, 1921. (Infectivity and survival of spirochaeta pallida in rabbits with observations on some strains from latent syphilis.)

"An experimental investigation of the latent syphilitic as a carrier," by Drs. M. F. Engman and F. Eberson, Journal of American Medical Association, 76:160-66, January 15, 1921. Preliminary communication.

"A study of the incidence of hereditary syphilis," by Dr. P. C. Jeans and Dr. J. V. Cooke, American Journal of Diseases of Children, 22:402-11, October, 1921.

"A study of 443 cases of hereditary syphilis with especial reference to the results of treatment," by Dr. Park J. White and Dr. B. S. Veeder, American Journal of Syphilis, 6:353-91, July, 1922. Part I. Social and clinical data. Part II. End results of treatment.

"Immunity studies in experimental syphilis. (Spirocheticidal properties of serums in latent and experimental syphilis) with some observations on immunity," by Frederick Eberson. Reprinted from Archives of Dermatology and Syphilology, 4:490-511, October, 1921.

"The transmission of complement-fixing substances from mother to child," by J. V. Cooke, American Review of Tuberculosis, 6:127-33, April, 1922. (Result of a study of the incidence of hereditary syphilis, and is therefore an indirect result of the Social Hygiene Board grant.)

University of Wisconsin Medical School

"An improved method for the preparation of primary arsanilic acid," by H. C. Cheetham and John H. Schmidt. Reprinted from the Journal of the American Chemical Society, 42:828-29, April, 1920.

"An automatic pipetting device," by W. F. Lorenz, Journal of Laboratory and Clinical Medicine, 7:54-57, October, 1921.

"The relation of chemical constitution of certain organic arsenical compounds to their action on the optic tract," by A. G. Young and A. S. Loevenhart, Journal of Pharmacology and Experimental Therapeutics, 23:107-26, March, 1924.

"The therapeutic use of tryparsamide in neuro-syphilis," by W. F. Lorenz, A. S. Loevenhart, W. J. Bleckwenn and F. J. Hodges, Journal of American Medical Association, 80:1487-1502, May 26, 1923.

"The treatment of central nervous system syphilis with a new arsenical," by W. F. Lorenz, M. D., Wisconsin Medical Journal, 20:336-37, December, 1921.

LIST OF THE SCIENTIFIC RESEARCHES THAT HAVE BEEN AIDED BY THE UNITED STATES INTERDEPARTMENTAL SOCIAL HYGIENE BOARD

California, Berkeley
University of California
Drs. Frederick Gay, Marjorie Cook
"Classification of gonococci and fixation reaction in gonorrhea."

California, Stanford University
Leland Stanford University Medical School
Drs. H. G. Mehrtens, Wm. McKay, Mr. A. Motzkau, Mr. C. A. McArthur, Mr. P. S. Williams
"The permeability of the meninges to antisyphilitic drugs—an attempt to increase their permeability."

Leland Stanford University Medical School
Drs. H. E. Anderson, H. E. Coe
"An investigation into more effective methods of treating syphilis."

Leland Stanford University Medical School
Dr. H. G. Mehrtens
"Quantitative estimation of arsenic in the spinal fluid following irritation of the meninges and intravenous injection of trysparsamide."

Leland Stanford University Medical School
Dr. William Ophuls
"An investigation into more effective treatment in acute and chronic gonorrhea."

Connecticut, New Haven
Yale University Medical School
Dr. George H. Smith
"An intensive study of methods for the isolation and identification of the gonococcus with a view to the determination of the homogeniety and heterogeniety of strains and their etiological relationships."

Yale University Medical School
Drs. M. C. Winternitz, Theodore S. Moise
"Serological reactions on experimental syphilitic infection of the rabbit."

Yale University Medical School
Drs. M. C. Winternitz, F. P. McNamara, Sidney Moise
"The demonstration of the syphilitic nature of unusual lesions encountered at the post mortem table."

Illinois, Evanston
Northwestern University
Dr. Frank Whitmore, Messrs. Vergil E. Meharg, Edmund B. Middleton
(a) "Synthesis of new organic compounds of mercury for use in treatment of syphilis of the central nervous system."
(b) "Synthesis of new substances of the general type R- HG-O. OO, R′ with variations to make new drugs more suited to their use in syphilis and gonorrhea."

Northwestern University
Dr. W. Lee Lewis, Messrs. C. D. Lowry, Frank H. Bergein, Harold C. Cheetham, C. S. Hamilton
"A synthesis of organic compounds containing arsenic of possible value in the treatment of syphilis of the central nervous system."

Illinois, Urbana

University of Illinois

Dr. Roger Adams, Messrs. J. R. Johnson, C. S. Palmer, J. L. Hall

"The preparation of new organic compounds which may have therapeutic value."

Illinois, Chicago

John McCormick Institute for Infectious Diseases

Drs. L. Hektoen, R. D. Herrold

"An investigation for the establishment, if possible, of a better and more definite standard of cure in gonorrheal infection in the male by means of improved methods of cultivation of the gonococcus, improvement in the provocative test, and by means of correlation of the results of fixation and other serologic tests."

Indiana, South Bend

The Clinic

Drs. R. V. Hoffman, M. W. Lyon

"(1) The relation of the Wassermann reaction to the complete and incomplete sterilization of syphilitic tissues; (2) An attempt to sterilize syphilitic tissue by constant saturation of the blood with drugs in tolerable doses."

Iowa, Iowa City

Iowa University (College of Medicine)

Drs. Henry Albert, Mary Erickson

"A selective medium for the isolation and cultivation of the gonococcus."

Maryland, Baltimore

Johns Hopkins University

"(1) Studies in asymptomatic neurosyphilis; (2) Studies in familial neurosyphilis, and (3) Studies in the treatment of syphilis."

Johns Hopkins University

Drs. Hugh H. Young, E. O. Swartz, E. C. White

(a) "Manufacture and investigation of a series of penetrating dyes in the treatment of chancroids."

Drs. Hugh H. Young, D. M. Davis

(b) "Experimental study of various methods of venereal prophylaxis with the object of developing simpler technic, more efficient and less expensive drugs."

Drs. Hugh H. Young, E. C. White

(c) "Development of new synthetic drugs for the treatment of gonorrhea."

Drs. Hugh H. Young, E. C. White, J. F. Moore

(d) "The manufacture and investigation of a series of new organic compounds in the treatment of syphilis."

Johns Hopkins University

Dr. J. Whitridge Williams

"1. The operation of a clinic for the scientific study and treatment of patients suffering from syphilis; (2) Study of available data now accumulated concerning presence of syphilis in families; (3) Study of positive Wassermann reactions among different groups of patients; (4) The effect of syphilis on prenatal and infant mortality."

Johns Hopkins University

Karl S. Lashley and John B. Watson

"A psychological study of motion pictures in relation to venereal disease campaigns."

Dr. J. Whitridge Williams

"A comparative application and analysis of some of the more popular forms of treatment for syphilis."

"Studies of the treatment of syphilis in families, with special reference to its prenatal application."

Massachusetts, Boston

Massachusetts State Psychiatric Institute

Dr. Harry C. Solomon

"An investigation of the changes produced in the central nervous system by the treatment of neurosyphilis."

Massachusetts State Psychiatric Institute

Dr. Harry C. Solomon

"Research on the family of the syphilitic (Social and economic effects of syphilis in special relation to the family)."

Massachusetts State Psychiatric Institute

Dr. Harry C. Solomon

"The clinical results in the treatment of general paresis. (Summary of results obtained in the treatment of general paresis at the Boston Psychopathic Hospital and state institutions of Massachusetts for a period of seven years)."

Massachusetts, Cambridge

Harvard University Medical School

Dr. Reid Hunt, Mr. W. G. Christiansen

"An investigation of the properties contributing to the toxity of arsphenamine, neoarsphenamine, and analogous products."

Harvard University Medical School

Dr. Reid Hunt, Mr. W. G. Christiansen

"An investigation of methods for preparing safer, cheaper and also new arsenicals in the treatment of syphilis."

Michigan, Ann Arbor

University of Michigan

Dr. A. S. Warthin, Mr. Allen C. Starry

"A research for an improved method of demonstrating the spirochaeta pallida in human tissues."

Minnesota, Minneapolis

University of Minnesota Medical School

Dr. A. D. Hirschfelder, Mr. Merrill C. Hart, Mr. F. J. Eucera

"Investigation of phenol-alcohol derivatives in relation to their antisepsis and chemo-therapy of the gonococcus and spirochaeta."

University of Minnesota Medical School

Dr. C. E. Nixon

"An investigation of the chemical and physical properties of the cerebrospinal fluid in the luetic and non-luetic."

University of Minnesota Medical School

Drs. W. P. Larson, J. M. McClendon

"A study of the permeability of bacterial membranes particularly the organisms of venereal disease."

Missouri, St. Louis

Washington University School of Medicine

Dr. Borden S. Veeder

"A study of hereditary syphilis with particular reference to the progress of the disease in the individual and the effect of the treatment."

Washington University School of Medicine
Dr. F. C. Jeans
"A study of hereditary transmission of syphilis."

Washington University School of Medicine
Dr. M. F. Engman, F. Eberson
"A laboratory (biological) investigation of the latent syphilitic as a carrier."

Washington University School of Medicine
Drs. White and Veeder
"Problems in prevention, immunity and treatment of syphilis, based upon observations made in a study of the latent syphilitic as a carrier."

St. Louis University School of Medicine
Dr. R. A. Kinsella
"Studies in the bacteriology of the gonococcus—its growth peculiarities, immunizing properties, classification, and its mode of infecting experimental animals."

Nebraska, Lincoln
University of Nebraska Medical College
Dr. Edwin G. Davis
"(1) Investigation relative to the development of an internal urinary antiseptic; (2) Investigation of the value of certain anilin dyes in the treatment of gonorrhea."

University of Nebraska Medical College
Dr. Edwin G. Davis
"The clinical value of the various acridin dyes for the purpose of internal urinary antiseptsis."

University of Nebraska Medical College
Dr. Edwin G. Davis
"The relative value of the various brands of acriflavine in treatment of gonorrhea."

New York, New York
Cornell University Medical School
Dr. John C. Torrey
"A seriological study of the gonococcus group."

Columbia University College of Physicians and Surgeons
Drs. Hans Zinsser, Oscar Teague, Mr. Olin Deibert
"Studies of the etiology of chancroids with special reference to bacteriology, diagnosis and serum reactions."

American Social Hygiene Association
"An attempt to evaluate the results developed from the scientific researches on venereal disease problems which are now being carried on in this country."

Albany Medical Department of Union University
Drs. George S. Graham, W. M. Baldwin
"An attempt to produce generalized infection in lower animals with treponema pallidum of gonococcus."

Albany Medical Department of Union University
Drs. Thomas Ordway, Dr. Arthur Knudson
"Studies on the nature of the Wassermann reaction."

Albany Medical Department of Union University
Drs. G. S. Graham, W. M. Baldwin
"A study of the effect of radiant energy upon experimental syphilis in the rabbit."

New York University and Bellevue Hospital Medical College

Drs. Wm. Park, Noble, Frankel

"Improvement in methods for determining infection as employed in cultures and complement fixation in subacute and chronic gonorrhea, and results of frequent tests in cases under treatment and detention."

Pennsylvania, Philadelphia

Jefferson Medical College

Drs. Randle C. Rosenberger, John I. Fanz

"A series of studies for the recognition and diagnosis of treponema pallidum in venereal diseases, and the effect of various drugs and materials, as germicidal agents against treponema pallidum."

Woman's Medical College of Pennsylvania

Dr. Bertha Meine, Dr. Rose Hirschler

"A serological study of syphilis in pregnant women and new-born children with reference to the efficacy of methods of diagnosis and treatment."

Wisconsin, Madison

University of Wisconsin Medical School

Drs. A. S. Loevenhart, H. C. Bradley, P. F. Clark, W. S. Stoval, W. F. Lorenz

"An attempt to prepare mercurial and arsenical compounds which have a predilection for the central nervous system, in the hope of finding drugs more useful than any known in the treatment of syphilis of the central nervous system."

THE AMERICAN SOCIAL HYGIENE ASSOCIATION

ADVISORY COMMITTEE FOR

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