Serology of nervous and mental diseases / by D. M. Kaplan.

SEROLOGY

OF

NERVOUS AND MENTAL DISEASES

BY

D. M. KAPLAN, M. D.

DIRECTOR OF CLINICAL AND RESEARCH LABORATORIES OF THE NEUROLOGICAL INSTITUTE, NEW YORK CITY; SEROLOGIST TO THE MONTEFIORE HOME

ILLUSTRATED

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1914

PRINTED IN AMERICA

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

Dedicated
to the work of
THE NEUROLOGICAL INSTITUTE
New York City

PREFACE

In reviewing the literature in book form it became apparent that there is no American work covering the subject of serology in nervous and mental diseases. Scattered articles of merit are to be found in general and special periodicals, but a collection of the material in one volume is sadly wanting. I, therefore, thought that it would meet with the approval of physicians, particularly neurologists and psychiatrists, to have a volume in which some of their queries might be answered. The chief stimulus to write such a book came from Dr. M. J. Karpas, of the Psychiatric Division at Bellevue Hospital, to whom I wish to express my sincere thanks. I am also indebted to Dr. H. Noguchi for photographs and suggestions. The coöperation of the Medical Officers of the Institute helped greatly in furthering the completion of this work, and I wish to close with thanks to them.

D. M. KAPLAN.

30 Beekmann Place,
New York City.
May, 1914.

CONTENTS

PART I—TECHNOLOGY

PART II

PART III

PART IV

SEROLOGY OF NERVOUS AND MENTAL DISEASES

PART I—TECHNOLOGY

INTRODUCTION

HISTORY OF LUMBAR PUNCTURE

THE credit for first withdrawing cerebrospinal fluid from a patient ought, properly, by right of priority, to go to an American physician, Dr. J. L. Corning, who performed the puncture in 1885.[1] Essex Wynter conceived the plan of diminishing intracranial pressure by performing ventricular puncture. Later, in a patient in whom the fontanels had prematurely closed, and it was desirable to diminish the intracranial pressure, the spinal route had to be resorted to for the purpose of withdrawing the cerebrospinal fluid. This was performed in 1889, and although the technic[2] was crude, it nevertheless served as a stimulus to other workers further to elaborate the study of lumbar puncture. The first paper by Quincke on the technic of lumbar puncture and the study of the cerebrospinal fluid appeared in 1891. The thoroughness with which the subject was treated, and the painstaking studies that followed on the steps of the German investigator, justify the coupling of his name with the operation of lumbar puncture, in fact, with the entire subject of research work done on the cerebrospinal fluid. Following closely the publications of Quincke appeared those of Sicard, Nissl, and others.

[1] "Hand-book of the Med. Sci.," W. Wood, vol. vii, p. 292.
[2] The fluid was obtained by performing a laminectomy.

ANATOMY AND PHYSIOLOGY

The spinal fluid occupies the space between the pia and arachnoid—the so-called subarachnoid space. It comes in contact with the periphery of the brain and cord, and probably communicates with the ventricles. The subarachnoid space is traversed by very fine connective-tissue trabeculæ, of which but little is known, although they may assume pathologic importance when they become thickened and adherent. Cerebrospinal fluid can be demonstrated as early as the fourth month of fetal life, at a time when the Pacchionian bodies are still absent. It is, therefore, unreasonable to suppose that these bodies have anything to do with the formation of cerebrospinal fluid. It is more likely, although this is not definitely settled, that the fluid is a true secretion of the choroid plexus cells, a theory advanced by Mott. Whether the fluid is to be considered as a true secretion or as a transudate or as both, can be ascertained from the opinions of noted workers on this subject. It has been proved that the spinal fluid in patients with icterus do not show discoloration in the ventricular fluid, whereas the spinal fluid is discolored yellow. The increase in globulin, as found in general paresis, exhibits a similar peculiarity. These facts tend to show, among other things, that a free communication between the ventricles and the subarachnoid space probably does not exist. The normal meninges permit the appearance, in the cerebrospinal fluid, of formalin after the ingestion of hexamethylentetramin. The circulation also gives to the fluid its specific syphilitic amboceptor. The appearance of blood in the spinal fluid after a hemorrhage in the ventricles cannot be considered as proof that there is a free communication between the subarachnoid and the intraventricular fluids, for it is likely that the trauma produced by the free extravasation of blood in the ventricles would also destroy normal barriers. As against this is the fact that small particles of sterile dyes injected into the spinal canal find their way into the ventricles. Some experimenters have suggested an outlet for the central canal in the conus terminalis (Kramer).

The chief function of the cerebrospinal fluid is a protective one, *i. e.*, the fluid serves as a cushion, preventing jarring of the structures surrounded by it. It also tends to neutralize substances that are to be considered as excretory, forming inert combinations of complex organic constitution. The presence of glucose in the fluid appears to furnish an energy supply to the nervous apparatus (personal communication by Mott).

RACHICENTESIS

Indications.—The chief purpose in obtaining cerebrospinal fluid is to secure, in doubtful instances, an aid to diagnosis. It is this feature alone that has made spinal puncture a frequent procedure, especially in neurologic and psychiatric practice. The progress made in the study of the fluid has furnished very practical and useful aids to treatment and prognosis. The not infrequent meningeal manifestations in children require that a definite diagnosis of the disease be made, which is often impossible without the aid of lumbar puncture. It has also been used for therapeutic purposes in such conditions where the symptoms were believed to be due to increased intracranial pressure.

Contraindications.—First in the list of contraindications to lumbar puncture must be placed tumors of the posterior fossa, particularly of the cerebellum. Where the necessity of studying the fluid is very great (establishing a syphilitic disease of the nervous apparatus), it is permissible to withdraw at most 2 c.c. of the fluid, and immediately replace the same with an equal quantity of sterile normal saline solution, or raise the foot of the bed and keep the patient in this position for twenty-four hours. It is needless to warn against puncturing patients whose physical condition in itself would preclude such a procedure.

Preparation of Patient.—It is best to secure a spontaneous bowel movement first, and if this is not successful, then a mild saline should be given on the morning of the day when the puncture is performed. In the case of ambulant patients, it is advisable to do the puncture in the evening, so that they may rest overnight. The aseptic precau-

tions consist in the ordinary cleansing of the lumbar and upper sacral region with green soap, followed by water, alcohol, and ether. It is not necessary to use a stiff brush, an ordinary piece of sterile gauze being sufficient for the mechanical work. Having thus rendered the part aseptic, a piece of sterile gauze is placed across the spot to be punctured, and secured by a strip of adhesive plaster.

Technic of Lumbar Puncture.—It is best to perform the puncture with the patient sitting on a chair sideways, so that the back of the chair is to one side of the patient. Place a pillow under the patient's abdomen, pushing it well back, and folding the patient's arms across it. Having instructed the patient to bend his spine into an arch backward, the operator runs his index-finger over the spinal column in an endeavor to locate the softest spot on a level with the posterior superior spines of the ilium. This finding of the most suitable point is a matter of training, and is more reliable than measurements made with a tape held over the spines. When the condition of the patient does not permit the use of a chair, the puncture may be done with the patient in bed, lying on one side, with his knees well drawn up over his abdomen. The more the back of the patient is bent, the greater will be the distance between the two lumbar spines, and the easier will it be for the operator to find the softest spot. Having found the spot, a slight impression is made over it with the thumb-nail (previously rendered sterile).

The needle to be used should be made of flexible and not of rigid material, as cases are on record in which the needle broke and had to be dissected out. The one commonly in use is about 11 cm. long and of 1 to 1.5 mm. bore.[1] It is provided with a stilet, which is withdrawn when the canal is reached. In neurotic patients it is safest to anesthetize the puncture spot with ethyl chlorid. The needle is inserted with a sudden thrust, exactly in the center, and straight forward. By going to one side and directing the needle-point toward the patient's left one frequently en-

[1] The so-called "Quincke set" is an expensive apparatus, and can readily be dispensed with.

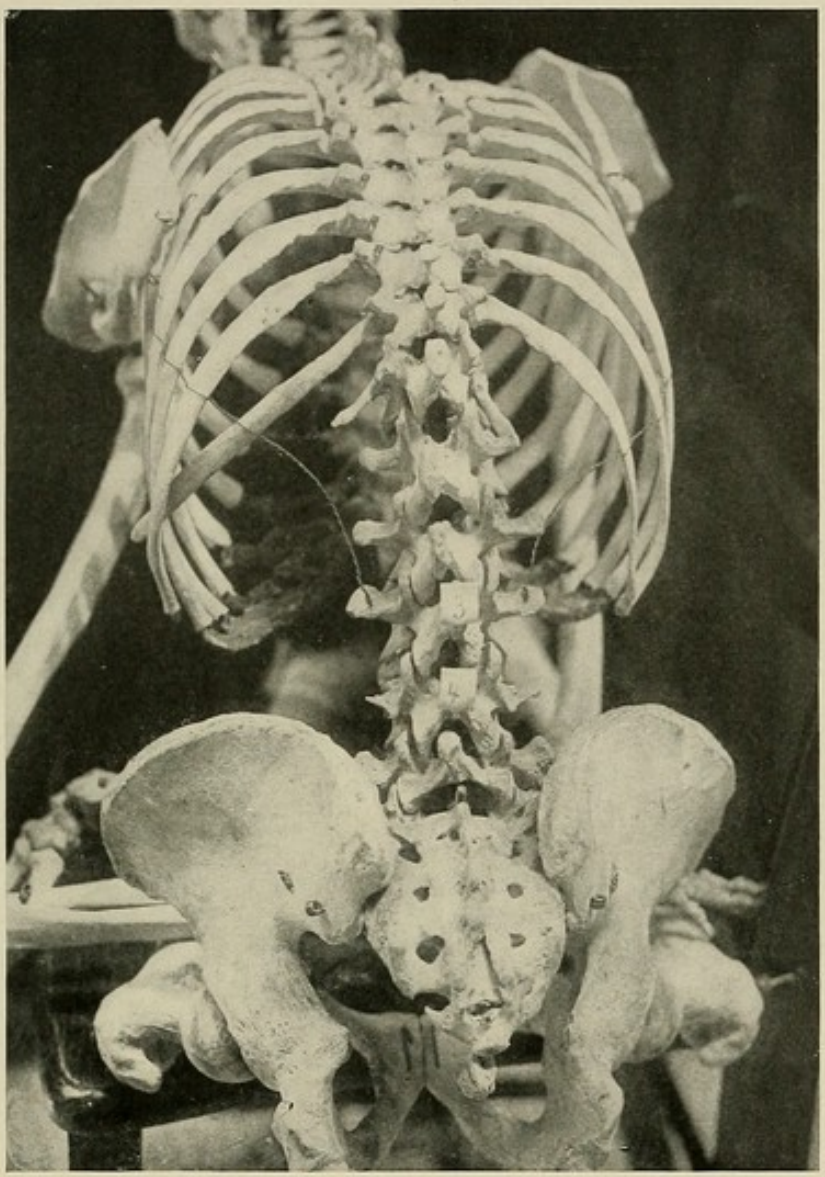


Fig. 1.—Skeletal relations of the lumbar puncture. Note the comparatively larger space between the third and fourth lumbar spines. The "soft spot" is usually to be found in this region.

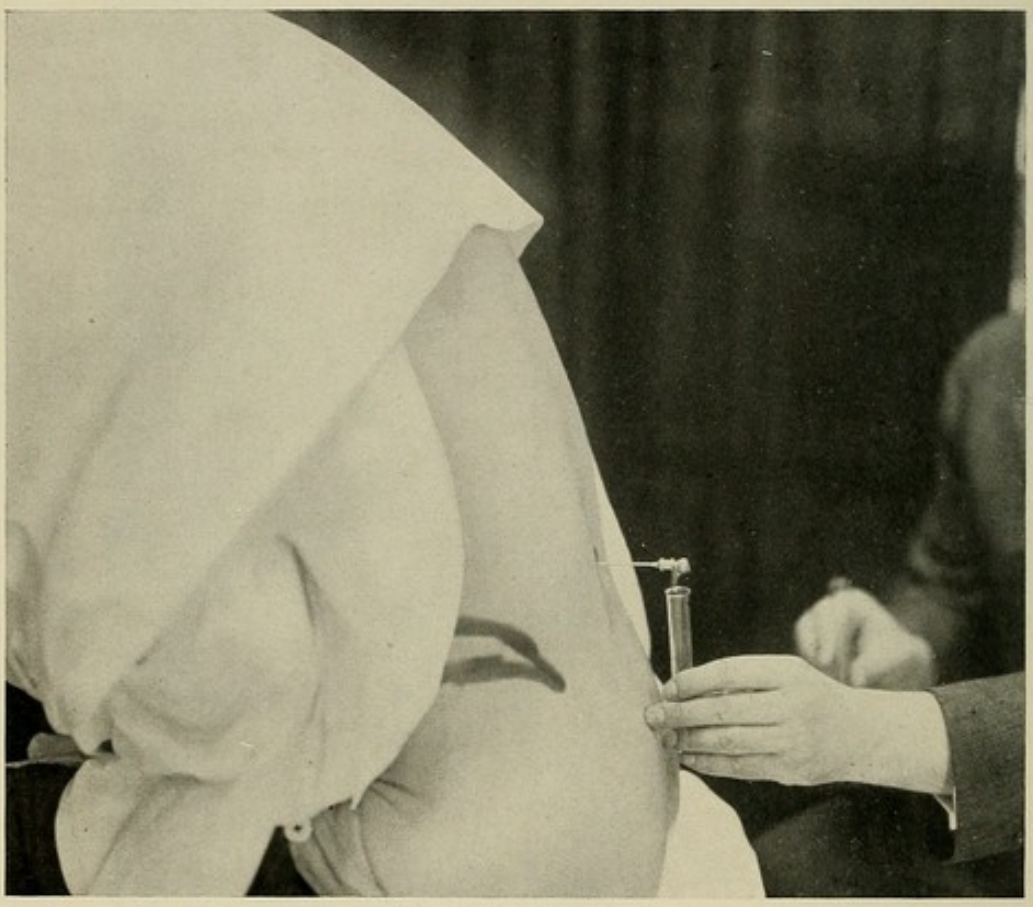


Fig. 2.—Posture of patient during lumbar puncture. Note the second test-tube in the operator's right hand. The space between the two dark lines corresponds with the posterior superior spines. The needle is in the space between the third and fourth lumbar spines.

counters obstacles that are not met when the median line and a straight thrust are used. It is sometimes desirable to ascertain the pressure of the spinal fluid; in such case an ordinary 3 mm. tube, bent into a U, with a small straight limb provided with a piece of rubber connecting tubing is employed. The long arm of the U tube is about 90 mm. long; the short tube, 30 mm. Before using it it should be filled with mercury up to 30 cm. A centimeter scale may be attached to it, and the rise of the mercury column measured after the cerebrospinal fluid begins to flow. Having obtained about 6 to 8 c.c. of fluid, the needle is quickly withdrawn, and the point of puncture covered with a strip of adhesive plaster. It is advisable to collect the cerebrospinal fluid in two test-tubes, in case the first tube shows blood contamination. Occasionally one is unable to obtain spinal fluid even when there is no doubt as to the needle being properly introduced into the subarachnoid space; this fact was determined by W. M. Leszynsky, who, having introduced a needle and entered the canal in the fourth space without obtaining spinal fluid, demonstrated the fact that a dry tap was the cause of the non-appearance by introducing salt solution through a needle introduced in a space higher up, which appeared through the needle that was left *in situ* in the previous puncture.

Phenomena Attending the Puncture.—It sometimes happens that, on withdrawing the stilet, the operator finds that no fluid issues forth; if the patient is instructed to take a deep breath, and no result is obtained, one of three things is at fault: either the needle has not gone deep enough or it has gone too deep (lodged in the intervertebral fibrocartilage), or else it has become clogged by a fibrin plug or by some substance detached by the needle during its transit from the skin to the subarachnoid space. In the first instance, and provided the direction of the needle is correct, a little further advance of the needle will cause the fluid to flow; in the second instance, withdrawing the needle will have the desired effect; when the lumen is obstructed, it is permissible to reintroduce the stilet and dislodge the occluding material. When blood is obtained with the first attempt, it is advisable

not to attempt puncture again, as most likely the fluid is contaminated, and is no better on a second trial than on the first. It is a peculiarity of some patients suffering from tabes or general paresis that the introduction of the needle is hardly appreciated. It sometimes happens that the needle strikes one of the nerve-filaments in the cauda equina bundle; this is followed by a more or less severe pain, affecting the area of the nerve distribution. There are instances on record where death occurred immediately after a lumbar puncture.

After-care of the Patient.—Some patients are so little affected by the lumbar puncture that it is hardly necessary in these instances to adopt any precautions whatever. It is, however, better and safer practice to keep the patient in bed at least overnight, where, if necessary, he can be seen by the doctor. Other patients, again, suffer from severe headache which may last over a week. Lowering the head, mild sedatives, an ice-bag, or any similar simple procedure often suffices to overcome this after-effect. If it does not abate, it is safe to give in one dose 40 gr. of sodium bromid, together with 20 gr. of iodid of potassium. If necessary this may be repeated in four hours. On the other hand, patients of a hysteric temperament are likely to suffer longer and more severely; such individuals may vomit or develop a nervous diarrhea and be otherwise miserable.

Disposal of the Obtained Fluid.—A great deal depends upon the care the fluid receives after it has been withdrawn. As the chief purpose of the puncture, in the majority of instances, is to aid in diagnosis or measure the progress of treatment, a fluid that is placed in the refrigerator overnight or for twenty-four hours may at times undergo a change sufficient to alter its entire composition. The best procedure is to count the cells within an hour of the withdrawal of the fluid; it seems that, when left overnight, some fluids suffer greatly, so far as the cell count is concerned. It is not altogether safe to add a few drops of formalin (4 per cent.) to the fluid, as such a procedure may, in some fluids, produce anticomplementary properties and thwart the result

of the Wassermann reaction. For bacteriologic purposes, the utensils employed should, it is needless to say, be perfectly sterile. In fact, for such work the entire procedure must be more carefully performed: the operator's hands must be treated as for an operation; the patient's back must be thoroughly cleansed; the test-tubes should be sterile and dry, and the fluid preferably submitted at once for bacteriologic analysis. If placed in the ice-chest, and with the addition of a few drops of a 1:3000 tricresol solution, cerebrospinal fluid keeps fairly well for the Wassermann test for three to four days.

GENERAL CONSIDERATIONS OF THE SPINAL FLUID

PHYSICAL PROPERTIES

Normally, the color of cerebrospinal fluid is that of clear water. At times the admixture of red cells gives it a pinkish hue, which, in view of the traumatic origin of the blood, need give rise to no concern. It is in such instances that the advantage of using two test-tubes becomes apparent. The fluid has a specific gravity that is not constant, and ranges between 1003 and 1009. It is absolutely tasteless and odorless.

In *pathologic* states the color may be unchanged, and, in fact, in the majority of diseased conditions of the nervous system the color is not distinguishable from that of normal fluids. It is not at all impossible for blood or its products to find its way into the subarachnoid space after a cerebral hemorrhage, provided, of course, that the meninges were involved in the bleeding; experience teaches, however, that such admixtures are quite rare, and that blood products are more frequently the exception than the rule in cerebral hemorrhage. As will be seen later, the change in color is of significance in certain conditions, and consequently it becomes important to be able to differentiate between the true color of the fluid and that due to the accidental admixture of blood which is sometimes unavoidable; in such instances the color due to cellular admixture is excluded by thorough centrifugalization. I have observed that some fluids, besides giving an intense protein excess reaction, also show a slight yellowish discoloration, no deeper in color than ordinary cedar oil (xanthochromia). Mestrezat distinguishes three forms of xanthochromia, according to its origin: (1) Origine serochromique; (2) origine hemolytique; and (3) origine icterique. In the majority of instances such fluids came from

paraplegic patients; I do not wish to ascribe this peculiarity to tumors of the cord or brain, although this abnormity was chiefly encountered in cord tumors, but would prefer to leave the pathologic significance of this most interesting finding for future observers to decide. At present much new matter is being obtained by the safer operative procedures, showing us in the living subject the cause for such deviation from the normal; I must say, however, that where the laboratory advanced the possibility of a tumor of the cord, the clinician having made this diagnosis before, the subsequent operation did not reveal such a condition. In one instance there was an endothelioma with cysts. In a few instances all that was obtained was a purplish discoloration of the roots of the cauda equina.

Aside from the color, the transparency of the fluid at times suffers from pathologic admixtures. Instead of the clear watery liquid, one sometimes, although rarely, withdraws a turbid, cloudy fluid that, in the majority of instances, is due to cellular admixture. This is sometimes obtained in severe purulent affections of the meninges of the brain or cord. That pure pus may be found is a possibility, though a rare one.

The changes observed in the pressure vary to such an extent, even in normal individuals with intact nervous systems, that it is hardly permissible to ascribe any great significance to its variations. Some tabetics show an increased pressure, whereas others do not; in fact, in some it is below the normal. It is, however, important to know to what extent the fluid can be withdrawn; in this instance the pressure serves as an index. If the pressure has fallen greatly below normal, in the sitting posture, and with the use of the water manometer,—less than 100 mm.,—then the danger mark is near at hand, and one ought to be prepared to inject normal sterile saline solution to replace the fluid withdrawn. Such a procedure was found necessary when a solution of magnesium sulphate was injected into the subdural space to overcome the spasticity of the lower extremities. The respirations in this patient fell to 8 or 9 a minute. Some interesting facts are being elicited in the differences in pressure in

attacks of epilepsy, but up to the present time (1913) no definite clinical benefit could be derived from this knowledge.

Concerning the specific gravity of fluids in pathologic conditions, such as meningitis or hemorrhage, the increase, if present, is due entirely to the protein excess and to the number of cells, and is proportionate to the increase of these two factors.

CHEMICAL CHARACTERISTICS

The reaction of the **normal spinal fluid** is slightly alkaline, and contains a little over 1 per cent. of solid matter. It is capable of reducing Fehling's solution, which reaction, according to Mott, is due to the presence of glucose. Of the basic elements, potassium is to be found in greater quantity than sodium, chiefly in the form of the salts of phosphorus.

The protein matter that is always found in traces in normal cerebrospinal fluids consists chiefly of globulin and albumose. Halliburton demonstrated the presence of traces of cholin in normal cerebrospinal fluids. This substance is a product of decomposition of cerebrospinal nerve matter, and is derived from the breaking down of lecithin and cephalin. In some fluids traces of lactic acid may be found.

Methods of Protein Determination.—Before considering the occurrence of protein excess, it is essential, first, to consider the methods of its detection and quantitative determination. This is very important for clinical purposes, especially as some methods give an excess, whereas others do not. This must be determined before a conclusion can be arrived at as to the significance of an excess in the work of an experimenter who reports this finding. The various methods for the determination of protein in the spinal fluid are about the same as those for the finding of this substance in other media. These methods, however, had to be modified for cerebrospinal fluid work, and others had to be devised for this purpose. Aside from the various tests of complex nature which are not suitable for the clinician, a few of these, however, on account of their simplicity, lend themselves to the needs of the practical physician. It is these tests that are, I believe, of interest here.

The much discussed *Phase 1 reaction* consists of the addition, to the normally reacting spinal fluid, of an equal quantity of neutral ammonium sulphate solution. This is a saturated chemically pure ammonium sulphate solution in hot water. The Phase 1 reaction of Nonne is said to be positive when, three minutes after the addition of the ammonium sulphate solution, a turbidity takes place.

In detail, the *reaction of Nonne and Apelt* is performed as follows: 2 c.c. of cerebrospinal fluid are mixed with an equal quantity of a neutral saturated solution of ammonium sulphate (purissimum, Merck), and compared, after three minutes, with another tube containing spinal fluid only; if there is no difference, or only a very faint opalescence, the reaction is considered as negative. If there is an opalescence or a turbidity, the reaction is said to be a positive Phase 1.

Zaloziecki, in performing the Nonne-Apelt reaction, uses only 0.5 c.c. of cerebrospinal fluid, carrying out the test in smaller test-tubes. I agree with him in the use of a smaller amount of fluid, as it does not in the least alter the result of the test, and leaves the remaining fluid for other reactions, such as the cell count, the Wassermann reaction, the gold solution, the Fehling reaction, etc.

A positive Phase 1 was considered by Nonne and Apelt as significant of a globulin excess, and also as evidence that the fluid was obtained from a patient whose nervous system was not normal. As Phase 2 was considered the appearance of a turbidity in normal fluids on the addition of heat and acetic acid. Owing to the uncertainty of reading the end-results with this method, its clinical application, so far as a globulin excess is concerned, is less popular than other methods in vogue.

The *Ross-Jones method* is a ring test, using ammonium sulphate as the precipitating reagent. Carefully float 1 c.c. of cerebrospinal fluid over 2 c.c. of concentrated ammonium sulphate solution; when a ring of hair-like fineness is obtained after three minutes, the reaction is considered to signify a globulin excess. This test is better suited for clinical purposes, as the end reaction is more constant, is less influenced by individual interpretation, and is sharper.

Ross and Jones consider the importance of estimating the thickness of the ring, the time of its appearance, and the performance of the test with diluted fluids.

The *Noguchi method,* which is very popular in America, gives very satisfactory results. Its technic is as follows: To 0.1 c.c. of cerebrospinal fluid add 0.5 c.c. of a 10 per cent. solution of butyric acid in physiologic salt solution. Boil this for a short time, and quickly add a quantity of a normal solution of sodium hydroxid equivalent to the amount of cerebrospinal fluid used. After this the mixture is boiled once more for a few seconds. An increase of protein matter is characterized by the appearance of a granular or flocculent precipitate, which gradually settles to the bottom of the tube. The greater the excess, the more pronounced is the precipitate. If the amount of protein matter is very small, the precipitate does not appear until after standing for two hours. Such results are not considered as an excess. Although very well adapted to qualitative work, this method does not give a sufficiently accurate gage regarding the quantitative relations of the excess.

Nissl's qualitative demonstration of globulin is made with a cold saturated solution of ammonium sulphate; his quantitative method entails the use of a centrifuge, after the addition of Esbach's reagent to the spinal fluid.

Sippy and Moody used colloidal gold, after the Lange fashion, and reported results that compared very favorably with those obtained with the Nonne method.

The *method of Lange* is performed as follows: Four solutions are prepared: (1) A 1 per cent. gold chlorid solution in very carefully distilled water, using absolutely clean utensils throughout; (2) a 2 per cent. potassium carbonate solution; (3) a 1 per cent. formaldehyd solution; (4) a 10 per cent. sodium chlorid solution. These solutions may be kept in stock, and are used from time to time to make up the indicator.

Preparation of the Gold Solution Indicator.—Into a 1000 c.c. flat-bottom flask of best Jena glass place 500 c.c. of freshly and doubly distilled water. The apparatus used for the distillation should not have rubber connections com-

ing in contact with the steam nor with the water. Add to 500 c.c. of the water 5 c.c. of the carbonate solution, and place on a wire gauze for rapid boiling. Half a minute after the addition of the carbonate solution add 5 c.c. of the gold chlorid solution, and permit the mixture to boil up quickly, using two Bunsens. As soon as the first bubbles of ebulition appear, remove the flask from the flame and add gradually $3\frac{3}{4}$ c.c. of the formalin solution; shake all the time in a rotary fashion until the fluid becomes a deep cherry red. The best way to control the color is as follows: In an ordinary $\frac{5}{8}$-inch test-tube place 15 c.c. of $\frac{1}{10}$ normal sodium hydroxid solution; add 0.2 c.c. of a 0.5 per cent. Congo red solution and 0.3 c.c. of a 1 per cent. alizarin solution. The intensity and the nuance of the color in the test-tube as viewed by transmitted light correspond exactly to the depth and color of the indicator in the flask, viewed in a similar way. The resulting solution should be absolutely clear—so clear that ordinary newspaper print can be read through it; it should not give rise to the formation of a bluish deposit of gold on the sides of the vessel after a few days' standing. Although the solution keeps fairly well, I prefer the use of freshly prepared solutions. Solutions with a yellowish shimmer should be discarded.

Performance of the Test.—Into each of 10 test-tubes place the salt solution made up to 0.4 per cent. freshly, from the 10 per cent. solution. Each tube with the exception of the first one receives 1 c.c. of the salt solution. Test-tube No. 1 receives 1.8 c.c. of the salt solution. Into tube No. 1 place 0.2 c.c. of the spinal fluid to be analyzed. Mix, and remove 1 c.c. of the fluid. Place this into tube No. 2, and continue the procedure until each tube receives a gradually weaker dilution of spinal fluid. Now add to each tube 5 c.c. of the gold solution indicator and mix well at once. Let the fluids stand for twenty-four hours at room temperature and then examine. A clear solution indicates a positive reaction. The gradation of colors is from an absolutely colorless to a red fluid. The first is marked as 5; the latter, as 0.

Kaplan's Method.—In my laboratory the procedure used

is as follows: Into a test-tube 1 cm. wide and 8 cm. long are placed 0.5 c.c. of the spinal fluid to be analyzed. It is heated until it boils up twice; then 3 drops of a 5 per cent. solution of butyric acid in physiologic salt solution are added, followed immediately by 0.5 c.c. of a supersaturated ammonium sulphate solution and the fluid set aside for twenty minutes. In adding the ammonium sulphate solution care must be taken to allow it to flow under the solution and not to mix the test-tube contents.

After about twenty minutes an excess manifests itself in the form of a thick, granular, pot-cheese-like ring. When no granular thick ring forms, the fluid may be regarded as normal. Every fluid that shows the ring just described is further tested as to the intensity of the excess. For this purpose four other tubes receive each 0.1, 0.2, 0.3, and 0.4 c.c. of spinal fluid respectively, and each in turn is brought up to the 0.5 c.c. mark with distilled water. The same procedure is followed as for the first tube. The tubes are set aside for twenty minutes and readings then taken. The quantity of protein matter permitting a ring to appear in the tube containing only 0.1 c.c. of spinal fluid is designated as 0.1 excess, and marks the greatest degree of increase. Fig. 3 shows a 0.4 excess. The chemical changes to be observed in pathologic fluids vary in different diseases and in different forms of the same disease. It is to be remembered, at the beginning, that no hard-and-fast laws exist for the finding of abnormalities in pathologic fluids, and that if one adheres too closely to the significance of laboratory data and disregards clinical findings, he will sooner or later be led into error.

Zaloziecki recommends highly the *Pandy reaction*, which he performs as follows: From 80 to 100 c.c. of acidum carbolicum liquefactum purissimum are brought up to 1 liter with distilled water. The mixture is shaken thoroughly and placed in the incubator for a few hours. After complete clarification at room temperature, which requires several days, the clear supernatant fluid is removed and used as the reagent. It should be kept at room temperature and evaporation avoided, as both tend to render the reagent opaque. A

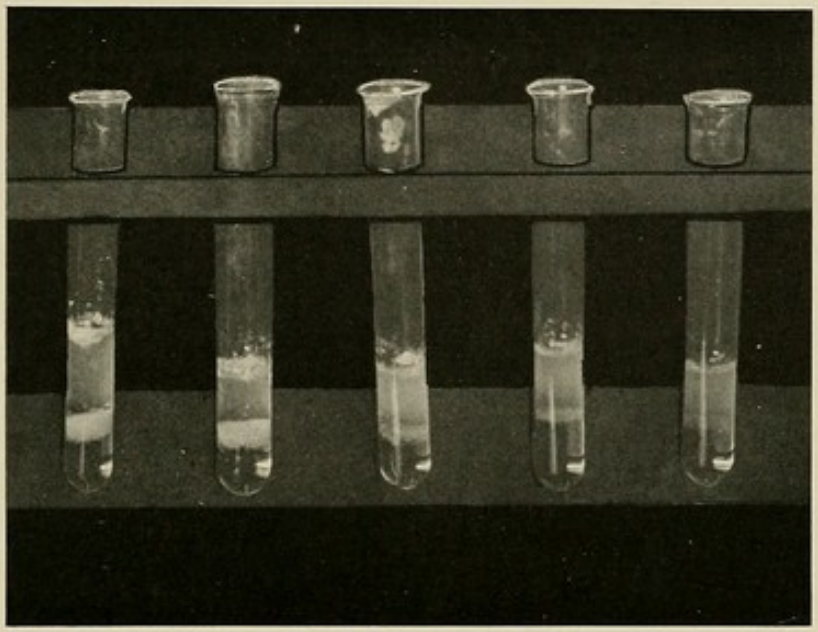


Fig. 3.—The writer's method of estimation of a protein excess. The above shows an excess obtained in the tube containing four-tenths of a cubic centimeter of spinal fluid and one-tenth of water, *i. e.*, a 0.4 excess.

drop of the fluid is permitted to trickle down the side of a watchglassful of the reagent. The fluid must be free from blood and centrifuged before using. A mild reaction is characterized by the appearance of a cloudiness in the liquid; a strong reaction shows a white precipitate. The finer results must be viewed over a dark surface. This reaction is chiefly produced by globulins, but may also be obtained with albumin in fluids containing a sufficient salt content.

As was previously stated, the admixture of blood products will alter the color of the fluid; besides this, such constituents will also change the qualitative as well as the quantitative relationship of the chemistry of the fluid. Hemorrhages into the nervous apparatus, permitting blood to appear in the fluid, although not giving it a distinctive discoloration, may be detected by the different sensitive chemical tests. In using benzidin, one must be extremely careful not to allow his hands to come in contact with the fluid, as perspiration, even in traces, is capable of giving the reaction. A yellow discoloration of the fluid is at times obtained in icteroid states. A pale, cedar-oil-color is sometimes obtained in cases of spinal cord compression. In one instance it was believed that the color was due to cystic fluid, the needle having entered the cyst. Upon operation it was found that an enormous endothelioma encircled the cord for about 9 inches, filling the entire vertebral canal; the tumor showed many cysts containing the same colored fluid as the specimen obtained by lumbar puncture. It is of interest to note that the fluid almost congealed upon boiling. It is not at all improbable that the color is a blood product, as the fluid in the case just cited gave a Berlin-blue reaction. In uremic states the quantitative relationship of urea in the fluid is thought to be proportionate to the increase of this substance in the blood. As the presence of cholin in the spinal fluid was demonstrated in normal states, and as its quantitative determination involves considerable technical experience, this finding loses in importance for the reasons just given.

In diabetes the sugar content may increase markedly in the spinal fluid. In dementia præcox this constituent is greatly reduced in quantity. In two cases of diabetic coma,

one in a girl of sixteen and another in a youth of seventeen, I was able to obtain marked acetone and diacetic acid reactions with the ordinary chemical tests.

Of the drugs that enter the spinal fluid after their administration the foremost and the earliest studied is urotropin. In some meningitides iodin can be detected after its administration. After prolonged narcosis chloroform was found, and some observers demonstrated the presence of alcohol in cases of acute alcoholism. Wechselmann, Zaloziecki, Sicard, and Bloch were able to demonstrate arsenic in the spinal fluid after the injection of salvarsan. They used the Marsh method and the cultural method of Abel. (Cultures of Penicillium brevicaule give a distinct odor of garlic with minutest traces of arsenic.) In a search for arsenic in patients similarly treated I was able to demonstrate the presence of arsenic in a number of spinal fluids. These tests were performed from two days to two weeks after the last intravenous injection of salvarsan and neosalvarsan. The inherent odor of the bread culture of the fungus is so strong in itself that one must possess the very finest sense of smell in order to be able to demonstrate a faint trace; in some instances an extraneous odor may give one the impression of garlic.

The observation of Pappenheim, that some fluids from patients with general paresis contain a leukotoxic substance, is interesting from an immunity standpoint.

CYTOLOGY

General Morphologic Considerations in Normal Fluids.—In the majority of instances the small lymphocyte is the chief constituent of normal spinal fluids. Here and there one may find a cell with a tail-like prolongation that, in my opinion, has no special significance, as it may be found in normal as well as in pathologic fluids. As a result of an unsuccessful puncture the normal hematologic constituents may find their way into the spinal fluid. This occurs at times regardless of the care and the experience of the operator who makes the puncture. At times the admixture is so slight that these findings may be disregarded, and the general morphologic

picture may in such instances be accepted as the true expression of the condition of the cerebrospinal fluid. At other times, when much blood is accidentally obtained, no definite conclusion can be arrived at because of the admixture.

The normal quantitative limits vary with the worker's method. In fact, the laboratories using the Fuchs-Rosenthal chamber are at variance as to the normal limits of the cell count. In view of the meager knowledge of the normal physiologic limits, such as the change in the cell count after a hot or a cold bath, after massage, during gestation, etc., one is compelled to be very conservative regarding the approximately true limit of the cellular content in the spinal fluid. In my experience, the maximum normal count can be placed at 8 per cubic millimeter. Regardless of the care exercised by French workers using the centrifuge method, their quantitative conclusions are not nearly so definite as are the opinions of those who use the counting chamber and pipet.

General Morphologic Considerations in Pathologic States.—That morphologic admixtures may be found in spinal fluids that belong among the curiosities of medicine cannot be denied; in this work only the usual cells encountered in conditions that are acceptedly pathologic will be dealt with, and where it is possible to attach a clinical significance to a given cell form, such opinion will be expressed. As previously stated, the majority of cells found in the spinal fluid are small, poor in protoplasm, and intensely basophilic lymphocytes. The nuclei of these cells are usually round, but may at times show a slightly oval contour. The protoplasm may seem to be entirely absent, and at other times may show a slight accumulation at one pole of the cell, or surround the nucleus with a narrow margin of lighter staining cell protoplasm. These small lymphocytes are smaller, as a rule, than the ordinary red blood-corpuscles, viewed with the same power lens; those that are larger and show more protoplasm may be considered as large lymphocytes. The differentiation between the small and the large has no special clinical significance, the former being present in much greater quantities than the latter.

One frequently finds, in pathologic fluids, cells that do not

take up the stain with their usual avidity for bases. It would seem that these cells have lost the power of absorbing the dye, and hence one may consider them as elements whose life is on the decline, cells that have served their purpose, and do not functionate any longer. Such cells may be found even in normal fluids, and tend to indicate the aging of the lymphocyte. It is to be observed that when a fresh meningeal irritation is present, the small, intensely basic lymphocytes predominate; the same fluid, obtained some weeks later, will show a generous admixture of the large forms plus the above-described poorly stainable small cells.

It is important for the worker with but a moderate experience to carry away with him a definite picture of these poorly staining cells, as it is frequently difficult to differentiate them from the slightly degenerated red blood-corpuscles that may be present in the same specimen. The old lymphocyte studied with the No. 6 lens is no larger than the red cell, but upon focusing shows a definite flatness; its entire body appears to be covered with small dots, which are not granules, but protoplasmic corrugations the points of which lend the impression of dots. The red cell is at once apparent by its gradual disappearance upon focusing, showing differently refracting rings as the cell disappears from view, the result of its biconcave nature. If the red cells are very old (degenerated) and have lost their biconcave form, they may, nevertheless, be distinguished from the old lymphocytes by the complete absence of the dotted appearance just described. Another feature is the color: the red cell tends to assume a pinkish hue, whereas, no matter what the age of the lymphocyte, its former affinity for basic dyes is still apparent in its tendency to stain gray.

An increase of lymphocytes may be observed whenever an irritation of the meninges is present. The amount of increase is dependent upon the degree of the insult. It is, therefore, commonly observed in all meningitides and in diseases of the meninges that are primarily or secondarily involved in luetic processes, such as tabes, cerebrospinal syphilis, and general paresis. It is reasonable to assume that in the

more active manifestations of these diseases a greater variety of cells and in greater numbers are present. To attach diagnostic or pathognomonic significance to any special cell form, with the exception of specific tumor cells, is theoretic and not borne out by proof. One variety of cells, however, the plasma cells of Alzheimer, deserve special mention and description. These are large cells, with a nucleus that stains very intensely with appropriate methods, showing marked chromatin staining. The protoplasm is apparently finely granular, and shows a tendency to lighter staining in the neighborhood of the nucleus. The method of obtaining this cell form, as described by Alzheimer, is as follows: The cerebrospinal fluid is treated, preferably immediately after withdrawal, with 96 per cent. alcohol; about 3 to 5 c.c. are placed in a centrifuge tube and allowed to rotate for about one hour at 1000 to 1200 revolutions a minute. At the end of this time all protein matter will be observed to have collected at the bottom of the tube, and with it, of course, also the cellular elements. At the end of one hour the 96 per cent. alcohol is replaced by absolute alcohol, then by ether alcohol, and lastly by ether, at intervals of thirty to forty-five minutes. The precipitated mass of protein matter is disturbed as little as possible after the alcohol centrifugalization, and carefully placed in a clean container with the other media. The hardened sediment is next placed first in thin and then in thicker celloidin, and after the latter is sufficiently hardened, is ready for cutting. The sections are made about 15 micra thick. The celloidin is dissolved in methyl-alcohol, and the specimen stained with the solution of carbol-methyl green-pyronin of Unna-Pappenheim. The staining should not last longer than a few minutes, and be applied with gentle heat, until slight steaming is observed. The specimen is then treated with water; 95 per cent. alcohol; absolute alcohol, each for a few seconds; next the specimen is transferred to xylol, and lastly it is embedded in Canada balsam. If the fluid is very poor in protein, it is advisable to add a drop of clear albumen, mix the fluid thoroughly, add the alcohol, and centrifuge.

According to the view of Alzheimer and those who worked with him, the finding of plasma cells in the spinal fluid is highly suggestive of general paresis. It must, however, not be forgotten that many cases of general paresis do not exhibit these elements in the fluid; besides this, it is not at all rare to find them present in cerebral lues. To place special significance because of this on a particular cell form is, in my opinion, unsafe.

Many other morphologic forms are to be found in the spinal fluid, such as large cells with eccentrically placed nuclei, large cells (plasma cells) with tails, cells with overlapping nuclei (neutrophiles?), etc. Of special interest in this connection is the leukocyte. From a hematologic standpoint, this term covers the three forms of granulocytes—the eosinophile, the neutrophile, and the basophile cells. The eosinophilic leukocyte is found but rarely in the spinal fluid, and then only when the fluid contains a large number of leukocytes, as in a very active acute meningitis, when the presence of blood, accidentally or pathologically, will sometimes disclose an eosinophile or two in the fluid. The basophile is rarely found in the fluid, and if present, it is usually the result of the same factors that are responsible for the presence of the eosinophile. The neutrophilic leukocyte is, on the other hand, a very common and important cell found in the cerebrospinal fluid. It may be seen in all acute forms of meningitis, such as tuberculous, purulent, epidemic cerebrospinal, and in abscesses that invade the subarachnoid space. In acute forms of cerebrospinal meningitis luetica the presence of these elements is an expression of the acuity of the inflammatory process; they gradually diminish in number as the process tends to become chronic, and in many instances disappear entirely. The so-called polymorphonuclear leukocyte, as seen in the counting chamber, shows one or more nuclei, which do not take up the stain with the avidity characteristic of the lymphocytes in their young forms, but appear rather like the old, worn elements previously described. This phenomenon is not due to age, but to the fact that the neutrophilic nuclei do not, as a rule, take up the basic stain as markedly as does the

lymphocytic nucleus. Besides these characteristics, the neutrophilic cells are much larger than the lymphocytes—about twice the size of the red cells encountered in the cerebrospinal fluid.

Some writers give elaborate descriptions of the various cellular elements to be found in the spinal fluid, using the schemata elaborated by Pappenheim, and describe neutrophilic and eosinophilic leukocytes, microlymphocytes, microlymphoidocytes, lymphoidocytes, large monocytes, endothelial cells, plasma cells, and daughter plasma cells. As there is no special benefit to be derived from so elaborate a classification, and as the search for these elements consumes much time, I will not enter into a detailed description of this cytologically interesting subject which was worked out by Szesci.

Origin of the Cells in the Spinal Fluid.—The origin of the cells found in the cerebrospinal fluid is by no means a settled point. Some workers claim that all the cells found in the cerebrospinal fluid can be traced back to the blood, and others that the cellular elements have a dual origin, some being histogenetic, others hematogenetic. That the last is the best contention will appear from the following exposition of the subject: It is to be admitted that, tinctorially, most of the cells correspond to the elements to be found in the blood. The granulocytes, with their specific granules, definitely prove their relationship to the similarly stained cells in the blood. On the other hand, careful histologic studies of the meninges in general paresis disclose marked infiltrations with plasma cells, which are widely different from any cells to be found in the blood. Besides these plasma cells, one often finds large cells with various nuclei, apparently collected during their sojourn in the spinal fluid. These cells are apparently macrophages of the spinal fluid, and serve as scavengers. They originate in the meninges, and are apparently sent into the fluid circulation in response to a call which is always some irritation, be it traumatic, chemical, or morphologic. These macrophages, stained by the Alzheimer method, frequently show in their protoplasm remnants of old red cells, portions of dead lymphocytes, and débris that has

lost all distinctive landmarks. Pappenheim is of the opinion that the cells in the fluid are purely hematogenous, and believes that the fact that their tinctorial properties differ from those in the blood is to be accounted for by the change a sojourn in a foreign medium would effect. Szesci, on the other hand, advances the opinion that the great majority of cells in the fluid are histogenetic, and that their origin may be traced back to a focus in the meninges that show a similar cellular infiltration; in short, that the pleocytosis is an expression of a cerebrospinal peri-arteritis. Fischer asserts that the pleocytosis obtained is only expressive of a meningeal irritation somewhere in the neighborhood of the puncture, and that the greater the number of cells obtained, the nearer to the site of puncture is the meningitis. Plaut's efforts, however, show that the fluid obtained at higher levels corresponds exactly, so far as the number of cells is concerned, with the specimens obtained from lower portions of the spine. These investigations were carried out with the aid of the counting chamber.

In order definitely to settle the dual origin of the spinal fluid cells it is only necessary to take into consideration the large fibroblastic elements. These cells are the largest to be found in the fluid; they possess a large nucleus, which stains poorly, and may contain one or two chromatin accumulations that may assume the appearance of nucleoli. One may at times find a fibroblast with two nuclei. The most marked differentiating feature is the cell-body; this is usually prolonged into a spindle form with fusiform extremities; at times a cell with two tails is seen. That such cells are not to be found in blood is not to be denied. It is safest to assume that cells, such as the lymphocytes and granulocytes, are hematogenous in origin, whereas the large fibroblastic elements, the plasma cells and their derivatives, are histogenic in origin. We know that all these elements are to be found in the pia, and the changes a cell may undergo when once it reaches the fluid is still an unsettled point that will require much investigation before a definite conclusion can be arrived at.

Methods of Cell Counting

The **French method** of counting cells in the spinal fluid will receive only brief mention, as it is now only of historic interest. Three or 4 c.c. of the spinal fluid are placed in tapering centrifuge tubes and permitted to centrifuge at the rate of 1200 a minute for forty-five minutes. The centrifugalization over, the tubes are next emptied and placed on filter-paper, upper side down, so that as little fluid as possible will trickle down the sides of the tube. Without turning the tube right side up the small, grayish accumulation of thrown-down cells are sucked up with a very fine capillary pipet. The cells are next spread upon a clean, dry slide in three equal drops. The drops are dried in the air, fixed for ten minutes in absolute alcohol, and stained with methylene-blue in the ordinary way for about ten minutes, washed, dried, mounted, and examined. The difficulties of this method are manifold: first, one does not always obtain the same quantity of fluid; this could, of course, be overcome by taking only 2 or 3 c.c. as a standard, and vigorously shaking the fluid before pouring it into the centrifuge tube. The second objection is the capillary pipet, which must necessarily be of the same caliber (the life of a fine capillary pipet at best is not very long). The drying in the air is another feature that ought to be dispensed with, as such treatment of the drop will inevitably distort the cells, making the subsequent morphologic analysis difficult.

The **Nissl method,** so far as the cell count is concerned, is almost the same as the French, and has the same disadvantages. The same idea has been elaborated by Fischer, Kafka, and others, but, as previously stated, the drying, the uneven sucking up of drops, and the irregularities of the centrifuge all introduce objectionable features, and hence these methods are not to be recommended.

The *method of Alzheimer* is a purely qualitative one, and, when used for this purpose alone, gives very satisfactory results. The only correct method for the estimation of the number of cells in the cerebrospinal fluid is with the counting chamber, as described by Fuchs-Rosenthal. The *chamber of Nageotte* is used extensively in France, but permits of too

great error in the final result, besides requiring too much time for the estimation of cells in one fluid. The chamber of the

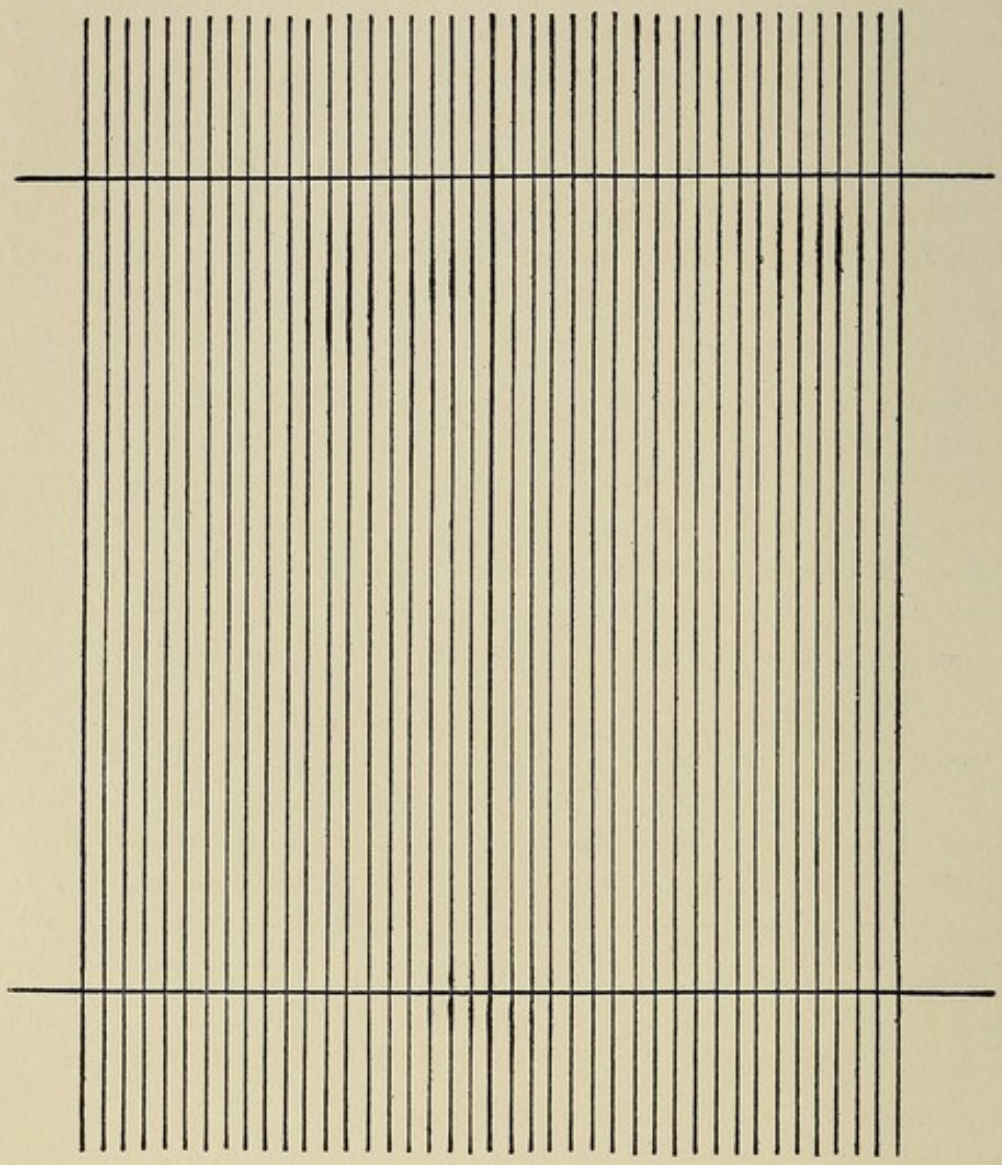


Fig. 4.—Counting chamber of Nageotte. The counting chamber is to be had in two depths, 0.5 or 1.0 mm. In counting, usually four long spaces are computed, which gives the number of cells in 5 c.mm.; this divided by 5 gives the result in 1 c.mm. Either acetic acid or the methyl-violet stain as used with the Fuchs-Rosenthal chamber may be employed. The above calculation is to be used with 0.5 mm. deep apparatus.

French worker and that of Fuchs-Rosenthal are shown in the accompanying diagrams (Figs. 4 and 5).

It is not absolutely essential for the actual cell count to employ the staining fluid, as the cells can be easily dis-

cerned with the use of ordinary 2 per cent. acetic acid instead of the dye. In my laboratory the methyl-violet stain is used not so much as an aid in counting the cells, as it is for the purpose of ascertaining which cells are fresh, thereby giving a clue to the age of the cells and the meningitic process itself; and, secondly, to determine the rapidity with which they disappear after judicious treatment. As a rule, the average cell in the spinal fluid is not a representative of the fully endowed functionating lymphocyte or polynuclear

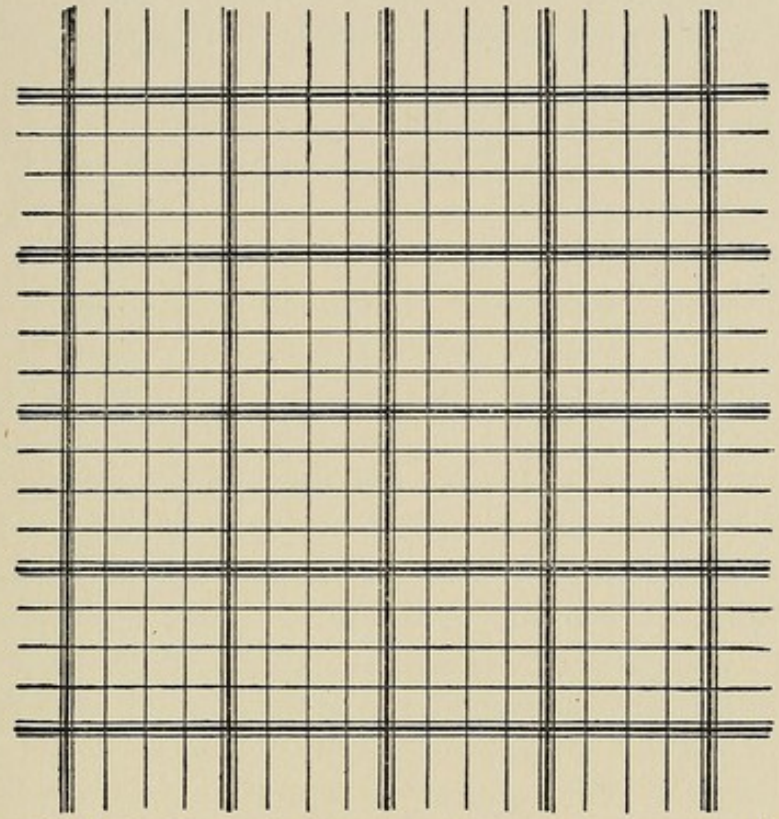


Fig. 5.—The Fuchs-Rosenthal counting chamber for cerebrospinal fluid.

cell; the elements found in the fluid are more or less devitalized by a prolonged sojourn in the cerebrospinal fluid or represent the normal expression of wear and tear, with the absence of certain characteristics possessed by normal youthful elements. If a counting chamber with a cellular fluid stained with the methy-violet dye is permitted to act on the cells for five minutes and then counted, it will be observed that the majority of the cells, in a case with a metaluetic nervous affection, such as tabes, will show that most of the

cells are only faintly colored, and that only here and there are elements to be seen that exhibit the necessary affinity for the dye, which gives them the blackish-blue color; the remaining cells range in depth of color from a very faint gray to a light blue. In my opinion the cells capable of taking up the stain also possess some of the other qualifications of a cell that is still in a position to exercise its functions; whereas the pale cell, I believe, is an element incapable of function, and is in a stage preceding its complete dissolution. With the aid of acetic acid one can, as a rule, determine the nuclear outline of a cell with much greater certainty than with the stained fluid.

The Fuchs-Rosenthal Counting Method.—The diagram of the chamber shown in Fig. 5 is 16 mm. square and 0.2 mm. deep; in these particulars it differs from the ordinary Thoma-Zeiss blood-counting chamber, in that the latter is only 1 mm. square and 0.1 mm. deep. The resulting count with the blood chamber gives the number of cells in $\frac{1}{10}$ mm. of blood; the Fuchs-Rosenthal chamber gives the number of cells in $\frac{16}{5}$ mm. This markedly reduces the errors in counting, as the final result is practically one-third of the entire number of cells counted. In counting the fluid cells the following procedure is employed: The test-tube containing the cerebrospinal fluid is vigorously agitated, which distributes the cells fairly equally through the medium. With an ordinary white blood-corpuscle pipet the staining fluid is sucked up to the mark 0.5, and then vigorously shaken again. After permitting the cells to absorb some of the stain, which requires about three minutes, a large drop is placed on the counting chamber, the cover-slip is adjusted, and the specimen is ready for counting. The stain used for this purpose is made up as follows:

Methyl violet	0.05
Glacial acetic acid	0.5
Aq. dest.	ad 25.0

In order to preserve the staining fluid and to prevent the formation of fungi I am accustomed to add a few drops of a 10 per cent. solution of phenol. When, in spite of this precaution, fungi and bacteria develop, it is best to make

up a new quantity of stain. This counting method requires very little fluid, consumes but little time, and can be carried out at the bedside of the patient. The cellular contour is not disturbed in the least, and the morphologic constituents of the fluid appear in their unaltered physiologic form. It is to be remembered that the fluid is to be examined as soon as possible,—preferably within one hour after the puncture,—as the cell content suffers through standing.

It is a matter of training to be able to distinguish the various cellular types from their appearance in the Fuchs-Rosenthal counting chamber; where, however, exactitude in determining the morphology of the spinal fluid is an essential feature, it is advisable to resort to the fixation and staining methods previously mentioned.

Interpretation of Findings

The Abnormal Cell Count.—The classification of Ravaut, who employed the French method, does not deserve special consideration on account of the wide margin of error inherent in the counting. Even the improvement of Nissl, who counted the cells in the entire specimen (a very tedious and time-consuming procedure), does not give as much information as the counting chamber methods. In my experience, the maximum limit for the normal cell count is 8 lymphocytes per c.mm.; the border-line count from 9 to 15 per c.mm.; the pathologic increase, 15 to 60 cells per c.mm.; hyperlymphocytosis, 60 to 250 per c.mm.; acute meningitic cell count, from 250 to 2000 per c.mm.

These cell counts are useful chiefly for the establishment of pathologic conditions in the meninges; secondly, as an aid to gaging the progress of a given remedial agent; in fact, the latter use, in my opinion, is the more important one, and the one that gives greatest satisfaction to the clinician. The border-line count, as all such findings are, be it a questionable Phase 1 reaction or a weakly positive Wassermann test, has no particular significance. Such a result, in the hands of a physician who does not know how to weigh laboratory reports, will sometimes be provocative of error if too much credence is given such a report. In order to be

able to determine the cell count in a given spinal fluid satisfactorily it is better to perform another lumbar puncture about ten days later, and count the cells again, in case the previous counting gave a border-line result.

In paretic individuals who are in their decline it is customary to find border-line counts; low cell counts are sometimes seen in cord tumors and in cases of cerebrospinal lues of the endarteritic form. The majority of instances in which the pathologic increase is obtained are in tabes, particularly in those forms of the disease that yield to specific treatment. To this cell count can also be added general paresis; in fact, this disease is the representative of the small-cell count pleocytosis. Pathologic increase in cells (15 to 60) is found in cases of untreated tabes. Properly treated cases of cerebrospinal syphilis of the gummatous and the meningitic types exhibit this degree of increase in their cell contents after appropriate therapy. The hyperlymphocytic cell count is found in tabes and in the milder forms of cerebrospinal syphilis. The purulent meningitides show the highest cell counts, and it is in these cases that it is not infrequently impossible to count the cells because of their number. The acute forms of cerebrospinal syphilis have also their place in this form of cellular increase; I have observed a case in which the cells numbered 1680 per c.mm. The lowest of these counts are at times, although but rarely, found in tabes. The influence of therapy on the cell count in different conditions in which a pleocytosis exists will be the subject of a later section, in which, also, the other reactions, such as the Wassermann test, the globulin excess, and the Fehling reduction, will also be considered.

A few remarks on the **bacteriology of the cerebrospinal fluid:** In order to secure an uncontaminated specimen for bacteriologic analysis, the fluid must be collected under strict aseptic precautions. Every utensil or instrument that may come in contact with the spinal fluid must previously have been sterilized. It is also essential, once the fluid begins to flow, to act as quickly as possible, as undue exposure to the air may contaminate the fluid and offset the resulting cultural work.

When a bacteriologic examination is required, it is best to make this alone, leaving other investigations, such as blood-pressure and collecting the fluid for chemical analysis, until a future time. It is, however, advisable to note the color and the transparency of the fluid as it flows into the test-tube, as it is sometimes possible to exclude a purulent process simply by observing the transparency of the fluid. When a diagnosis of an acute cerebrospinal meningitis has been made, it is best to bring the microscope and staining fluid to the bedside of the patient and then and there determine positively the existence of such a condition. The laboratory worker should bring with him the necessary antimeningitic serum, place the same in a vessel with warm water, to bring it to the temperature of the body, and if the resulting cell count shows the existence of a meningitis, regardless of the bacteriology, which is as yet undetermined, the serum should be injected at once, as the delay necessitated by the growing of the bacteria may permit the disease to progress beyond hope of repair. On the other hand, if the microscopic analysis shows an absolutely normal spinal fluid, one may wait to ascertain the result of bacteriologic analysis, and for the time being treat the patient symptomatically. If this method were resorted to more often, fewer spontaneous cures of epidemic cerebrospinal meningitis would have been reported.

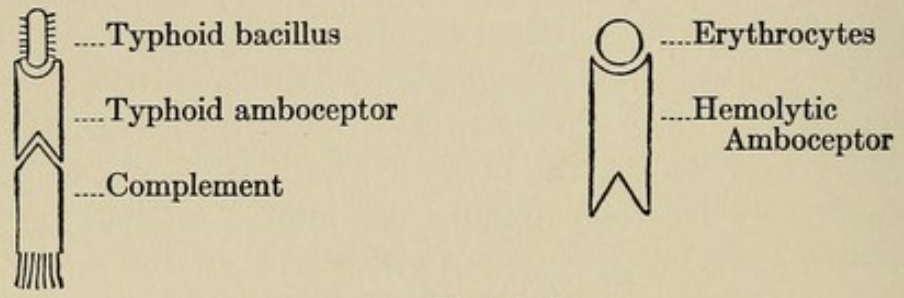
The search for tubercle bacilli is performed as follows: The spinal fluid is placed into a centrifuge tube, and three or four absorbent cotton threads are added; this is permitted to centrifuge for one hour, at the end of which time the collected mass on the bottom of the tube is poured into a Petri dish over a black surface, and the material enmeshed in the cotton threads is carefully extracted and placed on a glass slide. The fluid is gently evaporated, and stained by the Ziehl-Neelson carbolfuchsin method. At best, the search for tubercle bacilli, even if they are present, is a very time-consuming process, and should not be given up before the entire slide has been thoroughly examined. This may require an hour or two; if the fluid submitted for examination does not show a pleocytosis, half an hour is sufficient

for the microscopic work. The more painstaking procedure is suggested for fluids in which a pleocytosis was found. Of the microbic invaders of the spinal canal, the most difficult to detect is the tubercle bacillus. The other bacilli and cocci lend themselves much better for microscopic determination. Of these, the pneumococcus shows itself to greatest advantage; the Micrococcus intracellularis can also be readily detected; the influenza bacillus and the ordinary pus-cocci show definite microscopic pictures. Although the microscopy of a fluid and the finding of the invader are frequently sufficient for clinical purposes, one should not depend upon the result of such an analysis, especially when the exact biology of the microörganism is of interest. For accurate bacteriologic work, special methods are necessary, requiring the assistance of a trained bacteriologist. The fluid is best collected, under the precaution previously outlined, in a Petri dish, adding the nutrient medium, blood-agar, glucose-agar, or plain agar, and submitting the specimen to the specialist for further elaboration. In order to be certain that the proper technic and subsequent disposal of the collected fluid are properly carried out it is best to leave the entire procedure to the bacteriologist.

SEROLOGY

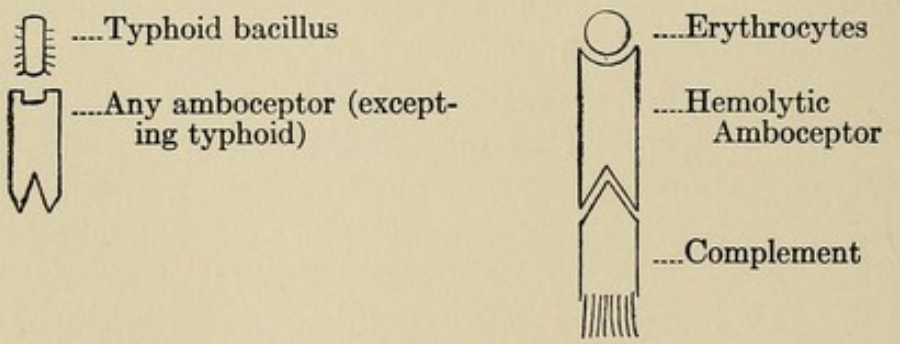
History and Development of the Wassermann Reaction.—The work of Bordet and Gengou, who in 1901 described the method of detecting antigens and introduced it into practice for many diseases, needs but to be mentioned here. By the term "antigen" is understood any substance capable of producing, in a susceptible living organism, a definite and specific response; this response is the formation of antibodies. The nature of the latter substances is still an unsettled question, but it is fairly well established that antibodies belong to the class of amboceptors. The entire reaction depends upon the mixing of a given antigen with its homologous, inactive (heated at 56° C.) immune serum and complement. In case the immune serum is of homologous nature with the antigen, the complement is bound or deviated; at least it is rendered ineffective for further use. This is established by the method introduced by Bordet and Gengou, who added a well-washed (serum-free) suspension of erythrocytes, together with a definite quantity of a specific hemolytic serum, which was also heated to 56° C. If the previously introduced complement is deviated or bound, no hemolysis will ensue, as no complement remains to complete the hemolytic reaction. When the complement is not deviated, hemolysis takes place and serves as a proof that the serum added to the antigen was not of a homologous nature. This method, therefore, serves as an indicator as to the existence of an amboceptor that may fit a given known antigen. Taking, as an example, a serum from a case in which typhoid is suspected, the following procedure would be used: The suspected serum is rendered inactive (heated for one hour at 56° C.) and placed in a test-tube; to this is added our known antigen (Bacillus typhosus); next a given quantity of complement is added (guinea-pig serum). In order to give this combination an opportunity to unite, the mix-

ture is placed in an incubator for one hour. If the serum is that of a typhoid patient (contains the homologous immune body), we expect a deviation of complement. After an hour's incubation the erythrocytes, plus their hemolytic amboceptor, are added to the same mixture and the test-tube is again placed in the incubator. If the complement is free, a proof that the serum originally subjected to the test did not contain the homologous antibody, hemolysis will take place in from fifteen to fifty minutes. If, on the other hand, the patient had typhoid, hemolysis, for obvious reasons, will not ensue. Pictured diagrammatically, the following scheme is helpful:



Figs. 6, 7.

This diagram shows theoretically the existing conditions when the patient's serum contains the immune amboceptor necessary for the binding of the complement. If the patient is not suffering from typhoid, and consequently does not possess the amboceptor, the following diagrams will tend to illustrate what happens:



Figs. 8, 9.

Hemolysis is the result of this combination, and is proof that the patient does not suffer from typhoid fever, as the

complement was left free to act on the subsequently introduced hemolytic system.

The next step in elucidating the foregoing phenomenon of complement deviation in typhoid was the study of similar deviations with various antigens. Wassermann, Neisser, and Bruck established the fact that apes treated with repeated injections of organic extracts from syphilitics showed, in their sera, substances that were capable of binding complement with organic extracts (antigen?) of syphilitic origin. Next, Detre, Wassermann, Neisser, and Bruck, as also Schucht, found that the same holds true with sera obtained from patients who were infected with syphilis. The early results were not very encouraging, as only a small percentage of cases gave this reaction. Citron, however, proved that the reaction is rarely obtained in recently infected individuals, as well as in old, symptom-free luetic patients. A similar absence of phenomenon was observed by him in well-treated syphilitics. This author, on the basis of the results obtained in Krauss's clinic, advised the performance of the test as a routine procedure in all cases where syphilis was suspected. The elaboration of the theoretic part of the reaction is due largely to the labors of Porges and Meier, Landsteiner, Mueller, and Poetzl, and later to Levaditi and Yamanouchi. These workers obtained, with the use of alcoholic extracts from syphilitic livers and other organs, very satisfactory substitutes for the still but little known syphilitic antigen. The contention at that time was that the entire phenomenon is an interaction of various more or less complex lipoids. Porges and Meier believed that the lipoid bodies were closely related to lecithin. Levaditi and Yamanouchi again ascribed the antigenic rôle of their organic extracts to bile salts. The experiments of Wassermann and Citron showed that, at least so far as animal experimentations show, there is no evidence that antigenic qualities can be ascribed to lecithin or allied substances.

These workers also proved that deviation of complement can be obtained with such substances as glycogen, albumose, pepton, lecithin, oil, gelatin, etc., a finding that was corroborated by the experiments of Landsteiner and Stan-

kovic. These results make it probable that the phenomenon of complement deviation is due to a change in the physico-chemical relationship of a molecule through the addition of another substance, a view also shared by Bordet and Gay in their conception of hemolysis.

If this is really so, then the interesting work of Seligmann finds an explanation—*i. e.*, that the reaction is a physico-chemical change of a colloid molecule when another substance ("Reagin," Citron) is introduced. This last investigator obtained complement deviation with a colloid iron hydroxid solution, with emulsions of mastic, with gelatin, etc. For the purposes of immunodiagnosis it suffices to know that whatever the colloid-like antigen may be, it is specifically influenced by homologous immune sera, and hence is very useful for the detection of unknown antibodies (Reagines).

At present the application of the phenomenon of complement deviation as a serodiagnostic method for the detection of syphilis receives more attention than for any other infectious disease, especially since the work of Citron established its significance for lues in general; Wassermann and Plaut, as well as Marie and Levaditi, for the presence of complement deviating substances in the cerebrospinal fluids of general paretics.

Technic of Blood-taking.—This procedure, in the hands of an expert, is accomplished in not more than one or two minutes from the beginning of sterilization to the finished bandaged, punctured arm. One who has no experience, however, will frequently lose much time and, in the end, have secured no blood for analysis, and, besides, the patient will have a bruised and aching arm. For these reasons it has been deemed well to describe the technic fully, and show how an apparently difficult puncture can be easily and successfully made. Special apparatus are unnecessary, and the method does not require a special procedure; the essential points to know are how to handle a vein and to become acquainted with the peculiarities of veins in general. The area of the puncture is first inspected; in my practice I prefer to use the left arm, for the simple reason that the vein selected

runs in the line of the needle puncture, *i. e.*, from right to left and upward, which is exactly the direction of the thrust of the needle's point in right-handed operators. The inspection should take in the general contour of the arm, and especially the bend of the elbow. The bend is carefully palpated, in case there are no visible veins, and if none are to be felt upon palpation, it is advisable to exert a slight pressure two to three inches above the bend. Sometimes the veins are so deeply situated that a tourniquet must be applied before the vein can be felt. For educational purposes I advise that one finger be trained for the palpation of veins; this advice may seem superfluous, but I have found that where others could not find a vein, the well-trained finger detected the slight resistance and the puncture gave blood at the first attempt. It is commendable to devote five minutes to getting the bearings on the venous distribution before attempting to puncture an arm. Most every one has witnessed the repeated puncturing of an arm until it resembles a sieve. One is to be particularly warned against trying to puncture a thin-walled, superficially lying vein that is not sufficiently fixed by perivenous connective tissue. The secret of success lies largely in the ability to select a proper vein to puncture. This is not always the largest one, but, on the contrary, the firm, thick, small, and well-fixed vein, which nine times out of ten will receive the needle-point without swerving and slipping from under; of course, if properly manipulated. The proper method of manipulating an arm for puncture can be divided into—(*a*) the selection of the vein; (*b*) rendering the vein prominent and harder; (*c*) fixation of the vein; (*d*) handling of the needle.

(*a*) As previously stated, the most sensitive finger is employed for palpation of the bend of the elbow. These suggestions, of course, apply to cases in which difficulty is experienced in finding veins for puncture. With slight intermittent pressure the finger palpates the deeper soft parts of the elbow; if a string-like resistance is obtained and the sense of touch is not delicate enough to distinguish a vein from a tendon, then a tourniquet is applied and the area again palpated. With the finger still on the suspected vein, the

tourniquet is suddenly released: if the finger is on a vein, then the swelling or the resistance will suddenly collapse; if it is on a tendon, the resistance will remain unaltered. Should no satisfactory vein be obtainable on the left side, then the right side should be tried; under no circumstances should the needle be plunged into a spot before ascertaining whether it is a proper vein or, perhaps, no vein at all.

(*b*) Having found what appears to be a vein, the next step is to make it fit for puncture. The area is rubbed gently with 95 per cent. alcohol, and the tourniquet is applied, as previously stated. In using a tourniquet, a simple piece of good rubber tubing is preferable to the instruments sold in the shops for the purpose. The tubing is of the caliber of a good-sized catheter, and 18 inches long. The pressure must not be too great, as in that case the artery may be obliterated; it is, therefore, advisable for beginners to feel the pulse before proceeding further. With the tourniquet in position, the next step is to bring out the vein as prominently as possible. This is accomplished by dropping from a bottle, a drop at a time, 95 per cent. alcohol on the spot to be punctured, gently rubbing the trained finger over the spot. When enough resistance to the finger is experienced, then the vein is ready to be punctured.

(*c*) All precautions can be frustrated if the vein to be punctured is not properly fixed by the operator's left hand. Care must be observed to prevent the vein from slipping from under the needle-point, as it often will. For this reason a firm hold on the vein should be obtained before the puncture is made. Figs. 10 and 11 illustrate graphically the points to be observed in this connection, and also demonstrate the reason why the left arm is more suitable than the right. With the thumb of the left hand over the vein, firm pressure is exerted on it, the entire attention being directed toward this spot, the object being to prevent slipping of the vein from under the thumb as well as to guide the needle-point. If the needle is in the vein lumen and has pierced all the coats of the vein-wall, the hand holding the needle will experience a sudden sense of diminished resistance, which, in the majority of instances, is followed by the trickling of

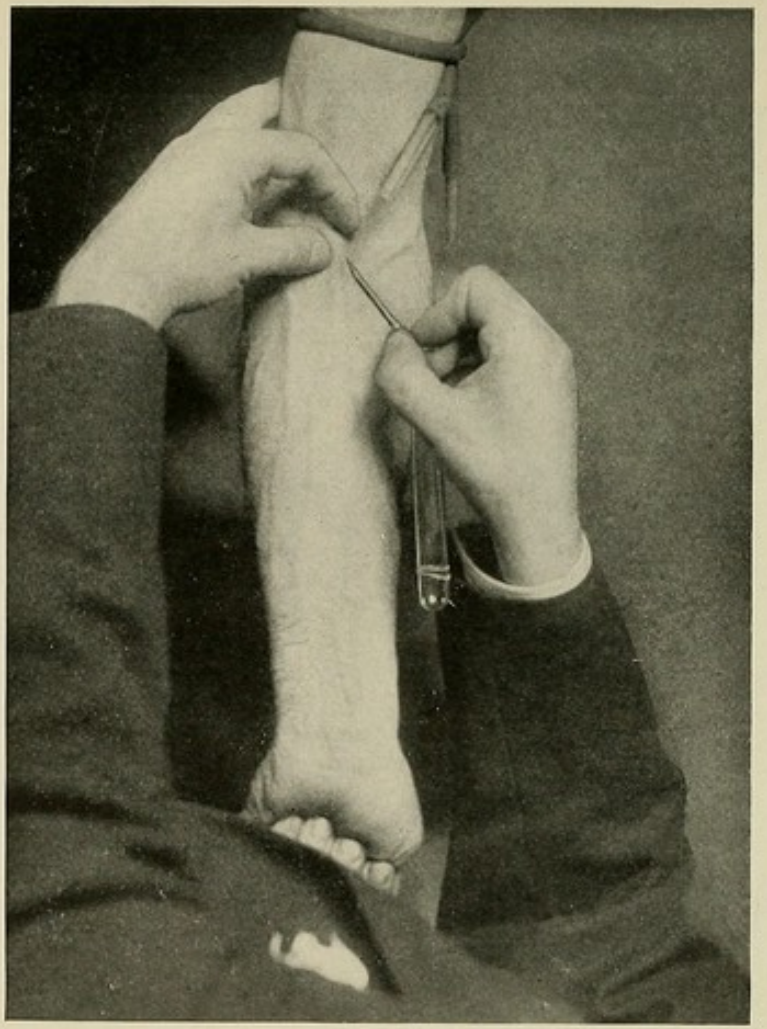


Fig. 10.—Faulty fixation of the vein. The two fingers can never hold the vein in place for proper puncture, as it will always slip from under the needle.

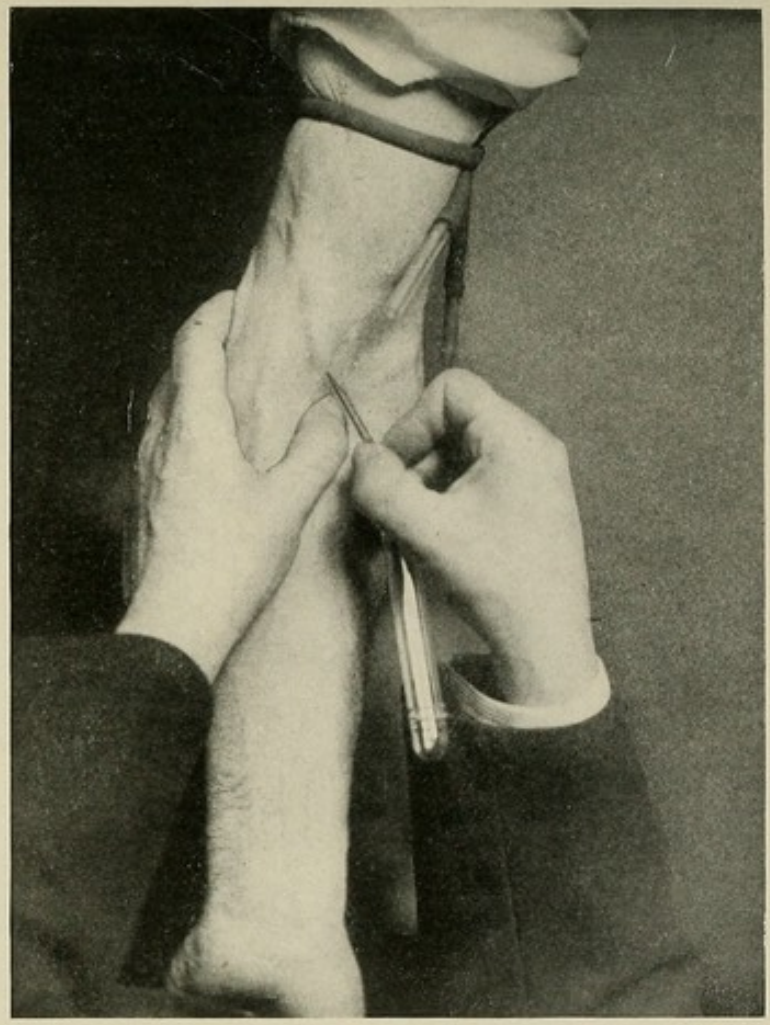


Fig. 11.—Proper manipulation of a vein during venipuncture. Note the thumb of the left hand and the relation of the needle-point to it. Also note the angle and the bevel of the needle; the latter is turned *up*, and not, as in the preceding photograph, *down*.

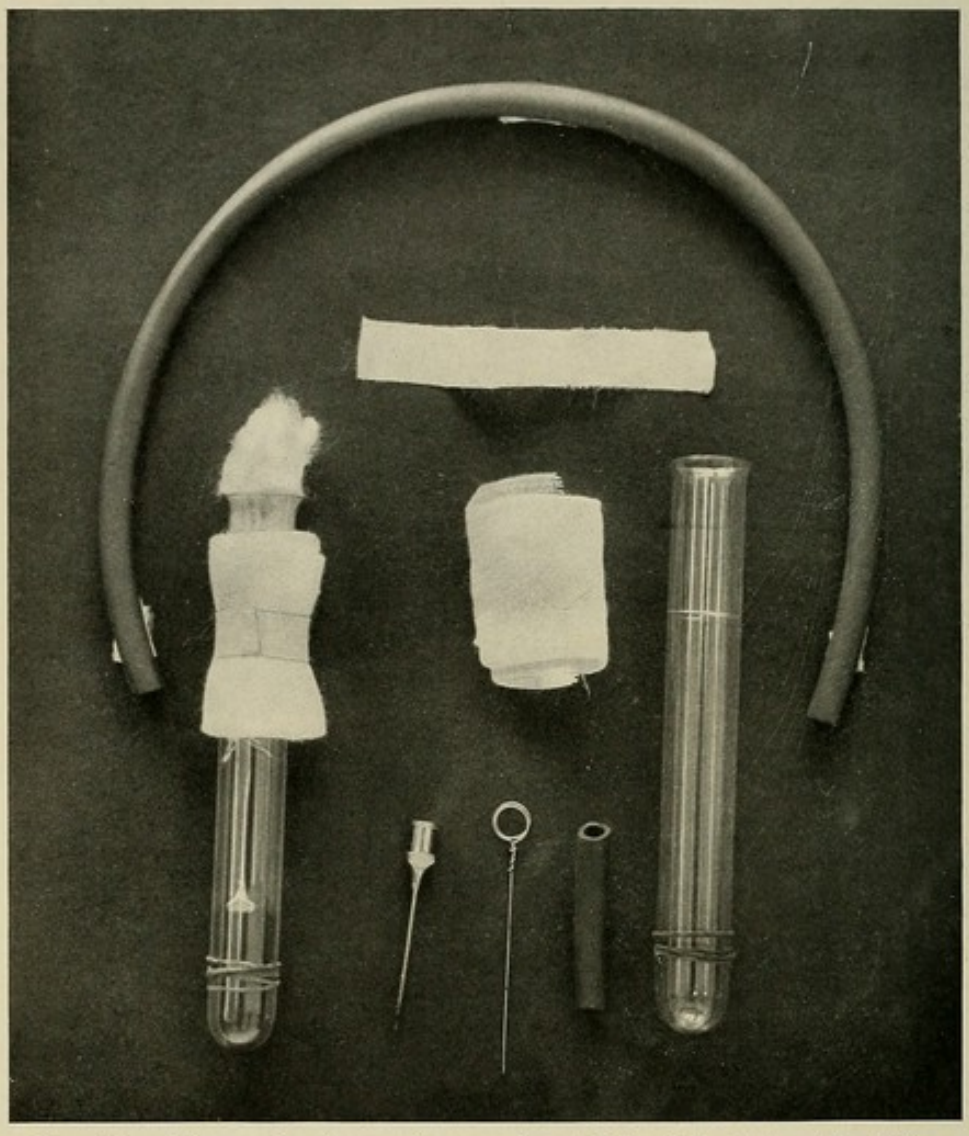


Fig. 12.—The author's equipment for taking blood for the Wassermann reaction, consisting of a rubber tourniquet 16 inches long and a test-tube outfit as seen on the left of the photograph, which shows the gauze bandage and the strip of adhesive. Inside of the tube is the needle, the hilt of which is inside of a rubber tube one inch long. The individual parts are shown to the right of the photograph.

blood from the free end of the needle. It is to be noted that in patients with tabes the blood flows very slowly, regardless of the large but flabby vein. The instrument used in obtaining blood for the Wassermann test is very simple, and can be carried with ease in one's vest-pocket. As shown in Fig. 12, it consists of an ordinary test-tube into which is placed a 19 gage needle $1\frac{1}{4}$ inches long. Around the test-tube is placed a piece of zinc oxid adhesive plaster half an inch wide and about four inches long. To this adhesive strip is attached a small gauze pad consisting of eight layers of gauze, about three-quarters of an inch wide and about $1\frac{1}{2}$ inches long. The adhesive and the gauze serve the purpose of a dressing after the blood has been withdrawn. The entire outfit is sterile. For safety it is best to carry the test-tube in a wooden or paste-board container, especially after the blood has been collected. The free end of the needle is provided with a piece of rubber tubing about one inch long, which is held in the test-tube while the blood is being withdrawn. Test-tube and needle can all be held with one hand.

(*d*) It sometimes happens that the needle, turned with the slant down, as in Fig. 10, will slip for this very reason, and, so to speak, glide along on the outside of the vein. The angle of the needle at times is faulty, and it will not penetrate. Therefore the direction of the needle's point is not to be at too great an angle, nor is the point to be too far from the fixing thumb. Having forced the needle through skin and vein-wall in one thrust and with a quick movement, the direction of the needle is slightly deflected downward and pushed further into the lumen of the vein for about 3 or 4 millimeters. Sometimes five to ten seconds elapse before the blood begins to flow, as said before, a condition frequently observed in tabes.

In collecting the blood for a Wassermann test I usually hold the test-tube and needle as in the accompanying illustration (Fig. 11). Sometimes one is sure that he is in the vein, but, nevertheless, the blood does not flow. This may be due to one of the following reasons: The needle may have gone through the other side of the vein-wall; in this case very gentle withdrawal for about 1 or 2 millimeters will

establish the blood-flow; the slant of the needle rests against the anterior vein-wall: in this case a slight bending of the needle upward without going deeper will be sufficient to cause the blood to appear. It sometimes happens that the needle passes between the layers of the vein-wall: a slight, gentle push will overcome this. For purposes of analysis about 6 to 7 c.c. of blood are sufficient. It should be emphasized here that during the manipulation of the vein the patient should make a fist and direct his attention away from the arm to be punctured. It is best to have the arm bandaged before permitting the patient to look around again. Before the collected blood is placed in the ice-chest it should be permitted to remain at room temperature for a few hours. This procedure will frequently obviate the necessity for centrifuging the blood to obtain the clear serum, a time-saving expedient not to be lost sight of where many tests are to be made. If the methods described for bringing into prominence a deeply situated vein prove futile, as is very often the case with babies and with patients with very stout arms and small, undeveloped veins, the following procedures are recommended: A bit of cantharides plaster, one inch square, is placed on the pectoral region of a baby, and left there for three hours. To prevent scratching and undue pressure a padding of absorbent cotton should be placed about the plaster. It is highly important that the formed blister is obtained intact during the removal of the dressing. With a sterile hypodermic syringe aspirate the formed serum, being at the same time prepared to catch into a test-tube any serum that may escape through the puncture made by the needle. Another and a more rapid way is to sterilize the area between the shoulder-blades, and, with an absolutely sterile scarifier, make a quick incision and aspirate the blood with a small Bier cup. This method is also applicable to children with inaccessible veins, as well as to adults and dementia præcox patients, who frequently prove very rebellious and make the ordinary ways of obtaining blood for the Wassermann reaction impossible.

Instrumentarium.—The chief and most frequently used instrument in performing the Wassermann reaction is the

pipet. For ordinary work, several dozen of 1 c.c. pipets graduated into $\frac{1}{10}$ and into $\frac{1}{100}$ are required. These should be graduated to the tip (as should all pipets for the test), and the distance from the tip to the mark 0 should not be less than 13 inches; this gives to each $\frac{1}{10}$ c.c. a distance of 1.3 inches. The error with smaller pipets is too great, and they should, therefore, not be used. The 10 c.c. pipets are those of the ordinary Mohr pattern, graduated into $\frac{1}{5}$ and into halves. For ordinary work one dozen of these suffice. Several gross of 5 by $\frac{5}{8}$ test-tubes, of good glass, not too thin walled; a few 50 and 100 c.c. graduated cylinders; one dozen 100 and 250 c.c. glass beakers with griffin-lip; half a dozen each of 250 and 500 c.c. Erlenmeyer flasks; a dozen wooden double row (6 in a row) test-tube racks to fit the test-tubes; a few large Petri dishes; ordinary needles for obtaining the blood; these are $1\frac{1}{2}$ inches long, and have a No. 19 bore (for children it is advisable to have a No. 20 bore needle). The free end of these needles is provided with a small piece of rubber about one inch long, which lies in the lumen of the test-tube when the blood is being withdrawn. Where no vein can be obtained, as in very young infants, a wet-cup is made use of and the blood sucked up with a sterile Bier cup. An incubator and a thermostat of good copper, double walled, the former to have two compartments, each provided with reliable thermoregulators. The latter is an important feature, and for this reason I recommend the Lautenschläger pattern. One razor; one Luer syringe, of 10 c.c. capacity one animal cage for rabbits and one for guinea-pigs; one centrifuge, capable of making at least 1500 revolutions a minute (the centrifuge is to be protected by a brass bowl, and should be provided with a rheostat); one dozen centrifuge tubes; one dozen ordinary drinking-glasses, with cotton on the bottom; a few blue pencils for writing on glass; one shaking apparatus. A half dozen each of 1 liter and $\frac{1}{2}$ liter glass-stoppered bottles; one ice-chest. (For the inactivation of the patient's sera and for the storing of the amboceptor small, thin-walled test-tubes should be used; for an average laboratory one gross of these suffice.) A blow-pipe outfit with good bellows; one dozen

Bunsen burners. Of chemicals and reagents, the following will be found useful: Squibb's sodium chlorid; alcohol, 95 per cent.; acetone, ether, tricresol, phenol, collodion, freshly distilled water. It is my opinion that a known syphilitic and a known non-syphilitic serum should be regarded as the biologic reagents in a laboratory equipped for making the Wassermann reaction. Laboratories far removed from abattoirs will have to keep their own sheep, a few rabbits, and a dozen or more guinea-pigs (the latter should be full grown).

Rationale of the Test and Its Specificity.—This was considered at length under the caption of History and Development of the Wassermann Reaction. It is based, as the previous exposition tends to show, upon a using up of complement and the detection of this phenomenon. Primarily it is an antibody-detecting biologic test. It is believed that the extract from organs containing spirochetes are as useful for the making of a specific antigen as the antigen of typhoid bacilli is for detecting typhoid. As no methods for the proper cultivation of the spirochetes of syphilis existed in 1906, making this method of preparing antigen impossible, the technic advanced by Wassermann and his collaborators was employed. It soon became apparent in America and abroad that the views held regarding the specificity of the reaction, and, in fact, the entire principle involved, had to be modified. Much and Eichelberg, who worked with watery luetic extracts, reported a positive Wassermann reaction in 50 per cent. of their scarlatina cases. These observers stated that although the reaction was not so vivid as the florid lues reaction, it was, nevertheless, positive. Weichselmann and Meier obtained positive reactions with the sera from lepra patients by using as antigens the watery extracts of luetic livers, alcoholic extracts of normal organs, and lecithin. A later, more extensive study showed that the majority of the florid tuberous leprosy cases gave a positive reaction with syphilitic extracts as well as with tuberculin. These authors reported that the maculo-anesthetic form of this disease was incapable of complement deviation. The same results were obtained by Slatineanu and Danielopolu.

Levaditi found a positive result in the cerebrospinal fluid from a patient with sleeping sickness. In 7 cases of scleroderma the writer was able to obtain a positive reaction in 6. These were cases of the advanced form of the disease, and showed an involvement of the face, hands, and knees. Morphea gives a negative result. I also called the attention of my co-workers to the fact that sera having the color of old Canada balsam (jaundiced?) will at times give a positive Wassermann reaction, and cautioned against assuming, as a result of the test, that the patient had syphilis.

These observations and many others detracted greatly from the specificity of the test, and made conservatism of interpretation an extremely important constituent of the laboratory worker's equipment. This conservatism is not only to be urged in regard to the entire significance of the test, so far as its specificity for syphilis is concerned, but should also govern every step of the performance of the test. The laboratory worker should never attempt to defend his position when the result he obtains does not coincide with the clinician's diagnosis; for the clinician is probably right, having a score or more reasons for his opinion, whereas the laboratory worker relies only on his reagents, and these have peculiarities still unknown to immunology. This will be discussed further in the section dealing with the attitude of the serologist. It may be stated here that the larger the experience of the serologist, the greater the specificity of the reports from his laboratory, and vice versâ.

Technic of Preparation of the Various Reagents.—The reagents used in the test are the complement, the amboceptor, the antigen, and the sheep's blood-corpuscles. Whatever the reagent used, no distilled water must be allowed to come in contact with it, else its presence may produce a hemolytic effect. Only salt solutions should be employed throughout the test. Squibb's NaCl (C. P.), 0.9 per cent., in fresh distilled water, is the solution used in the writer's laboratory. The first reagent to be considered is the complement.

Concerning the Complement.—For this purpose full-grown guinea-pigs are preferable to younger animals, since their

complemental powers are more stable, and sufficient serum is obtained from one animal to make about 40 tests. The smaller guinea-pigs will rarely give more than 2 to 4 c.c. of serum. The animal is held over a large Petri dish, and bled to death by severing the carotid artery with a good razor. This is practically painless, the procedure lasting about a second. At most the pigs do not suffer greatly, and are practically dead in a minute or two. In severing the carotid care must be taken not to injure the esophagus, as this may cause an admixture of gastric juice with the blood and minimize its ultimate value. It is important, in holding the guinea-pig, to keep the hindquarters well away from the Petri dish, as it sometimes happens that the animal will pass urine during the exsanguination and make the complemental power less uniform and efficient. The blood is collected in a sterile dish, covered with another larger vessel, and kept at room temperature overnight. I usually kill an animal the night before the test is to be made, and pipet off the clear serum the first thing in the morning. It seems to me that the complement left thus overnight gains strength and is more efficient than the guinea-pig serum used on the same day as the killing. Gay and Ayer determined the fact that sera left together with the coagulum for twenty-four hours gain in complemental powers.

Concerning the place of origin of the complement, I believe that the theory advanced by Metchnikoff cannot be maintained. This author believes that the complement is entirely dependent upon the breaking down of leukocytes. Experiments by Semnittzky, however, showed that leukopenic bloods do not contain less complement because of it. Further researches by Donath and Landsteiner showed that, on the contrary, exudates rich in leukocytes possess antihemolytic qualities. The chief argument against Metchnikoff's theory is furnished by Hoke, who found that leukocytes are capable of binding complement, and that when a serum (complement) is brought in contact with leukocytes, its complemental power is thereby diminished. Neefeld is of the opinion that leukocytes do not secrete, give off during coagulation, nor contain complement at any time. The

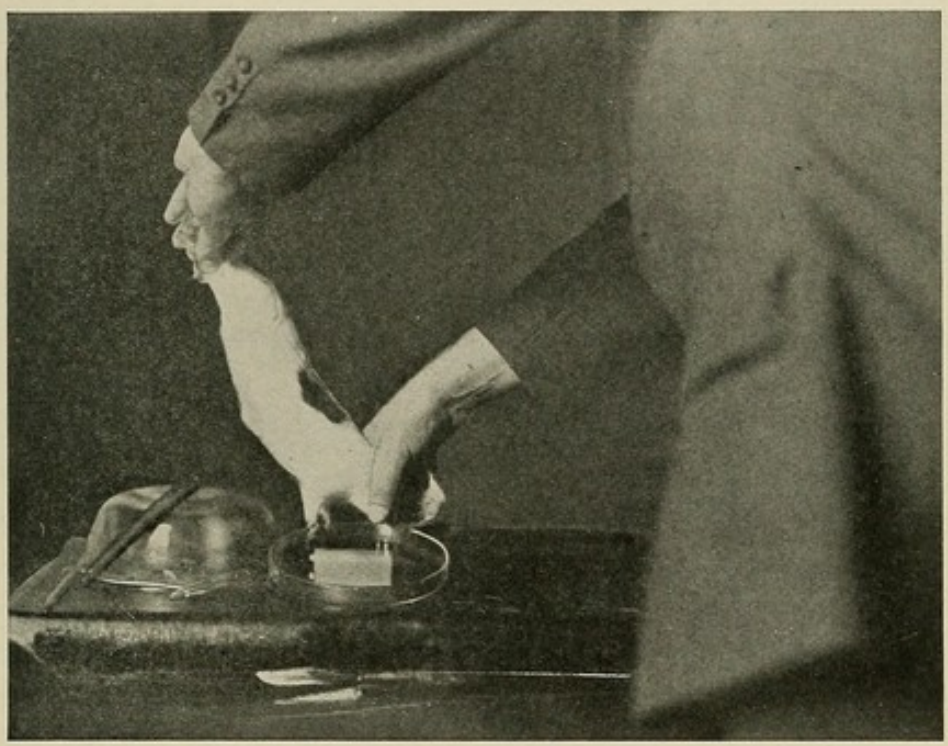


Fig. 13.—Holding guinea-pig for obtaining complement.

many studies that helped to overthrow one view did not, however, supply another one instead, and it is still an open question today where the complement comes from.

It seems to me that the existence of many complements (Ehrlich and Morgenroth) renders the finding of its, or rather their, origin a very difficult task, and one that will require much study. The function of the complement in the Wassermann reaction is to complete the work of the amboceptor, whatever its function may be. Without its help the hemolytic amboceptor, for example, cannot lake the red cell, although it is anchored to it. In the Wassermann reaction the amboceptor-antigen combination, if they fit one another, and only then, attract and take up the complement in the test-tube. No complement absorption takes place if the amboceptor is foreign to the antigen, and is still available for work when an opportunity is offered, such as by the subsequent addition of an amboceptor and an antigen that are homologous, *i. e.*, fit each other.

The Preparation and the Properties of the Hemolytic Amboceptor.—The hemolytic amboceptor is the only true antibody that one deals with in the Wassermann reaction. It is the reagent used in the second stage of the Wassermann test, namely, the hemolytic incubation. This phase of the reaction can justly be called the most important part of the test, as those who are unfamiliar with the work will commit errors more frequently here than at any other time during the test; this is because at this stage judgment is the chief prerequisite of the worker.

Whether one uses the antisheep or the antihuman system, the animal used to produce this amboceptor is always the rabbit. The making of a good amboceptor is very important, and not always a success. One finds rabbits that, for some reason, will not react in the production of an amboceptor of sufficient strength.

It is preferable to immunize male rabbits of about 5 pounds' weight. The process of immunization is as follows: The blood from a freshly killed sheep is defibrinated in a sterile vessel. The fluid blood is centrifuged at least five times, and washed each time with 0.9 per cent. NaCl solution.

The sheep-cells are poured into a 10 c.c. all glass syringe (sterile), and the rabbit's ear is prepared for the injection. The ear is washed with soap and water, shaved, washed with alcohol and ether, and the thumb of the assistant is placed at the root of the ear to impede the venous flow and thereby bring the vein out to its full extent. The needle of the syringe should not be very long, and of about 20 gage. Having dilated the vein as much as possible, the point of the needle is forced gently into the ear vein, preferably into the apex of the inverted V, and a slight up-and-down movement made to ascertain if the needle is in the lumen. In case it is not, the forward movement will be obstructed; besides this, a vein that is punctured will show a hematoma as soon as the piston of the syringe injects a drop or two of blood. It is useless to attempt to inject blood into a vein thus injured, as it will invariably collect on the outside, and result in a badly sloughing ear. Only when the needle can be freely moved and the few drops of blood do not produce a swelling should the blood remaining in the syringe be emptied into the vein.

The proper manipulation of the rabbit's ear requires a little practice, but more frequently furnishes a good amboceptor than the peritoneal method of immunization. I am accustomed to inject, the first time, about 3 c.c. of blood, to which are added 2 c.c. of NaCl solution. The second injection, of 5 c.c. of cells and 3 c.c. of NaCl solution, is given five days later, also intravenously, and the animal carefully observed. From now on the average rabbit begins to elaborate the required amboceptor and should receive all the care possible, including good food, such as fresh cabbage leaves, carrots, and oats, and fresh air and exercise. I know of instances in which six rabbits had to be sacrificed before a proper amboceptor could be obtained, hence the advisability of adopting the prescribed care suggested above. In the majority of cases the full value amboceptor can be had in from eight to ten days. On the eighth day after the second injection a little blood is obtained from the ear vein by a quick cut with a keen razor; this is centrifuged for about fifteen minutes, and the clear, supernatant serum collected for

Fig. 14.—Intravenous injection of blood for obtaining the amboceptor. Note that during the injection no lateral swelling of the vein takes place, a sign that all of the blood is properly injected.

a preliminary gaging. If the serum shows a hemolytic power capable of laking 1 c.c. of a 5 per cent. suspension of cells in a dilution of 1:1500 or 1:2000 in about thirty minutes, then the rabbit is ready for bleeding. This is best done on the following day, *i. e.*, nine days after the last injection. If the hemolytic power is not strong enough, then one ought to wait a day or two more and then test again. It is sometimes necessary to repeat the injection a third time and wait again, but it has been my experience that such rabbits do not furnish a good amboceptor, even if injected again and again. In such instances anti-amboceptor production must be thought of. Assuming that the hemolytic power of the rabbit's blood is great enough, the animal is exsanguinated the next day, and the blood caught in a sterile large glass bowl and kept covered for twelve to sixteen hours. The expressed serum is now ready for storing in the ice-chest. As will be noted, I do not use the method of heating at 56° C. I believe that, since the complement is easily destroyed by age, and since the dilution of the rabbit's serum is so great, it is not necessary to diminish the hemolytic powers of the amboceptor by a temperature of 56° C. My amboceptor was not capable of hemolyzing a 5 per cent. suspension of cells in an eight times concentration without the addition of complement. This, in my estimation, is sufficient proof that the trace of complement present either becomes inert after a short time, or is not sufficient, in its complemental powers, to complete the laking of the cells. I do not, therefore, inactivate my amboceptor. I believe that good amboceptors are often rendered useless by this preliminary inactivation—an observation that, I am sure, others will corroborate.

After the complete separation of the hemolytic immune serum it is placed in small sterile test-tubes,—2 c.c. in each, to which is added a tricresol solution 1:2000,—and the tops are sealed with the blow-pipe, permitting enough space so as not to heat the top of the serum. This is best accomplished by holding the tube between fingers level with the serum in it. Such a hemolytic amboceptor is serviceable for three to four months. Of course, it is not capable of hemolyzing

cells in the same titer as at the original standardization, but if this original titer was about 1:2000, then such an amboceptor can be used until none remains. A good-sized rabbit should yield from 50 to 70 c.c. of amboceptor.

The preliminary *standardization of the amboceptor,—i. e.,* the gaging before the animal is exsanguinated—is performed as follows:

PRELIMINARY STANDARDIZATION OF THE A. S. A.[1]

Complement.	Sheep Cells 5 Per Cent. in NaCl.	A. S. A. 1 C.c.	NaCl 0.9 Per Cent.	Result After Incubation at 37° C.
0.1 c.c.	1 c.c.	1:200	Up to 5 c.c.	Hemolysis usually in 5 minutes.
"	"	1:400	"	" " 6 "
"	"	1:800	"	" " 15 "
"	"	1:1600	"	" " 40 "
"	"	1:3200	"	" " 75 "

The rabbit's serum that furnishes an A. S. A. of the above potentiality is admirably suited for complement deviation. There are many instances in which it becomes necessary to employ very strong amboceptors, and unless one has a powerful hemolytic serum to begin with such an increase is often impossible. The amboceptor as standardized above is in actual use in my laboratory, and hemolyzes in a still greater dilution in one hundred and five minutes (1:6400). For the actual performance of the Wassermann reaction the foregoing standardization will not suffice. It is necessary to take into consideration every ingredient of the test-tube that makes up the complete reaction, as I was able to show repeatedly.[2] Where the above gaging only is made use of, a goodly number of positive reactions will be obtained from innocent persons. In order to avoid this I intend to gage my reagents in such a manner as to exclude, so far as possible, such interpretations; in fact, I would prefer to report many luetic sera as negative, for the sake of eliminating positive reactions in those who did not come in contact with this infection. As the normal patient's serum and the antigen used are in themselves in-

[1] Anti-sheep amboceptor.
[2] Kaplan, New York Med. Jour., September 7, 1912.

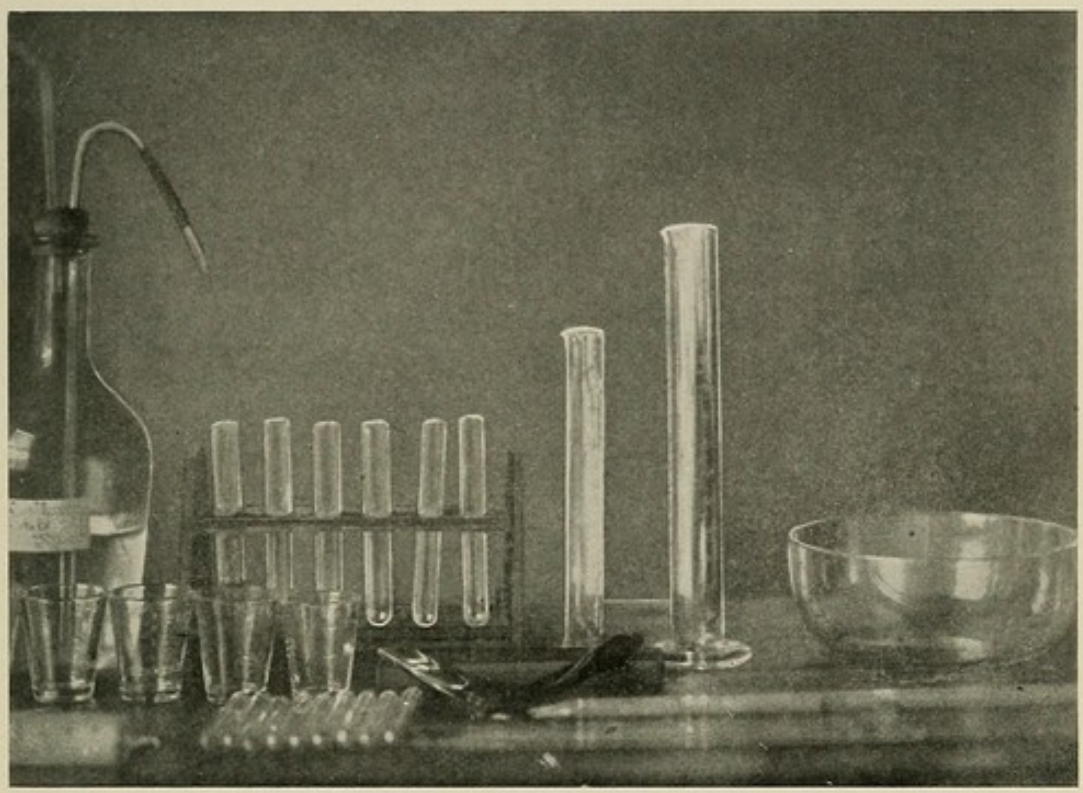


Fig. 15.—Instruments used in obtaining and gaging the amboceptor. The two long white lines in the foreground of the illustration are various pipets for measuring small quantities of serum.

hibitory factors, it is, therefore, necessary, in the standardization of the amboceptor, to take cognizance of these factors, and gage the amboceptor accordingly. The amboceptor previously standardized, gaged with the antigen and a normal serum, gave the following titer:

STANDARDIZATION OF A. S. A., TOGETHER WITH THE ANTIGEN AND NORMAL SERUM

Normal Serum.	Antigen.	Complement.		Sheep Cells.	A. S. A. 1 C.c. Sol.		Hemolysis.
0.2 c.c.	½ U.	0.1 c.c.	Incubate for 1 hour at 37° C.	1 c.c.	1 : 200	Incubate at 37° C. for hemolysis.	Complete in 7 minutes.
"	"	"		"	1 : 400		" " 11 "
"	"	"		"	1 : 800		" " 36 "
"	"	"		"	1 : 1600		" " 102 "
"	"	"		"	1 : 3200		" " 150 "
"	"	"		"	1 : 6400		Incomplete.

The standardization together with antigen and serum shows us that, not only is hemolysis slower in appearance, but also that the 1:6400 dilution did not hemolyze completely. It is also apparent that the 1:3200 dilution required two and a half hours for complete hemolysis; this is too long a period for actual work, and consequently cannot be considered in establishing the working unit. Since the principle underlying the establishment of the working unit requires that the dose should be twice the size of the dilution that hemolyzed the given quantity of cells in two hours, it becomes apparent that the A. S. A. unit for work is somewhere between 1:800 to 1:1000. Since the first titration would have given us an A. S. A. of much weaker power, and the chances of error with its actual use would also have been much greater, it is quite evident that the method of preliminary standardization is not applicable to actual work. Regardless of the care and apparent overdosage of the A. S. A., it has happened occasionally that the entire array of tests showed marked resistance to hemolysis. Although the standardization on the day of the tests gave a working unit of 1:600, the hemolysis was, nevertheless, very sluggish, and required a great deal of care to distinguish the true from the masked negatives. This occurred often enough to demand investigation. In my laboratory this phenom-

enon was designated as the low-power amboceptor, and would manifest itself on days showing more than the average barometric changes; on such days persons with rheumatic tendencies usually complain of joint or muscular tenderness. It was very interesting to note that the amboceptor unit changes considerably on such days, as the table below will show.

The Low-power Amboceptor.—The amboceptor used for this titration gave, on a day with the barometer at 755 and the temperature at 22° C., a maximum hemolytic power of 1:3200 in ninety-eight minutes. A few days later, with the barometer at 763 and the room temperature at 21° C., the following values were obtained:

Normal Serum.	Anti-gen.	Comple-ment.		Sheep Cells.	A. S. A.		Hemolysis.
0.2 c.c.	½ U.	0.1 c.c.	Incubate for 1 hour at 37° C.	1 c.c.	1 : 200	Incubate at 37° C. for hemolysis.	Complete in 14 minutes.
"	"	"		"	1 : 400		" " 19 "
"	"	"		"	1 : 800		" " 52 "
"	"	"		"	1 : 1600		Incomplete.
"	"	"		"	1 : 3200		No hemolysis after 2 hours.

The reason for the poor amboceptor work accomplished on these days was apparently made clear by the foregoing standardization, and, as a result of this, my Wassermann work is now performed after consulting the barometer, and if the atmospheric pressure is in the neighborhood of 765, the working unit is doubled. It is needless to emphasize the fact that proper controls were carried on while making the studies of the low-power amboceptor. As nearly as possible the same factors entered into the gaging of the amboceptor during both clear and cloudy days with a high humidity. It is extremely vexing to be called upon to explain a positive Wassermann reaction in a patient who does not exhibit the slightest sign of syphilis nor give a clue in his anamnesis; for this reason I believe it is much safer to gage the work so as to eliminate all possibilities of error in this direction, even if thereby one reports an inordinate number of negative results on known syphilitic subjects.

Of this, more will be said under the head of The Attitude of the Serologist. It seems to me that the peculiarity of the amboceptor just described tends to corroborate the belief expressed by some workers that the entire Wassermann reaction is simply a phenomenon of surface tension.[1] Before concluding this section I wish to add another point regarding the preservation of the A. S. A. Previous to placing the serum in test-tubes for sealing, it is advisable to add to each cubic centimeter of the immune serum some tricresol solution in a concentration not greater than 1:2000. It is best first to make a solution of the preservative in salt solution and then add it to the amboceptor. This will keep the serum in good condition for many months, and do away with the unpleasant odor that old amboceptors usually display. A sediment will always develop, but this does not interfere with the hemolytic power of the serum.

The Preparation and Properties of the Antigen.—The chief argument against strict conformance to the side-chain theory of the Wassermann reaction is the antigen. The number of substances that can be used for the purpose of binding complement with a serum containing the so-called syphilitic antibody and their great variability all tend to prove that strict specificity is not a part of the test, but, rather, that the entire reaction is more or less a fortunate coincidence of phenomena of which little has as yet been incontrovertibly established. It is a well-known fact that classic inhibition may be obtained with syphilitic sera using as antigens lecithin (Porges and Meier) or the salts of the bile acids, soaps, etc. (Sachs and Altmann), and other substances mentioned under the head of The History and Development of the Wassermann Reaction. All these things tend to prove that the antigenic part of the test is entirely a matter of choice, and it is well to admit, at this point, that the entire usefulness of an antigen, or, as I am accustomed to refer to it, "the inhibitory extract," is dependent on the carefulness and precision with which the extract was standardized. The finer details of standardization must be given

[1] G. A. Stephens: Brit. Med. Jour., April 5, 1913, pp. 697, 752.

close attention if one wishes to eliminate non-specific inhibition and avoid the humility that follows incorrect reports. The only property that one expects the inhibitory extract to possess is, as its name implies, inhibition of hemolysis; specificity is of secondary consideration. This is perhaps one of the reasons why so many heterogeneous substances are employed as inhibitory extracts.

Of the known properties of the antigen, very little can be said. The general view held regarding its ability to bind complement is that it possesses a molecule chemically related to lipoids, which, as is generally known, are substances capable of producing, under certain circumstances, the phenomenon of complement deviation. Besides this, there are other very interesting and important facts to be learned from the study of the substances used as antigens. Those who use liver extracts have observed a peculiar wave of potentiality in the extract in the course of time, and reported very good results by making use of extracts that were discarded as having become too weak, and, therefore, useless (Kaplan, Beneke, Stuehmer). The last-named author, using alcoholic extracts from guinea-pig livers, observed the following changes in them: Extract No. I was not treated in any way; Extract II was kept for twelve hours at 38° C., and, of course, was decomposed by bacteria; Extract III was kept in the ice-chest for fourteen days, and was also decomposed by bacteria; Extract IV, kept for nineteen days at 18° C., was decomposed by bacteria; Extract V, kept for four weeks in the ice-chest, remained sterile and dry. The various extracts showed the following properties:

Quantity.	Ext. I.	Ext. II.	Ext. III.	Ext. IV.	Ext. V.
0.25 c.c.	a	a	d	a	a
0.125 c.c.	b	b	b	a	a
0.06 c.c.	c	b	a	a	a
0.03 c.c.	d	c	a	a	a
0.015 c.c.	d	d	a	a	b
0.007 c.c.	d	d	a	a	c
0.004 c.c.	d	d	a	a	d
0.002 c.c.	d	d	b	b	d
0.001 c.c.	d	d	d	c	d

a = total inhibition; b = partial inhibition; c = incomplete hemolysis; d = complete hemolysis.

To estimate the inhibitory strength of the foregoing extracts one would have to consider the size of the dose and the result following. The smallest amount of extract capable of causing inhibition is the extract most suitable for the test. In the preceding analysis it is evident that Extract IV produced complete inhibition with only 0.004 c.c. of the extract. Extracts I and II were useless; Extract III, although useful in the smaller doses, was hemolytic to start with; Extract V, although dry and sterile, was not so potent as the decomposed Extract IV. I was able to demonstrate that old extracts, after having been discarded on account of impaired inhibitory action, were found to possess marked inhibitory powers a few weeks later. This was observed a sufficient number of times to make careful observations necessary before a given inhibitory extract is discarded as useless. Some authors believe that the extracts used for making the Wassermann test can be resolved into their different components by appropriate treatment: U. Friedmann demonstrated that the hemolytic component of the extract is soluble in water-free ether; F. Lesser found the inhibitory side-chain (if I may so designate it) soluble in ether. Ehrmann and Stern could separate the inhibitory molecule from its interfering side-chains. Joannowicz and Pick determined later that the unsaturated fatty acids were responsible for the hemolytic qualities of the extract, while the acetone-precipitable lipoids represented the inhibitory principle. J. Zeissler observed that extracts kept on ice for four weeks lose their hemolytic property, whereas the inhibitory qualities remain intact. All these observations suggest the complexity of the inhibitory extract and permit the conception that the antigen in the Wassermann reaction consists of a complex molecule of a lipoid nature, with an inhibitory nucleus and a number of side-chains, some of which are decidedly hemolytic in character. The hemolytic side-chain is decomposed in a comparatively short time, a fact that enables one to use the extract again, frequently in a smaller dose than at the original standardization. These data are very important in the consideration of the inhibitory extract, as they give one a means of effecting so-

called restoration of the useful properties it has lost. Diagrammatically, the entire process of restoration of the inhibitory power may be pictured as follows:

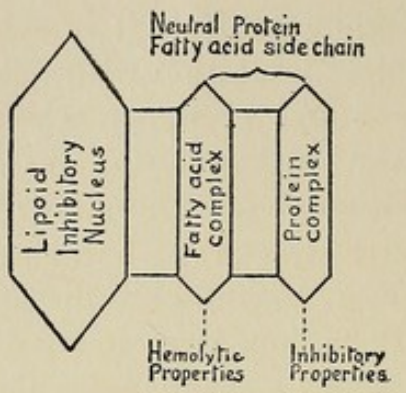


Fig. 16.

As the protein side-chain undergoes autolytic decomposition or bacterial putrefaction, the fatty acid complex is left attached to the lipoid nucleus, and the balance of power is in favor of hemolysis; such an extract is useless. In the course of time further decomposition takes place, and the fatty acid side-chain no longer interferes with the lipoid inhibitory nucleus. Although greatly decomposed and malodorous, such treatment frequently gives powerful inhibitory extracts in remarkably small doses. These changes, of course, take place in watery extracts only, the alcoholic extracts not being affected by bacteria and but very little by autolysis. Regarding the preparation of antigens, one may use either the watery or the alcoholic organic extracts, as he desires. In this work the various methods will be described, together with such observations as, in the writer's experience, were found of practical value, the object being to render the Wassermann reaction less difficult and more attractive.

Preparation of the Watery Luetic Fetal Liver Extract.—A number of luetic fetal livers are weighed and finely comminuted. To each gram of tissue 4 c.c. of 0.9 NaCl solution are added; to this is further added a sufficient quantity of phenol to make a 0.5 per cent. solution. This is placed in a dark container (an Erlenmeyer flask covered with black

paper), tightly stoppered, and vigorously shook in a shaking machine for twenty-four hours. I use the Spiegelberg apparatus, but any other instrument will answer provided the flask can be so placed as to prevent accidents overnight. Next day the entire mass is centrifuged and the coarser particles discarded. The opalescent supernatant fluid is the syphilitic antigen as prepared by Wassermann. This fluid is placed in a dark, rubber-stoppered bottle, and left in the ice-chest ready for use. In order to avoid contamination it is advisable to pipet off the amount to be used for the day, and, without exposing the bottle to sunlight, replace it in the ice-chest. With proper precautions, in my experience, such extracts can be used for months and retain their full strength. In America the question of obtaining luetic livers is attended with great difficulties, a fact the reason for which I am unable to state.

In order to render the extract less changeable, Marie and Levaditi suggest the method of pulverizing the luetic liver which has been dried *in vacuo*. This retains its inhibitory qualities remarkably well, and can be used until the last grain is exhausted. It is prepared by mixing the powder with salt solution in the proportion of 1:4 and extracted for twenty-four hours. The suspension is centrifuged, and the supernatant fluid is ready for use.

Of the alcoholic tissue antigens, the following are to be recommended: Landsteiner, Mueller, and Poetzl rub up to a fine consistence the muscular parts of guinea-pig hearts, and extract 1 gm. of this with 50 c.c. of 95 per cent. alcohol at 60° C. for several hours. This mixture is filtered, and the filtrate preserved in this state at room temperature. Michaelis and Lesser rub up in a mortar syphilitic or normal livers, and shake the mass at once, for five or six hours, with 10 parts its weight of alcohol. After standing for twenty-four hours the clear, supernatant fluid is pipeted off and kept in the ice-chest as the stock solution. For use they dilute 1 part of the stock solution with 4 parts of physiologic salt solution.

Noguchi's method of preparing the acetone insoluble antigen is as follows: Extract finely minced syphilitic or normal

liver with 10 volumes of 95 per cent. alcohol for about a week, at a temperature of 37° C. At the end of this time filter the alcohol and evaporate the filtrate by using a fan at a temperature of less than 40° C. This sometimes requires twenty-four hours or more. The residue is extracted with ether and permitted to evaporate. The residue of the ethereal extract is taken up with a small quantity of ether and fractionated with 5 volumes of acetone. A sticky, gummy precipitate forms, which adheres to the stirring glass rod. Pour off the supernatant acetone, permitting the remainder to evaporate. Collect the resinous mass into a dark bottle, and keep it air tight in the ice-chest. For making the test 0.2 gm. is dissolved in a little ether and brought up to 100 c.c. with 0.9 per cent. NaCl solution. This emulsion can be kept on ice without impairing its inhibitory qualities.

In my laboratory I use the following method: Guinea-pig hearts are weighed and minced in a meat-mincer. The entire mass, plus bloody fluid, is placed in a dark bottle, and ten times the volume of 95 per cent. alcohol added. This is kept in the incubator at 37° C. and shaken twice daily for four days. To this alcoholic extract cholesterin is added, thus: Four grams of Merck's cholesterin are dissolved in as little ether as possible and added to 96 c.c. of the alcoholic extract of guinea-pig hearts. This makes a turbid fluid which, on standing in the ice-chest, deposits cholesterin at the bottom of the container. For use the mixture is shaken and placed in the thermostat at 56° until the cholesterin dissolves, and 1.5 c.c. are brought up to 100 c.c. with 0.9 NaCl solution. In my work 1 c.c. of this solution will inhibit syphilitic sera, but is not in the least inhibitory with non-luetic material. I have also used the watery extract of syphilitic fetal livers whenever possible, preparing it according to the method of Wassermann.

It is immaterial what one uses for antigen, so long as the substance conforms to the requirements of the reaction, *i. e.*, to inhibit with luetic sera and not to interfere with hemolysis when the serum is not luetic. This question is settled by the standardization of a given extract.

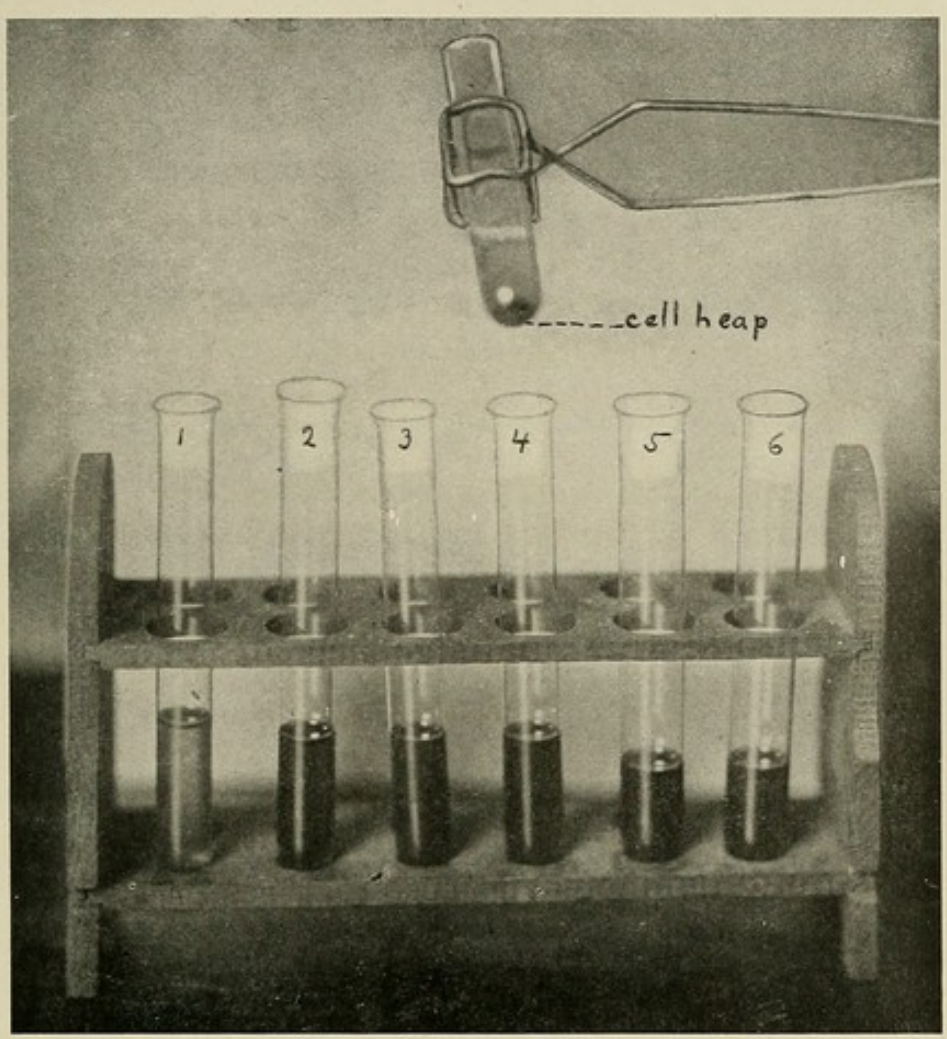


Fig. 17.—The Wassermann reaction, showing at the top the heap of cells which is significant of complete inhibition of hæmolysis. Test-tube 1 is the positive control of the reaction, and the others represent complete hæmolysis of the remaining controls of the reaction.

Standardization of an Extract to Be Used as Antigen.—Known syphilitic serum, 0.2 c.c.; complement, 0.1 c.c.; to this add extract in varying strengths; incubate at 37° C. for one hour; add 1 c.c. of sheep cells (well washed and made up to 5 per cent. with 0.9 NaCl solution); add two units of amboceptor, and note the time when hemolysis takes place in the tubes with the smallest amount of extract. If the extract is at all serviceable, then it ought to show complete inhibition with at most 0.2 c.c. of the extract. If it requires a greater amount to produce inhibition, the extract will most likely become useless in less than a week. The same procedure is repeated with a normal serum. In my laboratory the previously described antigen with cholesterin reinforcement gave the following titer:

Positive Series.		Negative Series.[1]
Amount of Extract.	Inhibition.	Inhibition.
0.6 c.c.	Complete	Slight
0.4 c.c.	"	Very slight
0.2 c.c.	"	None
0.1 c.c.	"	"
0.05 c.c.	"	"
0.025 c.c.	"	"
0.0125 c.c.	Incomplete	"
0.00625 c.c.	Hemolysis	"

The above antigen showed the ability to inhibit with syphilitic serum in the 0.025 dose, whereas by using 0.2 c.c. with the normal serum no inhibition was obtained. The rationale of the antigenic standard is admirably conformed with in the foregoing extract. Any substance that will inhibit completely with a positive serum in a dose that is not potent enough to do the same with a normal serum, even if the dose is three times larger, fulfils the requirements of an antigen for performing the Wassermann reaction. This practically covers the entire principle of antigenic activity

[1] The same quantities were used as in the positive series. Normal sera were used, otherwise everything as before.

as applied to the practical Wassermann laboratory method. Manifold theoretic considerations enter in the modus operandi of antigens, but these do not concern the practical worker, who is interested only in the clinical side of the question.

Various Inhibitory Substances Used as Antigens.—Aside from the use of non-luetic organic extracts for complement deviation tests in syphilis, other substances of known chemical constitution were made use of. Schuermann's method of preparing such an antigen is as follows: Lecithin, 0.3 gm. dissolved in 50 c.c. of absolute alcohol; sodium glycerophosphate, 0.3 gm. in 5 c.c. of 0.9 per cent. NaCl solution. Of this solution, 30 c.c. are mixed with 5 c.c. of lactic acid and 10 c.c. of ammonium vanadinate. The unit is established according to the standardizing schedule previously outlined. Porges and Meier make a 1 per cent. solution of lecithin (Kahlbaum), shaking it in 0.5 per cent. phenol-normal salt solution, which serves as a stock solution. With 0.05 c.c. of this solution most luetic sera inhibit and non-luetic sera hemolyze. This antigen is not to be recommended for practical work, as the margin of error on the positive side is too great for clinical purposes.

Sachs and Rondoni give the following formula for a useful antigen:

Sodium oleate (Kahlbaum)	2.5
Ovolecithin (Merck)	2.5
Oleic acid (Kahlbaum)	0.75
Distilled water	12.5
Alcohol, 95 per cent.	ad 1000.0

For use, the foregoing is mixed thoroughly with 0.9 per cent. NaCl solution in the proportion of one part of the extract to five of the salt solution. The usefulness of an extract depends entirely upon the results of the standardization; this is chiefly the distance between the complete inhibitory dose with positive sera and the non-inhibition with normal material. The greater this distance, the better the extract. and the fewer the errors that will be obtained by its use.

The Various Modifications of the Wassermann Reaction

In America the **Noguchi modification** is used quite extensively. The presence of a natural anti-sheep amboceptor in some human sera resulted in many negative results with some unquestionable syphilitic sera. To overcome this difficulty Noguchi devised the method of using human blood-corpuscles and a corresponding amboceptor for the indicator, instead of the anti-sheep system, as in the original Wassermann reaction. This method is to be recommended especially when it is difficult to obtain sheep cells in a fresh state. Noguchi uses the acetone-insoluble fraction of beef livers as his antigen. The blood for the work can be obtained from the patient's finger. Only a few drops are necessary. The entire contents of the test-tube, after the addition of all the reagents, amount to about 1.5 c.c. A water-bath is required for the fixation and for the hemolytic incubation. So far as results with this method are concerned, I can state, after having performed 4200 comparative Wassermann and Noguchi reactions, that the latter is slightly simpler than the Wassermann reaction. The transference of the reagents to paper I do not consider an advantage, but rather a drawback. It is my belief that, by furnishing the reagents to laboratory workers, they are deprived of the benefit of the experience to be gathered by gaging them, and is decidedly detrimental to obtaining correct Wassermann results. The sending of antigen and amboceptor paper to different workers, thereby making it easy for them, and reducing the Wassermann test to a mere throwing together of bits of paper, is not to be recommended. I believe that Noguchi has given up the saturation of paper strips, and now recommends the use of definite amounts of fluid reagent. All things being equal, the reaction is fairly reliable, and in my hands gave a positive error of 2.5 per cent.

Another modification is the **Bauer test.** This author omits the making and the standardization of the A. S. A., and relies entirely upon the natural anti-sheep amboceptor present in the serum of the patient. This is a very unreliable

and uncertain method, as the natural A. S. A. is not always present in a serum.

The **Tschernogouboff method** omits still more reagents, dispensing with complement as well as with amboceptor. This observer uses the natural amboceptor and the complement in the patient's serum, against guinea-pig erythrocytes, neglecting entirely the quantitative relationship of the reaction. The same can be said of the *Hecht modification*, which does not differ from that suggested by Tschernogouboff.

Margarete Stern adds a quantity of anti-sheep amboceptor to the active serum of the patient (not heated at 56° C.), and omits the guinea-pig complement. As the complement in human serum is a very inconstant ingredient, and is, on an average, much less potent than the guinea-pig serum, this modification also has its drawbacks.

Detre and Brezovsky used an anti-horse system. *Boas* recommended an anti-goat system. *Browning* employed an anti-ox hemolytic amboceptor.

Some time after the Noguchi method appeared, Tschernogouboff also devised an anti-human method similar to that of his predecessor. The latter's observations, however, lack the elaborateness of those of the Japanese worker, and the method is also, for other reasons, less reliable.

Close upon the trail of the Wassermann publications appeared a number of reactions that did not depend upon the phenomenon of complement deviation, but upon other physicochemical laws. *Porges and Meier* elaborated a method of precipitation, using 0.2 c.c. of a 1 per cent. stock suspension of lecithin; to this they add 1 c.c. of a 1:5 solution of the patient's serum in 0.9 per cent. NaCl solution. This mixture is placed in thin precipitation tubes and left in the incubator for a few hours. These authors report a faintly positive result whenever a finely granular opacity takes place in the tube. If a sediment is obtained in twenty-four hours, then the reaction is considered as positive; a total precipitation of the lecithin mixture is considered as strongly positive. As this reaction is obtainable with advanced tuberculosis, in tumors, lepra, trypanosomiasis, and

even occasionally in absolutely healthy individuals, it is not to be recommended as a test to be depended upon alone, without the use of the original Wassermann reaction.

A later study by *Porges and Salomon* advocates the use of a 1 per cent. sodium glycocholate (Merck) solution in distilled water. The solution is mixed, in equal parts, with an absolutely clear, inactivated portion of the patient's serum. This is placed in test-tubes of about 7 mm. inner diameter, which are large enough to hold 0.2 c.c. of each substance. The tubes are permitted to remain undisturbed at room temperature. If the serum is syphilitic, distinct flocculi will appear at the top of the fluid. Opalescence and the presence of traces of flocculi are not conclusive. As precautions, the following suggestions are offered: Do not form layers, as such treatment permits of the formation of rings. Incubation temperature is conducive to the development of bacteria. The solution must be freshly prepared. The addition of phenol renders the reaction less specific. The use of turbid or hemoglobin-containing sera interferes with the test. The end reaction is to be observed with the naked eye and by ordinary light.

The **water reaction of Klausner** is performed as follows: Into a test-tube of 5 mm. inner diameter and 7 cm. high place 0.2 c.c. of the patient's serum, which must be absolutely clear and blood free; this is diluted with 0.6 c.c. of distilled water. In a few hours—rarely more than fifteen—one notices, in luetic sera, a thick sediment. The more florid the lues, the sooner does sedimentation take place. After treatment a previously positive reaction may become negative.

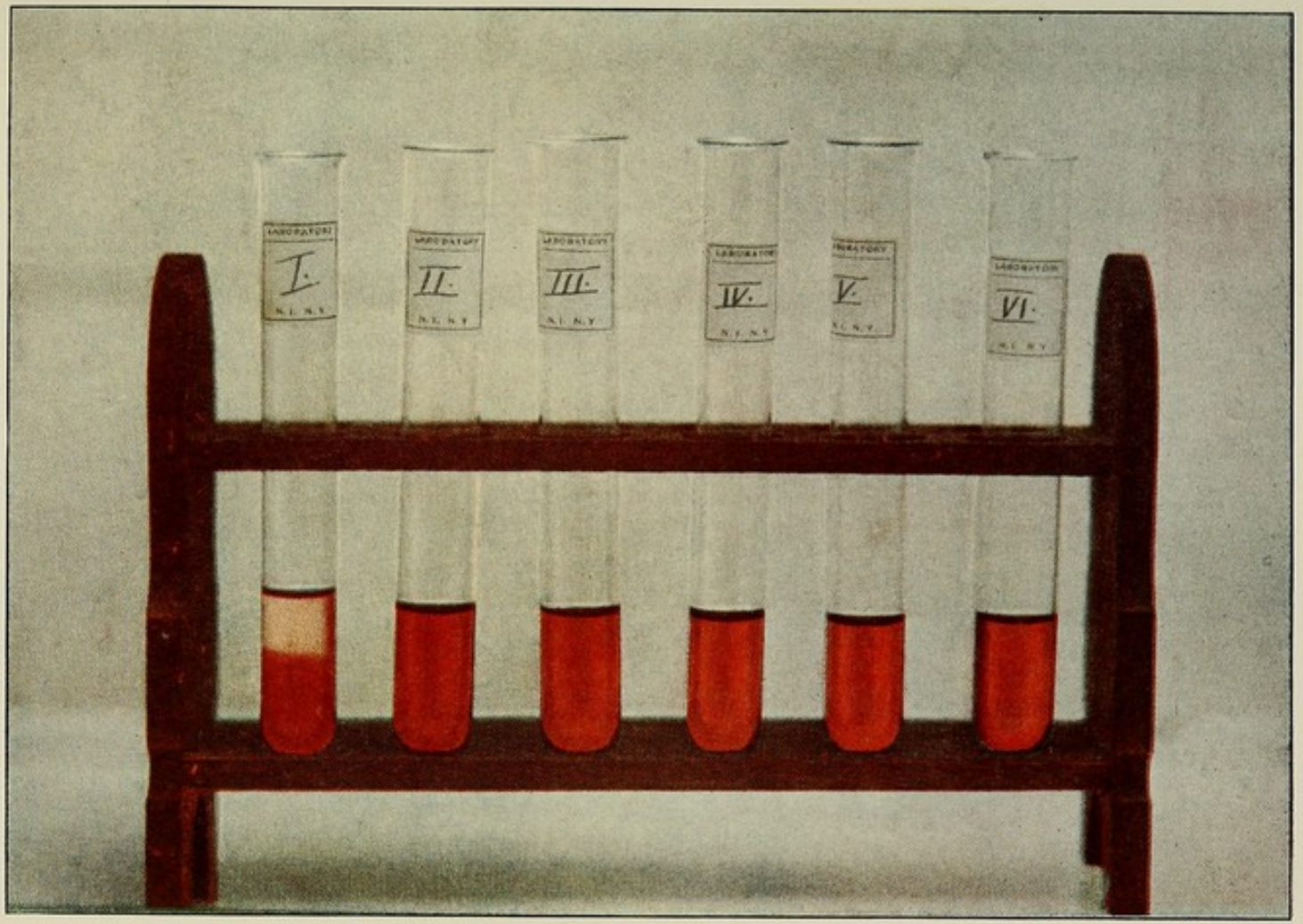
The Controls and Their Significance

The absence of standards and definite quantitative chemical relations requires the use of many controls in place of more exact procedures. It is necessary that the serologist be able to draw upon a mass of known material for his controls, otherwise his work is rendered very difficult indeed. The positive control serves as an index of the antigen's potency, and, as its name implies, is ob-

tained from a known syphilitic with a positive Wassermann reaction. For the selection of such a serum it is not advisable to make use of a patient who is "Wassermann fast" (see Wassermann-fast tabes), as these subjects react quantitatively with much less antigen than does the ordinary positive luetic, which quantity, when used on ordinary material, will result in a series of negative Wassermanns even on manifestly positive sera. To recapitulate: The positive control contains the ordinary positive serum plus the half unit of antigen, plus the complement, and, after the preliminary binding incubation, plus the sheep cells and two or three units of amboceptor.

The negative control is intended to guard against too large doses of antigen and partly also against too small quantities of amboceptor. For such purposes jaundiced sera, as well as lipemic sera, are not to be used. The same ingredients as above, with the exception that the serum be negative, are placed in the test-tube as before.

The amboceptor control corresponds with the amboceptor titration, as suggested by Citron, and serves to eliminate an amboceptor dose that is too weak for hemolytic purposes. The test-tubes in actual work contain complement and salt solution to start with, and after the preliminary incubation cells and the amount of amboceptor determined for the day are added. The control for antigenic interference is to determine whether the quantity of the extract is not too great, and whether it is capable of inhibiting hemolysis without the addition of the patient's serum. The tubes contain all the material except the patient's serum. The auto-inhibition control is the most important one of the series. Some sera, although negative, are very slow in hemolyzing, and it is, therefore, not advisable to read end-results before the auto-inhibition control is completely cleared, *i. e.*, shows total absence of inhibition. The test-tube containing this control contains all the material except the antigen, and serves to eliminate the not infrequent anticomplementary sera. On days when the barometer is at 765, the auto-inhibition controls are more frequently unhemolyzed than on other days.



Controls used in Wassermann reaction: I, known positive; II, control showing the presence of anti-sheep amboceptor; III, known negative; IV, auto-inhibition; V, antigenic interference; VI, amboceptor efficiency.

In the colored illustration test-tube No. 1 represents the positive control, and, as shown, is the only positive non-hemolyzed test in the rack. All the other test-tubes are clear, as they should be in a properly controlled reaction. The only test that must be repeated with every serum is the auto-inhibition control; otherwise the remaining controls serve for any number of reactions.

The Performance of the Wassermann Reaction

As a rule, the serologist begins his collection of sera for the Wassermann reaction on the day before the test is to be made. The blood is collected in an ordinary test-tube and placed at room temperature, to permit the coagulum to express the serum. The clear serum is collected in smaller tubes and appropriately labeled, and placed in the ice-chest until the next day. On the day before the test is to be made all the utensils that may come in contact with the serum should be sterilized. A large-sized guinea-pig is exsanguinated, with the precautions described under complement, and left overnight at room temperature.

The first task on the following morning is to obtain sheep blood and rid it of its adherent serum. This requires three or four washings with salt solution.

The next step is to collect the complement in a sterile centrifuge tube, and if there are traces of blood, it is necessary to centrifuge the serum. Having obtained the washed cells and the complement, the standardization of the amboceptor is begun. The method previously described in this section is to be followed exactly. Having standardized and ascertained the size of one unit, the next thing to do is to place all the sera in the thermostat at a temperature not above 56° C. The sheep cells are next diluted to a 5 per cent. suspension with 0.9 per cent. of NaCl solution; to this suspension is added an equal quantity of salt solution containing 3 to 4 units of amboceptor to each cubic entimeter of salt solution. The 4 unit dose of amboceptor is to be used on days when the barometer is near 765. The method of ascertaining the antigen unit is the one described on p. 71, and is to be so diluted that each cubic centimeter

of salt solution contains half a unit of the inhibitory extract.

After three-quarters of an hour's inactivation at 56° C. the various sera to be analyzed are removed from the thermostat, and disposed of as follows:

1. Place in each of two tubes, front and back, 0.2 c.c. of the patient's serum.
2. Add to each tube 0.1 c.c. of the guinea-pig complement.
3. To the front tube only add 1 c.c. of the antigen, which equals half a unit as ascertained in the standardization.
4. Bring up the mixture in each tube to 3 c.c. with 0.9 NaCl solution.
5. Place the rack with the tubes into the thermostat at 37° C., having previously shaken each test-tube. The incubation for complement binding should last one hour.
6. After one hour add to each tube, front and back, 2 c.c. of the blood-amboceptor mixture, and after thoroughly shaking, replace in incubator for the hemolytic incubation. From now on every tube must be closely examined every ten to fifteen minutes. As soon as the tubes in the controls, with the exception of the positive control, have hemolyzed, the negative sera are recorded and removed from the incubator. This gives the eye less work in running over the entire series of tests, especially when the number of bloods to be tested is great. Only those sera that remain unhemolyzed to the end of the process, and even until the next day, should be regarded as positive. The serologist should not attempt to give weakly positive reports or make use of misleading terms, such as four plus, three plus, or plus-minus. Patients either have or have not a positive Wassermann, and all other designations tend to render the situation more complex and uncertain to the serologist and more so to the clinician.

The Wassermann reaction on the cerebrospinal fluid is performed in the same way as the serum reaction, except that the fluid is not inactivated. The use of larger quantities of fluid is permissible only as a therapeutic guide, and should never be considered as a reliable index for the existence of a syphilitic neurologic disorder when the result is positive with

quantities greater than that which is used in the performance of the original Wassermann reaction. With large quantities of fluid, using as much as 1 c.c., one may at times obtain positive results in non-luetic individuals, and subject the patient unnecessarily to therapeutic measures that are uncalled for and will do him no good. This method will be discussed further under the head of Syphilitic Neurologic Disorders.

The Attitude of the Serologist.—Every serologist learns, sooner or later, that no matter how conscientious his working methods are, a number of errors cannot be avoided with the Wassermann reaction, and that some of the positive reports submitted were unquestionably on negative material. He must, therefore, accept the inevitable, and come to regard the entire test as only of secondary importance in making a complete study of a case of syphilis. The sooner the serologist arrives at this point of wholesome skepticism, the better for his reports, as only then will they contain the information desired—*i. e.*, is the reaction negative or positive?

This is practically all the physician requires to know; the explanations and fanciful designations of the end-result are absolutely unwarranted. There are some workers who pride themselves on their ability to report a positive Wassermann on every syphilitic serum. In my experience, the unerring positive is always accompanied by a long list of positive reports on distinctly non-syphilitic patients. This is amply illustrated by the many defenses advanced by serologists who never err in their recognition of luetic sera, by their ingenious logic in explaining how syphilis could be overlooked clinically, how the disease could remain latent or obscure, when their unerring positive reaction is obtained on a patient free from lues. It is, therefore, quite important to be acquainted with the private views of the serologist as to the significance he places on the Wassermann reaction, as to his opinion of his results in the reaction, whether absolute perfection is attainable in this test, etc. I believe that the attitude of the serologist is a greater factor in the value of a Wassermann reaction than is the standard-

ization of the reagents. The question of reliability resolves itself into this: a worker reports either too many positive Wassermann reactions in non-syphilitic persons, or too many negative reactions in those who were infected. Unless, therefore, the serologist determines on which side he intends to err, his results will, accordingly, be uncertain.

The function of the laboratory is not to diagnosticate syphilis; its duty is to report the results of a test-tube experiment that has only a certain amount of specificity. Syphilis should never be diagnosed in the laboratory, nor should the laboratory worker consider himself competent to give the final decision. It will, therefore, be necessary for the investigator to so arrange his working reagents that only those sera will be reported upon as positive that have withstood every attempt at negativation. Of course, it is possible to add so much of the amboceptor that even the positive serum of a patient with general paresis will eventually hemolyze. It is my experience that many weakly positive reactions are due simply to the use of too weak reagents, such as a poor (too old) complement, or the using of the Citron method of standardizing the amboceptor and of employing only two units. Using too much of the inhibitory extract is another factor in the production of weakly positive results or positive reactions on non-luetic patients. The reading of end-results must take into consideration all these points, and allowance must be made for the atmospheric pressure and meteorologic conditions. The careful worker will, therefore, in the course of time, consider a serum as positive only when it has resisted all the attempts at negativation just described—*i. e.*, the use of three or four amboceptor units, the employment of only one-half or even one-third of the inhibitory unit, the selection of vigorous animals for the complement, etc. It is absolutely necessary for the reliability of at least the positive Wassermann that the serologist should entirely disregard diagnostic responsibilities and merely submit the results of his test-tube analyses. He should frankly admit his mistake when a positive report is given on a non-syphilitic individual, and not defend his results by the arguments previously mentioned here. He

should make every attempt to negativate sera, and only when this is impossible should he report that a given serum is positive. By assuming this attitude I was enabled to report correct positive Wassermann results in all but 0.3 per cent. of positive results. The 0.3 per cent. were errors, as pointed out by the clinicians who treated the patients in question. The percentage of negative reports in syphilitic sera was naturally very large; nevertheless, when the number of recently treated syphilitics, as well as cases of old, quiescent tabes, is deducted from this list, the percentage of such reports is reduced to about 7 of the entire number of syphilitic sera.

In submitting a serum for analysis it is important, in order to obtain an unbiased opinion from the laboratory, to withhold the clinical findings in the case. The factor of personal equation is a very great one in reading end-results, and often influences the serologist to report as weakly positive, sera that would have been considered as negative had the serologist been unaware of the physician's opinion in the case. Of still greater significance is it to keep the laboratory in absolute ignorance of the clinical facts during the performance of scientific investigations with the Wassermann reaction, as the results from such premature knowledge are entirely derogatory to the reliability of the serologist's conclusions; it is absolutely impossible, in such instances, to leave personal equation entirely out of consideration. The possession of clinical facts previous to rendering results in a series of Wassermann reactions, as offered by some workers on the subject of specificity, or the introduction of new methods, makes the results of the research much less valuable than if the same work were conducted independently of such clinical knowledge. It is my advice, therefore, to those who wish to engage in experimental work, to reject all information that might interfere with the rendition of an unbiased and reliable conclusion. If this rule had been adopted before some reports were submitted the results would have been entirely different; biased opinion in these cases can be excluded with a fair degree of certainty.

The average serologist is oftentimes unable to differentiate

between an incomplete reaction, which should not be reported upon as positive, and the unquestionable, complete inhibition; in such a case the majority of laboratory workers will report positive findings instead of performing the test, as Zeissler suggested, with less serum, or, as I am accustomed to do, use more amboceptor. The desire to detect as many syphilitic sera as possible and thereby, so to say, show an increase in his efficiency, makes the serologist with a moderate experience commit many avoidable errors; such a worker, if he is in possession of facts suggestive of syphilis, is really afraid to report as negative the findings in such a patient, with the result that many innocent persons are made to carry the burden of a supposed infection, and, besides, are subjected unnecessarily to antiluetic medication. It cannot be denied that many individuals today carry the stigma of syphilis as the result of a superficial examination made by a physician before the days of the Wassermann reaction. It is to be deplored that today such occurrences are not only not diminished, but are actually increased, as a result of the serologist's attitude toward the Wassermann test. Attempts have been made to increase the sensitiveness of the test by using methods that are calculated not to make the number of negative findings greater, but, on the contrary, to make the number of positives as great as possible; the fact that the number of innocent sufferers is also increased is not considered. Such methods are the result of laboratory overzealousness and insufficient clinical knowledge. The work of Noguchi, although excellent from the standpoint of the laboratory expert, is sadly lacking in those clinical qualities that make the method he elaborated as useful as he would like to have it. The same can be said regarding the "Auswertungs Methode" of Hauptmann, who, in order to avoid the possibility of reporting as negative specific cerebrospinal fluids, uses quantities so large that a positive result is eventually obtained in some non-specific fluids.

The chief function of the laboratory worker, in my opinion, is not so much to detect every syphilitic, but to protect the non-luetic individual from a wrong diagnosis and useless

treatment. It should be the duty of every serologist to do his utmost to secure results that are characteristic of the unequivocal positive Wassermann, and he should consider himself as expert only when the number of positive reports on non-luetic sera approaches the zero mark, and not when his results with positive material approach the 100 per cent. efficiency mark. As previously stated, there are no two ways of performing and rendering results with the Wassermann reaction—either one is erring on the positive side, or commits the greatest number of mistakes on the negative side, and the latter is by far the lesser evil of the two. Clinicians ought to acquaint themselves with the views of the serologist before placing any confidence in his results. In concluding this very important section I would warn the clinician against the unerring serologist; in the present state of our knowledge of immunoserology such workers are a menace to physicians and patients.

PART II

THE SEROLOGY OF NERVOUS AND MENTAL DISEASES OF NON-LUETIC ETIOLOGY

GENERAL CONSIDERATIONS

NON-SYPHILITIC nervous and mental diseases have no direct connection etiologically with the spirochetes of syphilis. Although a patient with any one of the neurologic affections may have come in contact with syphilis either prenatally or postnatally, it is universally conceded that the disease in question is not syphilitic, although it may be argued that lues may have played a part as a predisposing factor. Whatever its relation to the diseases mentioned below, antiluetic therapy plays no very important rôle in their amelioration or eradication. This statement applies only to those cases whose serum and cerebrospinal fluid display a persistent negative Wassermann reaction; where the anamnesis and the physical examination reveal luetic manifestations, antiluetic measures are, of course, to be undertaken. On the other hand, one must not lose sight of the possibility of a coexistent lues of the viscera in a patient with any one of the acceptedly non-luetic diseases of the nervous system.

From a clinical point of view, the differentiation requires great analytic experience, as well as a sound consideration of the serologic data; it suffices here to mention the coexistence of lues in a profound neurasthenic or in a patient with multiple sclerosis, in which cases it may, perhaps, be excusable to think of general paresis in the former, and of cerebrospinal lues in the latter. That there are fine points of differentiation in both conditions one must admit; also that there are some cases in which even careful and experienced clinicians have failed to establish definitely the

nature of the malady. The purpose of the following exposition of the serology of non-luetic nervous and mental diseases is to give to the clinician additional means whereby errors may be eliminated by the performance of a series of tests which, together with the clinical findings, will complete the bedside and the laboratory picture of a given disease.

At the conclusion of each clinical picture the serology of the disease as found in the majority of instances will be given; this serologic picture will be designated as the "average formula." For the sake of brevity the Wassermann reaction will be designated as W. R.; the globulin, as Gl.; the cell count, as Pl. (pleocytosis); Fehling's reduction, as Feh. If normal or absent, the minus sign (−) will be used; if present or in excess, the plus sign (+) will be employed. In the case of Fehling's reduction, the presence of an excess of reducing substance (glucose?) will be tabulated as ++. This will also apply to a marked excess of globulin and to a hyperlymphocytic cell count. Instead of the word "serum," S. will be used, and C. S. F. will represent the cerebrospinal fluid.

MENINGEAL AFFECTIONS

Micotic Meningitis With Demonstrable Bacteria in the Fluid

Epidemic Cerebrospinal Meningitis.—That this form of meningitis is caused by the organism known as Weichselbaum's diplococcus, and that the pneumococcus of Fränkel is not a causal factor in epidemics of the disease, are accepted by most authorities. The serology of the acute form shows a marked increase in the cellular content of the spinal fluid, which may number several thousand to the cubic millimeter, and may even be so abundant as to make an actual count without great dilution impossible. The cells show great variety, with a large percentage of polynuclears, and the fluid is often purulent. The globulin is greatly in excess, and may be obtained in a fluid diluted 1:10. Other protein bodies are also present, and are demonstrable by suitable chemical methods. The reduction of the Fehling solution is absent, as a rule.

It is advisable for the serologist to come to the patient prepared to inject any of the remedies in use. The efforts of Wassermann-Kolle, Lepine, Jochmann, Flexner, Schoene, and others have placed at the disposal of the clinician immune substances capable of influencing this very fatal affection. As no time must be lost, and the patient's serious condition must be considered, the serum should be injected as soon as the diagnosis is corroborated by the microscope; hence the advice just given, to be prepared with everything necessary for the purpose. In a case in which I was called into consultation the equipment consisted of a microscope, staining fluids, counting chamber, 75 c.c. of Flexner's antimeningitic serum, and a lumbar puncture needle. As no lymphocytosis was obtained, the fluid was not injected. An interesting study of this subject was made by Sophian in a recent epidemic. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. ++; Pl. ++; Feh. −.

Influenza Meningitis.—In two cases of this disease I found the typical organism described by Pfeiffer. There was a moderate lymphocytosis in both instances, with an excess of protein. Fehling's solution was not reduced in one case, whereas the other gave a prompt reduction. The fluid that did not reduce the Fehling solution showed 82 polynuclear cells to the c.mm., besides 167 lymphocytes. The polynuclear content of the other was very low, showing only 3 polynuclears to the cubic millimeter. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. +; Pl. +; Feh. +.

Diphtheric Meningitis.—Bonhoff, Leede, and others were able to demonstrate the Klebs-Löffler bacillus in meningitis accompanying diphtheria. Aside from the presence of the bacterium, the other meningitic laboratory manifestations were also demonstrable: globulin excess, pleocytosis, diminished reducing substance, increased pressure.

Gonococcic Meningitis.—The gonococcus may invade the meninges. The literature contains observations made by Fürbringer, Deposse, de Josselin de Jong, and a few others, who found the gonococcus in the cerebrospinal fluid. That the gonococcus resembles the meningococcus of Weichselbaum very closely is true, and one may with justification

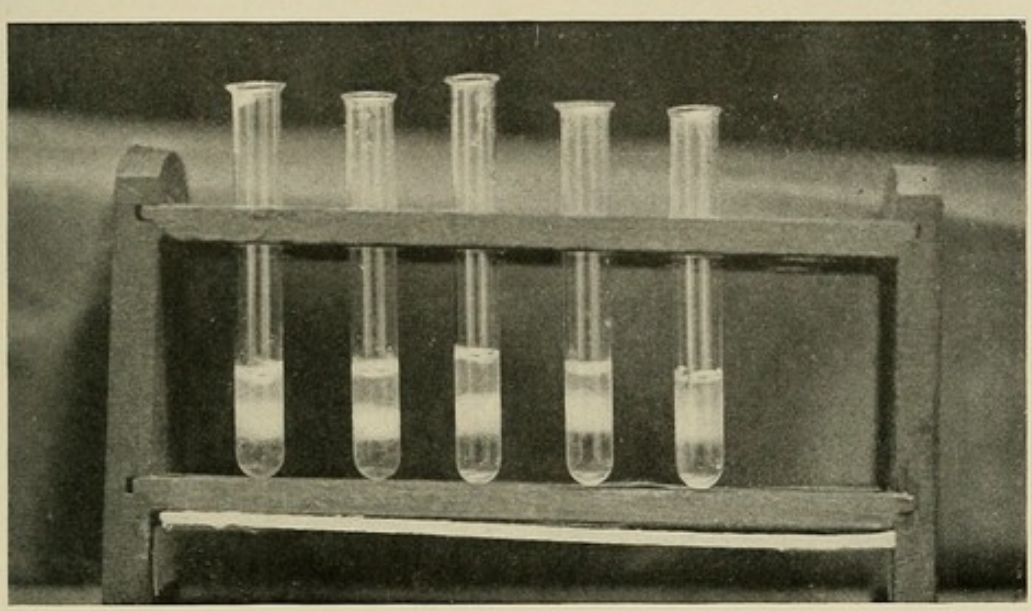


Fig. 18.—Protein excess as observed in a case of acute meningitis. Author's method, showing an excess in the tube containing 0.2 c.c. of cerebrospinal fluid and 0.3 c.c. of water The last tube, with only 0.1 c.c., also presents a faint ring.

question the genuineness of the observation; on the other hand, I have heard the opinion expressed by an authority whose judgment in such matters carries great weight, that a certain meningomyelitic process was of gonococcic origin, this remark having been made after opening the dura and making a study of the contents of the dural sac.

Typhoid and Paratyphoid Meningitis.—A genuine meningitis caused by either the typhoid or paratyphoid microorganism is a possibility, although a rare one. Lenhartz, Silberberg, Hugot, Boden, and others reported the finding of these bacilli in the cerebrospinal fluid. It does not necessarily follow that the meningeal symptoms frequently encountered in these diseases are the result of a micotic meningitis; the irritation, as will be pointed out further on, is, in the majority of instances, a reflex one, if one may be permitted to use the term in connection with a meningeal response to a general infection without being itself (*i. e.*, the meningeal structure) attacked by the bacilli.

Tuberculous Meningitis.—This form of meningitis is always secondary to a focus existing elsewhere, although during life, and even at the postmortem examination, the primary lesion may not be found. The serology of this disease is characterized by the presence of a lymphocytosis which may be very pronounced, or may be accompanied by an exceedingly small number of cells. When the condition is present in pure form, one usually finds the lymphocyte; when there is a mixed infection, the presence of polynuclear elements is demonstrable. In the case of a mixed infection, it is possible to estimate the extent of the inflammatory process by the number of polynuclear elements. As the meningitis subsides the polynucleosis also tends to diminish, and the previously absent Fehling's reducing substance gradually returns.

A pure lymphocytosis in a child should always suggest a tuberculous meningitis, and a diligent search for tubercle bacilli should be undertaken. With the milder forms of this disease the protein content is not markedly increased, whereas a marked excess—up to a 1:5 dilution—is obtainable in the severer forms, particularly where a mixed infection is

present. The search for the tubercle bacillus frequently consumes much time, and in the end the bacillus may escape detection. Some writers claim to have found this organism in over 90 per cent. of their cases of tuberculous meningitis, a fact not borne out by my own experience.

According to Trembur,[1] it is possible to increase the number of tubercle bacilli in a given tuberculous fluid by subjecting the obtained fluid to an incubation temperature for twenty-four hours, all precautions against contamination having been observed. The number may be so largely augmented that one can obtain without difficulty one or two good specimens from every six or seven fields.

Mestrezat lays great stress on the fact that the meninges in tuberculous meningitis present a greater permeability to nitrates than does any other meningeal involvement. He gives the patient 1 gram of sodium nitrate for every 30 kilos of body-weight, and analyzes the fluid three hours after the ingestion of the salt. In the normal state the amount of sodium nitrate obtained in the fluid ranges from 8 to 10 milligrams per liter. The amount obtained after the ingestion of 1 gram of the salt may vary 1 or 2 milligrams normally. In case of tuberculous meningitis, the quantity obtained may be anywhere from 40 to 85 milligrams. His tables show that after ingestion of the salt in any other form of meningitis the augmentation in the amount of nitrates in the fluid is strikingly small, as may be seen from the following examples:

Clinical Diagnosis.	Milligrams of Sodium Nitrate Found in the Fluid.
Tabes (6 cases)	9 to 13
Arteriosclerosis (2 cases)	12 to 14
Cerebellar glioma	8
Cerebral congestion	10
Syphilitic paraplegia	18
Multiple sclerosis	15
Tuberculous meningitis (9 cases)	43 to 85
Syphilitic meningo-encephalitis (semi-coma)	40 to 45
Cerebrospinal meningitis	38

In one case of this disease Hauptmann, using the "Auswertungs Methode," obtained a positive Wassermann reac-

[1] Trembur: Klin. Jahrbuch, No. 24

tion; this is to be considered as a result of the use of larger quantities of fluid than are employed in the Wassermann school; the possibility of syphilis as a factor in its production may be an argumentative subject, but cannot, in view of the clinical facts of the case, be considered. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. +; Pl. +; Feh. +.

Pneumococcic Meningitis.—In a case in which I had the opportunity to analyze the fluid showing this coccus, the cell count showed 84 lymphocytes per c.mm. and 8 polynuclear cells; the protein content showed a 1 to 3 excess, and the Fehling's reduction was prompt. This form of meningitis is not uncommon. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. +; Pl. +; Feh. +.

Meningitis of Otic Origin.—The presence of a meningitis in a purulent otitis media is not always to be demonstrated by lumbar puncture. When found, however, it adds an element of danger which greatly complicates the treatment, as well as rendering the prognosis much more grave. The severity of the meningitis is dependent upon the pathogenicity of the causal microörganism. As a rule, the infection that follows an otitis is usually a mixed one. On the other hand, it is not rare to have a serous meningitis as a result of ear suppuration. The serology in such a case is usually negative, or may be accompanied by an increase in protein without an accompanying lymphocytosis. Some cases improve spontaneously after the lumbar puncture, a point that may be utilized in the therapy of such cases (A. Bruce). Although the presence of pus and bacteria in the fluid obtained by lumbar puncture is significant in itself, it nevertheless does not help us to differentiate between meningitis and brain abscess. The performance of lumbar puncture in otic complications is not devoid of danger.[1]

The fluid usually contains cells and bacteria, and is turbid; this occurs, of course, only when the communication between the cavity of the skull and the spinal canal is open, which is not always the case.

The consensus of opinion of aurists is divided on the subject of lumbar puncture: some would employ it for diag-

[1] Grunert: Münch. med. Woch., 1905.

nostic purposes in every instance; whereas others would resort to it only in cases where the differential diagnosis demands it. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. +; Pl. ++; Feh. −.

Staphylococcus Meningitis.—The Staphylococcus aureus or albus may be the exciting cause in this form of meningitis. The condition is observed usually after injuries to the skull or during the course of sepsis. On the whole, it is a very rare form of infection, and is demonstrable only by careful cultural methods. One rarely finds the coccus in the smear preparation. When the opportunity for growth and propagation is favorable, the coccus may then be observed in the smear. The remaining serology is the usual meningitic pleocytosis, globulin excess, etc.

Streptococcic Meningitis.—This form of meningitis is generally secondary to a streptococcic invasion elsewhere. In the case of the Streptococcus erysipelatis, the meningitis develops, as a rule, after one or more of the cranial sinuses have become involved. The meningeal reaction is very severe, and goes hand in hand with the clinical manifestations, as well as with spinal fluid changes. In the streptococcic varieties of meningitis are to be found the most purulent spinal fluids.

Plaut described a Streptococcus mucosus which was first seen by Bonome. According to the former observer, small epidemics of this form of meningitis were observed by him, the mortality ranging from 40 to 50 per cent. In the sporadic forms of this disease the meningitis was secondary to an otitis media purulenta. Of these cases, every one proved to be fatal. The microörganism was demonstrable in the spinal fluid, and, besides showing the usual characteristics of an acute purulent meningitis, the cell count in one instance showed 30,720 cells per cubic millimeter, of which 90 per cent. were polynuclear elements. The streptococci capsules are seen in the smear, and appear in long chains, visible in every portion of the preparation.

The Streptococcus putridus was demonstrated in the spinal fluid as a secondary invasion from a focus in the ear, and in another instance in the course of puerperal sepsis.

The nature of the streptococci, with the possible exception of the Streptococcus mucosus, is best demonstrated by culture.

Remarks.—Besides the micotic invaders just mentioned, various authors have reported the finding, in the cerebrospinal fluid of the Bacillus coli commune; the Bacillus pyocyaneus; the Bacillus mallei; the Bacillus anthracis; the saccharomyces and the actinomyces.

In all forms of micotic meningitis the disease process may be confined to a very small area, giving rise to local manifestations only. If the process is well excluded from the general meningeal area and from the channels through which abnormal elements find their way into the spinal fluid, one may not observe marked changes in the fluid. Of course, an excess of globulin may be demonstrated, but even this may be lacking if the meningitis is in the frontal region, very small in extent, and well encapsulated. These circumscribed forms of meningitis may frequently escape laboratory recognition on one occasion, and at a subsequent puncture may manifest all the signs of a meningitic process, the result, most likely, of the extension of the process or of the breaking down of the protective barriers.

If the protective barrier breaks down, one no longer deals with a circumscribed disease, and the bacterium becomes apparent either culturally or in the smear. The latter finding marks the existence of a diffuse cerebrospinal meningitis. The terms "pseudomeningitis" and "meningismus" do not convey the necessary information, and are only misleading; equally meaningless is the term "meningitis sine meningitide" (Fr. Schultze). We are justified in distinguishing between the diffuse and the circumscribed forms of meningitis micotica, and I consider the absence of an accepted meningitic serology, such as a pathologic pleocytosis, globulin excess, etc., as the distinguishing feature between the circumscribed and the diffuse forms of this disease. The presence of these manifestations, and, above all, the finding of the exciting microörganism, remove the disease from the class of the circumscribed meningitides.

Non-micotic Meningitis

Secondary Meningitis or Meningitis Serosa.—In contradistinction to meningitis micotica we have meningitis serosa. The cellular increase in the cerebrospinal fluid in the course of a typhoid that presents meningeal manifestations is due most likely to a meningitis of this form. The bacteria are not, of course, demonstrable in the fluid. A general staphylococcus infection or certain infective endocarditides give rise to a serous meningitis. Other infectious diseases may also cause an increase in the number of cells in the cerebrospinal fluid without demonstrating the bacterium responsible for the increase. In cases in which it is absolutely necessary to differentiate between the infectious fever and the cause of the meningitis careful cultural methods of examining the blood and the spinal fluid are the only means by which light is shed on the subject. In the presence of a positive blood-culture in a patient with an infectious disease showing meningeal complications, the absence of the bacterium from the cerebrospinal fluid is generally sufficient to establish the diagnosis of a meningitis serosa (non-micotica).

It seems to me that further subdivision of the subject is only conducive to error, and I will, therefore, include under the heading of Non-micotic Meningitis or Meningeal Irritations all those conditions that are capable of giving rise to abnormalities in the cerebrospinal fluid, regardless of the fact that the irritation may have been transmitted through the wall of a bone cavity, without the actual inflammatory process coming in contact with the meninges. This will give us the meningitis serosa encountered during the course of an otitis media, frontal sinus disease, or disease of any of the cavities of the bones of the skull. The fluid is oftentimes altered but little, and at other times may give rise to a pathologic cell count. The globulin is but rarely in excess, and Fehling's reduction is always prompt. Besides these factors, there are also a number of vascular and other brain and cord manifestations capable of producing sufficient irritation to give rise to the above serologic changes. Of these, sinus thrombosis and brain abscess, as well as tumors,

are to be mentioned. The appearance of a cellular increase in the cerebrospinal fluid is dependent upon a number of factors, irrespective of the cause that has produced the secondary meningeal manifestations. If the iter from the irritating focus to the subarachnoid space and into the intradural canal is clear and uninterrupted, one will find various cellular elements in numbers corresponding to the degree of irritation. If adhesions exist, or even if a thick layer of brain tissue intervenes, then a pleocytosis, even of moderate degree, will hardly be found. A tumor or a deep cerebral abscess in the frontal region will rarely give rise to abnormalities; a similar condition in the pontocerebellar angle will frequently give abundant evidence of the presence of an irritation. If the meningeal irritation is very severe, one will find, besides a pathologic cellular increase, also a marked protein excess, and at times even a fibrinous network, a phenomenon encountered usually in acute meningitis.

Pleocytosis as a response to an irritation is to be considered as one of the earliest manifestations in the course of repair, and hence may be regarded as the first attempt by nature to guard against a spreading of the noxious process. The preponderance of phagocytic elements (polynuclear cells) serves as an index to the degree of irritation. The milder forms of irritation show, as a rule, only few polynuclear cells, the proportion of the latter increasing as the irritating process gains in extent and intensity. Hence the presence of cells in a larger number than normal is alone sufficient to serve as a danger-signal that something is wrong somewhere with the meninges. In treating various cerebrospinal conditions, the disappearance of the pleocytosis is also the surest index of the success of the treatment.

This dictum is true of all cases, with the single exception of tumors of the spinal cord. In the latter the presence of a large amount of protein and the absence of a corresponding pleocytosis would tend to show that the protein bodies found are chiefly specific tumor proteins, secreted by the tumor cells themselves. It is certainly very difficult to explain the absence of cells if the protein excess is accepted only as a meningeal response

Meningitis serosa is at times differentiated with difficulty from the circumscribed variety of micotic meningitis. Perhaps the absence of manifestations in any of the cavities of the bones of the skull, together with meningeal signs in the course of an infectious disease, ought to be significant guides in the establishment of a serous meningitis, provided careful cultural methods gave no evidence of the presence of a bacterium. It is extremely important for the surgeon, in particular, to be able to differentiate between a circumscribed meningitis micotica and a meningitis serosa, as in the former condition surgical interference may result in spreading the focus of infection, with the resultant general involvement of the meninges.

Hypertrophic Laminated Spinal Meningitis.—In one patient, previous to making the lumbar puncture, the diagnosis was tuberculous meningitis, being based on the signs at his apices and the gibbus in the dorsal column. The symptoms were so classic that only as a last resort was rachicentesis performed at the suggestion of the surgeon who subsequently operated upon the patient. The result of the rachicentesis was very striking, in that it gave no pleocytosis; in fact, not one cell was seen in the centrifuged specimen. The striking feature was the marked excess of protein matter, which congealed with heat into an albumin reaction. The presence of a possible tumor suggested itself, and the operation revealed a long plastic growth or, rather, what seemed to be a neoplastic formation. The specimen submitted for examination showed a tough, fibrous structure, which, even to the unaided eye, appeared to be finely laminated. The microscopic examination showed very few cellular elements.

Pachymeningitis Hæmorrhagica Interna.—In this condition the chief manifestation is the tinge of the cerebrospinal fluid, which is sometimes yellow or pinkish. The cellular elements are, as a rule, not striking; here and there an old red cell, more or less crenated and otherwise distorted, may be found in the fluid.

In cases where an abnormal (border-line) count is obtained, one may also detect a slight globulin excess.

BRAIN DISEASES

Cerebral Hemorrhage.—Although classified under the head of non-luetic diseases, syphilis is by no means rarely present in vascular affections of the brain. Depending upon the proximity of the bleeding vessel to the ventricles to the subarachnoid space, and to the iter e tertio ad quartum ventriculo, blood elements will be found in the spinal fluid. It is remarkable how little interference will produce cellular alterations in the cerebrospinal fluid; in fact, it seems that the first manifestation of an abnormal condition is the appearance of small cells in the fluid, with the exception of processes producing very gradual compression of the spinal cord. In the latter, the non-appearance of cells in the majority of instances is justly considered as paradoxic. In old brain hemorrhages some investigators have demonstrated the presence of chemical constituents in the blood. The presence of these elements is, in my experience, an exceptional finding, as the majority of fluids do not give chemical blood reactions in old hemorrhages, although some cells may show deposits of blood-pigment. Fresh blood constituents may find their way into the cerebrospinal circulation, with the proviso noted above. An excess of globulin is but rarely encountered, no matter what method of detection is employed. If it is present, syphilis is, perhaps, the causal factor in its appearance. In the ordinary simple arteriosclerotic hemorrhage of advanced age, the globulin content is, as a rule, normal. The serology of the serum may be positive or negative, and may or may not have any connection with the process responsible for the hemorrhage. It is quite different when a positive Wassermann is obtained in the cerebrospinal fluid, a result that invariably indicates that the vascular disease is a syphilitic one. Where the Wassermann is positive in the spinal fluid, cells are also present, while a globulin excess, with ordinary methods, may be absent. The Lange method of using colloidal gold for the precipitation of globulin-like substances in luetic diseases of the central nervous system will give the reaction of an excess more often than the usual Nonne-Apelt, Noguchi,

Ross, or Kaplan methods. The reduction of the Fehling solution is prompt in every instance of brain hemorrhage. Average formula: S.: W. R. − or +; C. S. F.: W. R. − or +; Gl. −; Pl. −; Feh. +.

Cerebral Thrombosis.—The hemiplegias and paretic conditions produced by the gradual occlusion of blood-vessels give us the serology of the etiologic factor responsible for their existence. If syphilis is the cause, one is apt to obtain a positive Wassermann reaction in the serum; here, as well as in other neurologic disorders, a positive Wassermann reaction in the serum bears only a secondary significance in the serology of the disease. In thrombotic brain diseases one is more often confronted with the question of syphilis than in the hemorrhagic cases. Nevertheless, a positive Wassermann serum reaction, in the absence of findings of a pathologic nature in the cerebrospinal fluid, need not be considered as final proof of the syphilitic nature of the thrombosis. Although suggestive of syphilis, when the test is positive in the serum only, its significance is greatly enhanced when the cerebrospinal fluid contains either an excess of globulin with a pleocytosis, or only the latter. In such a case the Wassermann reaction may be absent in the cerebrospinal fluid without reducing the significance of the collective findings. A positive reaction in the fluid is at times obtained in such cases, which, of course, settles the entire question of etiology and treatment. The increase in cells, if present, is usually of those of the small mononuclear variety, and, as a rule, it very rarely exceeds the pathologic increase; border-line counts are the rule, with a normal globulin content and a normal Fehling's reduction. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +. Luetic average formula: S.: W. R. +; C. S. F.: W. R. + or −; Gl.− ; Pl. +; Feh. +.

Cerebral Tumor.—The serology of cerebral tumors is almost negative. In the case of gumma one may find a positive Wassermann reaction in the cerebrospinal fluid, with a border-line or a pathologic cell count. I have never seen a pathologic increase or a hyperlymphocytic count. The significant serology of spinal cord tumors is not obtainable

with brain neoplasms, unless the latter are situated in the posterior fossa of the skull.

In estimating the value of a positive Wassermann reaction in the serum of a given case of brain tumor, one must be more cautious than in any other neurologic disorder. A positive Wassermann serum reaction was obtained in a case of brain endothelioma with a coexistent gumma of the liver. Only unquestionable spinal fluid positive Wassermann reactions should make one accept syphilis as the cause of the tumefaction.

The question of therapy is by no means settled by a positive Wassermann reaction in the cerebrospinal fluid and an increased cell count. Antisyphilitic treatment is to be resorted to only in case the tumor is not situated in the neighborhood of vital centers and when its size is small enough to encourage the hope that such treatment will effect its disappearance. In all other tumor cases surgery as practised today is a much more rational and satisfactory procedure than medical treatment. One must also not be misled by the successful negativation of the serologic findings by drug treatment; it should be borne in mind, especially in cases of brain tumor, that the patient is suffering from a neoplasm, and not from a positive serology. There are cases on record in which the patient, regardless of the fact that a negative serology was obtained as the result of drug therapy, succumbed to the tumor, which proved to be a gumma.

It must be conceded that inaccessible tumors of the brain are not helped by any form of treatment, whether the serology is positive or negative. As cases of sudden death have been recorded as a direct result of the rachicentesis in cases of brain tumor, caution must be exercised, particularly when the tumor is located in the posterior fossa of the skull. When it is absolutely necessary to make the puncture it is advisable, in order to avoid unpleasant consequences, to replace the removed fluid immediately by injecting an equal quantity of normal sterile saline solution, and to raise the foot of the bed about 12 to 15 inches. It seems that the tumor in the posterior fossa as the result of the removed

fluid encroaches upon the vital center in the floor of the fourth ventricle, causing respiratory or cardiac inhibition. The reintroduced saline solution may refill the cushion of fluid and thus obviate fatalities, and the raised foot of the bed will tend to deviate by gravity the line of pressure away from the vital centers. Average formula: S.: W. R. − or +; C. S. F.: W. R. − or +; Gl. + or −; Pl. −; Feh. +.

Cerebral Abscess.—In almost one-third of the cases of cerebral abscess the ear is the starting-point of the purulent process. Rachicentesis gives abnormal findings, as a rule, when the accumulation of pus gives rise also to a meningitic reaction. This, however, is not an absolute requirement, as there are instances in which a pleocytosis and an increase in protein were observed without a demonstrable meningitis. A well-encapsulated abscess of the cerebrum will give a negative result in the cerebrospinal fluid, no matter where it is situated. When a diffuse purulent meningitis is to be differentiated from a cerebral abscess, the performance of a lumbar puncture may frequently be of decisive importance. The former condition always presents a turbid fluid rich in cells (meningitic cell count), and shows a protein excess, as well as bacteria. All these pathologic constituents are to be observed only when the communication with the subarachnoid space is free; if it is shut off, one may find only a few cells (border-line count), with or without a mild protein excess. It is also important, in cases of diffuse purulent meningitis, to observe the behavior of the fluid toward Fehling's solution. At the height of the meningitis one obtains no reduction of the solution, which, however, appears as the acute stage gives place to a chronic condition. As the greatest difficulty is often encountered in differentiating between a diffuse meningitis and an abscess, the points just considered will prove of great usefulness. Average formula: S.: W. R. −; C. S. F. −; Gl. − or +; Pl. + or −; Feh. +.

Cerebral Softening.—This condition may give a positive serology in those cases in which lues is the etiologic factor. Where the softening is due to a simple arteriosclerosis, one may occasionally find only a few cells (border-line count), and rarely only a slight protein excess. In the luetic cases

the Wassermann reaction in the cerebrospinal fluid need not be positive, even when the "Auswertungs Methode" is employed. The reduction of Fehling's solution is always obtained. There are instances in which, as a result of the proximity to the meninges, a secondary meningitis is produced, with the usual serology in such cases. (See Meningitis.) Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Hydrocephalus.—In this condition one usually finds a normal cell count. The globulin is present in normal quantities only. It is to be conceded that occasionally one finds a fluid with a border-line or a pathologic cell count; these cases usually also give a positive Wassermann reaction in either the spinal fluid or serum or in both. This applies to the chronic, quiescent cases of hydrocephalus. In acute cases the cell increase may be decided and the globulin in excess. In such instances the pressure of the stream is an important point to be considered; Quincke reports cases in which the pressure was over 1000 mm. The objective symptoms frequently improve after an abundant withdrawal of fluid, which procedure is to be performed with caution and with the use of a manometer, not permitting the pressure to return quite to the normal. In post-traumatic hydrocephalus (concussion of the brain) the cerebrospinal fluid is usually increased in amount; the pressure is also increased, while the cells and the globulin content are, as a rule, normal. In this condition repeated puncture and withdrawal of fluid is frequently followed by improvement in the objective symptoms.

According to Quincke, the headaches of chlorotic individuals are due to a condition that he designates as hydrocephalus angioneuroticus. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Amaurotic Family Idiocy.—This disease belongs to the large group of hereditary or congenital diseases more or less closely related to the diplegias. Sachs believes that this affection is to be observed exclusively among the Jews. Properly classified, it ought not to be considered with brain diseases, as, according to Frey, the pyramidal fibers are

extensively atrophied, besides degeneration of the cortical cells.

But little, if any, serologic work has been done on this very interesting and obscure affection. I had the opportunity to study the serology in one patient, and could find no deviation from the normal in the serum or in the cerebrospinal fluid. In another patient, where the serum only was available for study, and gave a negative Wassermann reaction, the parents were also examined, with the result that the mother gave a positive and the father a negative Wassermann result. It seems to me that the positive reaction (syphilis?) bears no etiologic relationship to this disease. Had the spinal fluid Wassermann been positive, we would have formed quite a different conception of the entire process. In two other babies the serum Wassermann was found to be negative. It is to be hoped that in the future more extensive chemical studies of this form of infantile cerebrospinal degeneration will be made, especially on the spinal fluid. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

SPINAL CORD DISEASES

Spinal Spastic Paralysis (Lateral Sclerosis).—This is a well-defined clinical entity, and in the adult, considered from the serologic point of view, is entirely negative. When, however, syphilis is present as the etiologic factor of the lateral sclerosis, or is only a coexistent factor, great care is required for its proper interpretation. In the former one would expect cerebrospinal fluid abnormalities, with or without a positive Wassermann reaction in the fluid or in the serum or in both media; in the latter instance abnormalities in the fluid should, of course, be absent. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Congenital Spastic Paralysis (Little's Disease).—This is preëminently a disease of the motor area. That either the brain or the spinal cord may be implicated in the process is a possibility; the two are, however, usually found affected together, and the former more extensively so than the

latter. The most important etiologic factor in this condition is cerebral trauma inflicted during birth, which alone is sufficient to produce inhibition in the development of the pyramidal tracts. Only in very few instances can syphilis congenitalis be considered as a cause of the disease. The serology of the cerebrospinal fluid is usually negative. Not a single case among 6 analyzed by me gave a positive serologic result. In one instance the parents admitted lues, but gave a negative Wassermann reaction in the serum. In two other instances the parents denied lues and gave negative serum Wassermann reactions. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Senile Spastic Paraparesis.—As the name implies, this is a disease of the aged. In the majority of instances the changes are similar to those seen in arteriosclerosis of the vascular system of the spinal cord, and sclerotic changes are also seen near the vessels in the white matter of the cord. The involvement of the cerebral motor tracts by small foci may also give the picture of a spastic paraparesis. The serology is, as a rule, negative, as lues can be excluded in almost every instance. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.[1]

Combined Sclerosis.—A few such cases were observed at the Neurological Institute. All these showed more or less severe blood changes, although not one assumed the severity, so far as the morphology and numeric relationship are concerned, of the blood-picture of the so-called pernicious anemia. The changes were mostly confined to the red blood-corpuscles, which showed granular and hemoglobinemic degenerations, with or without a polychromatophilia. In one case a pronounced anisocytosis, and in another a marked macrocytosis, were the only abnormalities noted. The etiology in these cases was not determinable, although it was believed at one time that some toxic substance played the chief rôle. The serology of these patients was very interesting, in that three of them gave a marked increase in the globulin content of the cerebrospinal fluid,

[1] See Collins and Zabriskie, Medical Record, 1904; also B. Sachs, Revue of Neurol., 1905.

without an increase in the cell count; one gave a border-line pleocytosis. Syphilis could be excluded clinically, and if the negative Wassermann reactions can be taken as significant in these instances, also serologically. In these cases the globulin excess was so great that even a 1:10 dilution gave the reaction usually obtained with an excess. It will be shown further on that such findings are usually associated with a spinal cord compression.[1] Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. + or −; Pl. −; Feh. +.

Hereditary Ataxia (Friedreich's Disease).—So far as I know, there are no serologic records in the literature concerning the serology of this rare neurologic condition. One case analyzed by me gave absolutely negative findings. It may, however, be necessary at times to differentiate between this affection and cerebrospinal syphilis, a task which should not offer any difficulty in view of the serology of the latter disease. I believe that syphilis is rarely a cause of this disease. As its name suggests, heredity plays a more important part than anything else in the etiology of this nervous disorder. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Acute Myelitis.—In a case where the symptoms were ushered in somewhat suddenly, with pain in the region of the spleen and the signs of a transverse myelitis, which was for a short time regarded as a cord tumor, severe degenerative blood-changes were observed by me, and the observations reported together with those of Dr. Collins. The blood-picture was described as a promyelocytic leukemia. The blood-culture was negative (sterile). During his sojourn in the hospital the patient developed signs of pulmonary infarction, and died a few days later. The serology was negative, with the exception of a border-line count and a slight globulin excess. In post-infectious myelitis one usually finds such changes in the serology, with occasional red blood-corpuscles and blood-pigment in the cerebrospinal fluid. The Wassermann reaction is negative.

The reduction of Fehling's solution may be impaired and give a violet tinge to the fluid, and only a sparse de-

[1] Dana: Jour. Nerv. Dis., 1899.

posit of reduced copper will be seen on the bottom of the test-tube.

It cannot be denied that severe changes in the blood may exert deleterious influences on the cerebrospinal apparatus, and that the abnormal serology of these patients is to be considered as of the same significance as severe infections, which, as is known, frequently render the serologic findings abnormal. The qualitative study of the blood in these instances is a very essential feature of the entire clinical picture, particularly where the condition, in its clinical and serologic aspects, resembles a tumor. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. + or −; Pl. − or + ?; Feh. +.

Anterior Poliomyelitis.—In the acute form one usually finds border-line counts and a normal or slightly increased globulin content. The Wassermann is usually negative in the serum and spinal fluid. That positive Wassermann reactions may be obtained in the serum must be admitted; a similar result on the cerebrospinal fluid, however, should make one reconsider both factors, clinical and serologic, for when the Wassermann reaction is truly positive, I would not hesitate to doubt the clinical interpretation of the affection; on the other hand, if repeated serologic reports from different laboratories do not strictly coincide, then the serology should be discarded and poliomyelitis accepted as the clinical diagnosis. The positive Wassermann reaction obtained on the serum can be accounted for by a preëxisting congenital lues, but I am inclined to consider the serologic result as an error in the performance of the test, unless distinct signs of congenital lues are at hand. As the disease progresses and enters upon the prolonged chronic stage, one usually finds nothing abnormal in the serology with the exception of a positive Wassermann reaction in the serum in congenital syphilitics. There are no definite landmarks in the serology of poliomyelitis, nor does bacteriology help us in this instance, although a filterable toxic substance was obtained which proved to be noxious to monkeys. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

A very important contribution to our knowledge of this affection was given by Peabody, Draper, and Dochez. These observers find a variably high pressure, which, however, is not diagnostic. The cells are exceedingly numerous in the earliest stages of the disease, at which time the percentage of polynuclear elements may exceed 75 per cent. As the disease progresses the number of cells tends to diminish and may reach the normal or, at most, border-line counts. They find the highest counts in the preparalytic stage of the disease, the number of cells gradually diminishing to normal. Of 45 cases, 8 showed 50 cells and over per c.mm., while in the second week 23 gave normal counts. Of 40 cases in the third week, only one gave a count of over 50, while only 8 were above normal. As compared with the cell count, the globulin content is, as a rule, low in the first part of the acute stage, tends to rise during the second and third weeks of the disease, and then gradually falls. These authors conclude that the marked cellular increase is characteristic of the early stage of the disease, and that the higher globulin contents are significant of the more or less advanced form. The foregoing studies were conducted on children, but it must not be forgotten that acute anterior poliomyelitis was also observed in the adult, although no rachicentesis was performed. The danger in such instances is the suspicion of syphilis, which may defer proper treatment in due time.

Amyotrophic Lateral Sclerosis.—In this very interesting disease the serology is, as a rule, entirely negative. Although I had the opportunity of analyzing only 6 cases, I believe I am justified in making this statement, in view of the absence, in the literature, of anything to the contrary. Again, a positive Wassermann can be obtained in the serum of those who were infected subsequently to the development of the amyotrophic condition. It is an accepted fact that syphilis as an etiologic factor has no bearing on this affection, although it must be admitted that a lesion of the anterior horn cells and the pyramidal tracts can be produced by syphilis. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Progressive Muscular Atrophy (Spinal Form).—In this

disease, but in a few instances only, syphilis plays an etiologic rôle. This contention was advanced by Dana[1] in his statistics. In one patient only was I able to obtain a positive Wassermann reaction in the serum, the history of syphilis antedating the advent of the neurologic disorder. In another patient who gave a suspicious history a negative Wassermann was obtained on the serum, but another reaction, which will be spoken of further on, was positive. The cerebrospinal fluid was negative in 5 cases observed by me. I cannot state whether remedies directed against syphilis arrested the progress of this disease. Average formula: S.: W. R. − or +; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Progressive Muscular Atrophy.—In typical cases this disease shows no appreciable changes in the cord or nerves; the muscles are the seat of the pathologic process. The serology is entirely negative. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Progressive Muscular Atrophy (Neurospinal Form).—Although heredity plays an important etiologic rôle in this disease, syphilis is not considered as a factor. In two instances the serology was negative. The possibility of subsequent contamination with syphilis after the advent of the neurologic disorder must always be borne in mind. (See the section on General Considerations.)

In such an instance a positive Wassermann reaction demands great care in establishing the time relationship between the infection and the beginning of the neurologic disorder. In such cases also the Wassermann test should be performed more than once, and preferably by different serologists. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Multiple Sclerosis.—This disease is not nearly so prevalent in America as it is in Europe. I had the opportunity of analyzing 16 cases serologically. In only 3 was the Wassermann reaction positive in the serum, all having shown anamnesic factors of lues. Not one case gave a positive Wassermann reaction in the cerebrospinal fluid, the original Wassermann

[1] Dana: Jour. of Nerv. Dis., 1906.

method being used. The cells were always within the normal limits or, at most, gave the smaller of the border-line count. The globulin was never found to be in excess, and the Fehling reduction was prompt. It is my opinion, although supported by only 16 analyses, that it is safer to regard the finding of a positive Wassermann in the cerebrospinal fluid in this disease as a technical error than to assume that syphilis is the cause in a given case of multiple sclerosis. The obtaining of a positive result with the "Auswertungs Methode" is, in my opinion, of value only when the same is obtainable with the use of smaller amounts of fluid—as little as 0.1 c.c. The absence of a pleocytosis and of a globulin excess greatly minimizes the genuineness of a positive Wassermann reaction obtained in the cerebrospinal fluid in this disease. Concerning this, more will be said further on.[1] Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Syringomyelia.—In this condition one may obtain a marked increase of protein without a pleocytosis. As a rule, the Wassermann reaction is negative, as it has nothing in common with this disease. In one instance the fluid was colored a lemon yellow and did not give a Berlin-blue reaction. In four other cases the fluid was absolutely normal. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. − or +; Pl. −; Feh. −.

Hematomyelia.—A hemorrhage may take place in a preexisting cavity as the result of a syringomyelia. The condition is not a very common one, and is usually observed in those whose health is below par, and whose spinal cord is less resistant than normally. Whether syphilis can so alter the nutritive balance of the cord tissues as to make them less resistant to sudden or prolonged strain and thus induce rupture of a blood-vessel is not known. In two instances—one a girl of seventeen and another a man of forty-two—no abnormalities were observed in the fluid or the serum. The patients were studied a few months after the acute attack. What the serology would have shown had the fluid been analyzed immediately after the hemorrhage is merely

[1] See Kaplan: Deut. med. Woch., May 29, 1913.

presumptive. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Spondylitis Tuberculosa.—The serology of this condition depends entirely upon the extent of the involvement of the contents of the vertebral canal. A small tuberculous focus that does not interfere with the integrity of the meninges will, as a rule, give rise to no abnormalities in the cerebrospinal fluid; on the other hand, if great swelling and cord compression is produced, the fluid will be altered and will show an excess of protein matter (globulin?) and also a few cells. Not until a meningitis is produced will the fluid show a pathologic or a hyperlymphocytic count. In one case, described under the head of Hypertrophic Laminated Spinal Pachymeningitis, the etiologic factor was most likely a tuberculous focus in the vertebræ, and the laminated structure in that case could be regarded as a means of protection against invasion by the tubercle bacillus. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. + or −; Pl. −; Feh. +.

Tumors of the Spinal Cord.—Strictly speaking, any factor that is capable of exerting pressure on the cord shows the serology commonly encountered in tumors. New-formations in this region may be either extradural, intradural, or intramedullary. If the tumor is large enough to produce complete occlusion of the spinal sac below, the cerebrospinal fluid will be very scanty and at times no fluid at all will be obtainable.

Intradural and extramedullary tumors, as well as extradural new-formations, give rise to a paradoxic reaction in the cerebrospinal fluid; in 70 per cent. of cases analyzed by me a great excess of protein matter was obtainable. The reaction was so marked that a 1:5 and even greater dilution gave excessive response. Regardless of the great protein excess, a pleocytosis was but rarely encountered, and never exceeded the border-line count. In one case of gumma of the dorsal cord the cerebrospinal fluid likewise gave a positive Wassermann reaction. This patient showed 14 cells per c.mm.

Of the 31 fluids analyzed, 8 showed a xanthochromia

(citron-yellow color); 6 of these proved to be endotheliomata, and the yellow color of the other two was probably due to hemorrhages in tumors with cystic degenerations. It is possible, too, that the needle used in making the lumbar puncture may have entered one of these cysts.

In one of these two cases a few cells were observed that carried blood-pigment, as determined by the iron reaction; a similar result was obtained with the cerebrospinal fluid. The operation in this case revealed an intramedullary growth, with abundant hemorrhages, and cells that contained the same iron-reacting substance as was obtained by the puncture.

In one case of cord tumor with yellow fluid the liquid congealed in the test-tube and had the appearance of a thin pellicle which could be removed without destroying its contour. Of the above 8 cases with yellow fluid, 2 showed no reduction of Fehling's solution. The reaction of a protein excess without a pleocytosis is very characteristic of cord compression. The same serologic findings were, however, obtained in other diseases. (See Combined Sclerosis, Disease of the Cauda Equina, Syringomyelia, Spondylitis Tuberculosa.) The two last-named conditions may be regarded as productive of mechanical cord compression.

The question of treatment depends greatly upon the etiology of the new-growth; if the globulin excess is accompanied by a pathologic cell count and a positive Wassermann, as well as by a history of specific infection, the patient is to be given a course of antiluetic treatment. Where the diagnosis of an extramedullary growth is fairly certain and the subjective symptoms are very distressing, it is perhaps advisable to proceed surgically at once, and take up the treatment with specifics later.

It is a very dangerous procedure to attempt to remove tumors situated in the upper cervical or lower medullary region. The resulting edema and congestion, and at times post-operative hemorrhage, are fatal. Nevertheless, I know of at least three patients in whom an operation was performed in this region; in one of these an intramedullary growth was removed and the patient is doing well after three

years. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. ++ or −; Pl. −; Feh. + or −.

Disease of the Cauda Equina.—The cauda, being subject to the same diseases as the upper cord, will also show the same serology. In two instances in which the diagnosis of tumor was made and no growth was found at operation, the cerebrospinal fluid gave the reaction of a protein excess. The examination of the cauda showed a mild form of neuritis of the roots. No cells were found in the fluid. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. + or −; Pl. −; Feh. +.

Tumors of the Spinal Column.—Unless the contents of the vertebral canal are encroached upon, the serologic findings will be normal. Metastatic foci may produce sufficient irritation to produce the serology of a meningitis. It is sometimes possible to detect the nature of the malady by discovering atypical cells, which, together with other suggestive signs, should make one apprehensive of a metastatic process. The pressure of a growth of the bodies of the vertebræ may or may not give an excess of protein. If this is present, however, it favors the diagnosis of such a metastasis. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

NERVE AFFECTIONS

Multiple Neuritis.—*Alcoholic.*—In this form of neuritis the findings are at times so suggestive of locomotor ataxia that the term "pseudotabes alcoholica" seems to be justifiable in such cases. Even with extraordinary precautions it is sometimes very difficult to differentiate between this disease and neuritis alcoholica multiplex. It is needless to state that the typical cases are not included in this discussion.

In my laboratory it was not infrequently my task to decide for or against the existence of tabes, and sometimes even to take a stand against the diagnosis of the latter disease. I remember a case in which the history given by the patient was highly suggestive of lues, and the patient was, besides, decidedly alcoholic. The serology was entirely negative, and

a more complete analysis of the case proved the correctness of my contention. Such occurrences are not common, but they are, nevertheless, liable to arise in any well-equipped hospital. In this connection one must be particularly cautious not to consider a case presentation complete until a serologic report has been received, especially when the patient, in addition to his polyneuritic symptoms, shows also a mental disorder, as is the case with the Korsakow symptom-complex. A negative serology in such a patient is strongly suggestive of a non-luetic disease. In the latter disease, however, one may occasionally encounter a border-line cell count, and with it also a slight excess of globulin; more often the serology is negative.

The serology depends entirely upon the distribution of the pathologic process; it is by no means settled that the neuritides are affections confined to the peripheral nerves; it is not an unusual occurrence to find, with the pathology of the peripheral nerves, an ascending process in the ganglia, roots, and tracts which may be responsible for the abnormalities encountered in the cerebrospinal fluid. The importance of a positive Wassermann in this connection is self-evident, particularly if obtained on the spinal fluid; if obtained on the serum, its value is questionable.

I do not wish to convey the impression that the laboratory possesses a means of excluding tabes, even if the picture is not classic for this disease. It must be remembered that in tabes one may find a negative serology, as will be shown later, and to exclude this disease on the evidence of a serologic report is certainly not advisable. Although the difficulties are many, it is an extremely rare coincidence to find a patient who presents doubtful symptoms of locomotor ataxia, denies syphilis, admits alcoholism, and presents a negative serology without having been previously treated. In view of the facts presented above, it is, in my opinion, safe to exclude tabes, and search for other signs suggestive of some clinical entity other than locomotor ataxia. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Lead Neuritis.—In this disease the serology is absolutely normal, at least so far as I was able to ascertain. The mor-

phologic study of the red blood-corpuscles is a very useful guide in confirming the history and the clinical findings. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. − Feh. +.

Diphtheric Neuritis.—In two cases the cerebrospinal fluid showed no changes from the normal. The blood was negative to the Wassermann test; in one case the father of the patient had an infection.

Several workers found that the spinal fluid of some patients with a post-diphtheric neuritis showed a border-line count and an excess of globulin, and that this would disappear as the neuritic process subsided. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Diabetic Neuritis.—The spinal fluid occasionally shows an excess of glucose. Acetone may also be determined by the iodoform test. Some authors claim to have obtained diacetic and even oxybutyric acid reactions. In the terminal stages of the diabetic process it is possible to obtain all substances resulting from an insufficient catabolism of carbohydrates. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. − Feh. +.

Herpes Zoster.—The herpes occurring occasionally during salvarsan administration will not be considered here. The various forms of zoster having a posterior ganglionitis as their pathologic basis show an increase of cells in the spinal fluid. In those cases where a cell count of over 30 cells per c.mm. is obtainable the fluid may also give the reaction of a globulin excess. Fehling's solution is always reduced. The pleocytosis in this disease will frequently remain some time after the clinical signs have disappeared. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. + or −; Feh. +.

MISCELLANEOUS AFFECTIONS

Functional Nervous Disorders

Hysteria.—Hysteric attacks occurring in a patient who has come in contact with syphilis will, of course, give a positive Wassermann reaction in the serum, depending upon

the length of time that has elapsed since the last antiluetic treatment. The cerebrospinal fluid is entirely normal, even in those who suffer from a coincident systemic lues. After a severe attack the pressure is frequently increased. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Neurasthenia.—Some laboratory workers accept without question a positive Wassermann report on a cerebrospinal fluid that shows no other abnormalities. If the patient is suffering with a severe neurasthenia, he is unnecessarily doomed to years of treatment that, besides being unpleasant, may tend to aggravate his nervous condition. When, pending the report from the laboratory, the clinician has made a tentative diagnosis of severe neurasthenia, and the report of a positive Wassermann reaction on the cerebrospinal fluid is received, all doubt in the clinician's mind is dispelled and the patient is treated as is any other sufferer with neurologic syphilis. This state of affairs is still more aggravated if the patient had the misfortune to contract syphilis in addition to developing neurasthenia. The admission of an infection, together with the clinical signs and a positive Wassermann on the cerebrospinal fluid, although faulty, is sufficient to bias the diagnostic opinion of even the best physician. The possibility of an infection with syphilis in a true neurasthenic must be admitted; this, of course, could make his serum react in a positive manner to the Wassermann test, but it could never affect his cerebrospinal fluid so as to make it resemble the typical serology of a general paresis or cerebrospinal syphilis. It is well to emphasize again the fact that the laboratory should make it a rule not to report too many positives, or, as was pointed out in a previous section on the Attitude of the Serologist, the error committed in reporting a syphilitic as having a negative Wassermann in the serum is of much less consequence than to return a positive report on a patient who has never come in contact with lues. To report a positive Wassermann on a cerebrospinal fluid from a patient free from lues is inexcusable, more especially if the fluid shows no other abnormalities, such as an excess of globulin and a pleocytosis.

Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Psychasthenia.—The spinal fluid and serum show no deviation from the normal.

Psychoneuroses (Anxiety, Compulsion).—In one case of compulsion neurosis an increased pressure was observed. The serum reaction and the other cerebrospinal fluid reactions were normal. Syphilitic patients will give a positive serum Wassermann. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Spasmophilic States

The Epilepsies.—The field of idiopathic epilepsies is being gradually narrowed down to a small number of cases in which no changes in the central nervous system could be demonstrated postmortem. The development of our knowledge of internal secretory disorders makes it possible for us to treat some clinical manifestations that resemble to a marked degree the symptoms of the genuine disease, without exhibiting morphologic changes in the brain. In these so-called idiopathic epilepsies one or the other of the glandular extracts, as the case may be, will influence the convulsions in a way that will ultimately establish a definite opotherapy for these conditions, and the designation of "idiopathic" will sooner or later be discarded in these cases. I do not, therefore, speak of the disease in the singular number, but in the plural, being convinced that there are spasmophilic states that resemble very closely genuine epilepsy having pathologic changes in the brain, and that whereas treatment with organic extracts proved of great benefit in some of these cases, I believe they are caused primarily or indirectly by a disturbed equilibrium (oversecretion, undersecretion, or perverted secretion) in one or more of the glands having an internal secretion.

Serologically, there is very little of great moment in connection with the epilepsies. Recent studies of this disease tend to lay great weight on the significance of the increased pressure of the cerebrospinal fluid. This increase of pressure, however, is to be obtained after any great muscular exertion,

and particularly after convulsions. In genuine epilepsy one rarely finds an abnormal cerebrospinal fluid, although the presence of albumin, a globulin excess, and a border-line count were reported. In my experience, 4 out of 38 sera from epileptics gave a positive serum Wassermann reaction. The Wassermann reaction on the cerebrospinal fluid was negative in every instance, the original Wassermann method being used. In one case with a positive Wassermann reaction in the serum the cerebrospinal fluid also showed 23 lymphocytes per c.mm. The etiologic factor in this instance was most likely syphilis. In another case with a positive Wassermann the symptoms disappeared entirely after antiluetic treatment; the positive Wassermann, however, remained unchanged. The reaction was performed three times with the same result. In one instance the positive Wassermann was most likely an error. That syphilis plays an important rôle in some epileptics must be conceded, one of the cases just described being most likely an instance of epilepsy on a syphilitic basis. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. − Feh. +.

Chorea.—The various choreas of childhood or of adult life present little of interest serologically. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Paralysis Agitans.—Some authors have found an excess of protein in the spinal fluid. In a number of typical cases of Parkinson's disease no abnormalities could be detected. The calcium metabolism of one patient showed no deviation from the normal, and the spinal fluid was normal in every respect. In one patient a positive Wassermann on the serum was obtained on two occasions. In another patient the mineral chemistry of the cerebrospinal fluid showed no deviation from the normal control. In all, 14 fluids from such cases were analyzed by me. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Paramyoclonus Multiplex.—In one instance of this very interesting disease analyzed at the Neurological Institute the findings were in every way negative. It is not amiss here to mention a case observed in the Montefiore Home, that developed after surgical interference with the thyroid gland.

It is probable that in this case the parathyroids were affected by the procedure. Feeding with raw thyroid gave no relief. So far as I know no serologic work has been done on the disease.

VASOTROPHIC DISORDERS

Symmetric Gangrene (Raynaud's Disease).—In 2 out of 6 cases a positive Wassermann was repeatedly obtained on the serum. Although both patients denied having knowledge of the infection, both promptly improved after mercurial treatment. These patients showed an absolutely normal cerebrospinal fluid. The other patients were likewise in every way normal serologically. Of the latter group, two received very small doses of thyroid extract, with markedly beneficial results. Although this work is not a treatise on therapeutics, I would, nevertheless, in view of the gratifying results obtained, mention this fact here, with the hope that other suitable cases of this disease will be studied and treated in a similar manner. In one patient especially the results were particularly interesting; this patient was about to have his leg amputated (the other having been amputated before), but at the last moment he refused surgical interference. This patient was one of the two mentioned above as having improved so much that he walked out of the hospital, using the leg that was to have been removed with great ease. Average formula: S.: W. R. + or −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Scleroderma.—I had the opportunity to analyze 7 cases of this clinical condition. Four were being treated by the late Dr. Sigmund Lustgarten. It is a very interesting fact that every serum analyzed gave a positive Wassermann reaction. Three patients had their serum analzyed more than once, with the same result. In every instance the patient denied knowledge of the infection, nor could other luetic manifestations be detected in any of them. Although antiluetic remedies were tried in 4 cases, not the least change for the better followed. The Wassermann reaction was also studied after the mercurialization, without any abatement of the former intensity. The cerebrospinal fluid studied in two cases gave no deviation from the normal. I believe, from

the foregoing studies, that we are dealing with a clinical condition that is capable of giving a positive Wassermann reaction without being in any way related to syphilis. In one patient in whom a tentative diagnosis of scleroderma was made and was later changed to one of arteriosclerosis, the Wassermann reaction was negative. Average formula: S.: W. R. +; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Erythromelalgia.—In two instances the serology showed no deviation from the normal. In a third the condition was an accompaniment of tabes; this will be discussed further on under the consideration of Luetic Diseases. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Acroparesthesia.—This, as well as the condition just considered (erythromelalgia), cannot, properly speaking, be regarded as a particular disease having a definite pathologic basis. The serology in two instances analyzed by me was normal.

Disorders of Internal Secretion

Myxedema.—In two cases the serum was negative to the Wassermann test. The spinal fluid was not analyzed. Halliburton had the opportunity of studying a fluid from a case of myxedema, and states that he could not find mucin. Whether the substance present in the subcutaneous tissues of the myxedemic is true mucin is a point that has not been settled.

Exophthalmic Goiter.—In one instance giving a history of lues a positive Wassermann was obtained in the serum. In 5 others without any luetic manifestations and a negative history the Wassermann in the serum was also negative. The spinal fluid was not studied, as it was considered unsafe to perform a lumbar puncture in these patients.

Acromegaly.—In acromegaly, as well as in gigantism, the serology as obtained by me was normal. In one instance of dystrophia adiposo-genitalis (Fröhlich) with syphilitic involvement of the pituitary gland I had the opportunity to study the serology before and after treatment. The positive Wassermann gradually disappeared in the serum, and the spinal fluid remained the same as before treatment, *i. e.*,

normal. The hemianopsia, as well as the adiposity and the third nerve involvement, improved markedly.

According to Cushing, the hypopituitary individual shows an increased tolerance for levulose. In the Neurological Institute it is customary to administer to patients suspected of having this condition 1.3 gm. of levulose for every pound of weight of the individual. The urine is collected in separate marked containers, and the time of the appearance of the carbohydrate is observed. In a patient with a normal tolerance a distinct reduction of Fehling's solution should be obtained after the ingestion of this quantity of levulose. When the posterior lobe of the pituitary is involved in a pathologic process (posterior pituitary insufficiency), much larger quantities can be metabolized than those mentioned—1.3 gm. for every pound body-weight of the patient.

Mestrezat observed a case that showed the clinical picture of acromegaly in a patient with an ovarian cyst. The fluid gave a strong reaction with Fehling's solution and the pressure was increased. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

Addison's Disease.—The cerebrospinal fluid and the serum are normal. Bousquet and Derrien found acetone in the cerebrospinal fluid of a patient with this disease. The urine also showed a marked excess of acetone. The condition was fatal.

Myasthenia Gravis.—As some observers believe that the malady is the result of impaired thymic function, it may properly be considered here. In two patients the serology was entirely normal. In one of these metabolic studies revealed nothing unusual. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

THE PSYCHOSES

Constitutional Inferiority.—Since the perfectly normal man is very rare indeed, and as a standard of perfection has not as yet been established, a large number of human beings might be included in the class of inferiors. Kraepelin makes a distinct division between the insanities proper and

the types of disorder classified under the head of constitutionally inferiors.

In a paper entitled "A Consideration of Constitutional Inferiority" by H. W. Wright the subject is presented in a concise and comprehensive manner. The classification as offered by him, and quoted here with the author's permission, is as follows:

1. The Psychogenic Neuroses—(*a*) Hysteric psychoses; (*b*) apprehensive neuroses; (*c*) expectation neuroses.
2. Original Traits—(*a*) Neurasthenia; (*b*) constitutional pessimism; (*c*) constitutional irritability; (*d*) compulsive insanity; (*e*) erythromania; (*f*) impulsiveness; (*g*) sexual anomalies.
3. Psychogenic Personality—(*a*) Congenital criminality or moral insanity; (*b*) insanity of the emotions; (*c*) dipsomania; (*d*) habitual criminality; (*e*) morbid lying, morbid faking; (*f*) querulousness, habitual doubting.
4. Arrested Mental Development—(*a*) Idiocy; (*b*) imbecility.

In this broad grouping may be placed the backward schoolchild, whose condition has attracted a great deal of attention, particularly from the standpoint of therapy. Among specimens of inferiority may be included the habitual truant, the vagrant, the hobo, the tramp, the "Jack-of-all-trades," as well as the street tough and his gang.

The importance of the foregoing résumé of the classification of constitutionally inferior individuals becomes apparent when one takes into consideration the possibility of the development of a true deteriorating psychosis on the basis of the psychopathic constitution. This subject was covered in a masterful way by Dr. S. E. Jelliffe in his consideration of "Predementia Præcox" states.

The manifestation of these abnormalities depends upon two factors: first, defects of heredity; second, environment. In this exposition of the subject the hereditary factor will receive closer attention, as the serology of these defectives is frequently altered by hereditary antecedents.

The entire question resolves itself into the possible syphilitic factor which may have been responsible for the inferiority, and recently, also, attention has been directed to the influence internal secretory abnormalities may exert on certain predisposed individuals. The significant observation of Alzheimer, that juvenile paresis not infrequently develops in the course of inferiority on a constitutional basis, shows that syphilis in these cases must be the causative factor not only of the paresis, but perhaps also of the preceding psychosis. At least serologic investigations point very significantly in that direction. In 12 per cent. of my cases a positive serum Wassermann was obtained. The cerebrospinal fluid was analyzed in 8 instances, and, with the exception of one case, were all negative. The single exception gave 21 cells per cubic millimeter, a normal globulin content, and a negative Wassermann reaction. The value of the negative serum Wassermann in this instance is only of secondary importance. The history of the parents is much more significant, regardless of the negative result. Fournier speaks of another class that may properly be included in this consideration; these children he terms as "les enfants arrières"; in them slowly developing mental and physical defects manifest themselves in the developmental period. In these children dentition is delayed, they begin to talk late, are poor scholars, have a small vocabulary, and possess a poor memory. As they grow up they are far behind their companions, "toujours en retard," and although displaying here and there useful capabilities, they are lacking in originality, progressiveness, and brilliancy. They are not necessarily idiots or imbeciles—their somatic and psychic make-up does not permit of such a designation. Syphilis cannot infrequently be held responsible for the defect, and at times can be demonstrated physically (teeth, nose, glands).

That internal secretory disturbances produce psychic manifestations which most likely belong to the same group of cases as those classified under the head of Constitutional Inferiorities is becoming more evident, since completer studies of these secretory disturbances can be found in the literature. In Cushing's book on the pituitary gland one

meets with distinct types of mental inferiority where this gland is affected. I saw two cases of such deterioration in juvenile acromegalics. I also noted a hypothyreoid complex in two brothers, aged eight and ten years respectively, who were backward in school and showed a spastic gait and a low blood-pressure. Thyroid medication removed these stigmata of inferiority in a very short time.

The serology of this entire group can be summed up under two headings: First, those who give a positive serum Wassermann, whose parents deny an infection, and who give a negative Wassermann in their serum. Second, those whose parents admit an infection and whose serum is negative. The spinal fluid is but rarely involved, but an analysis of this fluid should never be omitted when practicable.

As regards the treatment, one should take into consideration the fact that it is possible for paresis to develop in those cases in which syphilis can be held responsible for the occurrence of the disease. Where the Wassermann proves positive, treatment should be instituted to remove the cause as soon as possible, and repeated analyses be made to detect any symptoms of a recurrence.

Idiocy and Imbecility.—That some cases of feebleminded-ness occurring in younger years depend upon a hereditary syphilis must be admitted, although most children who are effected by an extensive luetic cerebral process prenatally, as a rule, succumb to the marasmus produced by the infection. Only where the luetic process is so mild as to spare the life of the child do we in later years find the landmarks of mental enfeeblement known as idiocy or imbecility. It is not essential for the hereditary signs of lues to manifest themselves in the form of somatic symptoms; the display can be and often is, purely psychic. Where one is able to demonstrate pupillary abnormalities, the somatic factor alone is sufficient evidence of the cause of the trouble. Serologic investigation, however, should take in the systematic study of serum and, where feasible, also of the spinal fluid of the patient and parents. Plaut went even so far as to examine the brothers and sisters of the patient, and reported very important findings.

That such analyses will in the future give the therapeutist much concern is not to be denied, for the problem in a child with an idiotic mentality with a history of lues in the parents and a positive Wassermann in the serum of the patient will possibly require the treatment of the entire family, including the patient. Only in such a manner can prophylaxis be established, and the further mental deterioration of the imbecile child checked. A few very interesting case reports are to be found in the above-mentioned book of Plaut (see Literature). The material analyzed at the Neurological Institute disclosed the relationship of the syphilitic factor in the parents and child in very few instances. Very pronounced defectives were studied, as well as those who gave only slight symptoms. In the former a positive Wassermann could be obtained in the serum, but not in the cerebrospinal fluid. Where the fluid was also positive to the Wassermann test and showed a mild pleocytosis, the disease was considered as juvenile paresis and will be given in a separate paragraph.

There is no denying the fact that in the future serologic methods will shed a light not only on the etiology, but also serve as a guide to the best form of treatment. Systematic serologic analyses on inmates of institutions for mental defectives will, in the course of time, give sufficiently encouraging results to justify not only the establishment of serologic stations as a part of equipment of such institutions, but every child, before being admitted to these institutions, will be required to present a certificate from a competent serologist as to the existence or non-existence of a positive Wassermann reaction, and perhaps a study of the cerebrospinal fluid.

ORGANIC PSYCHOSES

Senile and Presenile Dementia.—As a terminal stage, and as an accompaniment of a more or less generalized arteriosclerosis, and never associated with syphilis, dementia of the aged is a disease possessing a negative serology. Although this condition may be included under the next subheading, it seems to me to deserve a place for itself. This is particularly true of cases of presenile dementia, since the studies of Alzheimer made it a clear clinical and pathologic

entity. Average formula for both: S.: W. R.—; C. S. F.: W. R.—; Gl.—; Feh. normal.

Psychoses Accompanying Organic Brain Diseases (Non-luetic).—This varied group of psychoses, so far as the serology is concerned, depends upon the factor producing the mental abnormality. We are, therefore, confronted with the findings that are obtainable in brain tumors, in brain abscesses, in cerebral hemorrhages, and in extensive cerebral arteriosclerosis. Besides these pathologic factors we must also consider the psychosis that is at times observed in multiple sclerosis. In the order mentioned, we occasionally find, in the serology of brain tumors, a pleocytosis; this, of course, depends upon the location of the tumor, which, in order to furnish a pleocytosis, must be close enough to the meninges in order to produce the necessary irritation. Next to be considered are the various abscesses, which may or may not give a pleocytosis, all depending upon location, extent, and integrity of the abscess-wall.

The simple arteriosclerotic forms give an absolutely negative serology. The psychosis that is at times an accompaniment of multiple sclerosis gives a negative serology. The globulin is, as a rule, within the normal, and Fehling's reduction is always prompt. In hemorrhage of the brain one is occasionally able to demonstrate altered blood constituents, and sometimes even the unaltered cells themselves.

The Wassermann reaction, where a visceral syphilis is present, will sometimes be found to be positive in the serum. In the cerebrospinal fluid the Wassermann is always negative, except for those peculiar findings in which large quantities of fluid were used and resulted in positive Wassermann reactions in some cases of undoubted multiple sclerosis. This could never occur where proper technic and the standard Wassermann were employed.

FUNCTIONAL PSYCHOSES

Manic Depressive Insanity.—Whether during the manic stage or during the depressed period, one rarely finds abnormalities in the cerebrospinal fluid. Syphilis of the other organs may be an accompanying feature and give a positive

Wassermann in the serum; the fluid, however, is always normal. If obtained after an acute maniacal attack, the pressure may be increased; the chemical and biologic findings, will, however, be normal. Certain mental phases of this disease may resemble certain psychic disturbances obtained at times in general paresis; this coincidence is discussed in the section on General Paresis, where the required information as to the serologic differentiation can be found.

Dementia Præcox.—The various forms of this disease (hebephrenic, catatonic, paranoiac) present, as a rule, a negative serology. Syphilis may enter as a complicating factor in some instances, and give a positive Wassermann reaction in the serum. This disease may also, in one of its manifestations, give rise to an uncertainty in the final differentiation between it and general paresis; a discussion of this will be found under the head of the latter disease.

I have collected the records of a number of cases of dementia præcox who were infected with syphilis, and hence gave a positive Wassermann reaction in the serum. The question of general paresis did not enter into the consideration of the diagnosis, as the clinical picture in these instances did not present diagnostic difficulties. Average formula: S.: W. R. —; C. S. F.: W. R. —; Gl. —; Pl. —; Feh. normal.

Anxiety Depression.—Here the serology is usually negative, except in the presence of lues of the viscera.

Paranoid States.—Very little is known of the serologic status of this disease. A few cases of this condition were analyzed and showed a negative serology in the serum and fluid.

TOXIC PSYCHOSES

Acute Alcoholism.—This mental derangement occurs as the result of an acute exacerbation of a more or less chronic condition. Besides this, it is possible for an acute alcoholic hallucinosis to develop in cases without a background of chronic alcoholism, occurring in an individual whose tolerance for alcohol is below the average, and one who has not been addicted to the prolonged use of alcoholic beverages. Occurring as a pure, uncomplicated toxic psychosis, the serology is correspondingly negative. With the aid of the

iodoform test Schottmüller and Schumm demonstrated, in acute alcoholism, appreciable quantities of aldehyd. This fact reflects greatly the degree of injury to the meninges caused by the overuse of alcohol.

Chronic Alcoholism.—The serology of this condition is negative.

The Korsakoff Syndrome.—This mental derangement is not necessarily due to alcoholic abuse alone; it may develop as the result of any intoxication, and may or may not be accompanied by polyneuritic manifestations. The term is not to be applied exclusively to those forms of toxic psychoses that are associated with nerve involvement, but is also applicable to a pure psychosis without such accompaniment. As it is at times difficult, in certain cases of this psychosis, to differentiate between this and general paresis, the importance of serologic aid will become apparent, as this alone can definitely decide the question. The differentiation will be described in the section on General Paresis. The real difficulty arises when a coincident visceral syphilis complicates the toxic psychosis. Here very careful weighing of the individual clinical and laboratory data are necessary in order to avoid error in the diagnostic interpretation of the complex. In such cases the serum, if positive, will have to be judged not only by the fact that it is positive, but the degree of inhibition and other characteristics of a positive serum reaction will have to be considered before the possibility of general pareis is excluded. This difficulty is only partially removed by a contemporaneous study of the cerebrospinal fluid. The finding of negative fluids in general paresis is by no means an impossibility, although their occurrence is rare. Average formula: S.: W. R. — ; C. S. F.: W. R. — ; Gl. — ; Pl. — ; Feh. normal.

Lead Psychosis.—This psychosis may present acute and chronic manifestations. The diagnosis is not furthered by a serologic investigation, as the cerebrospinal fluid in 2 cases of the chronic form showed no deviation from the normal findings. The presence of lead could not be demonstrated by Bernard and Troisier in a case of chronic plumbism. The diagnosis can be facilitated considerably by a mor-

phologic study of the red blood-corpuscles, which in such cases will frequently show the characteristic basophilic granulations.

Coal-tar Psychosis (After Prolonged Use).—After the use of large doses of antipyrin and acetanilid a patient developed an acute mania which gave place to a coma that lasted for ten days. After eliminative treatment the condition disappeared completely. The serology of the serum and fluid was entirely negative.

Morphin Psychosis (After Prolonged Use).—The serology is entirely negative.

Infective exhaustive psychoses occurring in the course of—

Tuberculosis.—For the occurrence of a psychic derangement in the course of tuberculosis (pulmonary, miliary, etc.), it is not absolutely essential for the tubercle bacillus to involve the meninges. Hence the finding of the bacillus in the cerebrospinal fluid is to be included among the exceptions, rather than among the expected findings. When these bacilli are demonstrated in the fluid during the course of a pulmonary tuberculosis, the aspect of the clinical condition becomes altered at once, and the gravity of the situation is correspondingly increased. Such a psychic derangement requires considerable diagnostic acumen in order to be able to differentiate between that which is exhaustive and that which is caused by the meningeal involvement by the tubercle bacillus. It is, perhaps, better judgment to consider the psychic disturbance in such a coincidence as a product of the activities of both factors—infective and exhaustive. With the exception of cases with meningeal involvement, the serology is negative.

Typhoid.—On several occasions the bacillus of Eberth was demonstrated in the fluid from patients with this affection. The psychosis that at times accompanies this disease may make manifest the presence of the bacterium in the fluid without increasing the dangers. Patients who gave positive morphologic and cultural evidence as to the presence of this bacillus in the cerebrospinal fluid showed in most instances no appreciable pleocytosis, nor were other cardinal signs of a meningitis found. It is more likely that

the phenomena responsible for the psychosis, when present, are purely chemical; in other words, the absorption of toxins is responsible for the patient's deranged mentality. These toxic substances, again, are not necessarily entirely the by-product of the life of the bacillus; it is highly probable that the increased metabolism of the febrile state is in itself capable of giving rise to a deranged mental activity as a result of the absorption of body toxins.

Postpartum Infections.—These infections are very prone to give rise to meningeal irritations, and, when present, will give the serology of a meningitis. On the other hand, chronic postpartum infections, those that, as a rule, do not prove fatal in a week or two, may give rise to a psychosis that, from an etiologic point of view, is purely exhaustive, and directly dependent upon the original infection of the birth-canal. So far as I was able to ascertain the serology of these latter cases is entirely negative.

Traumatic Psychosis.—The proper interpretation of this clinical condition gives rise at times to considerable trouble. The correct diagnosis can still further be deferred by the coexistence of syphilis with a psychosis caused by physical trauma. In such a case the positive serum Wassermann with a few cells in the cerebrospinal fluid (border-line count) is frequently sufficient to mislead the most skilled observer.

I had the opportunity to analyze such patients serologically, some presenting diagnostic difficulties that could not be overcome until a prolonged observation cleared up the doubt. Three patients presented the following findings:

A commercial man of forty-two, married; wife had two miscarriages; no living children. Patient sustained an injury to the head as the result of a fall. Upon examination presented lively knee reflexes; left pupil irregular; reactions normal; slight speech disturbance; poor memory as to the circumstances attending his accident, and general restlessness. Admitted lues. The Wassermann in the serum was positive; the cerebrospinal fluid showed a border-line count (12 lymphocytes per c.mm.) and a few degenerated red blood-corpuscles. Globulin, Fehling, and Wassermann nor-

mal. For the Wassermann in the cerebrospinal fluid 1 c.c. was used in order to exclude the chances of a faulty negative Wassermann; in other words, opportunity was offered for the fluid to react positively. The fact that the result was negative with 1 c.c. of fluid put the clinicians on their guard, and the final conclusion arrived at later was a diagnosis of traumatic psychosis and not of general paresis.

In another patient who was thrown from a carriage the following history was obtained: Patient, thirty-six years old, a coal-broker; married; no children; wife had no miscarriages. At nineteen the patient had been treated for some genito-urinary trouble for two years; was given drops and inunctions. Never had an ulcer on the glans. Remembers having a urethral discharge. After the injury patient was comatose for four days. Had bleeding under the conjunctivæ and from the ears and nose. A few months after a more or less complete recovery the patient became absent minded, his attitude toward his family changed, and he became neglectful of his business duties and showed a slight amnesia. The serology in his case was as follows:

Serum Wassermann negative; cerebrospinal fluid Wassermann negative; globulin normal; cells, a few lymphocytes and a moderate number of red blood-corpuscles. It was believed for a time that, in view of the history of two years' treatment and the peculiar change in the entire attitude of the patient, the diagnosis of general paresis would be a plausible one. The negative serology and the subsequent course of the disease showed the true nature of the malady.

In a third patient the following history was obtained: A broker, aged thirty-two, separated from his wife. Patient was perfectly well until October, 1910. Following an accident he became dizzy, had a convulsion, and soon passed into a delirious state, for which he showed an isolated amnesia. When admitted to the hospital (Ward's Island) he was quite elated, had no delusions and hallucinations, was inclined to be talkative, but coherent, and his answers were always to the point. His orientation was good and he showed no defect of memory. He was somewhat expansive,

but there was considerable basis for his ideas, and it was difficult to demonstrate absurdity or fiction.

During his stay in the hospital the patient was quiet and well behaved, but still maintained his former expansive ideas, which were probably exaggerated, but not entirely absurd. He was at all times amnesic for the acute period of his illness. At one time it was thought that the patient suffered from general paresis because of the history of syphilis, coarse tremor of the tongue, and on a previous occasion the limited range of his pupillary reaction; before his discharge his physical status revealed no neurologic abnormalities, and, moreover, fluid withdrawn by lumbar puncture proved negative.

His serology was as follows: Wassermann reaction in serum and cerebrospinal fluid negative; globulin normal; cells, one lymphocyte per c.mm. Fehling's reduction prompt.

The serology in traumatic psychosis, as can be seen from the foregoing exposition, is in itself not always conclusive; it is, therefore, necessary, in some instances, to wait until further clinical signs develop before a final conclusion is permissible. Although the findings are, as a rule, negative, it is frequently possible, in recent and in old traumatic cranial conditions, to demonstrate an increase in the cerebrospinal pressure, with an increased amount of spinal fluid. Although fairly constantly present, it, nevertheless, cannot be considered as pathognomonic of the above-described condition. Average formula: S.: W. R. −; C. S. F.: W. R. −; Gl. −; Pl. −; Feh. +.

INTOXICATIONS

Metabolic.—As a result of changes in the metabolic processes in the body, certain organic substances may appear in the cerebrospinal fluid due to faulty metabolization. We have, therefore, an accumulation of carbamid in uremia; of glucose, acetone, and diacetic acid in diabetic intoxication; of lactic acid in eclamptic seizures, and of bile-products in icteric states.

Uremic.—According to Mestrezat (see Literature), there are two different responses to be observed in the cerebrospinal fluid, which depend upon the renal involvement in

question. In case of mineral impermeability (to chlorids), an accumulation of chlorids in the body causes, besides the classic anasarcas, an appreciable increase in the chlorid content in the cerebrospinal fluid, without a corresponding increase in the urea content. The cases that present a renal impermeability to nitrogen, with an accumulation of nitrogen products of an excretory nature in the body, are the forms of renal insufficiency that give rise to uremic states. The physiologic limit of the urea content in the cerebrospinal fluid is 1 gm. or less per 100 c.c., hence the urea content of patients who are on the verge of or are undergoing a uremic attack may show 2 or more grams. The cases cited by this author are as follows:

Delirium in an arteriosclerotic patient, urea in cerebrospinal fluid	1.22 per cent.
Coma, alcoholic Bright's	1.50 "
Delirium, epileptic seizures in old hemiplegic	2.31 "
Coma in an arteriosclerotic	2.57 "

In 25 autopsies without involvement of the sensorium, with and without renal symptoms, the highest amount found was 0.95 gm. of urea per 100 c.c. of fluid. Widal and Froin were able to demonstrate as much as 4.5 per cent. of urea in the fluid of a patient with nephritis and in a uremic attack. Mestrezat is of the opinion that a cerebrospinal fluid with a urea content of 3 per cent. or more, associated with a uremic state, is of the gravest prognosis, ending, as a rule, in death. The remaining serology is generally negative, with the exception of those cases complicated by syphilis.

Diabetic.—In two cases of diabetic coma I was able to demonstrate acetone in sufficient quantity to give the iodoform reaction. After rallying slightly both patients died. The quantity of glucose in the spinal fluid is correspondingly increased, and may show as much as 18 gm. of this substance per liter of spinal fluid. The increase of this substance in the spinal fluid may be caused either by the hyperglycemia and increased permeability of the choroid plexus, or by a disturbance of the glycoregulatory apparatus. Diacetic acid is obtained rarely, and when found, signifies a profound intoxication.

Eclamptic.—In this condition the findings in the cerebrospinal fluid reflect greatly upon the rôle played by the renal integrity. The increase in chlorids found in the eclamptic states is similar to some forms of spinal fluid findings associated with anasarca. Besides this, various authors claim to have found appreciable quantities of lactic acid. For the detection of this substance Reichmann suggests the following method: 10 c.c. of the spinal fluid are treated with 5 parts of 95 per cent. alcohol. This is permitted to extract for twelve hours, and is then filtered and the residue washed with hot water repeatedly. The alcohol extract is collected *in toto* with a little hot absolute alcohol; this is filtered, the filtrate is condensed on a warm water-bath to dryness, and the residue treated with 3 drops of $\frac{1}{10}$ normal H_2SO_4; to this is added about 10 c.c. of ether and the mixture vigorously shaken. To a very dilute solution of Fe_2Cl_6 (one drop of the iron chlorid solution to 20 c.c. of water) in two test-tubes (one as a control) add the ether extract to one of them. If lactic acid is present, the solution in the test turns a pale yellow, showing a distinct difference as compared with the control tube.

Icteric.—The chief change in the spinal fluid, as well as in the serum, is in the color. Besides this, with proper chemical tests, one may find one or the other constituent of the bile. The most interesting, and, from a serologic point of view, the most important, occurrence is the behavior of sera from jaundiced patients to the Wassermann reaction. It is by no means rare to obtain a positive reaction in patients suffering from profound hepatic involvement without giving the slightest cue to the existence of lues. I had the opportunity to follow up such cases to the end without having been able to demonstrate postmortem any of the changes usually obtained with syphilis. This observation suggested to me an experiment which proved to me that the appearance of bile-products in the patient's serum may give rise to a non-specific inhibition. To the serum from a patient who on many occasions served as the negative control I have added gradually increasing quantities of fresh ox-gall. At a certain concentration the reaction proved strongly positive for

twenty-four hours in the incubator. In previous writings I have repeatedly pointed out the possibility of obtaining such a result without syphilis being present. The spinal fluid is less subject to such a pseudo-result, perhaps because the concentration of the bile-products in the cerebrospinal fluid is insufficient to produce this reaction. Colleagues have also related similar experiences, having on several occasions obtained positive Wassermann reactions on sera from patients with carcinoma of the liver. In one of my observations the positive Wassermann reaction appeared after a secondary involvement of the liver by a carcinomatous process, the reaction before this being absolutely negative.

Extraneous.—*Lead.*—The serology of this form of intoxication was practically covered in dealing with lead psychosis.

Mercury.—In acute mercurial intoxication traces of this metal, together with a mild pleocytosis, were found in the cerebrospinal fluid.

Carbon Monoxid.—In a case where suicide was attempted with illuminating gas the serologic analysis showed an increase of albumin in the spinal fluid and a pleocytosis consisting of 80 per cent. of polynuclear elements. Thin filaments were seen in the fluid, suggestive of fibrin. After twelve days the pleocytosis disappeared entirely (Legry and Duvoir).

Atropin.—An excess of albumin was obtained in a case of intoxication with this alkaloid.

Manganese.—A peculiar form of intoxication was observed by Dr. L. Casamajor among men who work in zinc mines. The ore is combined with manganese, which, in the course of separation, exists as a very fine powder. The patients showed, among other symptoms, a gait similar to that of paralysis agitans. The cerebrospinal fluid was entirely negative.

PART III

THE SEROLOGY OF NERVOUS AND MENTAL DISEASES OF LUETIC ORIGIN

TABES DORSALIS

In addition to the individual laboratory findings, the serology of this disease will also embrace the significance and interpretation of the different serum and spinal-fluid phenomena encountered in the various types of syphilitic involvement of the central nervous system. It is perhaps better to discard the old terms, "para" and "meta," as applied to syphilis, and to consider tabes, as well as other nervous diseases caused by the Treponema pallidum, as syphilis pure and simple. Noguchi demonstrated the presence of the Treponema pallidum in the brains of patients with general paresis, as well as in the spinal roots of one patient suffering from tabes.

In the serologic consideration of tabes, particular stress will be laid upon certain phenomena that have proved of great utility from a diagnostic, therapeutic, and prognostic viewpoint. These manifestations will be referred to repeatedly in dealing with this part of the serology of the luetic nervous disease.

For the clinical interpretation of the various neurologic entities of which this section treats I am greatly indebted to the Medical Officers of the Neurological Institute for their hearty coöperation. The routine serologic examinations performed on the great majority of patients who apply to the Institute for medical advice showed that syphilis of the nervous system may exist for many years without being

suspected by the physicians who had previously treated the patient. Vague pains and gastric disturbances are often treated for rheumatism and chronic stomach catarrh, and it is not until the serologic investigation discloses the true origin of the pains and the real significance of the stomach trouble that the etiology becomes clear. Some of these cases were differentiated from non-luetic diseases, at first with difficulty, but when the serology proved to be positive, there was no longer room for doubt. The juvenile form of tabes also offered great opportunity for errors in diagnosis. That syphilitic parents are capable of producing in their offspring unquestionable locomotor ataxia has been proved beyond doubt. The youngest case of tabes observed in the Neurological Institute was in a girl of six.

In the form of tabes which is monosymptomatic the diagnosis without serologic investigation would be made only with extreme difficulty. It seems that spinal fluid changes are almost as constant in tabes as is the Argyll-Robertson pupil or the absent knee-jerks, and it is, moreover, a gratifying coincidence that where the clinical diagnosis is most obscure and difficult, the laboratory is frequently able to furnish weighty evidence. It is needless to say that, so far as the diagnosis of tabes dorsalis is concerned, the laboratory does not play an active part, but it must be remembered that the serologic investigation in tabes is not always conducted for the purpose of clinching the diagnosis, but, on the contrary, from my experience, the reports are more often desired for the purpose of gaging the treatment. Occasionally prognostic suggestions are looked for from the laboratory, or the fluid is submitted for analysis in order to ascertain the possible transition of one luetic nervous disease to another.

The task of establishing types or laboratory standards for this disease required abundant material, and the results obtained had to be grouped together with the clinical diagnoses furnished after the reports were submitted to the physician in charge. These standards or types will be spoken of under the various headings of "usual serologic type," "hyperlymphocytic type," "negative type," etc. In making

this classification no hard-and-fast rules are laid down; the terms "always" and "never" are not used, and it is taken for granted that allowance will be made for exceptional occurrences. It is needless to emphasize the fact that in the compilation and classification of the various standards the greatest number of cases established the "usual serologic type"; that the exceptionally high cell count suggested the "hyperlymphocytic type," etc. The serology of the largest number of cases of tabes is to be observed in the "usual serologic type," which will first be considered.

The "Usual Serologic Type" of Tabes

In by far the greater number of cases of tabes the cerebrospinal fluid gives a negative Wassermann reaction. In speaking of the greatest number of cases, I am considering the results obtained from a study of 425 cerebrospinal fluids from various tabetics. The serum Wassermann is more often positive than negative. The globulin content of the cerebrospinal fluid is generally negative, an excess reaction in this type being seldom encountered. I do not consider those cases that may give a trace of globulin. The cell count ranges from 25 to 95, the two extremes, 25 and 95, being rather the exception than the rule. The majority of fluids gave a cell count that ranged between 37 and 73 cells per cubic millimeter. This observation shows that the serology of the form of tabes which I designate as the "hyperlymphocytic type" may include also specimens that show no globulin excess, as well as a negative Wassermann reaction, in the cerebrospinal fluid, a fact to be remembered when studying the "hyperlymphocytic type." Clinically, there is nothing to mark this serologic form of tabes; in fact, the first intimation that the patient is suffering from this laboratory type of disease is had when the rachicentesis reveals meningeal involvement. It is to be noted that these designations merely express the serology of the malady, which, as a laboratory entity, may have little in common with the evidences observed during the course of the disease, particularly in this type of serum and fluid analysis. The serologic formula of the "usual serologic type" is as follows:

Serum Wassermann Reaction.	Fluid Wassermann Reaction.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Negative.	Normal.	From 25 to 95.	Always prompt.

The cells number 98 per cent. of lymphocytes.

The "Hyperlymphocytic Type" of Tabes

It may generally be accepted as a fact that the more manifest the active evidences of the disease, and the more evident the painful phenomena, the greater is the cell count in the cerebrospinal fluid. This should not, however, be accepted as an invariable rule in the "hyperlymphocytic type" of tabes, for exceptions occur; *e. g.*, very active signs of tabes may occur without a corresponding cellular increase, and tabetics who are comparatively comfortable may show hundreds of cells. As has previously been stated, these designations apply to the majority of observations, and nowhere in this study of the serology of nervous and mental diseases are the terms "always" and "never" made use of. In the majority of instances, where the cell count in the cerebrospinal fluid is high, a positive Wassermann reaction in the serum will also be obtained. This finding, as an accompaniment of the "hyperlymphocytosis," is a fairly constant one—in my experience it occurs in 94 per cent.

With the higher cell counts one also encounters an excess of globulin, all of which point to the existence of a more or less active meningeal process. The spinal fluid Wassermann is positive in about one-half of the cases of this type. The pleocytosis averages, as a rule, less than 100 cells per c.mm., although here and there one may find as many as 200 and even 300 cells per c.mm. These findings are, however, the exceptions, and cannot be regarded as establishing the upper limit of the pleocytosis of this serologic variety of tabes.

Not infrequently one encounters what may be termed the intermediary variety of this form of tabes and the "usual serologic type," the connecting link being the positive globulin findings in the fluid, the Wassermann reaction being

negative in the fluid and positive in the serum. Because of the usually high cell count—over 60—this class of cases may, for the sake of brevity, be included in the "hyperlymphocytic type," with a consequent reduction of the positive fluid Wassermann to 54 per cent. of the cases.

Very exceptionally the pleocytosis may reach as high as 210 and 268 cells per c.mm. These figures represent actual observations on two cases; the serum Wassermann and the fluid Wassermann were positive, an excess of globulin being obtained in the latter. In two other instances the cell count was 192 and 240 respectively, but the fluid Wassermann was negative. The cells encountered were lymphocytes, with an occasional polynuclear or a polymorphonuclear cell. The lower count fluids presented a uniform lymphocytic picture.

The serologic formula of the "hyperlymphocytic type" is as follows:

Serum Wassermann Reaction.	Fluid Wassermann Reaction.	Globulin	Pleocytosis.	Reduction of Fehling's.
Positive, as a rule.	Positive in 54 per cent. of cases.	Excess.	60 to 96 (and more).	Always prompt.

The "Negative Type" of Tabes

The designation "negative type" is applicable to a very small number of cases presenting an absolutely normal serology. In my series only 30 cases gave these findings, which is equivalent to about 7 per cent. of the material analyzed. There are instances, however, that are almost negative, and differ from the absolutely "negative type" in that they present a more or less insignificant pleocytosis,—from 12 to even 32 cells per c.mm.,—the remainder of the serology being entirely negative.

It is well to note at this point that although the "hyperlymphocytosis" may be taken as proof of the existence of a meningeal irritation, the "negative type" serology, on the other hand, is significant of the absence of such irritation, and indicates the existence of a more or less purely degenerative

process. It must be borne in mind that some tabetics with a "negative type" serology nevertheless occasionally present the clinical picture of an active process, particularly pain, and respond readily to proper therapy. Although it may be difficult to reconcile negative serologic findings with a process that indicates an active ganglionitis, it is, nevertheless, plausible to believe that the active process may be confined to a locality which prevents spinal fluid contamination. It may also be possible that the exudative process affecting the ganglion in the intervertebral foramen is prevented from producing a pleocytosis in the cerebrospinal fluid by the formation of a barrier during the process of repair in the course of a previous inflammation. This latter will wall off the laboratory signs of inflammatory manifestations, including the pleocytosis, from the subarachnoid space. Thus may be explained the presence of active symptoms in a patient whose fluid presents a moderate cellular increase or even no increase at all. On the other hand, the nervous elements between the bony walls of the foramen and the nervous structures contained therein are so closely crowded that but little exudation or other inflammatory manifestation is necessary to produce pressure and, hence, pain.

The pleocytosis seen in herpes zoster rarely gives more than 40 or 50 cells per c.mm., and, furthermore, the absence of a cellular increase in this malady is of very frequent occurrence. Since more elaborate anatomic studies are lacking, one may select any of the contentions just set down or formulate another for himself as experience may teach.

The "relatively negative type" of tabes presents a borderline cell count, and may occasionally show but 25 cells per c.mm. Here and there I observed what may be considered the upper cell limit of this type, and counted 30 and 32 cells. The remainder of the serology is entirely negative. This "relatively negative type" was obtained in 21 per cent. of the cases studied. There is another variation of serology which shows a negative Wassermann reaction in the serum, a positive reaction in the cerebrospinal fluid, a normal globulin reaction, and a pleocytosis of from 20 to 50 lymphocytes per c.mm. This variety is obtained chiefly after treatment,

and, as will be shown later, presents a phase in the methodic negativation of the positive serologic picture in the course of its conversion to the "absolutely negative type."

The serologic formulæ for this form of tabes are as follows:

THE "ABSOLUTELY NEGATIVE TYPE"

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Negative.	Negative.	Normal.	3 to 8 cells.	Prompt reduction.

THE "RELATIVELY NEGATIVE TYPE"

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Negative.	Negative.	Normal.	12 to 32 cells.	Prompt reduction.

Wassermann Fast Tabes

In speaking of those cases showing great resistance to therapy I refer chiefly to the serology of the serum and only secondarily to that of the cerebrospinal fluid. Further on a suitable case will be described to show the permanency of certain serologic findings, and from this it will be seen that the reverse of the usual behavior of the entire serology takes place as a result of the treatment. A study of the manner in which a serology of the "hyperlymphocytic type" becomes gradually "negative" will disclose the fact that the cells in the spinal fluid are the first to be influenced; the globulin excess and the serum Wassermann are next affected, and become either weakly positive or entirely negative. This is not so, however, with the form of tabes under discussion. Here the cells in the fluid, the globulin, and the fluid Wassermann may become entirely normal, but the positive serum Wassermann remains uninfluenced. It has been maintained that the histologic nucleus about which tabo-paresis gradually develops may be present for a long time before clinical manifestations of the coexistent tabo-paresis become evident. It seems to me that serologic methods will enable

one to demonstrate the coexistence of such conditions much earlier than is possible at times with purely clinical methods. As examples of the condition the following individual cases are offered:

Mr. S. P., August, 1911, tabes. Initial serology as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Excess.	60 lymphocytes.

Following this report the patient was given mercury inunctions, from 2 to 4 gm. every third day. After the administration of 30 inunctions the serology at the end of September was:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Excess.	53 lymphocytes.

After this report the patient received 21 intragluteal injections of salicylate of mercury, and in December the serology showed the following improvement:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Normal.	50 lymphocytes.

In January, 1912, the injection of a full dose of salvarsan was given intravenously. In February the serology showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Normal.	41 lymphocytes.

Since then, until February, 1913, the patient received five intravenous injections of salvarsan, which resulted in the persistence of the positive Wassermann in the serum, the

fluid Wassermann became negative, and the cells fell to 17 per c.mm.

It is not essential for our purpose to start with the serology of the "hyperlymphocytic type"; cases presenting an equally strong resistance to treatment may be taken from the "usual serologic type," as the following case will illustrate:

Mr. St. was treated for three years for a gastric catarrh. Symptoms included Argyll-Robertson pupils, absent knee-jerks, and subjectively gastric crises. The serology performed in March, 1911, showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Normal.	42 lymphocytes.

Patient was given 24 mercury inunctions, and in May of same year showed—

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Normal.	31 lymphocytes.

June 2d he was given an intravenous injection of 0.6 gm. of salvarsan, and a serologic analysis was made. This showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Normal.	24 lymphocytes.

The clinical course could not be influenced by treatment, and although the patient received 8 more salvarsan injections intravenously, the serum Wassermann was not affected in the least.

The existence of "Wassermann fast" tabes is strongly emphasized in the studies of Swift and Ellis, who use the combined method of treatment, injecting salvarsan both intravenously and intraspinally. In an article which appeared in the Archives of Internal Medicine, September 15, 1913,

these investigators present the results of treatment in seven cases of tabes, in which they used the combined method. Of these seven patients, four presented the "Wassermann fast" phenomenon, in spite of the vigorous therapy to which the cases were subjected. The treatment, as carried out by these authors, is as follows:

Case 213.—O. W. A., aged twenty-nine; syphilis nine years; tabes, two and one-half years.

Date.	Serum W. R.	Fluid W. R.	Globulin Noguchi.	Cells.	Intravenous, Salvarsan.	Intraspinous, Serum.
1911						
June 23 to Aug. 2...	++	.....	.....	.....	5 x 0.2	
Aug. 5....	....	0.1±	—	110		
Aug. 10...	++					
to						
Oct. 20....	+	.....	.....	.....	4 x 0.2	
Oct. 27....	+	0.1++	—	75	0.2	25 c.c. of 40 per cent.
Nov. 3....	++	.....	.....	.....	0.2	
Nov. 21...	++	0.1++	.....	.....	0.2	20 c.c. of 50 "
Dec. 12...	++	0.1++	±	20	0.2	30 c.c. of 70 "
Dec. 19...	++	0.2++	±	19	0.2	25 c.c. of 40 "
1912						
Jan. 5.....	+	0.1++	—	22	0.3	30 c.c. of 50 "

From January 5, 1912, to February, 1913, the patient received 10 salvarsan injections intravenously, each of 0.3 c.c., and, in addition, 10 instraspinous injections of 30 c.c. of 50 and 40 per cent. serum. The last analysis in February showed a positive serum and fluid Wassermann, no cells, and a normal globulin reaction.

Similar findings were had in Case 893, in whom 10 intravenous and 4 instraspinous injections resulted, at the end of six months, in a ++ serum Wassermann, the fluid reaction being negative.

In Case 152 the relative "Wassermann fast" condition was obtained. The patient received, in the first year, 2.2 gm. of salvarsan in 12 intravenous injections, and then, in one month, 1.5 gm. salvarsan in 5 injections, plus 3 intraspinous injections, totaling 36 c.c. of the patient's own serum. In January, 1913, the patient suffered a relapse, which was re-

lieved in two months by giving 7 intravenous injections of neosalvarsan, totaling 5.8 gm., and 6 intraspinous injections, totaling 72 c.c. of the patient's serum. The resulting analysis in April, 1913, gave a $+\pm$ serum Wassermann, 7 cells, a globulin excess, and $\pm$ fluid Wassermann. In this patient, on one occasion, a negative serum Wassermann was obtained, and five times a $\pm$ result.

Case 113 is another instance in which salvarsan, mixed treatment, and neosalvarsan, as well as intraspinous therapy, resulted, after two years, in the production of a positive Wassermann in the serum.

In concluding the report of the results attained by them from the intraspinous serum treatment, the authors deplore the fact that their studies with general paresis were very limited, not permitting them, at the time this report was published, to formulate definite conclusions. In one patient with early paresis, and in one or two others who must be considered as border-line cases hovering between tabes and paresis, the treatment resulted in a rapid decrease in the pleocytosis and a moderate decrease in the globulin, but the Wassermann reaction was slower in showing a response to the treatment.

The foregoing findings relative to the inability of treatment to influence the Wassermann reaction in some cases, and the clinical opinion laid down as to the possible transition of tabes to general paresis is very interesting, more especially regarded from the viewpoint entertained by myself throughout these analyses.

Juvenile Tabes

This classification is based on purely clinical findings, but as the serology of the serum and spinal fluid is often the determining factor, it is proper to consider it here. In three cases of this form of locomotor ataxia the serum was positive in two, the spinal fluid Wassermann was negative in every one, there was no increase in the globulin content, and the cell count was 43, 35, and 17 respectively. The smaller count was obtained in the case that gave an entirely negative result with the other tests. In one case the serologic

investigation proved of great value in making the final diagnosis, as the extreme youth of the patient almost made such a conclusion impossible. It must nevertheless be admitted that infantile tabes is a possibility, cases having been described by Bruce, Collins, Maas and Hagelstamm, and others. In difficult cases the serologic corroboration is an important adjuvant to our methods of differential neurologic diagnosis, particularly when one bears in mind that such conditions as pseudotabes diphtheritica may at times evince a symptomatology closely simulating that of tabes. Although in this disease the previous history is frequently in itself suggestive of the cause of the condition, the fact must not be lost sight of that diphtheria may attack a child with a hereditary tabes in whom the cardinal signs of the spinal cord involvement prior to the diphtheric infection were not sufficiently severe to necessitate seeking medical advice.

In such a coincidence the danger would lie in placing too much credence on the history of an infectious disease of recent date, and omitting the lumbar puncture, which would settle at once the real etiology of the spinal trouble and indicate the proper line of treatment. The interpretation of neurologic disorders without the aid of serologic methods will in the future be regarded as negligence on the part of the physician, and will, besides, lead both patient and physician astray. Surprises are always in store for the physician who performs rachicentesis on all neurologic cases as a routine procedure, and the same applies also to the surgeon.

Monosymptomatic Tabes

The question of the specific origin of the fixed pupil is by no means a settled one. It cannot be denied that most of these pupils are of specific origin, and frequently constitute the initial sign of tabes. It is not at all uncommon to encounter patients who present an Argyll-Robertson pupil and yet have nothing else suggestive of tabes. The diagnosis of tabes in its incipiency is not always easy, particularly when the spinal fluid has not been analyzed. I have in mind three cases of this form of tabes: in one, Mr. L., all that could be found was a primary optic atrophy; no Argyll-Robertson

pupils; no Romberg; no Westphal; no pain; no other sensory disturbances. Syphilitic contamination was denied, and no clue to the etiology of the optic atrophy could be secured. The serology revealed the following picture:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Positive.	Excess.	160 lymphocytes.	Prompt.

From the foregoing serologic report there can be no doubt that syphilis is the cause of the atrophy, in spite of the denial of luetic infection and the absence of other corroborative signs of lues.

It is quite evident that a study of the serum and fluid will in some cases give a clue as to the etiology; in others, as to the diagnosis; and in others again, as to the line of treatment and the prognosis.

In another case the only symptom complained of was impotence of two years' duration. The difficulty came on gradually and is now (1913) complete. Patient denied syphilis; has one healthy child. The physical analysis gave no evidence suggestive of tabes; reflexes were normal, as were also the pupils. A band of hyperesthesia was elicited in the area covered by the first and second lumbar segments. The serologic analysis gave the following result:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Negative.	Normal.	67 lymphocytes	Prompt.

Here we have the type of serology that corresponds with that obtained in the "usual serologic type" of tabes. This case will be referred to again, as the results of treatment obtained are instructive.

In a third case the only disturbance complained of was a painful sensation at the head of the penis. This was later

shown to be a "penile crisis," and improved markedly after treatment. In this instance the serology was also positive, and aided in the final diagnosis of the case.

The Influence of Therapy on the Serology and Clinical Course of Tabes

Before discussing the changes in the serology effected by appropriate treatment, it will be well to give suggestions as to the advisability of therapy as may be indicated by a study of the serum and the cerebrospinal fluid. All are agreed on one point: that the posterior spinal sclerosis cannot be cured by treatment. Whether or not treatment can check the ascending tendency of the degeneration has not been settled. On the other hand, it has been quite well established that the inflammatory processes, whether they be mild or severe, can be influenced by specific treatment, and no matter how well chosen the remedy, more than this cannot be accomplished by any means. Therapy, therefore, resolves itself into a question of who shall and who shall not receive the treatment.

The selection of patients suitable for treatment must be made as the result of a thorough knowledge of the clinical and laboratory data. The active manifestations of tabes are, in the majority of cases, due to active processes in the meninges. These are chiefly of an inflammatory nature, and frequently affect the cerebrospinal fluid in a specific manner. This change in the fluid is readily demonstrated by serologic methods, and will guide the therapeutist in deciding for or against treatment. A purely degenerative tabes, *i. e.*, a tabes devoid of any meningeal manifestations, be they ever so mild, is not the rule, and, as previously stated, was seen in only 7 per cent. of the cases that came to the laboratory of the Institute. As was asserted elsewhere, purely degenerative tissue changes cannot be influenced by treatment, and as the "negative type" of serology represents the purely degenerative type of tabes, it is my contention that such tabetics should not receive the usual specific remedies, and are better without any treatment. If anything is to be accomplished, it must be by reëducation, hydrotherapy,

electricity, and not by the introduction of substances that are in themselves not altogether devoid of toxic properties. I know of cases in which the strenuous treatment was the cause of the rapid decline of the general health of the patient, one patient dying a few months after treatment was instituted. The foregoing contention applies to the "absolutely negative type"; the "relatively negative type," where some 15 to 30 cells per c.mm. are to be found in the spinal fluid, may be subjected to mild specific medication with benefit.

We will next consider the effect of treatment on those forms of tabes that present serologic evidence of a meningeal irritation. First in order is the "usual serologic type," with a positive serum Wassermann, a negative fluid Wassermann, normal globulin content, and a cell count of from 25 to 95 per c.mm. The chief object sought in the treatment of tabes is, of course, to influence pain or other unplesant subjective manifestations. Besides this, it is very gratifying to note the improvement in the serologic picture. In fact, having obtained improvement subjectively, it is the therapeutist's duty to follow up the case until the serology has become as nearly normal as it is possible to make it. That this can be done will be seen from the following description of a case of "monosymptomatic tabes." We will start with the "usual serologic type." On November 6, 1912, the serology was as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Negative.	Normal.	67 cells.	Prompt.

On that day the patient received an intravenous injection of neosalvarsan. On November 19th another serologic study revealed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Normal.	35 cells.

From November 19th to January 7th three neosalvarsan injections were administered, and on December 17th the serology showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Negative.	Negative.	Normal.	21 cells.

On the seventh of January, 1913, the serologic report gave:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Negative.	Negative.	Normal.	0

Upon studying the changes obtained in the serum and spinal fluid it will be observed that the case went through a stage of the "relatively negative type," and on the seventh of January showed the "absolutely negative type" serology. With the serologic negativation came the gradual return of the lost sexual power, which was preceded, on December 28th, by a disappearance of the band of hyperesthesia.

With insignificant variations in the change from positive to absolutely negative serologic pictures, all other reports follow approximately the same course. Regarding the clinical improvement, however, as much cannot be said, as very often the serologic picture becomes negative long before the clinical exudative manifestations have subsided.

The greatest benefit to the patient, and the source of most gratification to the physician, are to be obtained from the treatment of the "hyperlymphocytic type" of tabes. This type represents the serologic expression of an exudative process in the meninges, and the presence of inflammation and of syphilis. The serology, as shown before, may or may not give a positive Wassermann reaction in the cerebrospinal fluid (see Hyperlymphocytic Tabes), but the chief index to the exudative condition is the high cell count. The rapidity with which the cell count in the spinal fluid falls after appropriate treatment can almost be compared to the diminu-

tion in the leukocytosis after the opening of an abscess, and the relief to the patient is not infrequently as prompt.

One patient who suffered great pain and gave the classic "hyperlymphocytic type" serology showed the following picture:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Positive.	95 cells.

On January 3, 1913, the patient received 0.9 gm. of neosalvarsan intravenously.

On January 20th the laboratory report gave the following result:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Negative.	73 cells.

On January 25th another dose of neosalvarsan was given.

On February 9th the laboratory report showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Negative.	Positive.	Negative.	50 cells.

February 10th patient received a full dose of neosalvarsan.

February 20th the serologic picture was:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Negative.	Negative.	Negative.	10 cells.

In this instance the clinical course was extremely gratifying. The pain left the patient two days after the first injection, and did not return.

The negativation shown in the preceding schedules represents the usual serologic findings in the course of tabes following treatment. Occasionally cases are encountered that offer great resistance to treatment, and will not show a negative response, no matter how painstaking the therapy. These cases have been considered under the head of Wassermann Fast Tabes (p. 138).

The Serologic Interrelationship Between Tabes and General Paresis

The advent of a tabo-paresis is frequently determined much earlier by serologic investigation than is possible with clinical methods. The success obtained by the reduction of the pleocytosis is counteracted by the inability to render the serum Wassermann negative. It will be shown further on that the positive serum Wassermann in some cases of general paresis closely simulates the serum of an early case of tabo-paresis, and presents, in the majority of instances, a relatively insignificant pleocytosis. The two cases described under the head of Wassermann Fast Tabes both developed unquestionable clinical manifestations of tabo-paresis, the first patient having since died in an insane asylum in a paretic decline. At the time the first serologic investigation was made no clinical signs of paresis were demonstrable in either of these patients.

In consideration of general paresis it should be remembered that characteristics are to be obtained in the serum from a tabo-paretic that will enable one to classify certain sera as suspicious from the very beginning, without subjecting the patient to a prolonged course of treatment. This method is not, however, to be depended upon alone, and treatment is to be applied to the patient as a test before the final prognosis can be offered in a case of tabes. These suggestions apply only to cases where there is difficulty in the clinical interpretation, where the amount of treatment required by a patient is to be ascertained, or where it is important to render a prognosis in a peculiar case of tabes. It is a gratifying fact that biologic abnormalities precede the clinical by a time interval sufficiently great to permit of therapeutic

efforts heroic enough to ward off this disease, which is so hopeless when once it is apparent clinically.

RÉSUMÉ

Serologically, tabes presents four distinct types: The "Usual" type, the "Hyperlymphocytic," the "Negative," and the "Wassermann fast" types. The percentage of the different types is as follows:

The "Usual" serologic type	38.0	per cent.
The "Hyperlymphocytic" type	21.8	"
The "Negative type absolute"	7.0	"
The "Negative type relative"	18.6	"
The "Wassermann fast" type	8.5	"
Miscellaneous mixed forms	6.1	"

Serologic methods are essential to the proper interpretation of the rarer forms of tabes, such as the "juvenile" and "monosymptomatic" forms. The "Hyperlymphocytic" type of tabes, representing the serologic expression of meningeal irritation, is the form of tabes most amenable to treatment. The same holds true for the "Usual" serologic type.

Purely degenerative processes do not, as a rule, give the findings commonly observed in exudative conditions, hence treatment of the "Negative type" often falls short of its purpose. In a case of tabes in which all efforts fail to render the serum Wassermann negative, the advent of a taboparesis is to be thought of, although at the time no somatic or psychic manifestations may be demonstrable. In cases in which treatment is beneficial clinically, the result also shows an improvement in the serology, so that the pleocytosis tends to become less pronounced, the globulin excess disappears, the positive serum Wassermann becomes negative, and, lastly, the spinal fluid Wassermann also becomes negative. In the "Wassermann fast" type of tabes this result is not to be attained, and if it does occasionally occur, a recurrence is certain to take place after a short interval of time. The various serologic combinations in tabes as observed in these studies were as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
(*a*) Positive.	Positive.	Excess.	60 to 96 (63 cases).
(*b*) Positive.	Negative.	Excess.	30 to 88 (54 cases).
(*c*) Positive.	Negative.	Normal.	25 to 95 (162 cases).
(*d*) Negative.	Negative.	Normal.	12 to 32 (90 cases).
(*e*) Negative.	Negative.	Normal.	3 to 8 (30 cases).
(*f*) Negative.	Positive.	Normal.	20 to 50 } (26 cases).
(*g*) Positive.	Positive.	Excess.	16 to 47 }

The foregoing table includes all varieties observed, and also takes into account the treated and the untreated cases. Most of the patients from groups (*b*) to (*f*) received treatment, and only a few patients from groups (*a*) and (*g*) were subjected to adequate therapy before the analyses were made. The greatest number of cases who presented the "Wassermann fast" phenomenon after vigorous therapy were gathered from group (*g*). Although treatment of the "Negative type" offers little encouragement to the therapeutist, one must bear in mind the possibility of an exudative process running its course in a place where the spinal fluid does not actually come in contact with the area involved, and hence no marked cellular increase follows. This must not be lost sight of, particularly in those cases of the "Negative type" of tabes that exhibit considerable pain and other symptoms showing involvement of the ganglion on the posterior root (zoster). Treatment of this last form of the disease is often followed by distinct improvement, regardless of the absence of a marked pleocytosis.

A glance at the various serologic possibilities to be met in tabes will convince one that no hard-and-fast rules can be laid down to enable one to say beyond question that there is a combination of serologic findings that always indicates the existence of tabes. Clinical facts, collated with laboratory findings as shown in one complete picture, furnish the only possible means for correctly diagnosing a case as tabes. Not infrequently the laboratory is of no assistance so far as the serologic corroboration of tabes is concerned, as is the case when the "Negative type" is the form at hand. Fortunately, "Negative types" and clinically obscure tabes are

very rarely observed together, but when they do occur, it is safer to defer the diagnosis temporarily. The cases so far considered that really did offer clinical difficulties, such as the cases of monosymptomatic tabes and the few juvenile forms, showed sufficient serologic abnormalities to remove all doubt as to the genuineness of the tabes.

In studying the percentages of positive Wassermann reactions obtained in the serum of patients with tabes, it will be noted that here and there attempts have been made so to perfect the technic, or to introduce modifications, as would ultimately result in the possibility of securing 100 per cent. of positive Wassermann reports. If this object were really attained, what laboratory guide would the therapeutist have for gaging his treatment or determining the result of his efforts? There should be sufficient accuracy in the test to give a strong reaction with exudative tabes, a weak result when the disease is being properly treated, and a negative reaction at the conclusion of successful therapy, with the sole exception of the "Wassermann fast" type. All these important factors of the test would be lost if every tabetic were, from beginning to end, to give a positive result in his serum or fluid with a method incapable of error. Of course, an unfailing test would be a good thing where considerable doubt existed clinically; on the other hand, what guarantee could we have that the test is infallible? So far, all the modifications attempted have fallen short of their purpose, and only tended to increase the percentage statistics of syphilis, and render many an innocent sufferer miserable. My results in tabes gave the following figures:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Fehling's Reduction.
Positive, 68 per cent.	Positive, 21 per cent.	Excess, 30 per cent.	Present in 90 per cent.	Present in 100 per cent.

CEREBROSPINAL SYPHILIS

The serology of this varied luetic involvement of the nervous system depends, first, upon the anatomic distribution of the luetic focus and on its extent; second, upon the pecu-

liar tendency of the syphilitic virus to involve, selectively, to greatest degree the meninges in one patient; the inner walls of the blood-vessels in another, and in a third, to produce more or less extensive tissue changes of a gummatous nature. Collectively, these manifestations may be grouped, from the clinical point of view, under the head of cerebrospinal syphilis, or a further classification of the disease may be made according to its chief area of distribution—*i. e.*, purely cerebral or wholly spinal—regarding as cerebrospinal only those cases that present a symptom-complex embracing both anatomic entities. From a serologic point of view, it makes considerable difference whether the disease is purely cerebral or purely spinal, and it is still more important to determine whether the process is a purely meningitic, a gummatous, or an endarteritic one. The condition may also be markedly chronic, and consequently present serologic differences between this and the acute form. In the majority of instances, however, one is forced, from the manner in which the cerebrospinal fluid manifests itself serologically, to conclude that, in the great majority of instances, one is dealing with a pathologic state that is closely allied to the meningitides. This analogy is apparent in the absence in the fluid of the Fehling reducing substance, in the presence of a pellicle in the drawn fluid, in the great number of cells, and in the presence of polynuclear elements. These findings, while not the rule, nevertheless occur, and frequently enough not to be regarded as exceptional. In certain forms of the disease these findings are almost the rule, as in the acute syphilitic cerebrospinal manifestations. In the gummatous and the endarteritic varieties the process is usually milder, and, of course, devoid of the acute meningitic accompaniments.

Here and there serologic exceptions are encountered, as where it is clinically demonstrated that a high cell count ought to be found and it is not present, or that the Wassermann reaction is negative, although the patient did not receive treatment recently. These and other similar findings are mere coincidences, which tend to modify undue enthusiasm, and to render clinical evidence of greater value than test-tube revelations. On the other hand, the clinician who

believes that a neurologic study is incomplete without proper serologic investigation will be rewarded by finding, often to his great surprise, that what appeared to be a non-luetic disease, is unquestionably cerebrospinal syphilis. Such incidents are not rare, and clinical impressions without an accompanying serologic report are not infrequently erroneous, a result that could have been avoided if a laboratory had been consulted. It is to be hoped that with the routine performance of serologic tests in connection with neurology and psychiatry the clinician will be enabled to diagnose and treat his patient's malady more skilfully and successfully.

In the serologic report of a case of cerebrospinal syphilis the experienced neurologist, who is accustomed to interpret such findings, discovers so much of value from the point of diagnosis, treatment, and prognosis, that an omission of such a study would seem to be more than negligence. As a matter of fact, neurologists of experience do not omit serologic investigations any more than they would omit ophthalmologic examinations and sensory charting. Serology has, as it were, become an integral part of a neurologist's armamentarium. It is well to emphasize, at this juncture, that to attempt to treat cerebrospinal syphilis without making routine serologic investigations is to deprive the therapeutist of one of the most exact and most definite gages as to the success or failure of his efforts. This is especially true at the present day, when we are undergoing a radical change in our therapeutic conceptions as to the correct valuation of newly discovered drugs, and perhaps are in the formative period of an era that is laying the foundations for the establishment of an exact science—the treatment of syphilitic nervous diseases. It is by no means too much to expect, in the near future, that a distinct therapeutic formula will be devised for each and every syphilitic nervous disease, based on the conception of the complete clinical entity, both bedside and laboratory.

The older methods in vogue for the gaging of the efficiency of a certain remedy necessitated waiting for clinical improvement, subjective and objective, to take place; today this is considered by no means sufficient, unless the improvement is

accompanied by a corresponding change for the better in the serum and cerebrospinal fluid. The rapidity with which the serologic picture of a pronounced cerebrospinal syphilis becomes almost normal is the best guide as to the efficiency of a given method, and that method which will accomplish this in the shortest period of time will be the corner-stone for the building of a definite structure for the therapy of syphilis of the nervous system. This work is being carried on in various institutions, and the results are already very encouraging. These results will be dealt with more fully in another part of this volume.

The study of cerebrospinal syphilis, both at home and abroad, furnished various conclusions from the serologic point of view. Some (Hauptmann) busied themselves in elaborating methods, so that not a case of cerebrospinal lues would be overlooked serologically; others (Zeissler, Kaplan) attempted to do quite the reverse, *i. e.*, not to stigmatize one with this disease unnecessarily; others, again (Dreyfus, Kaplan), gave the serology of cases as affected by therapy. Plaut attempted to evolve a serology typical of cerebrospinal lues in contradistinction to general paresis; a similar attempt, but from a different standpoint, was made by Nonne. These studies will be considered subsequently, together with the similar findings as obtained by the writer.

THE "POSITIVE SPINAL FLUID" TYPE

In this form of cerebrospinal lues the spinal fluid gives a positive Wassermann reaction. The frequency with which this was observed by me warrants considering this form of serology of cerebrospinal syphilis under a separate heading. Out of a total of 184 cases of lues cerebrospinalis, 61 gave this serologic finding, *i. e.*, 33.33 per cent. According to the findings in the fluid, this variety includes the most pronounced examples of syphilitic cerebrospinal meningitis, as the cells may be present in such numbers as to exceed those in all the other luetic meningeal irritations. This is the serology that Plaut formerly held as significant of general paresis; he has since, however, altered his original opinion. The conclusions of Hauptmann, on the other hand, do not

admit of the existence of the negative fluid Wassermann form ("Plaut type" of cerebrospinal lues).

Neither the absence nor the presence of a positive Wassermann in the cerebrospinal fluid can serve as a guide to the diagnosis or exclusion of general paresis, nor can the Hauptmann experience be regarded as a rule without exceptions.

The Wassermann reaction in the serum is to a great extent positive in those cases that show the higher cell counts,—100 and more,—taking into consideration the possibility of obtaining a negative result in a well-treated case. In the untreated cases of this type the reaction is present in about 90 per cent. of the material as observed by me. The positive Wassermann in the serum of most cases is of the same degree of intensity as is obtained with the usual serologic type of tabes. The lower cell counts in cerebrospinal lues at times show a very intense Wassermann reaction, not infrequently simulating the "Wassermann fast" tabes serum. This reaction, however, does not merit a special classification, as it does not possess the clinical value of the one encountered in tabes. Phenomena are, however, encountered that could be regarded as the serologic transition from cerebrospinal lues to general paresis, the serology not infrequently being accompanied by clinical manifestations of beginning paresis, of which more will be adduced further on.

Certain prominent neurologists believe that a preëxisting cerebrospinal syphilis may prepare the soil for the future development of paresis. In view of our present development of the subject of neurologic syphilis, it is almost impossible to consider each of the syphilogenous nervous disorders as possessing an origin that is histologically entirely foreign to the other; it is much more logical to consider that the spirochete, from the earliest involvement of the nervous apparatus, injures the structure in a manner that is not specific, in so far as future tabes, cerebrospinal syphilis, or general paresis is concerned. In one patient the same organism will produce tabes; in another, general paresis; but the beginning lesion, from which the clinical and pathologic differences arise in the course of time, is essentially the same. The globulin is by no means always in excess, and if it is, this does

not always show an intensity corresponding to the degree of the pleocytosis. We are entirely at a loss at present to account for this discrepancy, as the factors that produce the globulin excess are not clearly established. In this form of serology the globulin excess reached 88.8 per cent. The cell count in the untreated condition, or in cases in whom treatment was remote, ranges from 100 to 1700 cells. The cells are in the higher counts of mixed type, with a large preponderance of the lymphocytes. The polynuclear elements, or the polymorphonuclear cells, when present in the fluid in large numbers,—from 40 to 200 cells per cubic millimeter,—also show an absence of the substance that, under ordinary circumstances, reduces Fehling's solution.

These findings, taken together, justify the assumption that a syphilitic meningitis is at the root of the serology, and that the cerebrospinal nervous system is pervaded by a specific exudate. This exudate is most likely responsible for the constriction of sensory nerves and pressure on motor tracts giving the clinical picture of the disease.

This serologic type of cerebrospinal syphilis gave the following percentages. The figures show the result of 61 analyses:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Fehling's Reduction.
Positive 55, or 90 per cent.	Positive 61, or 100 per cent.	Excess in 24, or 40 per cent.	From 160 to 1800 per c.mm.	Four fluids did not reduce, polymorphonuclears up to 260 per c.mm.

The absence of Fehling's reducing substance is not a constant accompaniment in cerebrospinal lues of any type, but when it is absent, this is always indicative of a very active exudative process.

THE "PLAUT TYPE"

This is the negative spinal fluid type, and is the form of serology first described by Plaut, comprising 58.2 per cent. of the material analyzed. This type also represents the

intermediary stage that the positive type must pass through before becoming negative as a result of treatment. Despite the fact that the Wassermann reaction is negative, the clinical intensity and the accompanying pleocytosis may be as pronounced in this as in the "positive type." In discussing the serology of tabes it was pointed out that the serologic and clinical manifestations are not always of the same degree of intensity in a patient. This holds true also for cerebrospinal lues. In fact, in the study of the fluids from patients with this disease the most astonishing findings were encountered, and the serology in some instances was the only clue as to the condition present. Diagnoses that were made previous to the serologic analysis not infrequently had to be reconsidered after a series of tests were made. In six instances the serologic study of the serum and fluid was responsible for the changing of the clinical diagnosis from general paresis to cerebrospinal lues, the further course of the disease and its amenability to treatment tending to confirm the latter diagnosis. In one instance, that of a negress of twenty-eight years who suddenly became ill nine weeks previous to admission to the Institute, there were very few sensory disturbances, and the reaction of degeneration was present; an unquestionable serology of cerebrospinal syphilis was obtained. The tentative clinical diagnosis before the laboratory examination was made was anterior poliomyelitis. The Wassermann reaction was positive in the serum, and the cerebrospinal fluid showed 940 cells per c.mm., with many polynuclear elements, a marked excess of globulin, and an absence of Fehling's reducing substance. After this report there was no doubt that the patient suffered from an acute exudative syphilitic spinal meningitis. Improvement followed specific medication. These instances emphasize the importance of performing the serologic tests as a routine in all neurologic manifestations.

Of the 184 cases that furnished the material for this study, 107 presented the "Plaut type" of serology. Eight cases gave no reduction of Fehling's solution, and also showed the presence of polynuclear elements. An analysis of the serology of this type is as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive in 94, or 89.7 per cent.	Negative in 107.	Excess in 66, or 61 per cent.	From 96 to 1400 cells.	Absent in 8 fluids, or in 7.4 per cent.

ACELLULAR TYPE

An acellular spinal fluid is rarely encountered, but it must, nevertheless, be mentioned, as it illustrates a seeming incongruity, and presents a formula that is somewhat difficult to explain extemporaneously. In the introductory remarks on cerebrospinal syphilis mention was made of the pathologic changes that the nervous system undergoes in this disease. It was pointed out that a meningitic, a gummatous, or an endarteritic process may involve the structures. The acellular type is representative of the endarteritic form, as it is incapable of irritating the meningeal structure, as is the case with the gummatous variety; nor are the walls permeable to diapedesis, as in the meningitic form, so that a condition is present that is favorable to the existence of very few cells, regardless of the presence in the fluid of biologic and chemical evidence of syphilis.

It must be borne in mind that the serology is not the result of therapy, and does not conform to the manner in which fluids become negative after having been positive. The retrogression of the positive serology after treatment does not take place in a haphazard fashion, but follows more or less definite laws, the positive fluid Wassermann reaction becomes negative long before the complete disappearance of the pleocytosis takes place. In very few instances have I observed the contrary, these being chiefly among general paretics, where, after vigorous medication, the cells disappeared entirely, leaving a positive fluid and serum Wassermann reaction. The globulin, as a rule, is always negative by the time the pleocytosis has entirely disappeared. The globulin excess without cells was described when dealing with cord compression (tumors, adhesions, spinal caries). The serology of the acellular type is, therefore, as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Positive.	Usually negative.	Absent or borderline.	Always prompt.

As previously stated, this serologic form of cerebrospinal lues is very infrequent, and was observed in the Institute's laboratory in only six patients, who gave no history of recent treatment.

The Influence of Treatment on the Serology and Course of the Disease

It may be said, at the very beginning, that the higher the cell count and the greater the number of polynuclear elements, the easier it is to influence the serology and alter the clinical picture of cerebrospinal syphilis by proper treatment. In cases in which there is an absence of Fehling's reducing substance the clinical result sometimes becomes evident on the very next day, and is closely followed by serologic changes for the better.

This form of lues cerebrospinalis will show results after any antiluetic remedy, so far as the serology is concerned, and it is even possible to obtain a diminution of cells in the fluid simply by making a lumbar puncture and withdrawing some of the fluid, a procedure which not infrequently effects an immediate amelioration of the patient's condition; in some of these cases the specific treatment acts more as a prophylactic, and gives the organic protective forces an opportunity to relieve the exudate. Subsequently, when the body becomes more or less saturated by the specific drug, the remedy will exercise its destructive properties on the syphilitic microörganism, and the opportunities for re-formation of the exudate are thus minimized. The destruction of the spirochætes,—at least those that may be reached by the drug through the patient's circulatory system,—tends to diminish the intensity of the Wassermann reaction in the spinal fluid and in the serum, which, when supplied in sufficient amounts at proper intervals, may result in a more or

less permanent negative serologic state and more or less permanent clinical cure. Of course, all that can be done is to relieve the active manifestations; organic tissue changes will not be influenced, but will remain as permanent evidences of the disease. When, however, the disease is detected in its very incipiency, which, with our modern methods, is not at all impossible, the timely institution of therapy will tend to reduce the formation of permanent tissue changes to a minimum, and thus prevent a crippling of the central nervous system. The "positive spinal fluid type" and the "Plaut type" of cerebrospinal lues, which show a thousand or more cells to the cubic millimeter and no reduction of Fehling's solution, with very few clinical manifestations, are, from a prognostic point of view, perhaps the most gratifying cases to treat. The following are a few examples of the serologic course after specific treatment:

Mrs. H., a Jewess, aged forty-two, housewife. On account of low intellectuality and poor environment her mental status offered analytic difficulties. With the exception of exaggerated reflexes and a few sensory changes, no other signs of cerebrospinal lues existed. Serology before treatment:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Strongly Positive.	Positive.	Excess, marked.	1680 lymphocytes; 260 polynuclears.	Absent.

An intravenous injection of salvarsan ("606") was given. Two weeks after the injection another analysis showed the following:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction of Fehling's.
Positive.	Positive.	Mild excess.	1240 lymphocytes; 20 polynuclears.	Present.

One week after the serologic analysis a dose of salvarsan similar to the first was administered, and the analysis, repeated a week after the second injection, showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Positive.	Normal.	480 lymphocytes.	Prompt.

A third dose was injected three days later, which was followed by a serologic analysis two weeks after the administration of the salvarsan. This showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Weakly positive.	Normal.	212 lymphocytes.	Normal.

The mental change for the better in this patient was marked after the first injection; the reflexes became normal and the sensory changes also disappeared. The subsequent history of the case showed that no permanent injury to the central nervous system remained after the treatment, and the patient is now in perfect health. I believe that here the timely diagnosis and treatment practically prevented permanent injury to the nervous apparatus, first, by partly evacuating the exudate, and, second, by preventing its reformation.

Mr. St., aged forty-seven, married, no children. Complains of intercostal pains; unable to sleep; poor memory; constipation. Physical status, exaggerated knee-jerks. Irregular pupils, sluggish reaction to light. Serologic analysis gave the following:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Negative.	Positive.	282 lymphocytes.	Prompt.

An intravenous injection of 0.6 gm. of salvarsan was given, and the serologic study repeated two weeks later. This showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Negative.	Normal.	174 lymphocytes.	Prompt.

Another injection was given as before, and the analysis on the serum and fluid, made one week later, showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Negative.	Normal.	88 lymphocytes.	Prompt.

A third injection was given a few days after the serologic study, which was followed by another analysis three weeks later:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Negative.	Normal.	43 lymphocytes.	Normal.

This was followed immediately by another injection as before, and a serologic study undertaken one week after the last treatment showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Negative.	Normal.	12 lymphocytes.	Normal.

The case just described is one of the "Plaut type," and although it does not present the intense meningitic phenomena that are at times encountered in this form of cerebrospinal lues, it nevertheless showed progressive improvement serologically as well as clinically.

A third case, originally diagnosed as general paresis, regardless of the laboratory report as to contrary serologic findings, was treated with specific remedies and showed the following progress. The serology before treatment was:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Positive.	Excess.	148 lymphocytes.	Prompt.

Twenty-four mercuric inunctions were given, each of 2 grams. The analysis made three weeks after the cessation of treatment showed the following changes:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Weakly positive.	Positive.	Normal.	130 lymphocytes.	Normal.

After this the patient made an extended tour, and upon returning, three months later, was given an intravenous injection of 0.6 gm. of salvarsan intravenously. A week after this the change was as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Positive.	Normal.	92 lymphocytes.	Normal.

The resulting serology justified further specific treatment, and the patient thereupon received a second injection of salvarsan. Two weeks after this treatment the serologic investigation showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Negative.	Normal.	19 lymphocytes.	Normal.

The readiness with which the patient's serology responded to the somewhat mild therapy and the clearing up of the clinical manifestations caused the diagnosis to be changed from general paresis to cerebrospinal lues, although the for-

mer diagnosis was adhered to long after the cessation of active treatment. The improvement in this instance was a lasting one. One may say, however, that lucid intervals are not uncommon in general paresis; be this as it may, if we can obtain a lucid interval for a general paretic and prolong the well-being of the patient, we certainly possess valuable measures, particularly if the serology can help us in the selection of the cases that will be most benefited by our efforts.

It must be admitted that, so far as the therapy of syphilitic nervous diseases is concerned, we have not, as yet, passed out of the experimental field, a fact that is borne out by the new therapeutic suggestions recorded in the medical press. The possibilities are very encouraging, and the newer methods should be employed where the older ones have failed. I am referring here to the recent work of Swift and Ellis and others, which will be considered in the section on Treatment. Although our progress in the fields of diagnosis, prognosis, and treatment has been marked, the prophylactic study of syphilitic nervous diseases is still virgin soil. That the physician of the future—and let us hope of the near future—will be able to foretell the onset of a neurologic syphilis in a patient who is in the secondary or florid stage of the disease is only a question of time, and therapeutic measures that will be elaborated for the combating of neurologic lues will most likely diminish likewise the number of tabetics, paretics, and cerebrospinal syphilitics. We are almost on the threshold of such a possibility. At present all are engaged in elaborating systems of therapeutics that will, in the shortest possible time, effect a change for the better, and tend to make this improvement as lasting as possible. Some of these methods are far more efficient than others, and are sure to gain universal recognition sooner or later.

THE TRANSITION OF THE SEROLOGY OF CEREBROSPINAL LUES TO GENERAL PARESIS

The contention that tabes, cerebral, spinal, or cerebrospinal syphilis, and general paresis, in their very incipiency, cannot be distinguished from one another is a fact that must be admitted. It may be said that during the early stage

of its existence no clinical signs are to be had of any neurologic disease, although the soil for its development is already prepared. This, so to say, "aclinical" lues of the nervous system may, even at so remote a date, show serologic evidence of its existence. Although corroborated by a few analyses, it may, however, serve as an interesting problem to be solved by the syphilographer, using the latter term in its broadest application, *i. e.*, one who encounters syphilis in all its manifestations, from the initial lesion of the disease to the malignant form of skin syphilis and to the paretic decline. If we assume that the original impetus is the same in all neurologic manifestations of syphilis, it is not difficult to conceive that one clinical entity may be transformed into another by gradual changes so minute as to go unobserved by the clinician. It is my contention that this imperceptible clinical transition can be detected by proper serologic studies.

It was mentioned in the section on "Wassermann fast" tabes that there the persistence of the test was considered as an index to the possible development, later, of a taboparesis. In a number of instances this fact was established. In regard to cerebrospinal syphilis or cerebral syphilis, the clue to the serologic transition stage is to be found in the peculiarity of the cell count and in the Wassermann reaction, and at times also in the globulin excess. It will be shown later that 1000 cells per c.mm. is unknown in general paresis, and that a count of 100 is not the rule in cerebrospinal lues. The cell count of cerebrospinal lues is, as a rule, high; in the untreated patient usually more than 100.

The therapeutic guide is the most certain differential point between cerebrospinal lues and the advent of general paresis, the characteristic feature being a marked persistence of all serologic abnormalities in the latter. In the attempt to reduce the pleocytosis the therapeutist will discover that no matter how vigorous the treatment, the cell count rarely diminishes below the border-line count, the Wassermann persists in the serum or fluid or both, and the globulin may show a slight excess. Such a patient should be closely observed for the corroborating clinical manifestations of gen-

eral paresis, as the deterioration is sure to appear sooner or later. All that can be done in such a state is to employ all means at one's disposal in deferring the approach of the much dreaded outcome.

RÉSUMÉ

The material analyzed consisted of 184 cases of clinically confirmed lues cerebrospinalis. Of these, 61 gave the serology of the "positive spinal fluid type" and 107 of the "Plaut type." Four cases showed irregular findings, and in 12 the serology was negative throughout. The latter were cases that were treated successfully, the majority having had one of the two positive serologic types before treatment was instituted. The number of cases that correspond serologically to the "Plaut type" could be materially diminished by employing the "Auswertung's Methode" of Hauptmann, which consists in the use of gradually increasing quantities of cerebrospinal fluid for the performance of the Wassermann test. Where 0.2 c.c. does not give the reaction, Hauptmann advises the use of 0.4 c.c., and so on up to 1 c.c. In my experience the use of this method did not materially diminish the percentage of the "Plaut type" of cases, so that I came to the conclusion that this type is a biologic reality, and is not due to the presence of a diminished amount of antibody, which is presumably overcome by the Hauptmann method.

In considering the Wassermann reaction in the serum, one not infrequently obtains a negative result even when the pleocytosis is accompanied by polynuclear elements and only a slight reduction of Fehling's solution, both of which are factors significant of an active process in the meninges. The percentage of the various components of the serology of this disease as found by me is as follows: (*a*)

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Excess.	160 to 1680.

Of these 61 cases, which represent the "positive fluid type," 6 gave a weakly positive Wassermann reaction in the

serum, and only 24 fluids gave the reaction of a globulin excess. With these exceptions in mind, this type represents about 33 per cent. of the serologic findings in cerebrospinal syphilis.

(*b*) The "Plaut type" gave the following numeric relationship:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Excess.	96 to 1240.

Of these 107 cases, 13 gave a weakly negative Wassermann reaction in the serum, and 41 showed no globulin excess in the spinal fluid.

(*c*) As a result of vigorous treatment, the serology of 12 cases showed the following:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Negative.	Negative.	Normal.	Normal.

The foregoing shows that only a very insignificant number of cases result in a restitutio ad integrum so far as the serology in cerebrospinal lues is concerned; there is no doubt that with a better knowledge of therapeutic procedure the number of such cases will be sufficiently increased to merit a classification of their own, and establish a serology of the successful post-therapeutic type. Each serologic item considered independently and exclusive of the negative serology obtained after treatment gives, in my experience, the following percentage relationship:

Serum W. R.: Positive in 88.7 per cent. of cases.
Fluid W. R.: Positive in 32.7 " "
Globulin: Excess in 50.3 " "
Pleocytosis: Present in 96.7 " "

The question of a pleocytosis must without exception be modified in cases where an endarteritic process is the factor

in cerebrospinal syphilis. Here a normal cell count or a borderline count will be found with a positive Wassermann reaction in the serum and fluid, and in half of the cases a globulin excess. The small number of positive Wassermann reactions in the fluid from patients with this disease will be received with considerable reserve by those who are accustomed to work with the "Auswertung's Methode." I fear that the use of too large quantities of fluid will increase the number of cases of cerebrospinal syphilis, so long as such a serology is possible without the presence of a pleocytosis, as is the case with lues of the brain and cord of the endarteritic type. It cannot be doubted that the real positive fluid Wassermann will inhibit hemolysis even when used in such small quantities as 0.05 c.c., and it is, furthermore, my belief that only such a spinal fluid will receive the same interpretation all over the world.

In considering the serologic changes effected by appropriate treatment it is important to remember the order of serologic progress for the better; it is very rarely, indeed, that the pleocytosis disappears entirely before the Wassermann reaction becomes negative in the fluid. Where opportunity is afforded for the persistence of a positive Wassermann reaction in the fluid, as is the case where larger amounts of fluid are used, a positive Wassermann reaction will occasionally be found where the cell count has entirely disappeared. To have effected the disappearance of a positive Wassermann reaction from a fluid is a considerable achievement. If such a fluid becomes negative after a special method of treatment, and the same serologic precautions in the performance of the test were observed as before the treatment was instituted, such therapeutic procedure must be regarded with favor. Where the Wassermann reaction in the fluid is only partly positive (after the use of 0.1 or 0.8 c.c.), the usefulness of the treatment is greatly diminished when the fluid becomes negative after its application. The performance of serologic tests must be regarded as only a small wheel in the mechanism of clinical diagnosis, and should never be considered except in conjunction with bedside findings. Here and there the laboratory diagnosis will vary from that

formulated at the bedside, and will occasionally also be justified in taking exception, but, as a rule, both sides agree in the essentials. Here and there the serology will give the first clue as to an impending general paresis, and although the clinician will not at the time find sufficient justification for such an assumption, he will, nevertheless, be on guard for the appearance of suggestive symptoms. This phase of serologic work is only in its infancy, and as statistics increase it will be given wider consideration.

The percentage of the various serologic types of cerebrospinal syphilis is as scheduled here:

The *positive spinal fluid type*—33.1 per cent.

The *"Plaut type"*—57.6 per cent.

The *acellular type*—9.3 per cent., inclusive of those cases that became acellular after treatment.

The foregoing also comprises a few cases in which the Wassermann reaction was positive in the fluid and negative in the serum.

Cerebral Syphilis

The purely cerebral distribution of the syphilitic process may manifest an acute or a chronic display of symptoms and a serology corresponding to the form of tissue change—meningitic, gummatous, or endarteritic.

The serology is greatly affected by the ease with which the spinal fluid receives impressions from the cerebral fluid. If obstacles preventing proper interchange exist, some cerebral luetic processes may entirely escape the serologist. In the majority of instances, however, the meningitic forms give to the fluid sufficient distinctive features to suggest the pathologic condition at hand. The cerebral distribution of the disease is entirely a matter of clinical differentiation.

The gummatous form of cerebral syphilis will in so far affect the spinal fluid as the process is either a superficially situated one or one deeply embedded in the brain tissue. The superficially located gumma gives serologic changes secondarily only by irritating the meninges, so that we are, in reality, dealing with a mixed form of disease—gummatous

and meningitic. If the process is situated deeply, the study of the cerebrospinal fluid will yield little evidence.

The purely endarteritic form of cerebral lues, like the spinal or cerebrospinal form, rarely gives a pleocytosis, although occasionally a positive Wassermann reaction may be obtained in the fluid.

From the clinical point of view we are dealing with the hemiplegic whose paralysis is due to a syphilitic cerebral lesion, which may occasionally be obscured by intercurrent acute manifestations of a hemorrhagic nature, giving in some instances the bloody fluid with red blood elements, in other cases only the dissolved coloring-matter. To this class belongs the erythrochromia of Mestrezat, who, as stated elsewhere, considers three forms of xanthochromia. The Wassermann reaction varies, and the same may be said of the globulin content. The other clinical form of cerebral lues is evidenced in the patient with a psychosis who not infrequently presents difficulties in the making of a differential diagnosis between cerebral lues and general paresis. In many instances definite symptom groups are sufficient to establish the correct interpretation of the disease; in others, again, the course of the disease sheds a light on the situation, but despite all these differential aids at our disposal, we are now and then confronted by a situation that does not lend itself readily to satisfactory elucidation. Here the serologic differentiation is at times of great value, provided, of course, that the technician is also an adept at interpreting serologic findings. Even then the serology may so closely simulate that of general paresis that, in order to establish a correct diagnosis, it would be necessary to subject the patient to a course of treatment and then carefully note the effect of the same on the serology. If the "Wassermann fast" condition is obtained, we are most likely dealing with a general paresis; on the other hand, if the Wassermann reaction becomes negative, it is safe to consider the case as one of cerebral syphilis.

There are cases on record in which paresis existed for a long time without evincing the characteristic progression that marks this disease, and, on the other hand, postmortem

findings have shown that luetic disease of the blood-vessels was present in subjects who presented the symptoms of general paresis. In our serologic methods, I am glad to say, we have progressed a little further regarding these confusing clinical entities, and where there is doubt as to the existence of general paresis, we can frequently clinch the diagnosis of this disease if we obtain a Wassermann reaction that is "fast," a cell count that is small, a gold curve that is characteristic, and frequently also a globulin excess. If the case were one of cerebral syphilis, the Wassermann reaction would become negative comparatively easily after therapy; the cells, which had been present in larger numbers, would disappear; the globulin, if present, would also become eliminated, and from the beginning there would be no characteristic gold chlorid curve. All these factors, properly interpreted, constitute to-day a valuable chapter in the clinical interpretation of syphilitic nervous diseases.

Spinal Syphilis

In this condition we are now in a position to study the cerebrospinal fluid as it may be affected by a local spinal process, a condition easily detected by serologic methods. With milder changes in endarteritic luetic spinal processes, we find in the meningitic forms marked changes in the cerebrospinal fluid. In the gummatous variety the changes may also be marked, but here the fluid is not so rich in cells as in the meningitic variety.

Here must be considered the spinal pachymeningitis hypertrophica on a syphilitic basis. The serology of this form is slightly different from the other two varieties in that the globulin may at times be present in very great amounts, a fact which may be explained by the apparent similarity between marked hypertrophic conditions that may give rise to considerable cord compression, similar to that produced by cord tumors. The cell count is low, although not so low as in the endarteritic form. In the meningitic variety the cell count may reach into the hundreds. As to the Wassermann reaction, the same may be said of the spinal as of the cerebral form, in that the reaction is present in about half of

the cases in the fluid, and to the extent of about 75 per cent. in the serum, these figures not including patients having received treatment.

GENERAL PARESIS

Of all the luetic diseases that affect the nervous system, general paresis requires the most care from a diagnostic, therapeutic, and prognostic point of view. The etiologic factor has been determined beyond doubt by Noguchi, who demonstrated the *Treponema* in the brain tissue of paretics. The diagnostic difficulties, however, that certain forms of this disease offer in differentiation are by no means removed. It is hoped that with the aid of serologic methods this much-desired factor will to a certain extent be attained. Therapeutically, general paresis has been the bugbear of those who were called upon to treat patients so afflicted. That serology will point out the form of general paresis that is amenable to treatment, and will, besides, warn the clinician of the impending advent of this dread disease, are desiderata likely to be attained.

The involvement of the brain by the Treponema pallidum is so peculiar as to make remedial agents of little avail in reaching the affected focus. Deeply placed within the brain tissue, the microörganism propagates, produces noxious substances that call forth the constant formation of specific reagines in the body of the host, a fact evidenced by the strong positive Wassermann reaction. The secondary meningeal irritation is very mild, calling forth few cellular elements, which must be regarded as protective agents. It is logical to expect that in order to influence the disease, it is imperative that the infective agent be reached first. As this agent is very securely hidden in the brain tissue, rather remote from vascular channels, it is clear that more strenuous methods must be employed in order to check the further propagation as well as the concomitant formation of toxins by the treponema. Hence the difficulty encountered up to the present time in checking the disease by ordinary therapeutic measures, such as are usually employed with more or less success in cerebrospinal lues and in exudative tabes.

It is small wonder that the prognosis from a therapeutic outlook in these cases was very pessimistic. The reason for the failures is to be found in the fact that the remedial agent did not reach the microörganisms, or that when it came in contact with them it was too weak to destroy the virus entirely, but permitted sufficient numbers of the infecting microörganisms to survive to give rise to the propagation of a new generation of treponemæ. As the result of the many failures that attended such efforts, they are rapidly becoming obsolete in the treatment of this disease.

The outlook at present for the successful treatment of active syphilis of the central nervous system is very bright; in fact, good results are already attained in the active manifestations of tabes, the patient being relieved of the pains in a manner that is remarkable. These data covering this part of the therapy will be considered in the section on Salvarsan and its Administration.

The Distribution of the Treponema Pallidum and its Detection

The distribution of the Treponema pallidum, to quote Noguchi, is to the gyrus rectus, frontalis, Rolandic area, and in some instances to the gyrus hippocampi and in Ammon's horn. The microörganisms are found in greater numbers in the cortical layers, and to a less extent in the nerve-fiber zone.

If the sections are properly counterstained with toluidin blue or thionin, it can be seen that a pyramidal cell is closely surrounded by one or more organisms, and in some instances are inserted even into the cytoplasm of the cell. An amorphous precipitate may be visible in the vicinity of some of the pyramidal cells; this Noguchi believes to be an exudate. These pyramidal cells show degenerative changes, as is evidenced by their altered contour, by swelling, and by the disappearance of their nuclei. The Treponema pallidum is very rarely found in the vicinity of blood-vessels, and almost never within the vessel-wall. Noguchi is not certain that he encountered the microörganism in the pia.

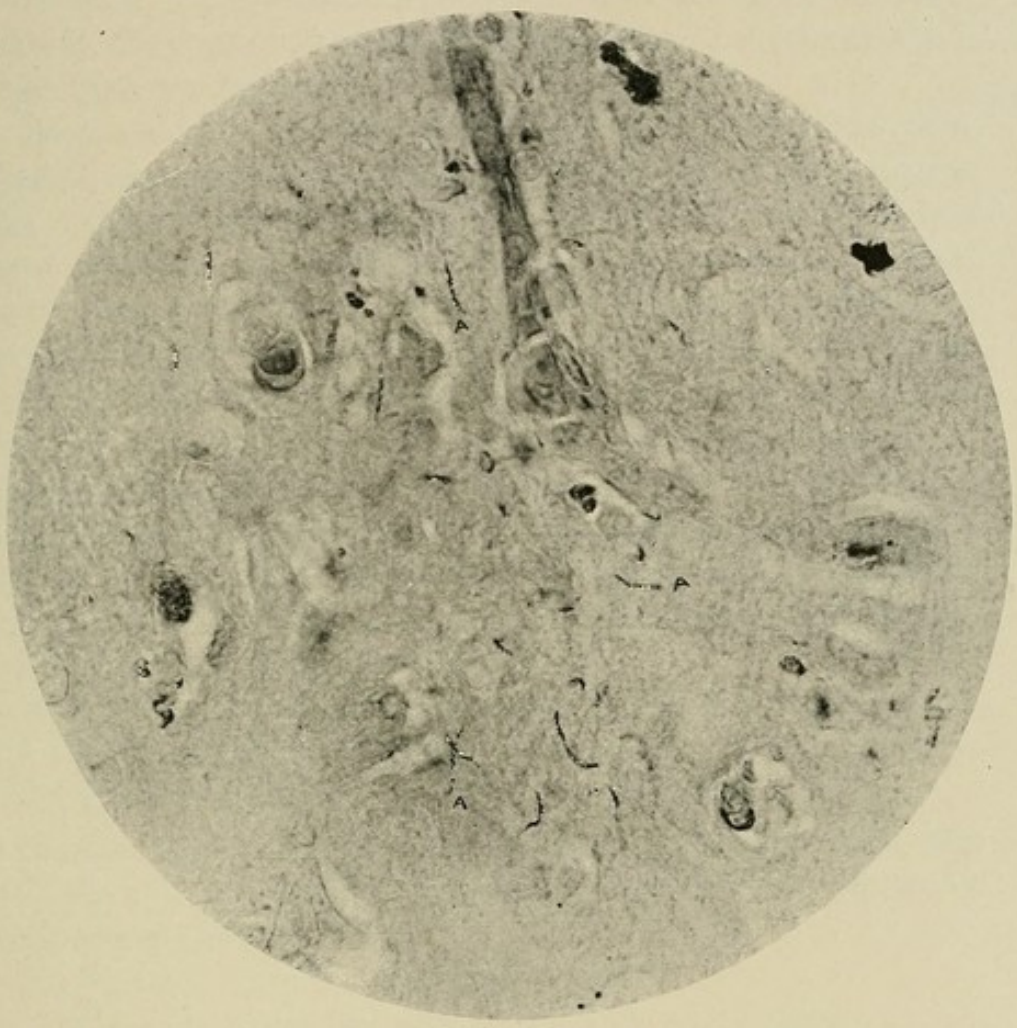


Fig. 19.—Showing Treponema pallidum (A) in the cortex of a patient who died of general paresis during a seizure. Stained by a modified Levaditi. Magnification 1100. (Courtesy of Dr. H. Noguchi.)

Although the technic of preparing tissue and sections for the study of the organism under consideration is not a serologic subject, it is so important that the author considers it necessary to describe the procedure in detail.

TECHNIC OF TISSUE STAINING

It is of the greatest importance that the tissue be completely fixed prior to impregnation. Specimens fixed for a year give excellent results.

Sections from one or more of the areas previously mentioned, and which have been hardened in 10 per cent. formalin, a slice of material measuring from 5 to 7 mm. in thickness, and being of variable dimensions otherwise, is put into a mixture consisting of 10 per cent. formalin, 10 per cent. pyridin, 25 per cent. acetone, 25 per cent. alcohol, and 30 per cent. distilled water. The tissue is allowed to remain in this for five days at room temperature. It is then thoroughly washed in distilled water for twenty-four hours. It is next transferred to 96 per cent. alcohol for three days, and again thoroughly washed with distilled water for twenty-four hours. After this the specimens are placed in a dark bottle, and receive the following treatment:

1. In 1.5 per cent. silver nitrate solution for three days at 37° C. (or five days at room temperature).
2. Wash in distilled water for several hours.
3. Reduce in 4 per cent. pyrogallic solution, with the addition of 5 per cent. formalin for twenty-four hours at room temperature.
4. Wash thoroughly in distilled water.
5. Transfer to 80 per cent. alcohol for three days.
6. Then transfer to 95 per cent. alcohol.
7. Place in absolute alcohol for two days.
8. Xylol, paraffin-xylol, paraffin.

The tissue is now ready for sectioning, the thickness of the section depending upon the degree of impregnation, and varying with different specimens of the brain. As a rule they are cut 3 micra thick, but when 5 micra in thickness the chances for finding more numerous specimens are increased.

The Theory of the "Wassermann Fast" Phenomenon

The serologic abnormity that first draws the attention of the laboratory worker to the initiation of a change suggestive of the onset of general paresis is, theoretically speaking, contemporaneous with the embedding of the treponemas in the brain tissue proper, having migrated by gradual stages from the meninges. The resulting serum analyses are, therefore, persistently positive, and remain so, in the majority of cases, regardless of the treatment usually administered. This is most likely the condition of affairs that exists in the "Wassermann fast" tabes, which, in my experience, is the serologic precursor of a taboparesis. It cannot be regarded as erroneous to consider cerebrospinal lues, tabes, and general paresis as originally one disease, each exhibiting different peculiarities of distribution of the microörganisms. It is also possible that a predisposition on the part of the individual infected plays a rôle in the production of the particular form of nervous yphilis, and the possible existence of more than one variety of treponema capable of producing lues must also be considered.

The general distribution in cerebrospinal syphilis speaks for the invasion of the meninges by the organisms; in general paresis, again, the organisms are more deeply placed; in the former disease the Wassermann reaction is rendered negative with comparative ease, the virus still being intravascular; in the latter the virus is protected by a wall of brain tissue.

If it were possible to attack the Treponema pallidum at the time when it begins to change its abode, or if tests could be devised for the detection of this more or less fatal transition, then we would possess a means of warding off the paretic attack. That a preëxisting cerebrospinal lues in some patients paves the way for the future development of general paresis was a theory advanced by Charles L. Dana years ago, and it became incumbent on the serologist to furnish a reaction or a number of reactions capable of directing the clinician's attention to the fact that the dangerous transition was at hand.

Although not established on an absolutely sure foundation,

it would seem that in the behavior of the Wassermann reaction, the globulin test, and the pleocytosis we have an index as to the possible onset of general paresis in a patient that may have been, and even yet is, afflicted with cerebrospinal lues. This question was touched upon in the consideration of cerebrospinal syphilis, and is to be elaborated here more extensively.

Before giving the serology of typical general paresis, the author wishes to emphasize the fact that the positive Wassermann reaction in this disease is somewhat different from the positive Wassermann result obtained in other syphilitic nervous diseases, unless they are undergoing a transition stage to general paresis. As is well known, the second part of the Wassermann reaction consists in the hemolytic incubation. The test-tubes containing syphilitic sera will begin to show a clear zone at the top of the tube, the cells gradually sinking to the bottom. The time required for this phenomenon to manifest itself is from ten to thirty minutes. Those who are accustomed to read Wassermann end-results will note that the sinking of the cells to the bottom takes place much sooner in some tubes than in others; in some cases this may consume even one hour or more. The tubes that show this early sedimentation are, as a rule, those containing sera from patients with general paresis. If the test-tube racks are gently removed from the incubator without the least shaking of the tube contents, it will be observed that the sera of general paretics show a lateral constric tion, similar in conformation to two parenthesis signs placed with their convexities toward each other,—)(,—the sides being entirely clear, and the top and bottom fluids being opaque and of an old-rose color. Not the slightest trace of free hemoglobin is to be detected in the fluid after twenty-four hours' standing, the supernatant liquid being of the transparency and color of clear water. In the vast majority of instances this will be the case when the serum is that from a patient with general paresis. It was previously emphasized that the cell count in cerebrospinal syphilis numbers, as a rule, over 100 cells per c.mm.; later we shall see that the pleocytosis in general paresis is only

very exceptionally above 100, and presents, in the majority of instances, less than 60 cells per c.mm.

In the course of treatment of a case of lues cerebrospinalis the serologic return to a more or less normal state follows certain well-defined paths, unless the patient shows a tendency toward the development of general paresis. This tendency is manifested by a marked fall in the cell count as a result of the treatment, but the Wassermann reaction remains uninfluenced. When the Wassermann reaction persists, and besides shows the peculiarity previously spoken of, the serologic evidence that the transition from cerebrospinal lues to general paresis is about to take place is at hand. The persistence may be either in the serum or fluid, and the latter may or may not show the reaction of a globulin excess. These serologic manifestations need not go hand in hand with the clinical evidences; on the contrary, many months may elapse before clinical corroboration establishing the justice of the laboratory's contention can be adduced. In one instance that came to the author's notice the paretic manifestations became apparent three years after the opinion had been advanced by the serologist.

The early recognition of the transitory stage, if it may be so termed, is much more important now than it was before the era of modern therapeutics, for the reason that it is sometimes possible, with the proper use of newer remedial agents, to check the further advance of the disease.

THE SEROLOGY OF THE FULL-FLEDGED TYPE

Under this head are included those cases that gave clinical evidence of the existence of paresis and some in whom the diagnosis was made only after the serologic report had been presented. Before the serology was submitted in these cases the diagnosis rested between cerebrospinal lues, cerebral syphilis, and arteriosclerosis.

This type of serology was encountered in 120 out of 261 cases of general paresis, and presented all the serologic characteristics mentioned in the introductory remarks. The findings were as follows:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Positive.	Excess.	17 to 50.	Prompt.

The pleocytosis of this type, together with the intensely positive Wassermann reaction and the globulin excess, is typical of the condition. On very rare occasions only is this picture present in a case of tabes, and when such is the case, it becomes the physician's duty to employ strenuous methods to overcome this type of serology, as it means, very often, a tendency toward the development of a general paresis.

Other Serologic Combinations

In a number of patients, 63 in all, the cell count ranged from 62 to 78 per c.mm. Some of these patients received vigorous treatment and showed some improvement as a result. In 29 others the serology was somewhat different, and may for the time be considered as of a type that is less pernicious than is the full-fledged type just considered.

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Negative.	Excess.	65 to 80.	Prompt.

The serology here outlined resembles slightly that which one might expect to find in a case of cerebrospinal syphilis of the Plaut type after a course of treatment. It is more often the case, however, that during the course of treatment the serum Wassermann becomes negative before the fluid Wassermann reaction, particularly when the cells in the fluid show a marked reduction in numbers. In addition to the apparent resemblance of the serology of cerebrospinal syphilis to the Plaut type, the French school (Marie) believes that the very incipiency of the paretic serology manifests itself in a picture analogous to that of the 29 cases above cited, *i. e.*, the serum is positive and the fluid negative. The French, however, do not consider that the upper limit of the pleocytosis is also of significance, a point

that must be remembered in determining the logical construction of a transitory serology from the one disease to the other. This French opinion will be dwelt on more fully further on. It should be borne in mind that the negative Wassermann reaction in a patient's cerebrospinal fluid with clinical evidence of general paresis removes it, so far as the serologic interpretation is concerned, from the full-fledged type of the disease. Even if the French teaching is true only in part, it nevertheless holds out some hope to the paretic who presents the so-called early type serology, which may be regarded, following Dana's reasoning, as the transition from a cerebrospinal syphilis. This form of serology may, therefore, be considered as favorable for the employment of therapeutic measures, a contention that was corroborated by the improvement that followed treatment of cases presenting this type of serology. The developments in the treatment of nervous diseases of syphilitic origin are so promising at the present time that great hope is entertained as to the ability, in the future, of warding off indefinitely the fatal paretic deterioration. Of this, more will be adduced in the section on Salvarsan and its Administration.

The attitude of Plaut, in his book on "The Wassermann Sero-diagnosis of Syphilis in its Application to Psychiatry," is very significant in connection with the stand taken by the author. On page 86 of the American translation of 1911 Plaut is quoted as saying that one does not go too far in accepting as true the statement that paretics, at the time of onset of the disease, are still syphilitics; these conclusions being based on the fact that in so far as the intensity of the Wassermann reaction is concerned in the serum, these patients manifest the same symptoms as patients in the florid stage of syphilis, and differ clearly from those in the latent tertiary stage. The phrase "at the time of onset" is very significant, at least it appears so to the author, for it is at this time that the Wassermann reaction is very strongly positive in the serum, and may not show a positive result in the cerebrospinal fluid at all—a fact that links more closely together the interrelationship of the serology of general paresis and cerebrospinal syphilis, particularly the

type described by Plaut. Besides the type of serology that gives a negative Wassermann reaction in the cerebrospinal fluid there is another that, similarly, does not show a globulin excess, as may be seen from the following table:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Negative.	Negative.	30 to 83.	Prompt.

This serology was obtained in 25 cases, and it was deemed better to consider two patients as in the transition stage from cerebrospinal syphilis to general paresis. These two cases showed 81 and 83 lymphocytes respectively, and reacted very favorably, both clinically and serologically, to treatment. The cell count diminished markedly, the Wassermann reaction became negative after three months of therapy, and the patients were able to resume their vocations, reporting regularly every three months for serologic analysis.

Another combination of serologic findings must be reported, as these cases exemplify the French type of the advanced disease:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Positive.	Positive.	15 to 29.	Prompt.

This serologic study disproves the contention that general paresis always gives a positive serum Wassermann reaction. This form of serology most frequently occurs in the later stages of the disease, and is encountered most often during the paretic decline, in patients who are afflicted with bedsores and whose mentality is entirely shattered.

Plaut observed eight cases with very slight pleocytosis and a serology similar to that described among the serum negative findings elsewhere. In the author's experience only 14 such serologic findings were obtained, but Plaut's series is introduced here chiefly to point out his contention that 5 out of his 8 patients were, in his opinion, cases of beginning paresis; on the other hand, the same worker

describes one of the cases that at autopsy proved to be an ordinary case of advanced paresis. Later he makes the assertion that he has observed enough cases of beginning paresis with a very decided cellular increase. This latter view is entirely in accord with our findings at the Institute, *i. e.*, that a decided pleocytosis marks the early paretic; a slight pleocytosis and a negative serum Wassermann, on the other hand, in the majority of instances are significant of the advanced form. The full-fledged type expresses the serology of the fully developed form of the disease as found in the greater number of cases. The last form of serology to be described will seem almost an impossibility to those who have worked with serologic methods that tend to make the Wasserman reaction more sensitive, as the findings are entirely negative:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Negative.	Negative.	Normal.	5 to 11.	Prompt.

A computation of the percentage of the various serologic posibilities will show that this form is the one least likely to occur, and the 10 cases collected that presented this serology include 3 who received very strenuous treatment, each having had over 18 intravenous injections of salvarsan. These patients improved after the first ten to twelve injections, so that it was thought advisable to push the treatment until the serology would become negative. The foregoing findings show the result of the treatment, these being practically normal. The serology of the remaining 7 does not give any particular evidence, but serves to emphasize the previous contention that one is not justified in making rules that are hard and fast and that permit of no exceptions. There is only one uncontrovertible rule, and that is that a positive serology is not compatible with a nervous disease of non-luetic origin; on the other hand, a negative serology may be obtained in a syphilitic nervous disease. In general paresis the various serologic combinations showed the following proportions:

Serum W. R..	Positive.	Positive.	Positive.	Positive.	Negative.	Negative.
Fluid W. R...	Positive.	Positive.	Negative.	Negative.	Positive.	Negative.
Globulin....	Excess.	Excess.	Excess.	Normal.	Excess.	Normal.
Pleocytosis ..	17 to 50.	62 to 78.	65 to 80.	30 to 83.	15 to 29.	5 to 11.
Reduction...	Prompt.	Prompt.	Prompt.	Prompt.	Prompt.	Prompt.
	120 cases, or 46 per cent.	63 cases, or 24 per cent.	29 cases, or 11 per cent.	25 cases, or 9.5 per cent.	14 cases, or 5.3 per cent.	10 cases, or 3.8 per cent.

The French Conception of Serologic Progression

Marie and his pupils formulated a series of reactions as exhibited by the disease in its various stages. These workers obtained different serologic results in the beginning of the disease, these differing also from the analyses obtained in cases in which the disease was fully developed and during its decline. Although other workers, including the author, could not corroborate Marie's finding in every instance, it must nevertheless be accepted as an established fact, although in some instances contrary results were obtained. Of the patients whose serology is shown in the foregoing table, some of the 29 in the third column were in a moribund condition, and one of the 14 in the fifth group showed clinical signs of the very earliest advent of the disease. The facts taken together, making allowance for exceptions that all laboratory data are entitled to, present a guide that can be accepted for occasional use in the classification of the stage of the disease. Discrepancies will naturally be encountered, but this is no argument for disregarding the very interesting and useful observations of the French investigators. The serologic progression from the early stage of the disease to its final deterioration is as follows:

	Incipient Stage.	Fully Developed.	Paretic Decline.
Serum W. R.....	Positive.	Positive.	Negative.
Fluid W. R.....	Negative.	"	Positive.

The globulin content, pleocytosis, and the reducing power were not considered in the studies; at least no special significance was attached to them. If we were permitted to formulate a serologic succession of events from the material analyzed by the author, the following arrangement of the

entire serologic chart, taking into account the work of Marie as well, would give the following result:

	Incipient Stage.	Fully Developed.	Paretic Decline.
Serum W. R.....	Positive.	Positive.	Negative.
Fluid W. R.....	Negative.	Positive.	Positive.
Globulin.....	Excess or not.	Excess.	Frequently normal.
Pleocytosis.....	More than 60.	60 or less.	Less than 40.
Reduction.....	Prompt.	Prompt.	Prompt.

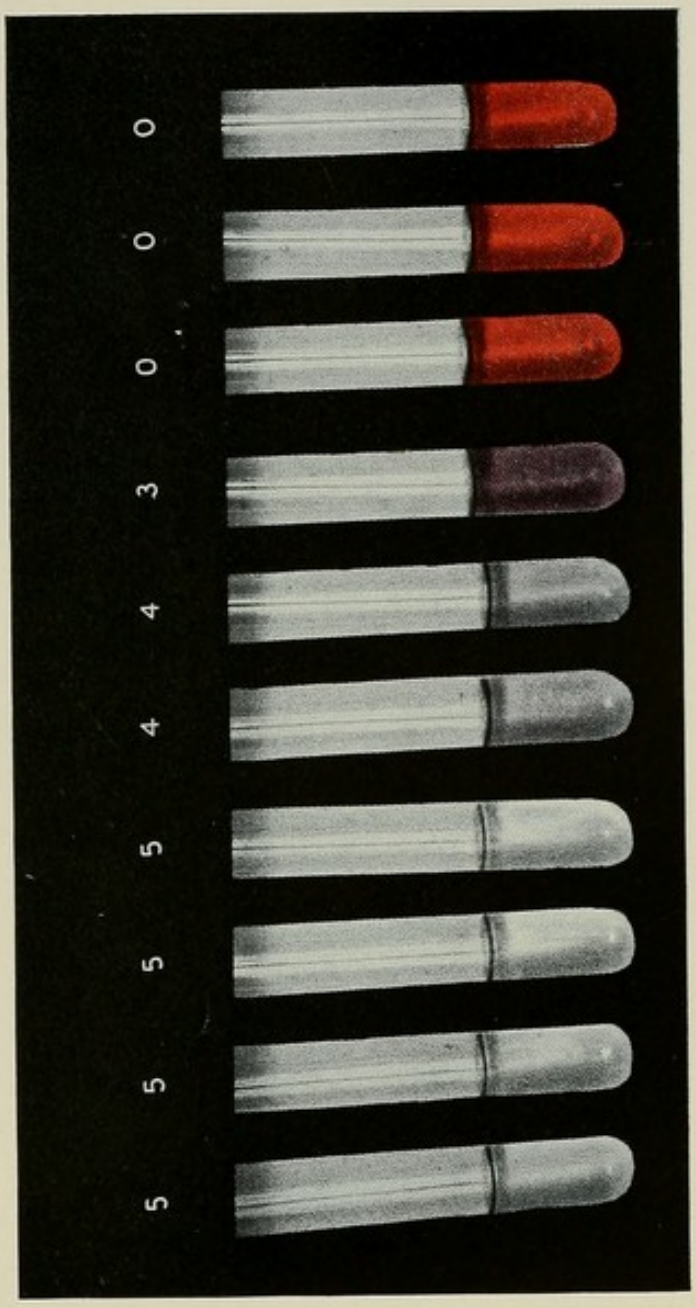
Although when these observations are given considerable latitude they are useful, when viewed critically they will furnish sufficient grounds for argument, as many exceptions to the formulæ here laid down will be found. The number of cells per c.mm. alone will give rise to much speculation, as some observers will claim that in a certain patient more than 100 and even 200 cells were counted in the spinal fluid. All these exceptions must be admitted, although the serologist who has had sufficient neurologic training will perhaps question the genuineness of a general paresis that exhibited over 200 cells per c.mm. in the cerebrospinal fluid. Nevertheless, such cases are seen, just as scarlet fever without a rash is occasionally encountered, or as typhoid bacilli may occur in the blood-stream without giving rise to the disease. In the greatest majority of cases, however, these findings will hold good and prove of the greatest utility to the clinician.

The Gold Chlorid Curve

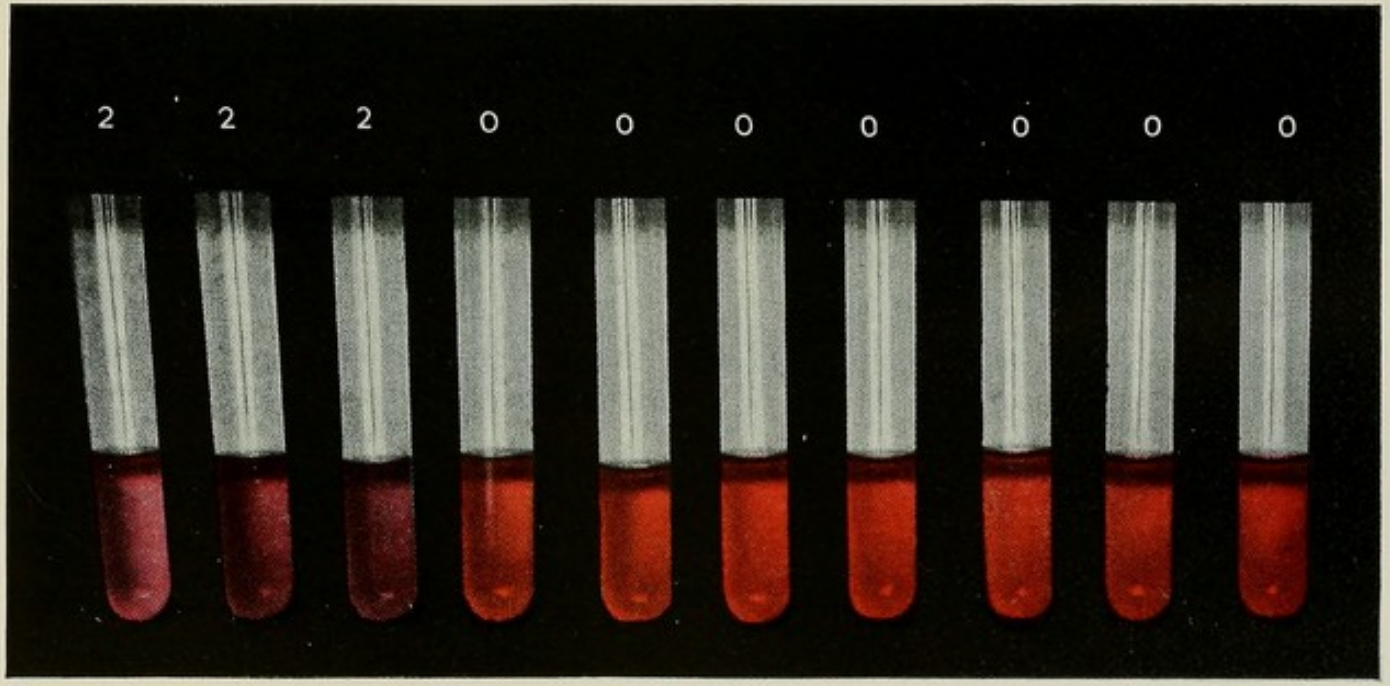
Since the studies of Lange concerning the significance of the precipitation (Ausflockung) of colloidal gold in the cerebrospinal fluid of syphilitic patients, a few papers have appeared in America, all attaching great diagnostic significance to the appearance of the reaction.

In the experiments undertaken at the Neurological Institute it became apparent that although no great amount of specificity could be placed on the precipitation in all cases of neurologic lues, a definite reaction, however, could be observed in paresis and in some cases of tabo-paresis. The tech-

PLATE II



A typical "step-ladder" curve as obtained in a case of general paresis.



Negative result in a case of tabes. This precipitation of colloidal gold is frequently the occurrence in tabes and in some cases of cerebrospinal lues.

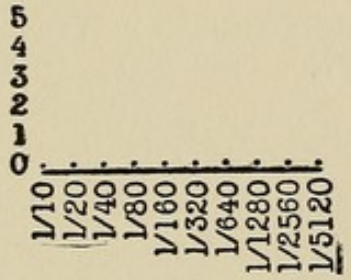
nic of the test was described in the first part of this volume, but it is deemed advisable to describe here the meaning of the curve and the color changes, as well as the dilutions.

The color of the gold solution, as stated elsewhere, is a deep red without the least trace of brown. From 9 to 12 tubes of various dilutions of cerebrospinal fluid, from 1 : 10 to 1 : 2560 or more are prepared. The red gold is placed in each tube, and permitted to remain at room temperature over night. The next morning some tubes will show definite color changes, which are designated as follows:

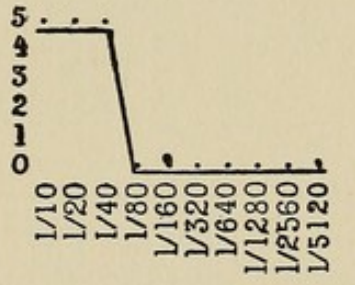
Complete precipitation showing a water-clear, colorless fluid equals.. 5
The slightest tinge of a steel gray is designated as..... 4
A somewhat deeper shade than the above or bluish tinge as..... 3
A reddish blue or bluish red as..... 2
A red color, slightly different from the original color, as..... 1
No change in color as..... 0

The numbers are arranged from 5 down to 0; the dilutions are arranged from left to right, starting with the 1 : 10 tube.

An absolutely negative curve would present the following characters:



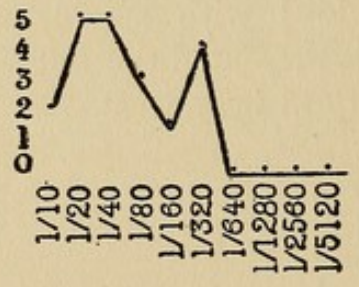
The curve obtained with spinal fluids from patients with general paresis presented the following general appearance in the majority of instances:



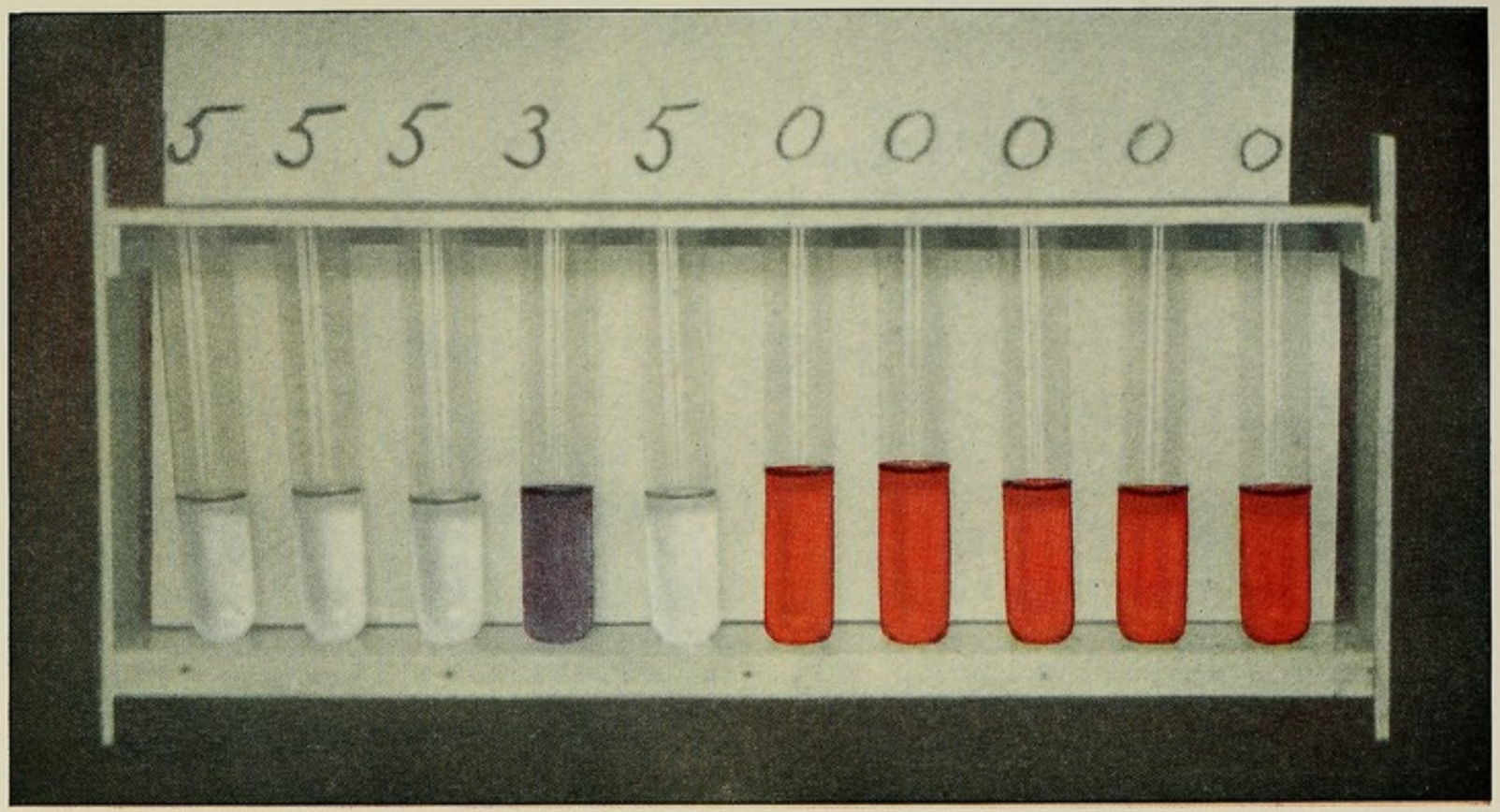
From the previous explanatory remarks, it will be seen that there was no change in the first curve from the original color

of the colloidal gold, which is a rich red in every tube; the curve obtained in general paresis, however, presented an absolutely clear series of three tubes in the first three dilutions; then a drop to 0, or no color change. This drop and the general resemblance to a step or series of steps suggested the name "step-ladder curve," by which term this particular form of precipitation of the colloidal gold is known in the author's laboratory. Although very suggestive of general paresis, it is not to be regarded as characteristic without considering the other accompanying features of the serology of this disease. Emphasis must, however, be placed on the fact that up to the present this curve has been very constantly found in this syphilitic nervous disorder. The intensity of the positive Wassermann and the other serologic findings, and, especially, the clinical corroboration that is always to be had when the fluid gives this reaction, make this curve one of the most important aids in formulating a diagnosis of general paresis. It is also demonstrable in the majority of cases of tabo-paresis, and, like the other findings, is not easily affected by therapy.

The curve was also obtained in a case of multiple sclerosis, while in six others it was absent. In cerebrospinal lues the curve does not show the uninterrupted series of colorless tubes in the first dilutions, but displays a rise, then a fall, and then another rise, so that the continuous feature is not observed. The following may serve as an example of such a curve:



At present sufficient results are not at hand to justify the contention that a diagnosis of syphilis of the nervous system can be made after securing the colloidal gold reaction. In the author's experience paresis and tabo-paresis give characteristic precipitations with gold chlorid, in that the first

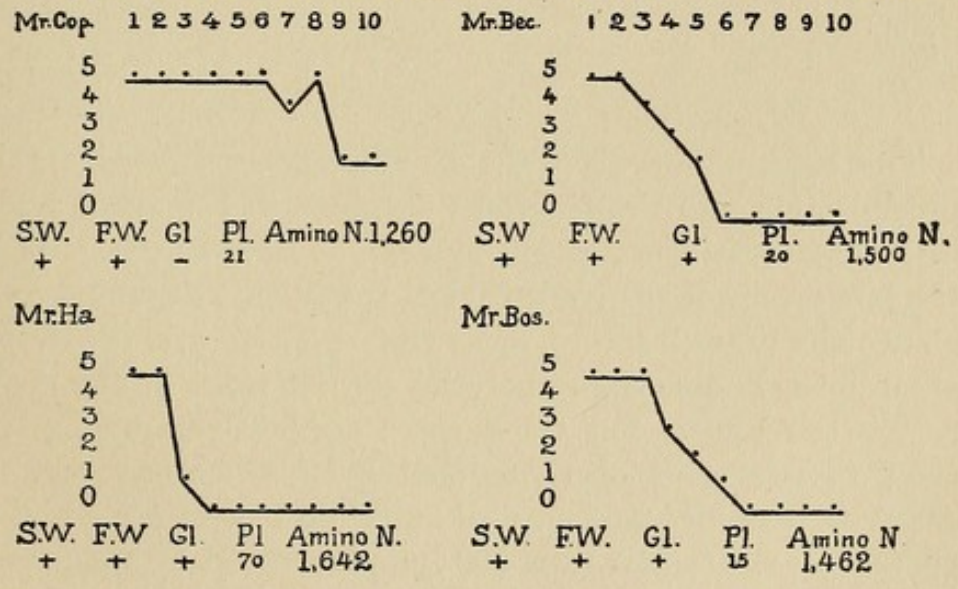


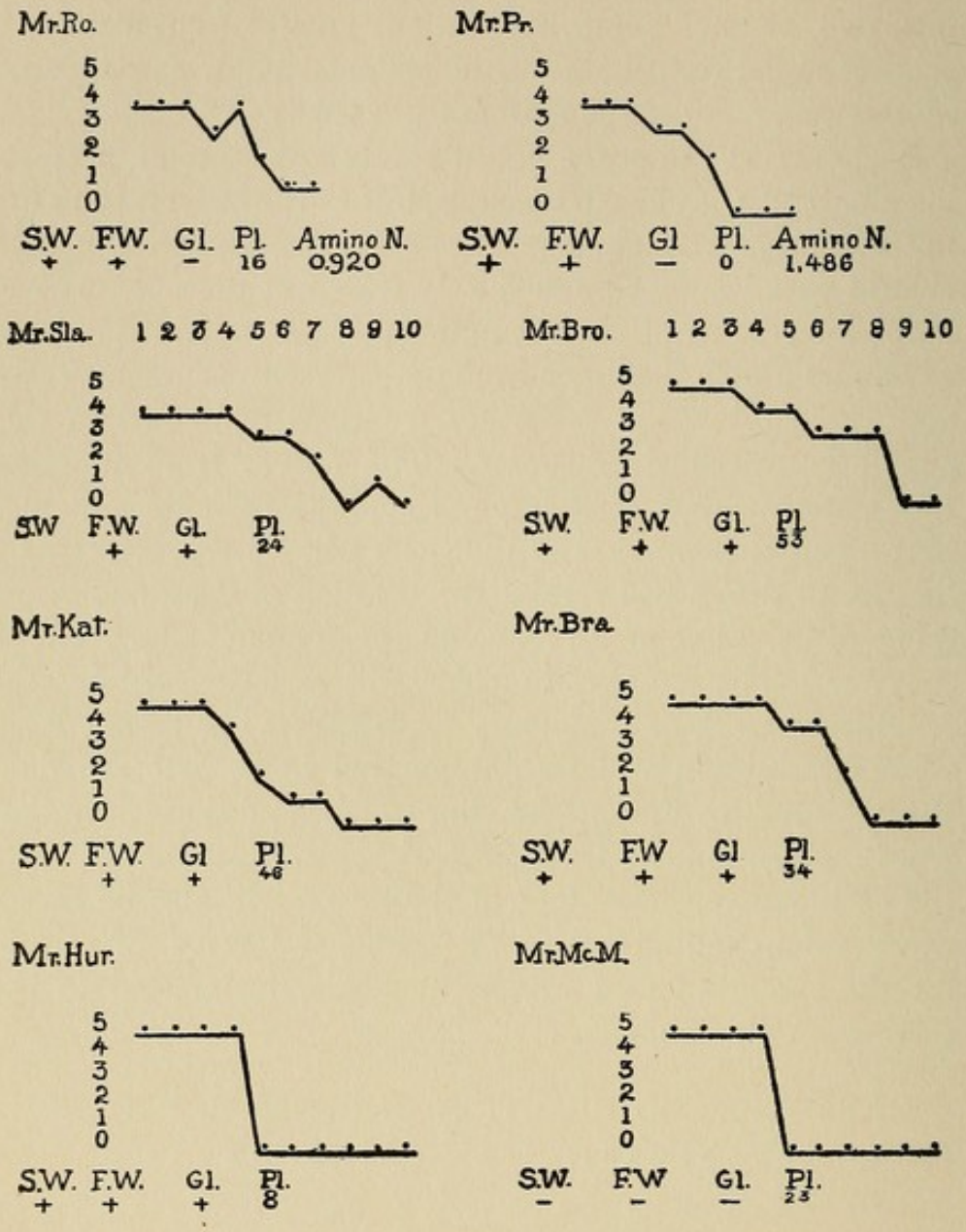
Precipitation of colloidal gold. Although the above is a positive curve, it is not characteristic of general paresis. In the latter the complete precipitation is uninterrupted. An interruption may, however, take place, but only after very intense treatment.

one, two, or more tubes, *i. e.*, in the greater concentrations, show complete precipitation of colloidal gold, as evidenced by the clear color of the fluid in these tubes.

A change in the curve is but rarely apparent after treating a patient with general paresis, but as the observations are not extensive enough, the effects of therapy on the gold chlorid curve cannot be definitely stated at present. It will be of interest to observe a number of "step-ladder" curves as obtained with the fluids from patients with general paresis, and also to describe the other reactions employed in this syphilitic neurologic disorder. The curves from tabetics, tabo-paretics, and cerebrospinal syphilis patients will also be presented below. The dilutions will be represented by figures, so that 1 will represent a dilution of $\frac{1}{10}$, 2 one of $\frac{1}{20}$ 3 one of $\frac{1}{40}$, 4 one of $\frac{1}{80}$, 5 one of $\frac{1}{160}$, 6 one of $\frac{1}{320}$, 7 one of $\frac{1}{640}$, etc. The changes in color will be expressed by the numbers 5 to 0, as previously explained. The serum Wassermann reaction will be abbreviated to S. W.; the fluid Wassermann, to F. W.; globulin, to Gl.; and the cell content will be given under Pl. (pleocytosis). In a number of cases the amino-nitrogen content of the serum will also be given, expressed in milligrams of nitrogen per 100 c.c. of serum, for the significance of which the reader is referred to the section on this subject.

GOLD CHLORID REACTION IN GENERAL PARESIS

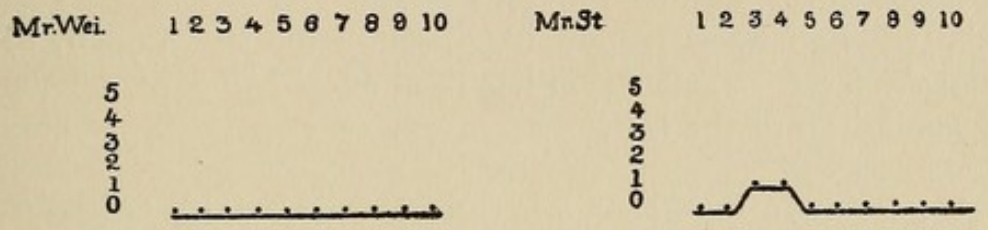




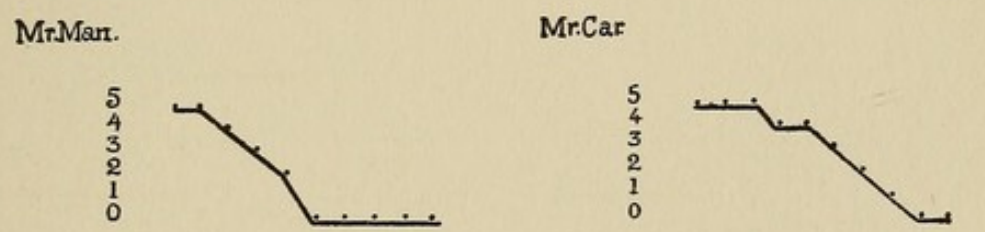
The contrast between the genuine general paresis gold precipitation and the reactions obtained in the other syphilitic diseases of the nervous system, at least as observed in the laboratory of the Neurological Institute, will reveal at a glance the importance of these tests. There are, of course, exceptions, in that some paretics do not react in the characteristic manner, but these cases are few, comprising less than 10 per cent. of those analyzed. Only one case of cerebrospinal lues and one of multiple sclerosis gave this curve. In the former over 500 lymphocytes per c.mm. were

obtained, which, in the author's opinion, is quite sufficient to exclude general paresis, and, so far as multiple sclerosis is concerned, the author believes that one is rarely called upon to decide between this disease and general paresis, so that the curve obtained will not, and in the given instance did not, influence the diagnosis of multiple sclerosis in the least.

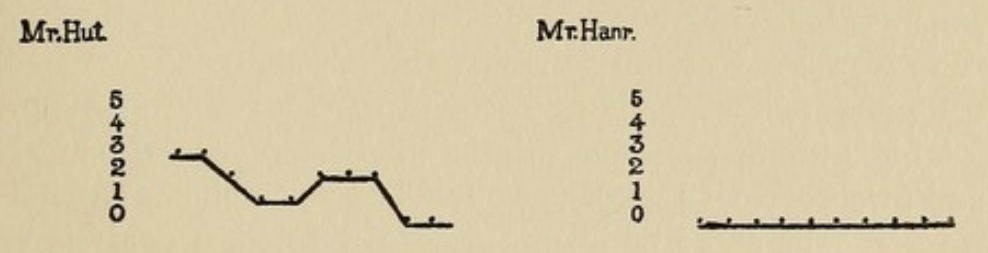
The precipitation in tabes shows, in the majority of instances, the following curves:



The advent of paresis or tabo-paresis is represented by a curve that is very suggestive of the general paresis curve, being another corroborative biologic phenomenon in favor of the earlier appearance of laboratory signs in the very beginning of paresis rather than the development of clinical symptoms.



In cerebrospinal lues the curve is also quite different from the general paresis "step-ladder" appearance.



The opinion of Lange and of those who followed him in experimenting with fluids from patients with syphilitic affections of the nervous system, that there is a specific pre-

cipitation of the colloidal gold in cerebrospinal fluids from such patients, must, as the result of Dr. McClelland's and of the author's experience, be modified considerably before it can be accepted in toto. The curve does not depend upon the protein content of the cerebrospinal fluid, as some fluids without an excess showed the curve and some with a very marked excess gave no curve whatever. A similar result was obtained with tabetics who gave no reaction of an excess, and also with patients with cord tumors, who showed the presence of a marked protein excess. The *raison d'etre* of the reaction must remain in abeyance for the present, as no satisfactory explanation has been offered to cover all the peculiarities of the test.

THE SEROLOGIC DIFFERENTIATION BETWEEN LUES CEREBROSPINALIS AND GENERAL PARESIS

As the result of a wide experience with neurologic material, coupled with the services of a serologic laboratory, Nonne made the attempt to differentiate, serologically, between the two diseases—cerebrospinal lues and general paresis—that at times present difficulties to the clinician. His serologic analysis of the two diseases is as follows:

PARESIS OR TABO-PARESIS.	CEREBROSPINAL SYPHILIS.
Serum Wassermann positive (in almost 100 per cent.). Spinal pressure frequently increased.	Serum Wassermann positive (in nearly 80 to 90 per cent.). Spinal pressure often increased.
Phase 1 positive (in nearly 95 to 100 per cent.).	Phase 1 only exceptionally absent.
Lymphocytosis (in nearly 95 per cent.).	Lymphocytosis, like phase 1, usually present.
Wassermann reaction in fluid positive in about 85 to 90 per cent., using 0.2 c.c.	Wassermann reaction positive in about 10 per cent. of fluids, using 0.2 c.c.
Using larger amounts—plus in 100 per cent.	Using larger amounts—nearly always plus.

This attempted differentiation between general paresis and cerebrospinal syphilis, as offered by the eminent German worker, falls short of its purpose. Upon close analysis of Nonne's table, one is at a loss to determine upon what special feature in either disease he places the greatest reliance. In both conditions the blood-serum is very rarely negative

to the Wassermann test. The same is true of the spinal fluid. The phase 1 is present in one to the extent of 100 per cent., and in the other it is only exceptionally absent. The same is true of the lymphocytosis. The only possible differentiating feature is obtained when but 0.2 c.c. of spinal fluid is used in testing for the Wassermann reaction, for then it will be obtained in almost 90 per cent. of cases of general paresis, and in only 10 per cent. of those of cerebrospinal syphilis, a feature that is obliterated when using larger quantities.

If the clinician should be compelled to seek the laboratory's aid in clearing up a difficult case of neurologic syphilis, and particularly if he sought to differentiate between general paresis and cerebrospinal syphilis, the author is convinced that very little help, if any, would be obtained from the table just given. The points of difference, as they appear from an analysis of the material collected in this exposition of the subject, would be as follows, not including cases that were treated with specific remedies:

UNTREATED CASES OF

General Paresis.	Cerebrospinal Syphilis.
Serum Wassermann plus in 90.9 per cent.	Plus in 88.7 per cent.
Fluid Wassermann plus in 75.3 per cent., using from 0.2 to 0.5 c.c.	Plus in 32.7 per cent.
Globulin excess in 86.7 per cent.	Excess in 50.3 per cent.
Pleocytosis, as a rule, less than 100 cells per c.mm., and obtained in 96.2 per cent. of cases.	Pleocytosis usually more than 100 per c.mm., and present in 96.7 per cent. of cases.
Fehling reduction prompt in 100 per cent.	Sometimes absent.
"Step-ladder" gold curve obtained in over 90 per cent. of cases.	Present in less than 5 per cent. of cases.

Juvenile Paresis

The occurrence of juvenile paresis, which must be considered as a disease produced by syphilis in the parents, disposes, in the great majority of instances, of the possibility conceived by some workers that, for the production of this disease, a special variety of the Treponema pallidum is necessary. In the cases observed and reported upon by Plaut no luetic parental data could be obtained. That

such parents may have had syphilis in some form that was kept from observation as the result of proper treatment is possible, but this is not the case with paresis, which is sooner or later diagnosed with accuracy and easily elicited from the anamnesis. In other words, juvenile paresis is not necessarily dependent upon the existence of paresis in the parents, but may be the result of any variety of syphilis, whether vascular, visceral, or osseous.

The following case is that of a youth of twenty, an errand boy, born in the United States. He was brought to the Institute on account of trouble with his eyes:

Previous History.—One of five children, who are all healthy. A brother next older to the patient is a periodic drinker. Patient went to school at five, but did not progress well. When about six he began to play truant. In his ninth year the patient complained of an inability to see print or to write. Began to smoke cigars at ten, and left school at thirteen. Associated with men of questionable character. His father having been in the liquor business, the boy began to use alcoholics to an inordinate degree. His eye-sight kept getting worse. When examined physically he showed no pupillary response to light; right pupil very irregular. Corneal sensibility reduced in both eyes; mobility normal; no nystagmus; no diplopia. Vision R., no perception; L., $\frac{5}{200}$. Fundi, simple optic nerve atrophy, more marked in right. Mentality that of a boy of nine (Binet test). Cannot repeat test sentences correctly. Station normal; some tremor of upper extremities; apparent ataxia of lower extremities. When told to perform certain acts, often did the opposite. Complete pharyngeal anesthesia. No tremor of tongue. Abdominal and epigastric reflexes present and equal. Knee-jerks elicited with difficulty. Flexor plantar response. The changes in the reflexes are not accompanied by any palsies, such as might be present in a multiple neuritis. Teeth show Hutchinsonian characteristics. Facial asymmetry.

This case, although presenting distinct irregularities, was, upon the strength of the serologic report, diagnosed as one of juvenile paresis. He gave a positive serum and fluid

Wassermann, an excess of globulin, and 8 cells per c.mm., together with a typical gold chlorid curve. (See Mr. Hur under Gold Chlorid Test.) The assurance the physician receives from such an analysis is self-evident, and removes all doubt from his mind as to the underlying cause of the disease. This patient emphatically denied all knowledge of an infection. The patient's mother shows diminished intelligence, has pupils that do not react to light, and gave a positive Wassermann reaction in the serum.

The Influence of Therapy on the Serology of General Paresis

This subject is discussed not so much with the purpose of showing what improvement can be accomplished clinically in this disease,—a subject that will be presented in a subsequent part of this volume,—but, rather, for the purpose of showing to what extent one can change the serology or render a positive Wassermann negative by instituting strenuous therapeutic measures. A careful study of the "Wassermann fast" quality of general paresis will shed a great deal of light upon the conception of the serologic progression of a syphilitic disorder from cerebrospinal lues or tabes to general paresis. Bearing in mind the Darwinian dictum that "*Natura non facit saltum,*" it is incumbent upon the physician to regard as important the "Wassermann fast" quality of his patient's serum. Even though the patient may at this time show no clinical manifestations of the disease, such as speech, memory, or character defects, the serum, nevertheless, takes on a peculiarity that is present most strikingly in general paresis. This similarity is in itself sufficient to warrant placing the patient under rigid observation and treatment; in other words, it is the physician's duty to overcome as quickly as possible the "Wassermann fast" tendency of the patient's serum. It is the author's conviction that the treatment that is capable of overcoming a positive Wassermann reaction in the fluid and serum is much more valuable and of greater significance to the patient than is the complete removal of the pleocytosis. The latter is only a sign of meningeal irritation, whereas the

former is "the writing on the wall" that will sooner or later claim its victim. Timely and vigorous interference may in some instances avert, or at least postpone, the danger.

Patient O. presented before treatment the following serology:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Positive.	Positive.	11 cells.	Prompt.

Upon receiving this report treatment was instituted, and 0.6 gm. salvarsan was administered intravenously. The serology obtained five weeks later showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Positive.	Positive.	11 cells.	Prompt.

A similar dose of salvarsan was administered one week after the last serologic examination, and another serologic analysis made after two weeks. This showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Positive.	Positive.	Positive.	10 cells.	Prompt.

A third intravenous injection, given immediately after the performance of the tests, followed by a serologic study one week after the treatment, gave:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.	Reduction.
Weakly positive.	Positive.	Positive.	7 cells.	Prompt.

Despite the normal cell count obtained in the fluid, the treatment cannot be considered successful, as enough factors still exist in the patient's body to supply sufficient

"reagins" for the persistence of the positive Wassermann in the fluid and to a lesser extent in the serum.

With the ordinary methods of introducing salvarsan into the system, and with the present dosage, number of injections, and duration of treatment-free intervals, the disease process still continues its progress unabated, as is shown by the persistent Wassermann. The foregoing serologic study is only one of many in which approximately the same result as the one cited was obtained. Concerning the different methods of treating this malady, the reader is referred to the section on Treatment.

Resume and Remarks

An analysis of the serology of general paresis conveys the impression that of all syphilitic diseases of the central nervous system, this disease, when it does present a positive Wassermann in the serum in particular, and in the spinal fluid, to a lesser extent, will give the reaction in its greatest intensity. It also possesses the quality that has been termed "Wassermann fast," in that it is very difficult to secure a negative result by means of treatment. This peculiarity is occasionally present also in the other syphilitic diseases of the nervous system, and when it occurs, is to be considered as a "*Signum mali ominis.*" The transition from cerebrospinal lues to general paresis is preceded by the "Wassermann fast" reaction, and the same is true also of the transition or the advent of a tabo-paresis. The decrease in the number of cells in a case of cerebrospinal syphilis, without influencing the positive serum Wassermann, bears out the conception of Marie of the serology of general paresis in its early stage, particularly when ushered in with a cerebrospinal lues of the "Plaut type."

In the light of modern research serologic methods permit us to differentiate between cerebrospinal lues and general paresis, provided the typical serology is obtained where the clinical opinion is uncertain. Where the serology is dubious, as it not infrequently is, a waiting policy is best, or therapy may be instituted regardless of the uncertainty that exists as to the final diagnosis. Treatment may, in fact, help consider-

ably in deciding for one or the other disease, as was suggested on a previous page. It is not at all difficult to ascertain the cause for a persistent Wassermann reaction in a paretic patient. If we regard the luetic process from the locality affected, we will see that in general paresis the amount of protection given to the Treponema pallidum is much greater than in the other syphilitic diseases of the nervous system. If the process is situated in the cerebral cortex proper drugs injected into the veins will have little chance of reaching the walled-in, inaccessible microörganisms; hence the formation of necessary reagins for the existence of a positive Wassermann is ideal and almost constant.

The process that permits the appearance of a "Wassermann fast" state may be regarded as a migration of the treponema from accessible to deeper, inaccessible brain portions, establishing a depot for reagins, and forming the histologic nucleus for a future general paresis. How long a time a "Wassermann fast" state must exist before clinical features of the disease manifest themselves, or, expressing the hypothesis in its histologic equivalent, how much of the brain substance must be involved before paretic symptoms present themselves, is a problem worthy of investigation.

It may safely be predicted that the gold chlorid curve ("step-ladder curve") will occupy a prominent place in the detection of the foregoing tendency, as evidenced by the presence of this reaction in tabo-paresis. It is not characteristic of syphilis of the nervous system in general, but is very constantly present in general paresis. Tabes does not give it and neither does cerebrospinal lues.

In the study of psychiatric material one is frequently called upon to differentiate between post-traumatic psychosis and general paresis. In these cases one must consider the possible coexistence of a visceral lues, a fact which should not confuse the investigator. If the fluid is negative, the chances are against the diagnosis of general paresis, although negative fluids are not impossible in general paresis. If doubt exists, the gold chlorid is made use of, which would, in the

majority of instances, decide the diagnosis; if, however, this proves unsatisfactory, then the resistence to therapy of the positive serum Wassermann should be taken into account. With our present development of serologic methods, it is hardly possible to err in the exclusion of a non-luetic disease of the nervous system.

In the alcoholic psychosis (pseudoparesis) one finds no difficulty in differentiating the condition from general paresis, and the same is true of the manic-depressive psychosis. Some paranoid forms of general paresis may give rise to confusion, although the interpretation is not difficult.

The Serology of Early Lues and its Significance

Frequent mention was made, on previous pages, of the early involvement of the nervous system by the syphilitic process. It is not at all a rash statement to make that in many cases the Treponema pallidum is present in the vicinity of the brain and cord at as early a date as is the ulcus durum. This fact has been brought out by many clinical observers, among the earliest being Ravaut. Plaut mentions the fact that he observed a syphilitic cerebral meningitis in a patient whose initial lesion had not yet healed. The autopsy showed a nodular syphilitic meningitis limited to the base. The serum of this patient gave a negative Wassermann reaction.

In the future the syphilographer will be able, with the aid of serologic methods, to classify his syphilitic patients into groups, such as those who will possibly develop syphilis of the nervous system, and those who are not likely to. Cases in which the changes in the serum and fluid justified a diagnosis of cerebrospinal lues in a patient not entirely free from syphilitic rash are not rare. The number of patients with an initial lesion still active who would show a cell count and a positive fluid Wassermann has never been determined. It is plausible to believe that the Treponema pallidum permeates the entire system of a patient in the beginning of the disease, gradually settling in various tissues, which will later determine the type of luetic affection, as, *e. g.*, visceral, vascular, cutaneous, nervous, etc. The

factors that determine the permanent involvement of the nervous system are still unknown. It is, however, a safe procedure to treat the patient with a positive spinal fluid more energetically, and continue the therapy until all pathologic constituents have disappeared from the cerebrospinal fluid. This applies particularly to the "chancres céphaliques" of the French, who give a large percentage of cases of involvement of the nervous system. The possibility of diminishing the number of cases of tabes, cerebrospinal lues, or general paresis is in the hands of the physician who sees the initial lesion and bears in mind the early possibility of involvement of the central nervous system, and the concomitant evidence to be found in the cerebrospinal fluid in such cases.

If the prophylactic treatment of syphilitic diseases of the nervous system is ever to become a certainty, it will have to be introduced by the syphilidologist or the genito-urinary specialist, who, as a rule, see such cases first. With this aim in view, it will be just as necessary for these physicians to acquaint themselves with the various serologic manifestations of lues, particularly of early lues of the nervous system, as it is obligatory for the neurologist to know the changes that occur in the cerebrospinal fluid. In an instructive study of the changes that take place in the cerebrospinal fluid in the various stages of syphilis, Wilhelm Gennerich has arrived at the very important conclusion that in many cases of primary lues the cerebrospinal fluid shows evidences of infection, which, according to his opinion, is an expression of the peculiarity of the syphilitic virus, in that it shows, by involving the nervous apparatus, its tendency to spread and permeate the human body. This tendency to extension is inherent in the Treponema pallidum, whether held in check by immune processes or by appropriate therapy. Hence the active manifestations that occur in a luetic after a comparatively symptom-free period. The temporary inertness of the virus is to be noted in ophthalmologic practice, where, suddenly, an eye muscle becomes affected; here, apparently, the natural immune protection which sufficed to keep the treponema dormant and confined for a prolonged period was

suddenly relaxed, with a resulting activity of the micro-organisms. Such occurrences are frequently the mode of infection in congenital lues. It is sufficient to know that the syphilitic virus can lodge in the meninges very early, remain dormant for a time, and later manifest its presence by a cranial nerve palsy, an Argyll-Robertson pupil, absent knee-jerks, defective memory, or a speech disturbance. These abnormalities, if detected in their incipiency, are not infrequently amenable to abortive treatment. One of the most reliable signs of an involvement of the central nervous system is the pathologic status of the cerebrospinal fluid.

In presenting a case of cerebral syphilis that occurred six months after the initial lesion, Gregory and Karpas quote Lannois, Fournier, Mingazzini, Oppenheim, Nonne, and Gowers, all of whom reported cases of cerebral lues occurring from six weeks to eighteen months after the chancre.

Nonne speaks of a case of basal meningitis that occurred four months after the infection in a patient who still presented a papular eruption. It must be remembered that the papular form of syphilids is more apt than any other early luetic lesion to show future involvement of the nervous system.

The case reported by Gregory and Karpas contracted lues in the early part of May, 1912. On June 29th papules appeared over the entire body, and the mucous membrane of the throat was congested. The patient was first seen by the neurologists on October 6th of the same year. It is highly probable that the cerebral manifestations were present in a latent form before the patient presented a dull and drowsy appearance and a partially paralyzed right side. The papular eruption was present, although it had disappeared for a time as a result of antisyphilitic therapy. The pupils were unequal and slightly irregular. Reaction to light and accommodation were sluggish. The right side of the face was paralyzed, and the nasolabial fold was obliterated. On the right side a clonus and a Babinski reflex were elicited. The patient was bedridden and required constant attention. He vomited and complained of headache. His serologic analysis gave the following results:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Positive.	Excess.	618 lymphocytes per c.mm.

The serology here is unquestionably that of cerebral lues of an active exudative type.

This case is interesting not only because it serves as an example of early involvement of the nervous system, but also from the therapeutic possibilities that exist in such cases. This patient received, from October 19th to December 18th, 7851 grains of potassium iodid, $10\frac{1}{4}$ grains of mercury salicylate, and 1.2 gm. each of salvarsan and of neosalvarsan. The subsequent serology showed:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Weakly positive.	Positive.	Normal.	17 per c.mm.

Dreyfus' studies show that of 22 cases of secondary syphilis, 17 exhibited pathologic changes in the cerebrospinal fluid. It is important to note the fact that in these cases Dreyfus could find no symptoms suggestive of an involvement of the central nervous system. He cites the case of a female who contracted lues in January, 1912, and a month later presented a maculopapular eruption. There were no signs of involvement of the nervous apparatus, but the serologic analysis showed that the fluid was abnormal, as may be seen from the following table:

Serum W. R.	Fluid W. R.	Globulin.	Pleocytosis.
Positive.	Negative.	Slight.	458 cells per c.mm.

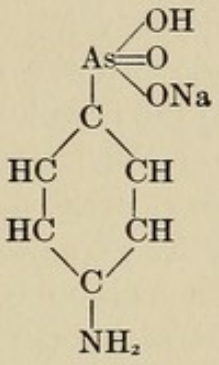
The importance of making early serologic tests by those who see syphilis in its first stages is self-evident. In these patients it cannot be doubted that proper tests will greatly diminish the statistics of the future of cases of tabes and general paresis, as well as of cerebrospinal lues.

PART IV

THE THERAPEUTIC USE OF SALVARSAN

HISTORY AND DEVELOPMENT OF SALVARSAN

THE history of the development of salvarsan and its application to the treatment of syphilis must be considered together with the development of organic arsenical preparations. Of these, *atoxyl* deserves first mention. Chemically speaking, this substance is para-amido-phenyl-sodium arsenate, and structurally it shows the following constitution:



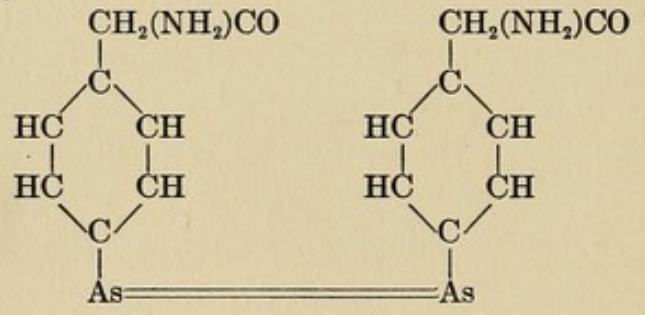
Atoxyl was used extensively in the treatment of infections due to the trypanosomes. Schaudinn, the discoverer of the microörganism of syphilis, advanced the hypothesis that the organism known as the Spirochæta pallida stands in close relationship to the trypanosomes. Working on this hypothesis, Uhlenhuth experimented with atoxyl in fowl spirillosis, and obtained sufficient success to warrant its trial in experimental syphilis. Here must be mentioned also the contemporaneous efforts of Neisser and of Metchnikoff, who proved the great value of atoxyl in the treatment, and even in the prophylaxis, of animal syphilis. These results were chiefly responsible for the employment of atoxyl in the treatment of human syphilis. The beneficial results obtained in some instances of lues, particularly in those

forms of the disease designated as malignant, served as a stimulus to the clinician and experimenter.

The clinician soon discovered the fact that atoxyl, while possessing marked curative qualities, also produced in some instances by-effects serious enough to preclude its use in certain forms of lues. The gastro-intestinal irritation, nephritis, and occasional blindness that followed the use of this remedy greatly minimized its therapeutic utility. Even very minute doses were frequently followed by symptoms of a toxic nature, so that Buschke expressed the opinion that, owing to its great toxicity, the usefulness of atoxyl is almost nil, a view with which many foremost clinicians were in accord. In spite of these failures, Uhlenhuth and Manteufel still maintain that atoxyl is a valuable remedy in human syphilis. These investigators have suggested combining atoxyl with mercury.

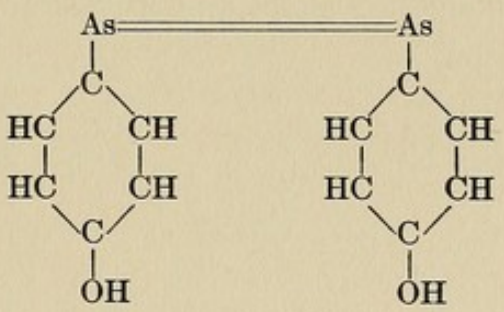
Ehrlich established the very important fact that during the course of his studies with the trypanosomes the combined use of mercury and the arsenical preparation increased the sterilizing potency of the latter to a marked degree. The reports on the animals treated with this combination showed that very large doses were necessary to secure a curative effect, and that the method could not, therefore, be utilized in the treatment of human syphilis. As a result, the use of atoxyl was discontinued.

Another drug was next tried for a short time, and better results expected on account of its greater stability; this was *arsacetin*. Although less toxic than atoxyl, this chemical substance did not fulfil the requirements of an ideal remedy for lues, and was likewise discarded. We are now approaching the chemical relatives of salvarsan, and the first of this group is *arseno-phenyl-glycin*. Its chemical constitution is as follows:



This substance is of interest from the chemical point of view, in that it illustrates the trivalent state of the arsenic molecule. It should be remembered that the arsenic in a pentavalent state is less active in exerting its toxic influence on the spirillum group than when it is in a trivalent state. This is due partly to the fact that in a molecule in which all the valences are satisfied the desired influence is less likely to take place than when some of the valences are not satisfied, a fact that is somewhat analogous to the readiness with which oxygenation can be obtained with an oxygen molecule as it exists in H_2O_2, where the O molecules interchange valences and hence are in a less stable chemical state than when the O is attached to two separate univalent molecules, or one bivalent molecule, as is the case in H_2O or in CaO. It is well known that in the two last-named substances the oxygen is separated with much greater difficulty than in the case of hydrogen dioxid. The same holds true to a certain extent of arsenic in a trivalent condition; this interchanges valences with its fellow on the other side, thus minimizing the affinity to the benzol ring, from which it separates when the suitable opportunity is at hand. Arsenophenylglycin was used with some success in combating recurrent fever.

Arsenophenol is another chemical compound that was tried with a view to obtaining a satisfactory spirillocidal substance. Its formula is the simplest of any of the organic arsenicals, and shows the following structure:

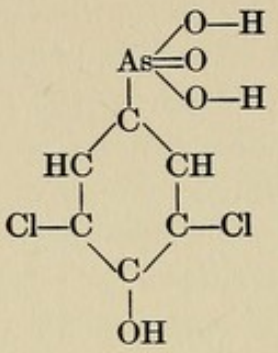


In this the arsenic is also in a trivalent state, and is very active against the fowl spirilloses. It is, however, very readily oxydizable, and must be kept in vacuum tubes. In spite of this precaution, it is necessary to reduce the sub-

stance before it is actually used, and for this purpose hydrogen sulphite (H_2SO_3) is recommended.

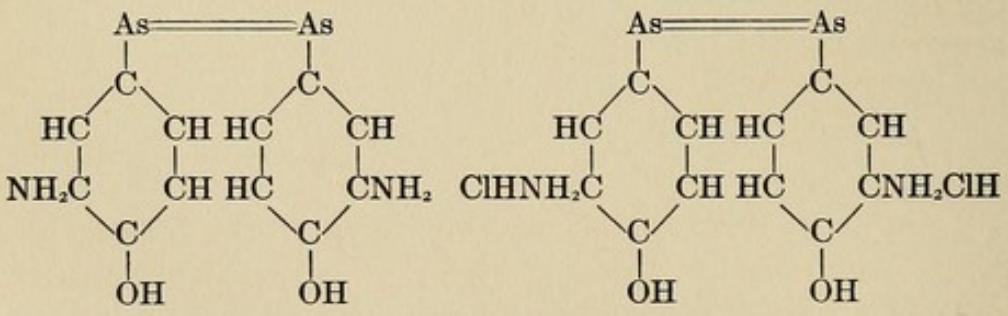
Tetrachlor- and *tetrabrom-arsenophenol* are substances structurally similar to arsenophenol, containing four molecules of Cl and Br in the 3 and 5 positions respectively. As compared with the halogen-free substance, their activity is less marked.

Dichlorphenylarsenious acid:



This substance is readily soluble in water, and can be neutralized with ease by using a sodium carbonate solution. The *dosis tolerata* for healthy mice is 1 : 75, whereas the curative dose is 1 : 100. There is, therefore, a considerable margin of safety between the tolerant and the curative dose, an item that is of the greatest importance in considering the value of any drug. A considerable drawback to its use lies in the fact that it is capable of producing disturbances in the nervous system. This in itself is sufficient to preclude its use in the treatment of spirilloses or allied infections.

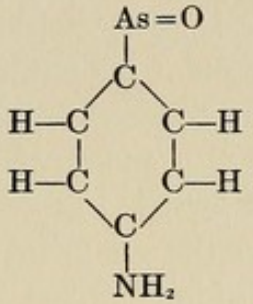
Dioxy-diamino-arseno-benzol and its hydrochloric acid salt:



The first of these substances was designated by Ehrlich, for purposes of brevity, as "592." It is a light-yellow powder, which, on account of the property it possesses of being very

readily oxidized, must be kept in sealed vacuum tubes. This substance is soluble in water rendered alkaline with NaOH. The hydrochloric acid salt of this substance ("606") is readily soluble in hot water, is strongly acid, and is absorbed with difficulty by the tissues. This latter peculiarity makes it unsuitable for therapeutic uses, at least in its acid form.

Another remedy possessing great spirillocidal power is *amidophenylarsenoxid.* The chemical structure of this substance is:



Of this substance, 0.03 gm. is tolerated per kilogram of fowl. The quantity required to rid the fowl of spirilla is only $\frac{1}{20}$ of this amount, a fact that makes this arsenical combination of great therapeutic significance. The comparative usefulness of the various chemical substances here considered will be seen from the following table, showing the dose tolerated and the dose required for sterilizing the fowl:

	Dosis Tolerata.	Dosis Curativa.	Proportion.
Atoxyl	0.06	0.03	$\frac{1}{2}$
Arsacetin	0.1	0.03	$\frac{1}{3}$:3
Arsenophenylglycin	0.4	0.12	$\frac{1}{3}$:3
Amidophenylarsenoxid	0.03	0.0015	$\frac{1}{20}$
Dioxydiamidoarsenobenzol	0.2	0.0035	$\frac{1}{58}$

A glance at this table shows that the last two substances possess the ideal qualities required of a therapeutic agent, and of the two, the last is the most potent.

The principle involved in the conception of "chemotherapy" as elaborated by Ehrlich consists of the finding of a remedial agent that possesses, first, properties injurious

to the "causa movens" of a given disease, and, second, one that, when introduced into the animal organism, will produce as little disturbance as possible. These properties are possible only after standardization and after a careful consideration of the effects of a given substance in animal experimentation.

The "chemotherapy" of the past was based more or less upon empiricism, and embraced only a few remedial agents whose properties were well defined. Mercury and the iodids were regarded as specifics for syphilis; quinin, for malaria; and later, atoxyl, for sleeping sickness. These substances were utilized as the result of experiments made in the past, and were not dependent upon the painstaking standardization that characterizes the chemical substances introduced into therapeutics by Ehrlich and his followers. This investigator differed from the chemists who considered "*Corpora non agunt, nisi fluida,*" and established as a chemotherapeutic principle that "*Corpora non agunt, nisi fixata.*" This conception is only a part of the original teaching of Ehrlich regarding immune processes in general. His theory of immunity maintains that definite receptors in the body-cells must be present before a certain substance can be "anchored" by the cell. In tetanus, for example, the cells of the nervous system possess a greater affinity for the poison elaborated by the bacterium than does any other body-cell; this is due to the fact that they are endowed with "receptors," which other cells do not possess. When arsenic is introduced into the body it is fixed ("anchored") by certain cell-receptors; when mercury is introduced, it in turn is fixed by other receptors. It is possible to produce chemical substances that carry side-chains that are capable of being fixed by certain cells only or by certain bacteria if need be.

It was the original intention of Ehrlich to produce a substance that would carry in its complex makeup a molecule or a group of molecules that would be anchored by the invading microörganism to a much greater extent than by the body-cells of the infected animal. Thus when the microorganism fixes (anchors) the given molecule, it also carries

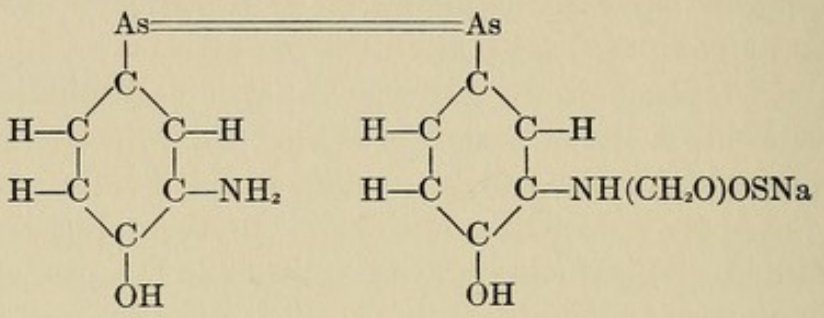
with it the remainder of the chemical substance, whatever that may be; at the same time, the side-chain that is anchored or is responsible for the anchoring of the entire molecule need not possess any of the properties of the entire molecule or of any part thereof. For example, when the molecule of "606" is anchored to the treponema of syphilis by its OH or its NH_2 side-chain, or by both, it must later contend with two molecules of arsenic, which, being in a trivalent condition, can exercise to a marked degree its toxic effects on the microörganisms. The side-chains as they exist in "606" are much more readily taken up by the Treponema pallidum than by the body-cells, as is shown by the dosis tolerata as compared with the dosis curativa.

The chief point to be observed in the introduction of chemicals into a living organism is that the infective agent will fix the given drug, and, as a result of this fixation, it will die, or, as is the case with some chemicals, reproduction will be inhibited. This quality was established in the production of dioxydiamidoarsenobenzol, in that it is fixed by its amido-oxy-group (haptophore group of the molecule) by the Treponema pallidum, which is killed by receiving the molecule in its economy, a fact that was demonstrated by animal experimentation as well as by clinical observations.

From the encouraging clinical reports received as the result of experiments carried out on many thousands of cases and on animals before the drug was placed in the hands of the general medical profession, Ehrlich believed at the time that in the "606" molecule he had discovered a means of ridding, by a single administration, the human organism of the cause of syphilis. This conception of a "Therapia sterilisans magna," although established in individual cases, did not wholly come up to the expectations of this eminent investigator.

Syphilis cannot be cured with one injection of salvarsan, and the physician who attempts to assert definitely how many injections are required is merely doing so as the result of conjecture, as there are no standards as yet that would establish the number of treatments required in a given case of syphilis.

In many instances the reports showed that it is not an altogether easy task to prepare the substance for injection, and that some chemical preparation that would require less handling would be most acceptable. With this end in view, Ehrlich resumed his search for a more ideal substance, and as the result of his nine hundred and fourteenth experiment he gave us neosalvarsan ("914"). This substance is a definite mixture of sodium-3 diamino-4 dihydroxy-1 arsenobenzene methanal sulphoxalate (according to the New and Non-official Remedies, Jour. Amer. Med. Assoc., 1913). The chemical formula may be represented as follows:



This substance contains in three parts by weight approximately the same amount of arsenic contained in two parts by weight of salvarsan. Salvarsan and neosalvarsan are dispensed in sealed tubes, containing varying quantities. Neosalvarsan may be obtained in tubes containing from 0.15 to 0.9 gm. Salvarsan may be had in amounts up to 0.6 gm., which represents the full dose usually given to adults. The ampules of salvarsan are filled with an indifferent gas, such as N, in order to obviate chemical changes. It must be remembered that salvarsan is readily decomposed, forming substances of a toxic nature, and must consequently be used as soon as an ampule is opened, not permitting it to remain in too prolonged contact with air. It is best to prepare the solution at the bedside and use it at once.

The following extract concerning the properties of these two drugs is taken from the Journal of the American Medical Association:

Salvarsan contains 31.57 per cent. of arsenic. It is a yellow, crystalline, hygroscopic powder, very unstable in air. It

is readily soluble in water, particularly when hot, yielding a solution with an acid reaction. The addition of sodium hydroxid solution to an aqueous solution of salvarsan, in the ratio of two molecules of sodium hydroxid to one of salvarsan, precipitates the free base, namely, (NH_2OH,-C_6H_3As : As,C_6H_3OH,NH_2). On the addition of an aqueous solution of sodium carbonate to an aqueous solution of salvarsan a precipitate is produced which is insoluble in an excess of the reagent. An aqueous solution of salvarsan is not affected by the addition of dilute hydrochloric, nitric, or sulphuric acids.

When salvarsan is heated with an alkaline solution of potassium permanganate, the permanganate solution is reduced and ammonia is given off. The addition of ferric chlorid solution to an aqueous solution of salvarsan produces a brownish-violet color, which gradually changes to a dark red; finally the liquid becomes turbid.

Silver nitrate solution added to an aqueous solution of salvarsan acidified with dilute nitric acid yields a dark-yellow precipitate which rapidly becomes black.

The addition of concentrated nitric acid to an aqueous solution of salvarsan produces a yellowish-white precipitate. On further addition of the acid the precipitate redissolves and the solution becomes dark red.

Neosalvarsan is an orange-yellow powder possessing a peculiar odor. It is very unstable in the air. It is readily soluble in water, yielding a yellow solution which is neutral toward litmus. Upon standing the aqueous solution becomes dark brown, forming a brown precipitate.

A freshly prepared aqueous solution of neosalvarsan (1 : 100) yields a precipitate on the addition of mineral acids.

If silver nitrate test solution be added to an aqueous solution of neosalvarsan (1 : 100), a brownish color should be produced, quickly followed by the formation of a black precipitate.

If ferric chlorid test solution be added to an aqueous solution of neosalvarsan (1 : 100), a violet color should be produced, which soon changes to a dark red.

If to 10 c.c. of an aqueous solution of neosalvarsan (1 : 100)

5 c.c. of dilute hydrochloric acid be added and the mixture heated, the irritating odor of sulphur dioxid will be evolved.

If to 10 c.c. of the aqueous solution of neosalvarsan (1 : 100) 5 c.c. of diluted hydrochloric acid be added, the precipitate collected on a filter and treated with zinc dust and warm, diluted hydrochloric acid in a test-tube, and if paper moistened with a 5 per cent. cadmium chlorid solution be held in the mouth of the tube, the paper should be stained yellow within a few minutes. (Distinction from salvarsan.)

EARLY METHODS AND RESULTS

Because of the marked instability of salvarsan and neosalvarsan, it is well to see that the ampule containing the drug is intact, and that the powder is of a yellow, and not of a gray or brownish, color. Any drug not up to this standard must be regarded as deteriorated, and hence dangerous for therapeutic purposes.

In the early methods only salvarsan was used, the drug being given intramuscularly, subcutaneously, and intravenously. For the muscular and subcutaneous injections acid solutions, alkaline solutions, neutral emulsions, and paraffin mixtures were employed. These various methods of giving the drug will now be considered briefly and in order:

The Acid Solution.—The equipment necessary for the preparation of the acid solution consists of a 25 c.c. graduated cylinder with a ground-glass stopper. This cylinder contains a number of medium-sized glass beads, about 30 in all. A small 25 c.c. griffin-lip beaker with a cotton plug, and, lastly, distilled water, are also required. These must all be sterile before using.

For intramuscular injection the drug is prepared as follows: Having placed the salvarsan in the cylinder, add at once boiling sterile distilled water and shake vigorously. The drug dissolves readily, a yellow fluid resulting. Pour the fluid into the beaker, and it is ready for injection.

This form of treatment was usually followed by intense local reactions, and for this reason is not to be recommended.

The Alkaline Solution (*Alt*).—The equipment for the preparation of this solution is similar to that used above,

with the addition of a 4 per cent. sodium hydroxid solution, an additional graduated cylinder of 25 c.c. capacity, and a graduated 1 or 2 c.c. pipet. Everything used must be sterile.

First prepare an acid solution as previously directed. To this add 0.5 c.c. of the sodium hydroxid solution for every 0.1 gm. of the drug. Shake vigorously. This produces a yellowish, at times a brownish, opaque fluid; to this add the alkali drop by drop until the opacity vanishes. It is not advisable that an absolutely clear solution be produced by the addition of more alkali, as the slightly opaque fluid is less irritating than a very clear fluid would be. This alkaline solution is also used for intramuscular injections, as suggested by Alt. This mode of administering salvarsan is less irritating than the injection of an acid solution.

The Neutral Emulsion (*Michaelis*).—The same utensils are required here as in preparing the alkaline salvarsan, and, in addition, a bottle containing 1 per cent. acetic acid solution and another containing 0.5 per cent. solution of phenolphthalein in 70 per cent. alcohol are also necessary. Everything used must be sterile.

The first step consists in preparing a perfectly clear alkaline solution, as previously described; add two or three drops of the phenolphthalein solution; this results in a red coloration of the fluid; finally add, drop by drop, 1 per cent. acetic acid solution. The salvarsan is precipitated as very fine, yellowish flocculi, and the acetic acid is added until all traces of pink color disappear from the mixture. The emulsion is poured into the beaker, and the cylinder is rinsed with a little distilled water and this added to the contents of the beaker. The emulsion is now ready for use, either subcutaneously or intramuscularly.

Neutral Emulsion (*Wechselmann*).—Apparatus required: Mortar and pestle; 15 per cent. NaOH solution; glacial acetic acid; $\frac{1}{10}$ normal NaOH solution; 1 per cent. acetic acid; red and blue litmus-paper; a platinum loop; a small centrifuge with sterile centrifuge tubes; sterile physiologic salt solution; sterile distilled water. The salvarsan is rubbed up in the mortar with 1 or 2 c.c. of the 15 per cent. NaOH solution,

which dissolves it. Glacial acetic acid is added a drop at a time, which results in the formation of a glutinous yellow mass that is diluted with 1 or 2 c.c. of sterile distilled water, and carefully neutralized with the decinormal NaOH solution, using the platinum loop for transferring a drop to the litmus-paper. This causes the formation of sodium acetate, which must be removed before the emulsion is ready for use. The centrifuge serves the purpose of showing that the neutral salvarsan in the centrifugalized fluid is at the bottom of the tube, the clear fluid on top representing the sodium acetate; this last is poured off and discarded. The remaining salvarsan at the bottom of the centrifuge tubes is taken up with from 4 to 6 c.c. of sterile water, and the emulsion is ready for use, either subcutaneously or intramuscularly.

All the methods here outlined of administering the drug have the peculiarity of producing in a few days painful swellings, and at times quite extensive infiltrations and necroses take place. The subcutaneous and intramuscular methods are not to be recommended, as by the intravenous administration of the drug all local manifestations that are encountered by the other methods described are avoided.

Oil and Paraffin Mixtures.—It has been demonstrated that these mixtures, when kept in dark containers, do not deteriorate for some time. This cannot, however, be depended upon, as the slightest decomposition of the original salvarsan is capable of producing marked toxic manifestations. It is, therefore, best to prepare the drug immediately prior to use, and not to utilize any drug that is left from a previous preparation.

In preparing these mixtures salvarsan is rubbed up in a mortar with some one of the following substances: Liquid paraffin, the finest sterile olive oil, oil of sesame, or sterilized liquid vaselin. The quantity of any one of these substances is measured, so that 1 c.c. of the oil or paraffin is added to each 0.1 c.c. of the drug. This mixture may be injected in toto, or, as Kromayer suggests, 0.1 to 0.2 of the drug (1 or 2 c.c. of the mixture) may be injected every second day. When the latter method is to be employed, the drug must be kept in a sterile dark bottle. Before using

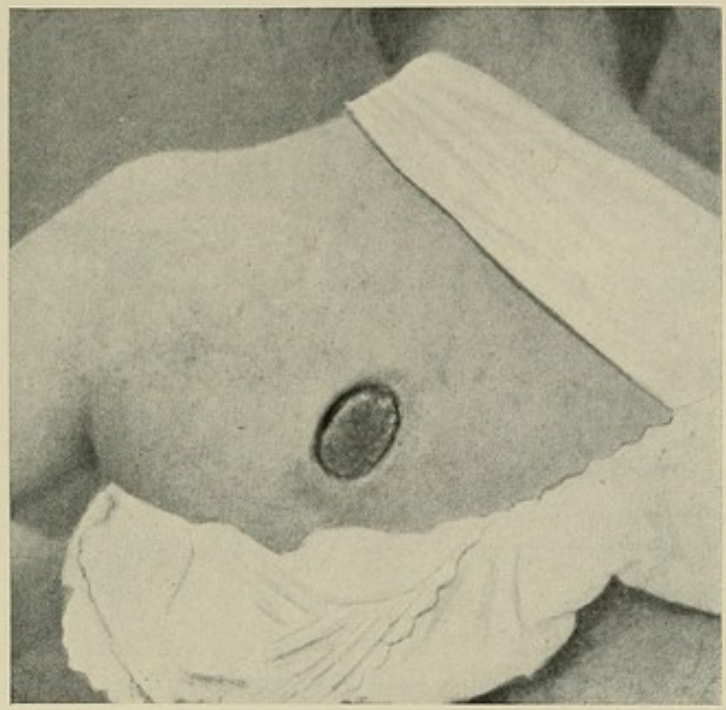


Fig. 20.—Necrosis resulting from an intramuscular injection of a neutral solution of salvarsan.

it, the drug must be rubbed up thoroughly, as a heavy sediment collects at the bottom of the flask.

Although the injection in itself is painless, a few days after the treatment sensitive infiltrations develop that will at times persist for weeks.

DOSAGE

Males receive in general about 0.6 gm., whereas female patients are given 0.5 gm. of salvarsan. This dosage is the same whether the mixture be acid, alkaline or neutral, or oil or paraffin. Weak patients with organic diseases of a grave nature should receive smaller doses—0.3 or 0.4 gm. of salvarsan.

For infants suffering from congenital syphilis the dose is from 6 to 10 milligrams of salvarsan for every kilogram of body-weight, so that a child weighing 4 kilograms would receive from 0.024 to 0.04 gm. of salvarsan. To older children, weighing from 20 to 30 kilograms, 1 centigram of the drug is given for every kilogram of body-weight.

INJECTION OF THE DRUG

For the oil and paraffin emulsions it is best to use a syringe with an asbestos plunger; for the watery mixtures an ordinary Record syringe will suffice. The substance is injected through a cannula, care being exercised that the cannula does not injure a blood-vessel. This may be accomplished by introducing the cannula without the syringe attachment, and turning it around a few times to be certain that no blood-vessel is near. Having taken this precaution, the substance may now be very slowly injected. The best site for making the injection is in the gluteal region. The small of the back (erector spinæ group of muscles) is also an excellent injection area, as absorption from this region is very rapid. After receiving the injection, it is well to keep the patient in bed for a few days.

The Intravenous Injection.—The advocates of the intramuscular or subcutaneous route belong to the early days of the use of salvarsan, when the conception of a "therapia sterilisans magna" still prevailed, and the belief existed that this could be accomplished with one or two injections of the

drug. The enormous number of applications of salvarsan that were made quickly dispelled the belief that a cure would follow one or two injections, and hence the intramuscular and subcutaneous methods were discarded on account of the unpleasant local manifestations that resulted. The comparatively easy technic of the intramuscular method made this form of administration popular with those who were not acquainted with the manipulation of veins, or who had had unfortunate experiences with attempted intravenous injections. As a result, some physicians effected a compromise, and advised the use of both methods, giving one intramuscular and later an intravenous injection of the drug. This combined method was said by some to have great possibilities.

The wide notice the drug received resulted in attempts to use salvarsan in every possible way, and today, after more than five million doses of this remedy have been disposed of, the intravenous method holds first place in efficiency, safety, and, with some practice, ease of administration. Further on certain methods will be described that tend to increase the efficiency of the drug by injecting it in the particular part affected; a method will also be given that tends to establish a form of fractional sterilization.

The best manner of using salvarsan is an attainment to be achieved by future therapeutists, when more factors will enter into the method of using the drug. This particular sphere of activity confronts the neurologist, who is guided by clinical as well as by important laboratory data as to the progress of treatment.

The intravenous method held out much more hope for the ultimate realization of Ehrlich's conception of a "therapia sterilisans magna," but that this will be the result not of one but of many injections is also a well-established fact. In the intravenous method of administering salvarsan we possess the key to the entire therapeutic structure of syphilitic therapy, which, it is hoped, will be accomplished in the near future.

The following description shows in detail the instruments required, the preparation of salvarsan and of neosalvarsan, and the preparation of the patient for receiving the injection.

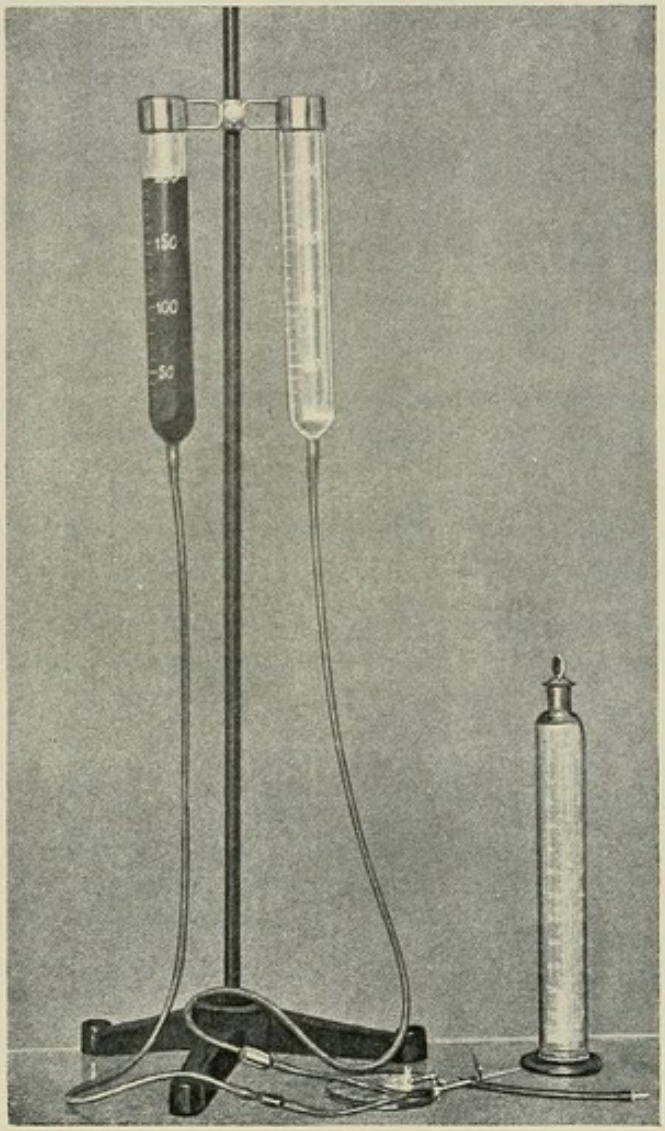


Fig. 21.—The Weintraud-Assmy intravenous apparatus.

Instruments Required for Intravenous Injection.—As a general precautionary measure it should be remembered that anything used in the preparation of salvarsan must be scrupulously clean and sterile. It will, therefore, be stated at the beginning, and repeated further on, that after having been used the entire apparatus is to be cleansed at once—needle, container, rubber tubing, etc. It is a generally accepted fact that the fewer the parts of an apparatus and the simpler its working mechanism, the better suited it is for use. This applies especially to the salvarsan outfit. Occasionally some worker will prefer an apparatus to which he has become accustomed, and which would require much time for one to learn if he had never used that particular apparatus before. In these cases it is useless to advise the purchase of a new outfit. The description that follows embraces general principles, and shows the apparatus the author considers of most value because of simplicity and ease of handling.

The instruments to be used may be divided into those that are required for dissolving the drug and those employed for the injection of the solution. Mortars and pestles are not necessary for the intravenous method. The drug may be dissolved in a 350 c.c. graduated, glass-stoppered cylinder, and poured from this into the injecting apparatus when ready for use. For the injection of the solution any apparatus the physician is accustomed to use will answer, provided it has an attachment that will permit of the interruption of the salvarsan flow and the substitution of normal sterile salt solution. The reason for this will be discussed later, under the head of Symptoms Accompanying the Injection. An apparatus that possesses all the advantages is seen in the Weintraud-Assmy outfit, which consists of:

One buret holder.
One holder for two graduated cylinders (nickeled).
Two graduated cylinders of 200 c.c. capacity.
Rubber tube leading from each cylinder.
Two glass connecting pieces.
One nickeled two-way cock.
A steel needle with point beveled obtusely.

In the author's work the following apparatus was used, which is a slight modification of the one employed at the Rockefeller Institute Hospital; it consists of a 400 c.c.

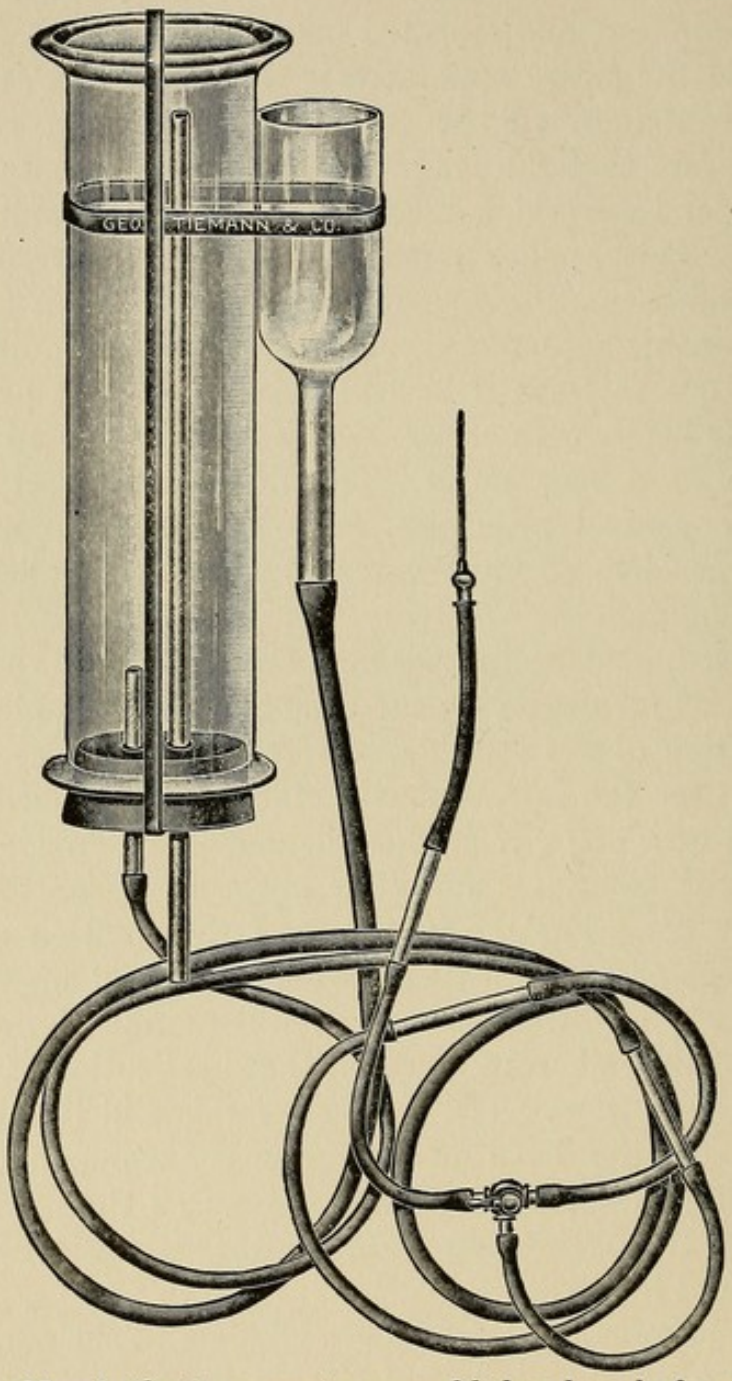


Fig. 22.—Author's apparatus assembled and ready for use.

cylinder, provided with two rubber stoppers, one solid and the other having two perforations. The stopper with the perforations has one short glass tube and one long one,

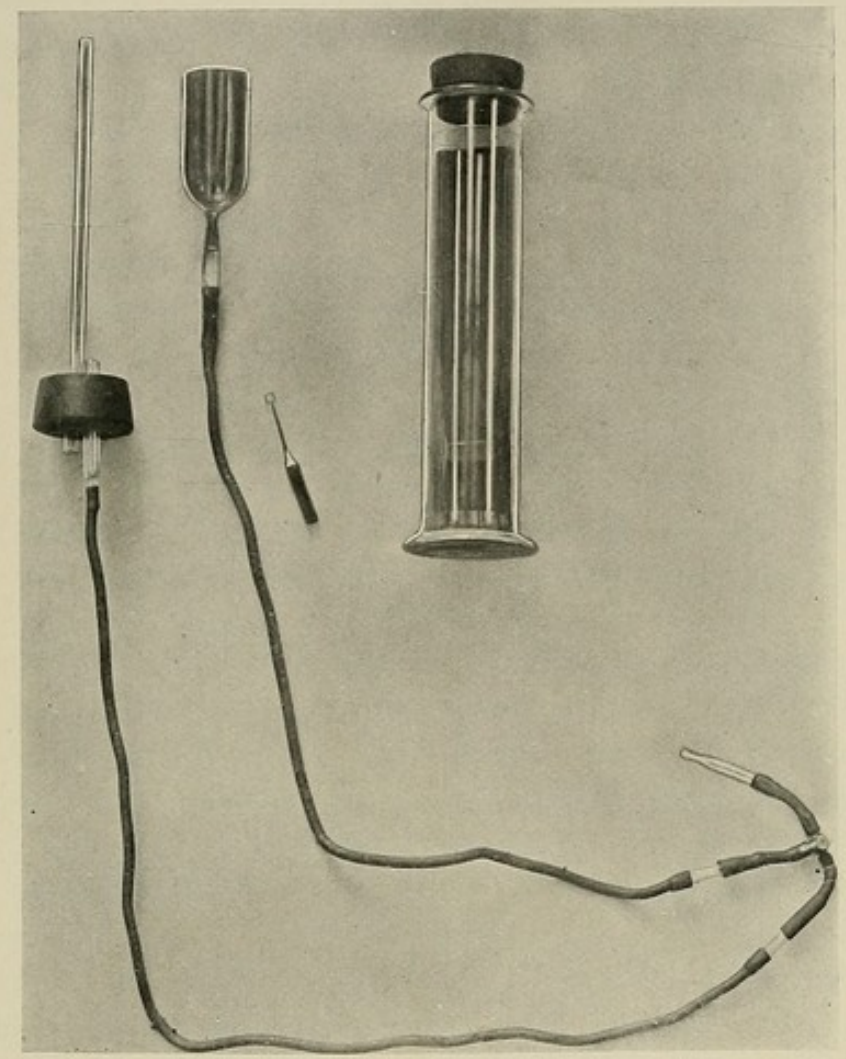


Fig. 23.—The apparatus used by the author. From left to right, long air tube and near it the short salvarsan tube; the carbon filter for the salt solution; the needle; the cylinder and rubber stopper. At the bottom the three-way cock and delivery glass tube.

as may be seen in the illustration (Fig. 23). The short glass tube has a rubber attachment connected with a three-way cock through an intermediary glass connecting tube. A 50 c.c. carbon filter is seen at the right of the long tube, which is also provided with a rubber tube that runs to the three-way cock. To the free end of the three-way cock is attached a piece of rubber carrying a delivery tube. All rubber-glass and rubber-metal connections are securely tied with cord or silk to prevent slipping or leakage. Two rubber bands—a large and a small one—prevent the accidental falling out of the rubber stopper when the apparatus is filled with the solution and turned over. The advantage of this contrivance lies in the fact that it eliminates the need for a separate mixing vessel, the drug being mixed in the same cylinder from which it is delivered. Having dissolved the drug and shaken it, the solid stopper is replaced by the perforated one, and secured with the larger rubber band; the apparatus is now turned over, having turned the three-way cock so that it will deliver from the carbon filter only. The outfit is suspended by the attached tape and the carbon filter adjusted, securing it to the side of the cylinder by means of the smaller rubber band. Saline solution is poured into the carbon filter, and the air expelled by lowering the delivery tube. The procedure of expelling the air is to be repeated, having turned the cock so that it will deliver salvarsan, the air contained in the rubber tubing also being expelled. Before using, the cock must be directed to the saline delivery, as it is advisable to begin with the saline, and have the glass connecting tube filled flush to the tip with the salt solution.

Special instruction must be given regarding the use of the needle. The author does not recommend the use of the Schreiber needle or of any but an ordinary straight needle, and cautions against using those possessing special curves, cumbersome attachments, too wide a lumen, or a special stilet and cannula. It is safest to grow accustomed to manipulating the simplest needle, such as the one shown in the illustration of the salvarsan outfit (Fig. 22). This is an ordinary Yale-Luer needle, with a No. 19 bore, and is $1\frac{1}{4}$

inches long. These needles are very serviceable, cheap, and a dozen can be used for months, even where many injections are given daily.

The other apparatus shown in Fig. 24, the Fox-Trimble, does not meet the requirements on account of the absence of an attachment for the salt solution. The same may be said of the Iversen-Wolbarst outfit (Fig. 25), which has the

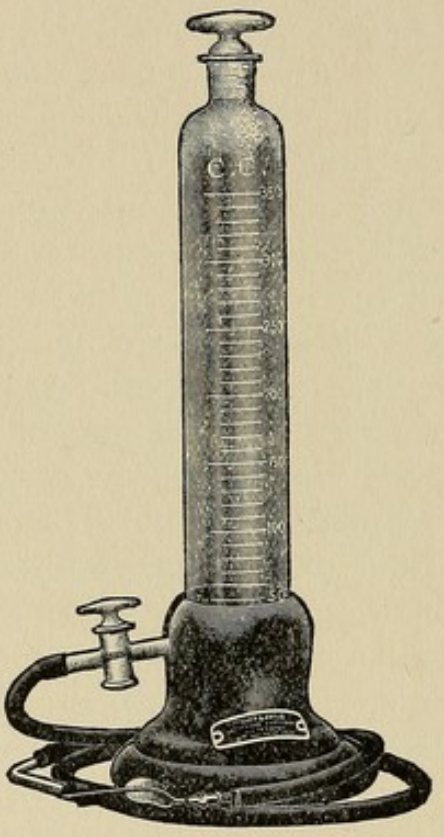


Fig. 24.—The Howard Fox and W. B. Trimble apparatus for the intravenous injection of salvarsan. The Schreiber needle is shown at the bottom of the cut.

additional disadvantage that it requires an air-bulb, driving the solution into the vein.

Besides the delivery apparatus, the tourniquet may be included as a part of the salvarsan injecting outfit. This need not be an elaborate affair, and the artery clamp may be eliminated. With a little practice one can learn how to apply the tourniquet, which consists of an ordinary piece of irrigation tubing, and be able to ascertain at a glance whether or not it is too tight. An extra supply of needles should be

carried in case of emergency, and more saline solution than is required for one treatment should also be at hand. The

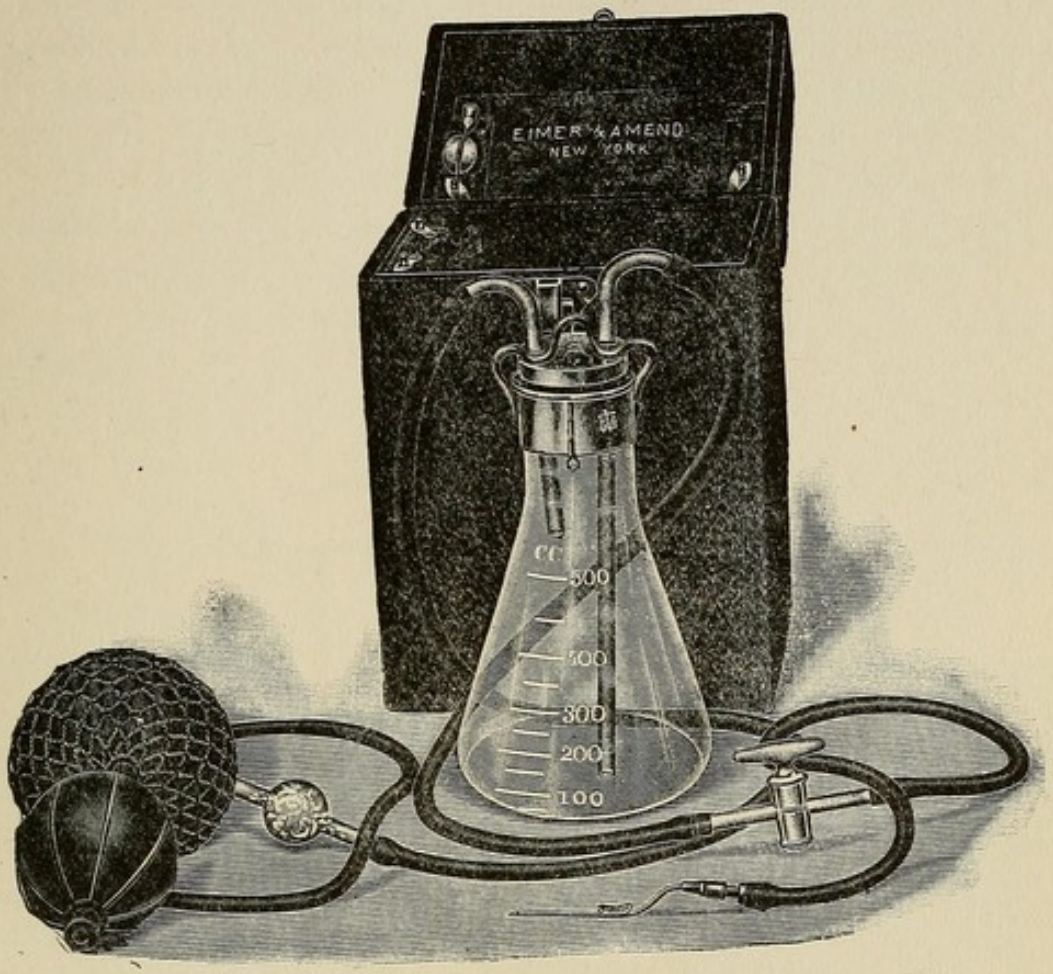


Fig. 25.—The Iversen-Wolbarst intravenous salvarsan apparatus. The Schreiber needle is not part of the outfit.

additional equipment consists of a rubber sheet, sterile gauze pads, towels, alcohol, ether, and collodion.

PREPARATION OF SALVARSAN

An important requisite is the employment of freshly distilled sterile water in preparing the solution of salvarsan for intravenous use. In order to have this at hand a water still is indispensable. It must be remembered that unless this rule is rigorously adhered to, satisfactory results cannot be expected. A very simple still can be installed in a physician's office near a water faucet and a sink, and enough water can be had for a dozen salvarsan injections if need be.

Such a water still is shown in Fig. 26, and, from the author's experience, is a very satisfactory and inexpensive apparatus. Having secured enough distilled water, 350 c.c. are next placed in an Erlenmeyer flask of 500 c.c. capacity, and boiled for five minutes. This is sufficient to render the water sterile for use with salvarsan. While still very hot, 100 c.c. of the water is placed in the container. (See p. 215.) The ampule of salvarsan is meanwhile kept in 95 per cent. alcohol to sterilize the surface of the container; the file is also placed

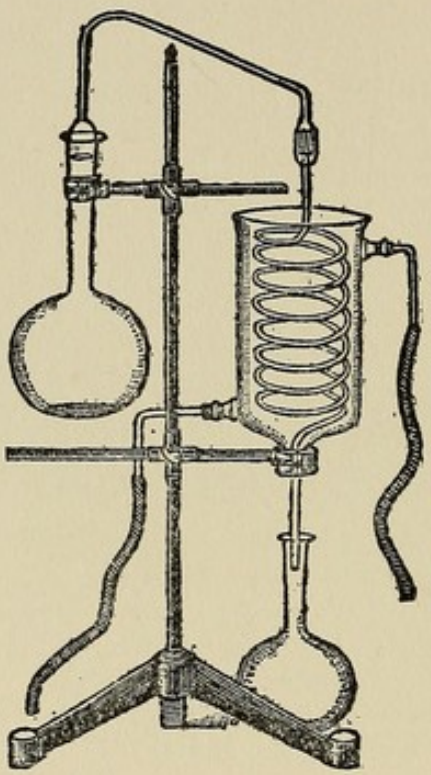
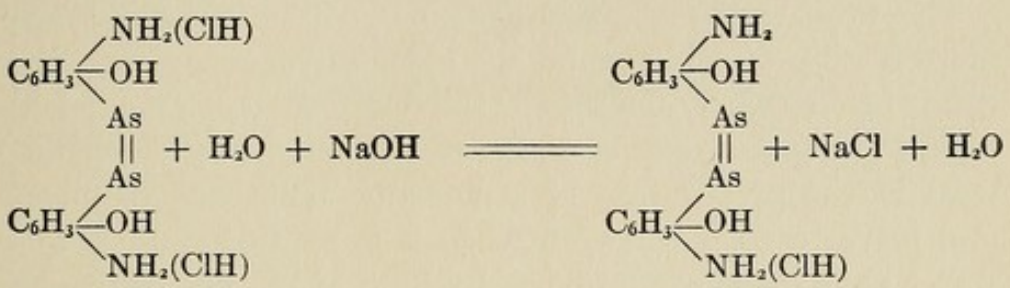


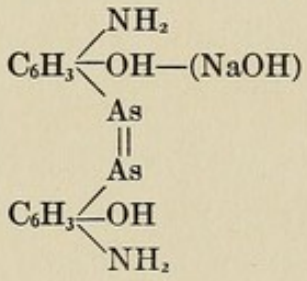
Fig. 26.—Muencke's distilling apparatus for office use. The cut does not show the Bunsen burner.

in the same fluid. After removing the ampule from the alcohol and drying it, with a firm pressure against the glass with the file rasp the neck and break it off by striking the tip firmly. Pour the contents into the container with the hot sterile distilled water, close tightly with the rubber stopper, and shake the contents until every trace of undissolved drug is gone. This sometimes requires from one-half to one minute's shaking. The next step is to neutralize the dichlorhydrate salt, which is accomplished by the gradual addition (drop by drop) of a 15 per cent. NaOH solution.

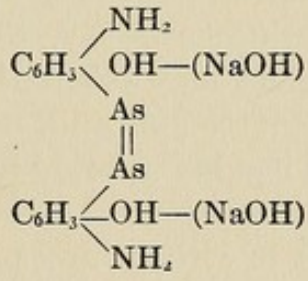
This step must be carried out with precision, as too alkaline or insufficiently neutralized solutions are harmful. After thorough shaking and inspection of the delivery cylinder to ascertain that no particles of undissolved drug are adhering to the cylinder wall, the 15 per cent. NaOH solution is poured into the cylinder drop by drop until about 11 or 12 drops have been instilled. Having replaced the rubber stopper, shake the contents vigorously. This addition of the alkali forms the mono-acid product, which is still in a state of solution. The reaction that takes place is as follows:



The futher addition of NaOH to the foregoing solution produces the neutral suspension by neutralizing the other ClH molecule. The addition of a few more drops produces the alkaline suspension, which has the following formula:



On adding a few drops more,—usually up to 16 or 19,—the suspension clears up, when the solution is ready for use; its formula is as follows:



The drug was utilized in every one of the foregoing formulæ. We know today that the only safe and least irritating preparation is the slightly alkaline solution. The subcutaneous and the intramuscular methods are far less effective than the intravenous, and the physician who does not employ the last-named method cannot be said to have used the drug in its most potent therapeutic form; neither is he justified in criticizing the drug because of certain failures that he may have experienced, as his method of using the drug was not the one capable of accomplishing the greatest good for the patient.

The Preparation of Neosalvarsan.—This powder is much more readily dissolved than the older salvarsan. Place the drug in a container, and for the full dose—*i. e.*, 0.9 gm.—add about 175 to 200 c.c. of water of the same quality as was used in the preparation of salvarsan. The drug dissolves and leaves a clear solution, when it is ready for use. The water used for the solution must be cold, as hot water decomposes the drug and renders it toxic. No neutralization is required, a fact that makes it a very acceptable preparation for those who do not possess the required technic for handling glass apparatus and chemicals. Neosalvarsan can also be given in concentrated form through an ordinary large Luer syringe by dissolving the substance in 20 c.c. of sterile distilled water and injecting it into the vein.

PREPARATION OF THE PATIENT FOR INJECTION

Although in the great majority of instances no special preparation of the patient is necessary, it is, nevertheless, best to administer the drug on an empty stomach. Having instructed the patient to refrain from luncheon, the drug is injected in the evening, before bedtime. It is also well to direct the patient to empty his bowels some time before the contemplated treatment,—say, the night before,—so that no toxic substances may be absorbed from the gut and give rise to unpleasant complications. When proper precautions are observed in administering the remedy, its use has proved to be so free from untoward manifestations that many physicians now inject it without any preparation whatever.

For the last two years, since the method of using salvarsan

and the general information regarding the drug have been placed on a surer footing, the author has not observed a single grave complication. In using the drug the peculiarities of the remedy and the patient's condition as well must be considered. It is bad practice to administer a small dose at prolonged intervals to a patient with active cerebral lues, as this is very often the cause of a neuro-recidive or a Herxheimer, and it is just as bad to administer a perivenous infiltration, an insufficiently neutralized solution, or a too strongly alkaline solution. Whenever possible, it is best for the patient to be in bed when the treatment is given; an operating-room is entirely unnecessary.

THE TECHNIC OF INJECTION

Where the administration of salvarsan or of neosalvarsan is a routine practice, the injection of these remedies does not rise above the dignity of a hypodermoclysis. To those who use the drug very infrequently, however, the injection will prove an operation of considerable difficulty. Some therapeutists with considerable experience in making the intravenous injection declare that the method of introducing the needle in injecting salvarsan is precisely the same as that followed in obtaining blood for testing for the Wassermann reaction. It may be stated here that on more than one occasion the needle had to be withdrawn from the vein, regardless of the fact that blood was flowing freely. It must be remembered that for making the Wassermann test it is not necessary for the point of the needle to be entirely in the vein in order to secure enough blood for the test, whereas in introducing a fluid like salvarsan it is very important that the point of the needle should be entirely within the lumen of the vein and nowhere else. In fact, the most important part of the injection consists in the proper introduction of the needle, as it may be partly outside of the vein, or may go too deeply or not deeply enough, or it may enter between the layers of the vein wall or between the vein wall and the perivenous tissues. The greatest source of error lies, therefore, in the improper manipulation of the needle. The chances for making this error are considerably enhanced by the use of

peculiar needles devised especially for the injection of salvarsan—needles that have a peculiar curve with a flat piece of metal attached to them, of which the Schreiber needle, illustrated in Fig. 25, is the prototype. In order to manipulate such a needle the physician must train his fingers to grow accustomed to handling a bent instrument.

No better needle can be used than an ordinary straight one with a stilet to prevent rusting. A very important point in the introduction of the needle is the peace of mind of the operator, a desideratum particularly essential in difficult cases with poor veins. For this reason alone the author believes that an attachment for giving the salt solution should always be a part of every apparatus used for the injection of salvarsan. When the operator knows that salt solution will be used,—a method incapable of producing untoward local effects even when the perivenous tissues are infiltrated,—his confidence will be more conducive to the proper handling of the needle than if no preliminary salt injection were used. For this reason, therefore, it is of the greatest advantage that the apparatus carry a container of salt solution that can be used at any time during the injection.

To return to the introduction of the needle: Although this procedure was fully considered under the head of Technology, this did not include the method for introducing drugs. For this, as was previously emphasized, a special technic is required. It is most essential, before making the puncture, that the operator be absolutely certain that the vein has the proper prominence, is well fixed, and that the vein selected is the most suitable one the patient possesses. It is good practice, therefore, to spend a few minutes in selecting a vein and judging which arm is best suited to receive the injection. If it is possible to use the left arm, this should be selected by right-handed operators in preference to the right. The reason for taking this precaution lies in the fact that the largest and most superficial vein at the bend of the elbow runs in a direction from right to left and upward, which is exactly the line of force used by a right-handed operator in puncturing a vein. Where the veins in the left arm are defective and the right arm is more suitable, it

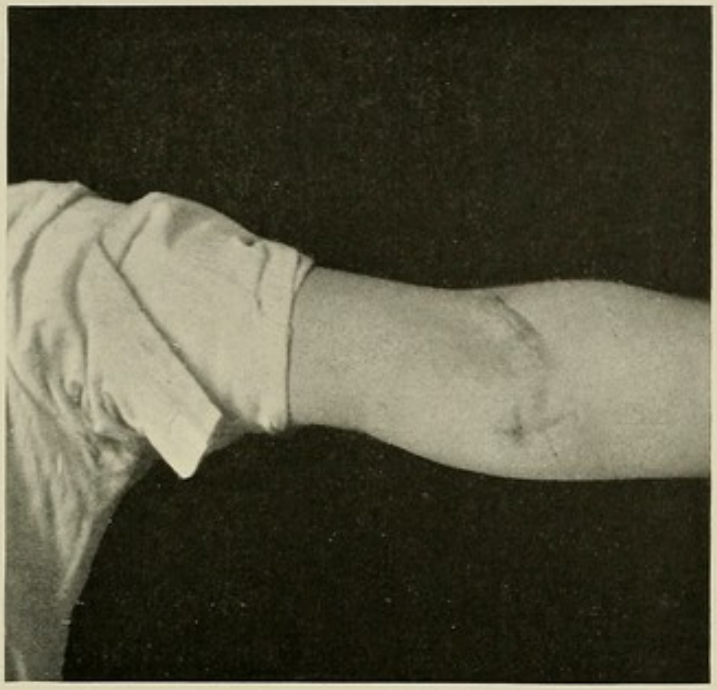


Fig. 27.—Appearance of scar four months after an infiltration of the perivenous tissues with salvarsan, due to improper introduction of the needle. The needle had to be removed and inserted into another vein exposed by an incision; the scar can be seen below.

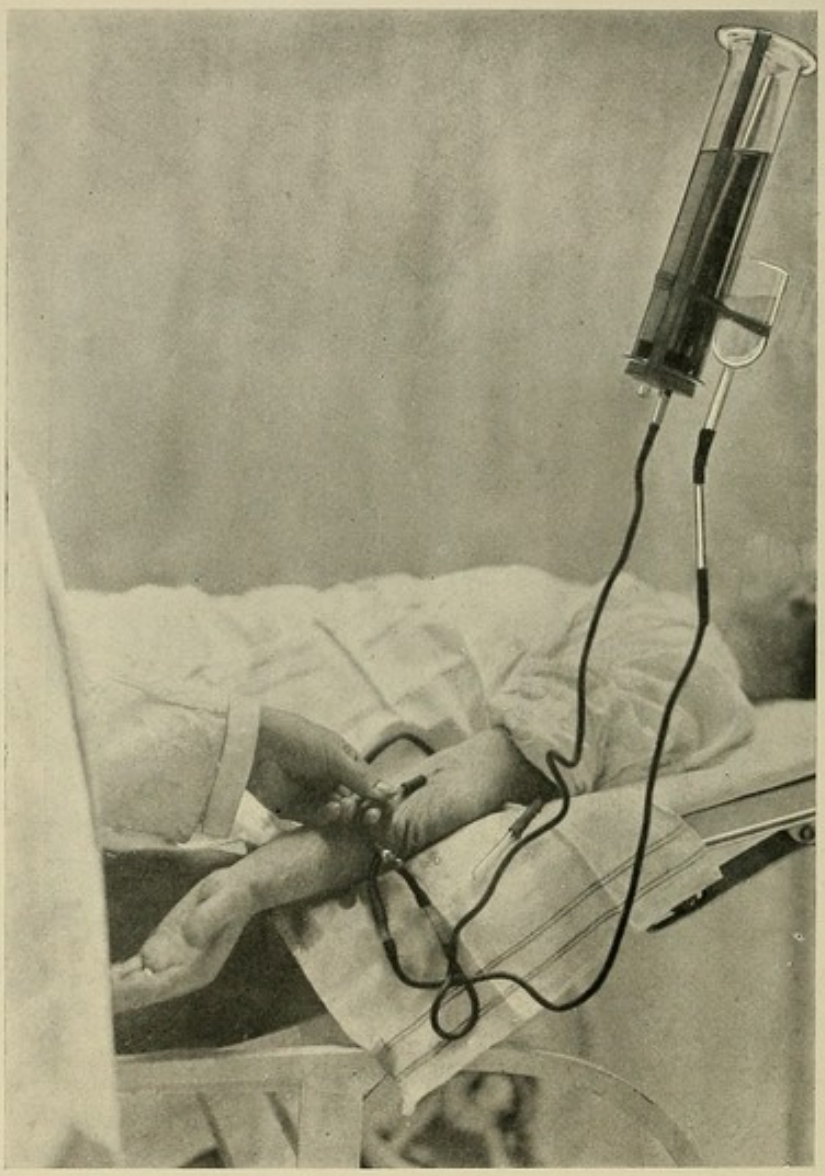


Fig. 28.—Intravenous injection of salvarsan. Note the three-way cock near the operator's hand, also the two rubber bands and the carbon filter containing sterile normal salt solution, fixed to the side of the large cylinder with one of the rubber bands.

becomes necessary for the operator so to place himself that the same direction of force may be exerted in puncturing the vein as was just described. Use every means to render the vein prominent (see Technology); grasp the arm firmly, and have absolute control of the area to be punctured.

In preparing the drug the author's apparatus possesses some advantages over the other salt-carrying three-way-cock outfits. The method of use is as follows: Pour the required amount of water in the cylinder, using hot water for salvarsan and cold for neosalvarsan. Having properly dissolved the drug, place the perforated rubber stopper tightly over the opening, securing the same with two stout rubber bands; in order that the bands may not slip from the bottom of the cylinder, it is best to attach adhesive plaster to the rim of the vessel. Place a sterile towel over the opening, having first secured the salt-carrying carbon filter; turn the three-way cock so that it will deliver salt, and then invert the entire device. Hang the apparatus on a hook, place some salt solution in the carbon filter, and drive out all air from the rubber tubing by raising and lowering the glass point of the delivery attachment. The cock should now be turned so as to deliver the drug, and the air expelled from the rubber tubing leading to the delivery cylinder. Turn the cock back again to the salt delivery tubing, and the apparatus is ready for use.

Having properly cleansed the bend of the elbow and rendered the veins as prominent as possible, with four fingers of the left hand of the operator under the elbow of the patient and with the thumb holding the vein firmly in place and in close contact with the overlying skin, place the point of the needle directly in front of the thumb, bevel up, and with a firm, steady thrust push the point into the vein. As soon as a sense of diminished resistance is experienced by the right hand not the slightest force must be used any longer, and the needle must be kept in exactly the same place, without the slightest deviation from the original position. When the blood begins to flow, collect some in a test-tube for a Wassermann reaction. Insert the delivery point into the rubber attachment of the needle, and permit about 25 c.c. of the salt solution to flow into the vein. If no

bulging occurs, the needle is probably in the right place; if the slightest swelling occurs about the vein, the needle is not properly inserted, despite the fact that the blood may have flown very freely. Once infiltration takes place, the vein is no longer fit to receive the salvarsan,—at least for the present injection,—and another vein must be selected for this purpose. The physician should never, under any circumstances, attempt to inject salvarsan where bulging has taken place with salt solution.

It occasionally happens that the needle is in the right position, and yet the salt solution does not seem to flow into the vein; this can be seen through the glass connection piece of the delivery point, which shows a trace of blood. This is sometimes due to an intravenous pressure that is greater than the pressure in the delivery apparatus; if the apparatus is elevated, thus increasing the pressure, the saline solution will begin to flow, and the blood from the connecting tube will disappear.

Having ascertained to his satisfaction that the point of the needle is in the vein, as shown by the steady flow of the saline solution and the absence of bulging, the physician now turns the cock to deliver the drug; this can be accomplished by the free hand of the operator, taking care not to change the position of the needle in the slightest degree. The turning of the salvarsan solution into the vein causes bubbles of salvarsan to rise in the air vent of the apparatus, so that the operator has at all times a gage as to the rapidity of the flow, and can tell at a glance whether or not the apparatus is functionating properly. The introduction of a full dose of salvarsan (0.6 gm.) should take about fifteen to twenty minutes; for the administration of neosalvarsan less time is required. One should not attempt to increase the rate of flow by pushing in or withdrawing the needle, as such manipulation may interfere with the success of the injection, either in whole or in part. Occasionally one may be permitted to turn the point slightly on its long axis so as to change the relation of the bevel to the vein wall; this must, however, be done with the greatest caution. When the flow is interrupted, a fact

that can be ascertained by the cessation of the bubbles rising in the air-vent tube, it is well, in order to reëstablish the flow, to turn on the salt stream before attempting to correct or improve the position of the needle.

The apparatus used by the author is very simple and permits of mixing in the same container that delivers the liquid; the water necessary for the solution of the drug can be carried in the same cylinder, and the rate of flow or its cessation can be ascertained at a glance. This last is a very important feature, and one that the other apparatus do not possess. Another advantage not possessed by other appliances is the ability to inject a pure solution of salvarsan without the least admixture of bits of glass or other insoluble débris that are at times present in a solution of salvarsan. No matter how careful the preparation of the drug, one will only in rare cases obtain an absolutely clear solution, and the delivery glass tube projecting slightly above the rubber stopper permits the impurities to settle on top of it, and these are not injected into the vein.

After the requisite amount of remedy has been injected, the saline solution is again permitted to flow into the vein, so that at no time does the salvarsan come in contact with the perivenous tissues, and after a few cubic centimeters have been introduced the needle is quickly withdrawn and the site of puncture bandaged. The aseptic precautions are the same as those observed in performing hypodermoclysis.

ILL EFFECTS ACCOMPANYING THE INJECTION

In the vast majority of instances the entire procedure is attended by very little discomfort. Extremely nervous patients may complain of faintness and require smelling salts. Only rarely will a patient complain of pain in the arm-pit corresponding to the site of injection. At times the continuous flow of salvarsan against a slightly injured wall on the opposite side of the vein will cause a smarting pain at the point of injection. This, as well as the pain in the axilla, can be readily overcome by stopping the flow of salvarsan and turning on the saline solution. Saline, there-

fore, plays a threefold rôle—it relieves the anxiety of the operator, it gives him a simple aid in ascertaining the accuracy of the needle's position without injuring the patient, and when, in the course of injection, accidents such as those mentioned do occur, he can always use the salt solution with impunity.

Studies on the variation in the blood-pressure were conducted by Sieskind from the service of Wechselmann, and showed that, in the majority of instances, the blood-pressure is lowered. This is in accord with the observations of Nicolai, who finds a lowering of the blood-pressure after the subcutaneous injection of arsenical preparations. This lowering is not very marked, and is not sufficient to justify the exclusion of salvarsan.

Some patients experience an increased flow of saliva during salvarsan administration; this disappears, however, in less than an hour.

AFTER-CARE OF THE PATIENT

After receiving the injection it is best for the patient to remain in bed. It may, at times, be permissible to give the injection in the physician's office, provided the patient is robust and does not present active manifestations of the disease, such as crises or lancinating pains. The author has had no difficulty in sending patients to their homes, even when they had to travel an hour or more. In selected cases this may be done with impunity, provided the full strength of the drug was not injected and when neosalvarsan was used. With full doses, and with salvarsan, it is better to give the injection at the patient's home. It is quite unnecessary to send the patient to a hospital to receive the injection.

In order to avoid the intestinal irritation which some patients seem to develop a small dose of Epsom salts may be administered, which will remove the irritating drug as it is eliminated from the system. This is particularly indicated in those cases where habitual constipation exists.

When the injection is given at bedtime, no dietetic orders need be given; where, however, the treatment is given during

the day, it is best to direct that solid food should be omitted until the following day. A small portion of soup or a cup of weak tea may be permitted a few hours after the treatment. Some patients are by nature very restless, and for these a small dose of a mild sedative will do no harm. The ordinary case needs no special attention, particularly when neosalvarsan is administered. The morning following the injection an analysis of the urine must be made, a precaution that should also be observed before making the injection.

Where facilities for performing the Wassermann reaction are at hand, as is the case in the majority of hospitals and in medical centers, the specimen of blood obtained during the introduction of the needle should not be discarded, but be utilized for making an analysis. The greater the number of Wassermann tests performed on a patient, the greater the good that will redound to the patient and to the physician. It is impossible at present to treat a case of syphilis intelligently without making a number of Wassermann tests. This will be discussed more fully under the head of Indications and Contraindications.

The treatment of a patient who shows pathologic manifestations after receiving the injection will be given in the section on Post-salvarsan Manifestations.

INDICATIONS AND CONTRAINDICATIONS

Indications.—In this connection only neurologic cases will be considered. The clinical and serologic symptoms requiring treatment will be considered together. It is fairly well established that the syphilogenous diseases of the nervous system all demand specific treatment, and the active varieties of these diseases require more attention than do the more or less quiescent types. Preëminently among the former is cerebrospinal syphilis.

In cerebrospinal lues, particularly with an abundant pleocytosis, the therapy must be correspondingly active, and this regardless of the behavior of the Wassermann reaction, as but little in the way of therapy need be given to overcome this index of existing syphilis.

The next to be considered is tabes. The serology of this disease is varied, and phenomena are seen that resemble cerebrospinal lues on the one hand and general paresis on the other. Again, there are instances in which biologic tests give no clue as to the existence of neurologic syphilis.

In this disease one must be satisfied with removing subjective sensations, as the objective pupillary and reflex abnormalities cannot be regarded as removable by therapy. Here serologic analyses are of the greatest moment, both as an index to treatment and from a prognostic standpoint. The higher the cell count in the spinal fluid in a given case of tabes, the greater the benefit that will be derived from antiluetic medication, and the quicker the result obtained. This was pointed out in the description of Hyperlymphocytic Tabes, which is, from a prognostic viewpoint, the most satisfactory type of tabes to treat.

Where the Wassermann reaction persists, treatment cannot be said to be concluded, and such "Wassermann fast" tabetics are best kept under surveillance until the reaction becomes negative, or, in other words, indefinitely. It is remarkable that where the "Wassermann fast" phenomenon is obtained, the patients, as a rule, can tolerate enormous quantities of salvarsan, administered at regular intervals, from 20 to 30 injections being readily borne.

The question of treating a tabetic that evinces no active serologic signs depends entirely upon the clinician's judgment and upon the subjective manifestations of the given case. Where marked discomfort is experienced from crises and shooting pains, the remedy may be employed and in some instances will be of benefit. The patient who presents the serologic and clinical combination under consideration most likely suffers from a pathologic change of an exudative nature, that runs its course entirely within the intervertebral foramen, as is suggested in Part III of this volume.

Whether or not a patient with general paresis should be treated specifically is as yet an open question. In view of the fact that but little is known regarding the effects that may be secured from salvarsan and neosalvarsan, it is justifiable to try out this form of treatment on such patients. As

will be shown further on, some improvement, clinically at least, is occasionally attained.

The same serologic consideration is to be given the selection of cases for therapy as applies to other syphilitic diseases of the nervous system, *i. e.*, the greater the cell count,—say, over 60 or 70 per c.mm.,—the more will the given patient be benefited. If the serology shows the combination of findings suggestive of the early stage of the disease, when comparatively little deterioration has taken place, this would point to the use of specific medication. In general it may be said that less hope can be offered to the case with a persistent positive Wassermann with a low cell count than to the patient who shows the early serology, or a high cell count, or whose Wassermann becomes negative after receiving a series of intravenous injections. It is a well-known fact that in rare cases the absent knee-jerks have returned and in general paresis the defective memory and the speech disturbance disappeared. The greatest caution must be observed in stating positively that this or that case is beyond improvement, the better plan being to experiment with the different methods and with the new remedies, either alone or in combination with mercury; of this, more will be adduced later.

Having once secured complete negativation of the serologic picture, the patient should be advised to return once every two or three months to ascertain if there is a recurrence. A return of pathologic findings is an index to further therapy.

Contraindications.—If one considers the fact that during the comparatively short time that has elapsed since the original publication of Alt (in March, 1911),—a period of three years,—over 5,000,000 doses of salvarsan and neosalvarsan have been used, it is small wonder that one still bears in mind the untoward effects produced by the remedy. The ill effects obtained and published in three years naturally present a formidable array of danger-signals, which are responsible for much hesitation in the use of the drug. If the physician will pause to consider the fact that millions of doses of this remedy have been used, he will see that the

element of danger in the use of salvarsan is no greater than in the use of mercury, quinin, or morphin. If the number of accidents per thousand administrations of the last-named remedies were calculated, the proportion would be no greater than follows the use of salvarsan or neosalvarsan. In a comparatively short time after its introduction accidents were reported from the use of the drug, but it was later shown that the method of administration (depot formation, use of impure water, improper selection of patients, etc.) was more to blame than the toxicity inherent in the drug. Our knowledge of the use of salvarsan having increased, the complications following its injection are becoming fewer and fewer, so that the contraindications pointed out by some writers are being regarded somewhat lightly, and only the indication is regarded as governing its use. In the author's experience the drug has proved a harmless one—much more so than the extensive literature on the subject would indicate. The contraindications to its introduction must be few, and, moreover, these must be generally recognized.

The weeding out of cases for salvarsan therapy may be divided into two classes: (1) Those to whom salvarsan is to be given with great caution only, and (2) those to whom salvarsan cannot be administered at all. To class 1, properly speaking, belong those patients who are to receive the drug, but who will require close watching; these cases are the early forms of cerebral lues with cranial nerve manifestations of an exudative nature—cases that usually come first to the ophthalmologist or aurist. In these cases, even if a small dose is injected, we may in a short time have to deal with a cerebral Herxheimer reaction (see Post-salvarsan Manifestations), which, considering the importance of the locality, in the case of the eighth nerve, the pons and medulla, would demand that extreme caution be exercised in advising the injections, more so since we know that one injection is as efficient in a case of cerebral lues as is a single injection of mercury salicylate. One injection, therefore, will tend only to increase the number of failures in this use of salvarsan, and be prejudicial to the treatment. Many of the so-called dangers are, in reality, due to the mode of administration,

which the statistics of 1913 seem to corroborate from the fact that since the necessary precautions were more carefully observed, and since the administration of salvarsan was generally performed with greater skill, fewer casualties took place. With these points in mind, the real danger of administering salvarsan and the contraindications from a clinical point of view are few indeed. It frequently becomes necessary to treat patients with a high blood-pressure with salvarsan. The author treated one patient with a blood-pressure of 240, and obtained no ill effects beyond nausea and vomiting. The organs of excretion were normal. Where the blood-pressure is much below normal, the use of salvarsan is dangerous, its injection being followed by a temporary lowering of the pressure. Such patients must be observed carefully, and if the pressure becomes low enough to cause symptoms of distress, an injection of a few minims of adrenalin chlorid may be used with advantage.

In neurologic practice one is not infrequently called upon to treat tabes with beginning optic atrophy. These patients, even if they do display active clinical and serologic manifestations, should receive salvarsan or neosalvarsan with the greatest caution. It is advisable to administer at first a very small dose of neosalvarsan and carefully observe its effect on the optic nerve, both subjectively and objectively. Any change for the worse, be it ever so mild, precludes the further use of the drug. It must be remembered that the amaurosis resulting from salvarsan or from neosalvarsan is very refractory to treatment.

Of the contraindications to the use of salvarsan should be mentioned: Severe uncompensated heart disease—where on the slightest exertion, and even while resting, there is more or less dyspnea, particularly when the pulse shows irregularities. Coronary sclerosis, particularly when accompanied by a urine of low specific gravity (contracted kidney), and containing albumin and casts. Emphysema and chronic bronchial affections that affect the heart should be treated with the greatest caution, and with small doses only. Even if syphilis is present in a patient with advanced diabetes,

carcinoma, or tuberculosis, salvarsan should not be given, as miracles cannot be expected to follow its use.

Aortic aneurysm in the very advanced stage will not be benefited by salvarsan, and its administration may be the direct cause of the patient's demise. This contraindication is removed when the condition is less advanced and when the remainder of the cardiac apparatus is intact. If the luetic focus is near an important and vital center, such as the vagus or other important medullary centers, the use of salvarsan is very dangerous on account of the possible production of a Herxheimer reaction in this region, causing almost certain death. This will be considered more fully together with the Herxheimer reaction.

Where an early cerebral lues manifests itself by headache, vertigo, defective memory, apoplectic seizures that leave permanent paralyses in their wake, salvarsan should be given with great caution, as its use may result in added insult to the brain.

THE WATER ERROR

The early literature on salvarsan and its by-effects contains many references to, and examples of, the toxic effects of the drug, This resulted in extensive experimentation to ascertain the cause of the toxicity, and it was subsequently shown that the trouble was not inherent in the salvarsan, but in the water used in making the solution. McIntosh and Fildes and Dearden, from the laboratory of William Bulloch, working with various ordinary and bacterium-free saline injections in rabbits, came to the conclusion that it was not the salvarsan, but the bacteria contained in the media used to effect its solution, that should be held responsible for the ill-effects of the drug.

As a result of the suggestions of Ehrlich and Wechselmann, Yakimoff and N. K. Yakimoff learned the effects upon animals of the injection of solutions containing the toxins and endotoxins of bacteria. These investigators found that the injection of small doses of salvarsan together with the endotoxin of Bacterium coli commune in mice infected with trypanosomes proved much more toxic than did endotoxin-free injections. These writers established the toxicity

for the endotoxins of Bacterium coli commune, for the Bacillus pyocyaneus, Staphylococcus aureus, Pneumobacillus Friedländeri, Bacillus subtilis, and Bacillus tetragenus.

The addition of these endotoxins to salvarsan injected intravenously will result in a toxic effect, multiplying this toxicity for mice from two to eight times. The same amount of endotoxin injected without the addition of salvarsan is without bad effect on the animals. The increase of toxicity produced by different bacteria also varies, the endotoxin of Bacterium coli being the most dangerous of all, and that of Bacillus tetragenus least toxic. The reason for using freshly distilled water is apparent from the foregoing report, and the precaution of always using this should be strictly followed. The simple boiling of old distilled water may result in the injection of sufficient endotoxin together with the salvarsan to produce all the untoward effects unjustly ascribed to the drug.

THE FATE OF THE DRUG IN THE ORGANISM

The presence of the injected drug is demonstrable at once in the blood drawn from the other arm; it may also be demonstrated in the urine voided during the operation or immediately following it. Sufficient data are recorded to show that the excretion of arsenic begins at once, and continues for a long time. The duration of this period of excretion depends greatly upon the condition of the excretory organs of the patient, and upon the method of introducing the drug; it remains in the body much longer after an intramuscular than after an intravenous injection. In from three to four days the arsenic can no longer be found in the urine, but it may still be present in the feces after five or six days. Some writers have found arsenic even after four weeks, and Finger reports its presence nine months after a single salvarsan injection. The elimination of the drug is so rapid that it is imperative to use repeated doses before an effect can be observed.

The ordinary tests for the presence of arsenic in the cerebrospinal fluid after an injection of salvarsan gave, as a rule, negative results. The reports of Wechselmann,

Sicard and Bloch, and Zaloziecki, using the Marsch-Bertrand apparatus, as well as the biologic method of Abel (see below), showed that arsenic is present in the spinal fluid of patients treated with salvarsan. This is to be expected, and to say that the drug does not reach the spinal fluid, in view of the fact that the serology is markedly changed in every way, is to establish an unexplainable paradox. The presence of arsenic in the fluid puts all controversy as to the modus operandi of the negativating forces to an end: it simply attacks the microörganisms *in situ*.

By using the biologic method for detecting arsenic, the author was able to demonstrate its presence in the vomitus of a patient treated with salvarsan.

THE DETECTION OF ARSENIC

The chemical detection of arsenic will be described after the biologic detection has been considered; the biologic method was employed by the author in his studies of arsenic elimination.

This method is dependent upon the growth and proliferation of a thread-like fungus, which, when brought in contact with a substance containing arsenic, gives off a strong, garlic-like odor. The reaction is, therefore, only qualitative, as the sense of smell of the individual worker must be considered. The chemistry of the reaction depends upon the formation, in part, of hydrogen arsenid, AsH_3, and largely on the production of diethylarsin, $AsH(C_2H_5)_2$, when the fungus is brought in contact with an arsenic-containing substance. The presence of the chemical substances just mentioned is responsible for the garlic-like odor.

The fungus, Penicillium brevicaule, grows very readily upon doubly sterilized potato, as well as upon white or brown bread. The growth is very persistent, and a dried-up potato culture eight months old will still give, upon reculture, a vigorous growth of fungi. The fungi grow at room temperature or at 32° C. in the incubator. In the course of time the growth becomes yellowish and then brown, a fact that does not interfere with the arsenic-detecting properties.

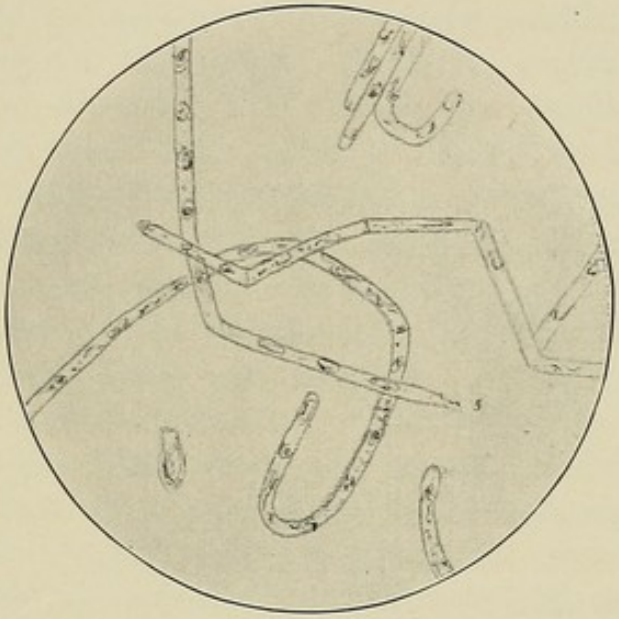


Fig. 29.—Penicillium brevicaule. (No. 6 Leitz, ocular 4.)

The technic is very simple, and does not consume more than five minutes of the worker's time. Having obtained the spinal fluid in the ordinary way, it is poured upon a culture previously grown on white bread (preferably two days old) in an Erlenmeyer flask, and stoppered tightly with a rubber stopper. It is permitted to remain thus tightly stoppered for forty-eight hours before the stopper should be removed for the detection of the garlic-like odor. Repeated opening of the flask tends to diminish the intensity of the odor. The delicacy of the test surpasses that of the ordinary Marsh test, as it is capable of giving the odor of garlic when $\frac{1}{300}$ milligram of salvarsan is brought in contact with it, and as salvarsan contains only a trifle over 31 per cent. of arsenic, the test is, therefore, sensitive to $\frac{1}{1000}$ milligram of arsenic. The author was unable to detect the odor in fluids from patients treated with one dose, but when frequently repeated doses of salvarsan or neosalvarsan were given, the odor could be obtained in from forty-eight to sixty hours. The test was performed in the following manner: The bread-containing Erlenmeyer flasks were sterilized twice and carefully inoculated with the Penicillium brevicaule fungus. At the end of the second day of growth these flasks were ready for use. Having obtained the spinal fluid, 10 c.c. was placed in the flask and stoppered with a rubber stopper. The cases that had received the foregoing method of treatment usually showed the reaction, provided not less than 8 c.c. of the fluid was used in making the test. After making three intravenous injections no trace of the drug could be demonstrated in the fluid, but after the fourth or fifth treatment the odor could readily be obtained. The incubation was carried out on top of the incubator, at a temperature varying between 27° and 30° C. In performing this experiment care must be taken not to introduce air bacteria while transferring the potato culture to the Erlenmeyer flask.

The Marsh Test.—Nascent hydrogen converts arsenic compounds into gaseous hydrogen arsenid, AsH_3. This can be decomposed by heat, the arsenic being deposited as a dark, mirror-like coating on cold objects. This is practically the

basis of the Marsh test. Where minute quantities of arsenic are to be sought for, it is necessary to have at least a liter flask, and a larger amount of zinc is required than where the search is for larger quantities of arsenic.

To begin with, all reagents must be arsenic free. The liter flask is provided with a separatory funnel that reaches to the bottom of the flask. As the liberated gas will contain moisture, it is best to pass this through a U-tube, which is immersed in cold water, and through another tube containing dried calcium chlorid. The moisture that is not condensed in the first U tube is absorbed in the calcium tube. The dry gas now passes through a horizontal glass tube of hard

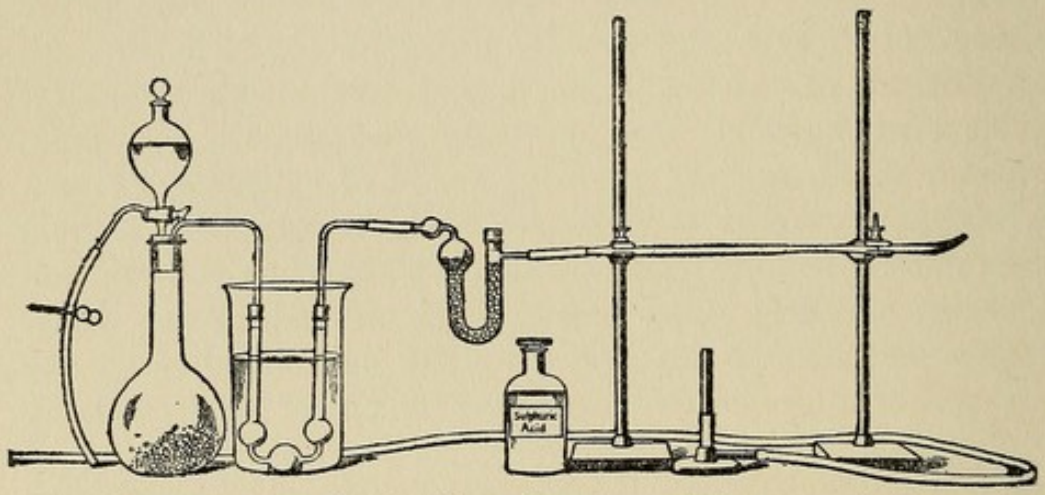


Fig. 30.—Apparatus for the detection of a minute amount of arsenic by Marsh's test (Rockwood).

Bohemian glass, which melts with great difficulty. After all the air has been driven off from the apparatus, this tube should be heated to redness with a Bunsen burner, and the heating continued for half an hour, in order to prove the purity of the reagents used; when satisfactory, the apparatus is ready to receive the material to be tested for the presence of arsenic. If the reagents are not pure, a brown or black mirror will immediately be deposited beyond the flame. The mirror of arsenic is rendered more apparent if the glass tube beyond the flame is constricted to a small diameter, which is also the case with the free point of the tube. If the arsenic is not decomposed at the constriction, which is often the case, it can be detected by the flame at the point of the

tube with a cold porcelain surface, upon which the mirror collects.

In order to remove the exhausted acid without the admission of air it is advisable to have a third glass tube inserted through the rubber stopper, with a bent end to which a rubber tube possessing a clamp is attached. This removal can be effected by opening the clamp and closing the exit tube for a second, when the fluid siphons off. Where very minute amounts of arsenic are present, it may be necessary to manipulate the apparatus for several hours. The test is sensitive to $\frac{1}{100}$ milligram of arsenic. The reaction is interfered with or prevented by the presence of oxidizing agents, organic matter, and the salts of the heavy metals, particularly of mercury.

The nascent hydrogen gas is generated by the action of chemically pure H_2SO_4 upon arsenic-free, finely granulated metallic zinc.

Other tests requiring the use of electric apparatus have also been devised; these will not be described here, the reader being referred to special works on analytic chemistry for a discussion of them, as well as for the corroborative tests for the detection of arsenic.

THE COMBINED INTRAVENOUS AND INTRASPINOUS TREATMENT

In an article which appeared in the British Medical Journal, November 15, 1913, F. W. Mott speaks of treating syphilis of the nervous system by a method conceived by Fisher, who in the spring of 1912 elaborated it in the Rockwood Hospital in Kingston, Canada. Fisher at that time administered to his patients salvarsan intravenously, and after having succeeded in rendering their sera negative to the Wassermann test, would inject this serum intraspinously every week for three months; after this the patient would receive the same treatment every two weeks for four months. Mott observed very gratifying results from this method of treatment, so that he had Fisher come to London to continue his studies on patients in the Claybury Hospital.

TABLE SHOWING RESULTS OF COMBINED THERAPY

Name.	Diagnosis.	Duration of Symptoms.	Duration of Syphilis.	Results of Analyses Before Treatment.				Duration of Treatment.	Method of Treatment.						Results of Analyses After Treatment.			
				Serum Wassermann.	Cerebrospinal Fluid.				Salvarsan.		Neo-salvarsan.		Serum (Intra-spinous Inject.).		Serum. Wassermann.	Cerebrospinal Fluid.		
					Cells. Per C.mm.	Globulin Reaction.	Wasser-mann.		Number of Injections.	Total Dose.	Number of Injections.	Total Dose.	Number of Injections.	Total Dose.		Cells Per C.mm.	Globulin Reaction.	Wasser-mann.
							C.cm.	Months.		Gm.		Gm.		C.cm.				C.cm.
1296 H. C.	Tabes (jmperfect).	3 years ??	24 years.	+	113	±	0.8 ++	1½	4	2.0	. .	. .	4	48	±	12	+	1.0 −
1204 F. G. B.	Tabes (advanced).	3 years ??	?	−	47	+	0.6 ++	2	6	2.8	. .	. .	4	48	−	7	+	1.0 +
1271 H. B.	Tabes (advanced).	11 years ??	18 years.	+	25	++	0.4 ++	2	4	2.0	1	0.45	4	48	±	11	++	1.0 ++
1219 L. P.	Tabes (moderately advanced).	5 years ??	?	+	233	±	1.0 ±	2	5	2.5	. .	. .	5	60	+	7	−	1.0 −
1211 J. H. T.	Tabes (moderately advanced).	8 years ??	15 years.	+	40	++	0.2 ++	2	5	2.3	. .	. .	5	60	+	14	++	0.2 ++
1159 O. K.	Tabes (advanced).	4 years ??	12 years.	++	112	++	0.4 ++	2	5	2.4	. .	. .	4	48	++	10	+	0.4 ++
1141 J. A. B.	Tabes (imperfect).	2 years ??	32 years.	++	33	+	0.8 ++	2	4	2.0	. .	. .	4	48	++	10	+	1.0 +±
1177 A. T.	Tabes (imperfect).	1 year.	8 years.	± ?	114	+	0.4 ++	2½	4	1.3	3	1.3	6	64	−	12	+	1.0 −
1136 R. S. P.	Tabes (imperfect).	4 years.	?	++	47	++	0.4 ++	2½	6	2.9	. .	. .	6	72	++	14	+	1.0 ++
1118 W. S.	Cerebrospinal Syphilis.	8 months.	6 years.	++	182	++	0.2 ++	2½	6	2.8	. .	. .	5	60	++	14	+	0.6 ++
1098 F. H. H.	Tabes (moderately advanced).	4 months.	12 years.	± ?	24	±	0.1 ++	3	5	2.4	. .	. .	5	60	±	5	+	0.4 ++
1140 A. D.	Tabes (advanced).	2 years.	14 years.	++	57	++	0.6 ++	4	5	2.5	5	3.7	8	96	++	3	+	1.0 +±
1111 C. M. A.	Tabes (moderately advanced).	12 years.	17 years.	±	92	±	0.4 ++	4	4	2.0	4	2.8	8	96	±	3	±	1.0 ++
1199 H. G.	Tabes (imperfect).	8 years.	?	−	25	+	0.6 ++	4½	3	1.5	7	5.0	7	84	−	3	+	1.0 −
1042 H. S. R.	Tabes (advanced).	5 years.	?	++	42	±	0.2 ++	4½	5	2.5	6	3.9	10	120	+	2	−	0.8 ++
1097 F. H. P.	Tabo-paralysis (early).	1 year.	8 years.	++	225	++	0.1 ++	5½	6	3.0	7	5.1	10	118	++	12	+	0.2 ++
1032 U. C. B.	Syphilitic Myelitis.	16 months.	?	±	50	+	0.2 ++	5½	6	3.0	9	6.9	13	156	++	2	±	1.0 +±
559 J. S.	Tabes (moderately advanced).	18 months.	8 years.	+	30	+	1.0 +	8	. .	. .	11	8.0	6	71	−	6	±	1.0 −
883 M. N.	General Paralysis (early).	1 year.	21 years.	++	46	++	0.1 ++	8½	7	3.5	9	6.7	10	120	++	4	++	0.1 ++
485 C. M.	Tabes (moderately advanced).	1½ years.	19 years.	−	130	++	1.0 ++	8	14	4.8	2	1.8	9	107	−	2	±	1.0 −

In the Münchener medicinizche Wochenschrift of 1913, Nos. 36 and 37, appeared an article describing the results obtained by treating locally (intraspinally) 12 patients suffering from syphilitic diseases of the nervous system. The experimenters, Homer F. Swift and A. W. M. Ellis, conducted their observations at the Rockefeller Institute Hospital. This method is described in brief as follows:

The patient receives an intravenous injection of 0.5 gm. salvarsan, in the majority of cases, given in the usual manner. One hour after this administration enough blood is withdrawn from the patient's vein to give at least 15 c.c. of serum. The blood, obtained under aseptic precautions, is permitted to coagulate, and is then placed in the ice-chest overnight. Next morning the separated serum is very carefully decanted off into a centrifuge tube, and permitted to centrifuge for about half an hour. The clear supernatant serum is pipeted off from the few red cells at the bottom, and poured into a graduated cylinder up to the 12 c.c. mark, and then brought up to 30 c.c. by the addition of sterile 0.9 per cent. NaCl solution. This is placed in a 56° C. thermostat for thirty minutes, to avoid danger of contamination, and the mixture of serum and salt is ready for intraspinous injection.

The solution is injected at body temperature. With the patient lying on his side, in bed, near the edge, the back is rendered aseptic in the ordinary manner, and the area to be punctured anesthetized with 2 per cent. sterile novocain solution. The lumbar puncture needle is introduced in the usual manner, and about 30 c.c. of cerebrospinal fluid is withdrawn, or a quantity that will reduce the intraspinous pressure to about 30 or 40 millimeters. This is gaged with a 3-millimeter glass tube graduated in centimeters and millimeters. When the desired pressure is reached, the connection with the gage is discontinued. The serum-salt mixture having been poured into a Luer syringe (large size) carrying at the delivery point a sterile piece of connecting rubber tubing about 12 inches long, this is now attached to the lumbar puncture needle, taking care not to introduce any air; the mixture is then permitted to flow gently into the

subdural space. The use of the gage is not essential, the only requisite being that the quantity removed equal the quantity introduced; if the patient complains of discomfort, the further withdrawal of fluid had best be stopped, and the mixture introduced before 30 c.c. has been withdrawn.

The table on page 240 gives the results, in part, of the investigations carried out by Swift and Ellis.

The results are very interesting and instructive. The most marked changes were chiefly in the cerebrospinal fluid. The serum Wassermann, however, was not greatly changed. In the great majority of instances the positive serum reaction remained positive, and only in three instances was the result weakly positive. Regarding the great diminution in the pleocytosis, one must be very conservative in ascribing the fall in the cell count entirely to the result of the intraspinous therapy. Although it is perhaps only partially responsible for the diminution, the possibility of diminishing the cell count by the removal of large amounts of fluid, such as is the custom in intraspinous therapy, must not be lost sight of. From the serologic point of view, the cases of tabes correspond to the "Wassermann fast" type described in Part III of this volume. Why the globulin content should not be influenced in the greater number of instances is not clear, in view of the fact that the cell count became, in the majority of cases, almost normal. The method of giving intraspinous injections was elaborated by Drs. Swift and Ellis, the intention being to bring to the cerebrospinal circulation direct the arsenic contained in salvarsan. The authors of the combined method claim that after giving intravenous injections alone hardly any arsenic reaches the spinal fluid.

THE "INTENSIVE INTRAVENOUS" METHOD

In studying the chemistry of salvarsan and its effects upon microörganisms more or less closely related to the spirochetes of syphilis, it became apparent that when trypanosomes are treated with small doses of atoxyl, it is possible to render them atoxyl-fast. A subsequent dose of atoxyl large enough to kill the non-atoxyl-fast trypanosomes will have no effect on the atoxyl-fast strain.

Ehrlich demonstrated that such a strain of trypanosomes is still susceptible to the effect of arsenophenylglycin. If these trypanosomes are treated with minute doses of arsenophenylglycin, a strain of microörganisms will be produced that are atoxyl as well as arsenophenylglycin-fast. This strain of trypanosomes is, however, promptly killed with para-amidophenylarsenoxid.

The significance of the foregoing biologic facts lies in the manner in which these spirillocidal chemicals act. They all contain arsenic, and can be attached to the trypanosomes by either the amido (NH_2) or the hydroxyl (OH) group. Other groups are spirillotropic, such as the glycin (CH_2-(NH_2)CO) molecule of arsenophenylglycin, of which perhaps the acetic acid radicle plays the important part of the haptophore group. These facts must be remembered in order to form a clear conception of what may occur when patients are treated with salvarsan or neosalvarsan. If the Treponema pallidum is capable of becoming salvarsan-fast, what should be done, and how can such a phenomenon be demonstrated? These questions can be touched upon only superficially, and open up a field of experimental possibilities that may, in the future, serve as a beacon-light to the exact scientific eradication of syphilis. At present one must be content to attempt the elaboration of what may serve as a nucleus for future workers.

In the Neurological Institute and from the service of the Second Division a method of treatment was devised that has given very gratifying results in a comparatively short time—in some cases in less than one month. The results secured, clinically and serologically, were such as to promise much improvement in cases that were previously treated with salvarsan without being benefited. By this method neosalvarsan is given in 0.45 doses intravenously, two days being allowed to intervene between injections. Five injections are given unless contraindications develop. During the two intervening days the patient receives inunctions of mercury, if necessary. Out of a total of 35, all but one showed improvement clinically. Of these 35, only 20 presented themselves for subsequent serologic observation, and of these,

only 3 patients retained their plus Wassermann, these patients being paretics in the well-advanced stage. Of these 3 patients, one had a second series of "intensive treatment," after which his Wassermann became negative.

In the treatment of diseases of the nervous system one must bear in mind that the pathologic process caused by syphilis presents two phases: one is the actual disease, which is an exudative process of greater or lesser intensity; the other is the result of the syphilis, *i. e.*, the production of degenerative changes in the nervous system. The therapeutist must remember that the degenerative process cannot, as the result of treatment, be converted into the normal or nearly normal, and it remains for him to do the best he can under the circumstances—treat the exudative manifestations of the disease. This treatment has been described in the third part of this volume.

The evanescent palsies, the pains, even the memory defect, the hand-writing, and the speech of the paretic may all be influenced by therapy, which must, therefore, be considered in those cases as produced by an exudative and not by a degenerative process. The Argyll-Robertson pupil, the absent knee-jerks, and the Romberg symptom are the manifestations of degeneration, and are not, therefore, amenable to therapy.

As the changes that take place in cerebrospinal, cerebral, or spinal lues are related to a purely exudative pathology, be it meningitic, gummatous, or endarteritic, the results of treatment are consequently better than in tabes or in general paresis, for in these diseases we are confronted by degenerative changes in addition to the accompanying exudation.

As the pleocytosis is a fair gage of the extent of the exudation, the method of treatment that will render 20 or 30 cells normal as well as negativate the positive Wassermann is of greater utility than a method that can only reduce the cell count of those cases that present a pleocytosis of 100 or more. The treatment that will convert a positive Wassermann into a negative reaction in a patient with general paresis has effected a better result than a method that can accomplish this only in a case of ordinary tabes or cerebrospinal syphilis, with-

out being able to influence the former disease. The author consequently considers the "intensive method" of treatment a distinct advantage over other methods of administering salvarsan or neosalvarsan, as it shows results clinically and serologically superior to any that have come to his knowledge up to the present time (February, 1914). The following table was compiled by Dr. Stephenson, to whom the author is indebted for its presentation:

RESULTS OF "INTENSIVE TREATMENT"

No.	Name.	Diagnosis.	S. W.	F. W.	Gl.	Pl.	Therapy.	S. W.	F. W.	Gl.	Pl.
1.	O. G.	Tabes.	+	+	+	34	1 series.	—	—	—	10
2.	Ham.	Tabes.	+	+	+	27	1 series.	—	—	—	0
3.	Kal.	Tabes.	+	+	+	77	1 series.	—	—	—	0
4.	Mur.	Cerebro-spinal lues.	+	+	+	117	3 inject.	—	—	—	28
5.	Sau.	Cerebro-spinal lues.	+	+	+	93	1 series.	—	—	—	48
6.	Sch.	Tabo-paresis.	+	+	+	40	1 series.	W.+	W.+	W.+	11
7.	Man.	Tabo-paresis.	+	+	+	70	1 series.	—	—	—	16
8.	Bra.	Paresis.	+	+	+	34	1 series.	+	+	+	16
9.	Kin.	Paresis.	+	+	+	63	1 series.	+	+	W.+	60
10.	Fur.	Paresis.	+	+	+	32	2 series.	W.+	W.+	W.+	32
							Three months apart.	—	—	—	34

The clinical reports show that all the patients but patient No. 8 showed improvement. With the exception of the paretic cases, the other syphilogenous nervous diseases treated all showed serologic improvement. Paretic No. 10 showed an improvement in his serology after a second series of injections. Considering the limitations that the treatment of such diseases are subject to, the results are as good as can be expected at present. The possibility of rendering the trypanosomes resistant to one drug, and being able, at the same time, to destroy them with an arsenic-carrying chemical substance possessing a different spirillotrophic haptophore group, was spoken of on a previous page. This phenomenon is described in connection with the various methods of therapy so

as to impress upon the therapeutist the possibility of its occurrence in the human organism, and with the Treponema pallidum.

The author had the opportunity of treating patients with neosalvarsan by the "intensive method," and in some cases the positive Wassermann could not be rendered negative. The possibility of the existence of a neosalvarsan-fast strain of microörganisms occurred to the author, and gradually increasing doses of salvarsan were given intravenously in a second series: the initial dose given was 0.4 gm.; after two days' interval 0.45 gm. was given, and so on until 0.6 gm. was injected. During the salvarsan-free days the patients received two inunctions of mercury daily. The four cases thus treated, who all presented a positive Wassermann before the salvarsan series, all gave a negative Wassermann reaction in the serum: one after two, one after four, and the remaining two after five injections. One of the patients improved sufficiently to enable him to return to business. All patients were clinically paretics.

The entire subject of treatment of the syphilogenous nervous diseases with salvarsan or neosalvarsan is to be regarded as still in the experimental stage. One of the facts established by the modern therapeutist is that mercury cannot be dispensed with no matter how brilliant the success that attends the treatment with the newer remedies. Salvarsan and substances allied to salvarsan accomplish definite purposes, which, although resembling the action of mercury to some extent, still do not possess all the curative qualities for which mercury is known, so that the greatest success will be obtained when the old and the new remedies are combined. Enough has been written regarding the subject to justify the combined treatment of syphilitic nervous diseases, the mercury being used in the form of inunctions, and the neosalvarsan being administered intravenously. If the desired results are not secured after the patient has had a treatment-free period of two weeks, it is advisable to institute a series of salvarsan injections, as previously suggested, and, in addition, prescribe inunctions of mercury twice a day. This method usually negativates the pre-

viously positive Wassermann in the serum and fluid, and, as a rule, is followed by clinical improvement. If the patient does not respond to this strenuous therapy, an intraspinous injection may be given tentatively, and repeated at definite intervals until the Wassermann reaction becomes negative. As the negativating powers of the intraspinous method are not very great, it is sometimes better to permit the patient to retain his positive serum Wassermann without treatment, so long as his clinical status is good enough to justify such a procedure. A watchful eye must, however, be kept on the serologic status of such patients, and any return of a pleocytosis or the return of an excess of globulin is to be promptly met by a series of injections.

POST-SALVARSAN MANIFESTATIONS

Local Reaction From Intramuscular and Intravenous Injections.—Any irritating effect produced by salvarsan can be detected by the subjective complaints of the patient and the objective signs at the site of the injection. One of the many necroses described in the literature as following the use of the drug is pictured in Fig. 20. A lesion produced by salvarsan heals with great difficulty; the author had a slight scratch on a finger that was brought in contact with the drug; this remained painful and did not heal for two weeks. Although the irritating properties of the drug may be neutralized by oil, paraffin, etc., instances are, nevertheless, recorded in which necroses occurred, and many cases of painful swelling are seen.

The improper administration of the intravenous injection—*i. e.*, the drug being driven into the perivenous tissues—results in reactions similar to the intramuscular manifestations, and in some instances sloughing may follow. If an improper injection has been given, this becomes manifest at once, as the perivenous salvarsan infiltration makes itself felt immediately. Small infiltrations—of a few drops only—will result in an arm that will be painful for a few days only and a black-and-blue discoloration. Such an arm should not receive another injection until the pain and discoloration have disappeared. In these cases it may be that the vein will

become thrombosed and rendered useless for an inch or more. Where many injections are necessary, it is evident that conservation of the patient's veins is quite important. Many patients display veins of which only one or two are suitable for receiving the treatment. A black-and-blue discoloration is sometimes produced by an extravasation of blood; this is, however, painless, and never causes thrombosis.

Neurotic patients at times complain of pain in the axilla; this lasts only for a short time,—an hour or two,—and disappears without special treatment.

General Reactions.—(*a*) *Headache.*—The headache that follows the injection of salvarsan is frequently not so much the result of the drug as due to the nervousness of the patient. Neurotic headaches often occur during the injection of the drug, and usually in patients who are getting their first salvarsan treatment. In cases of cerebral syphilis, where headaches are habitual, an aggravation of this symptom is an unpleasant accompaniment of the therapy, it being impossible to decide whether the pain is due to an increase in the exudative luetic process or to causes that bear no relation to the treatment, such as constipation, anxiety, and an empty stomach. The headache due to an aggravation of the cerebral process usually occurs in from ten to twenty-four hours after the administration of the drug, whereas a headache due to other causes manifests itself much earlier.

For this casual occurrence of headache none of the coal-tar remedies ought to be prescribed, and it is better to wait or to treat the causal condition if any is found to exist.

(*b*) Although very rarely a distressing symptom, one is sometimes called upon to treat *nausea.* A little hot water every ten minutes, given largely for its psychic effect, is at times sufficient to relieve the condition. Some patients display this symptom every time they are injected, whereas others, again, manifest it only as a result of many short interval treatments, as when a series is given.

(*c*) *Vomiting.*—This symptom will at times require a hypodermic injection of $\frac{1}{8}$ grain of morphin for its relief. Hot tea is also useful. The vomiting, as a rule, does not last long, and need give the physician no great concern.

(*d*) *Diarrhea.*—This symptom may at times prove quite troublesome, although it is never of an alarming nature. The complication is perhaps best met by the use of prophylactic measures, such as thorough clearing of the bowel before treatment by mild catharsis, or by administering a small quantity of Epsom salts an hour after giving the intravenous injection. These diarrheas occur in patients who, as a rule, are not subject to flux, and may even be seen in patients who are habitually constipated. If the measures suggested fail and the diarrhea is becoming very distressing, one is justified in resorting to the ordinary methods for its relief, such as morphin and atropin or bismuth and chalk. Clearing the lower bowel by means of an enema at times has the desired effect.

(*e*) *Chills and Fever.*—The chills and fever that formerly occurred immediately after injections of salvarsan are very rarely encountered at the present time, since freshly distilled water is employed in the preparation of the drug. They are still less frequently seen when neosalvarsan is used. The latter drug gives rise to fewer manifestations than does the older salvarsan, the same precautions being used. In the author's experience a hot-water bottle and a cup of hot tea are all that are required for the relief of this condition. The fever is rarely high, although cases are on record in which a temperature of 104° and even 105° F. was observed. As previously stated, these complications are becoming fewer with a better understanding of the technic, a more careful selection of patients, and the adoption of proper and timely precautions.

The reaction is usually accompanied by a trace of albumin, and rarely by a hyaline cast or cylindroid in the urine. Where the renal reaction is more severe, one must be very careful in using the drug again, as a severe nephritis may develop.

(*f*) *Skin Manifestations.*—Morbilliform and scarlatiniform eruptions may follow the use of neosalvarsan or salvarsan in from two to forty-eight hours, or they may appear as late as a week or ten days after the last injection was given. The reaction is chiefly a toxic manifestation, and only partly a reaction of a syphilitic organism to the introduction of

arsenic. These dermatologic manifestations are usually accompanied by considerable itching, more or less pronounced edema, and frequently by fever. The temperature may rise to 104° or even 105° F. For this complication, eliminative therapy is recommended, together with local applications of zinc stearate. As the reactions are at times very severe, all the precautions necessary in acute illnesses are to be observed in these cutaneous post-salvarsan manifestations; these include attention to diet, elimination, and stimulation.

The Herxheimer Reaction.—This very interesting post-salvarsan manifestation will be discussed at length from the neurologist's point of view, the studies of Milian being followed in detail:

The Herxheimer reaction is an inflammatory reaction produced in syphilitic tissues through the influence of specific treatment. This reaction may manifest itself not only after the intravenous administration of salvarsan or neosalvarsan, but also after the injection of mercury salicylate, calomel, sodium cacodylate, etc. Every luetic lesion, whether cutaneous, mucous, or visceral, is capable of reacting in such manner. We may have a liver reaction or a renal complication, with transient icterus in the former and albuminuria in the latter. The nervous system responds similarly.

The occurrence of the Herxheimer reaction has been variously explained by different authorities; *e. g.*, liberation of a syphilis-endotoxin causing a hyperemia (Thalmann); excitation of the treponema by an insufficient dose of the drug (Ehrlich, Iversen, Wechselmann, Loeb, etc.). Individual irregularities in the vascular tonus (Fränkel and Grouven). Mercury and salvarsan act in a manner similar to tuberculin (Julius Baum). The reaction is comparable to the tuberculin effect in lupus (Richard Kalb).

The theory regarding the reaction that has gained the widest credence is that expressed by Ehrlich, Iversen, Wechselmann, Loeb, etc.

Symptomatology.—The cutaneous reaction is manifested by an inflammatory train of symptoms giving rise to edema, redness, pain, and even to fever, these usually following

the first injection. The mucous patches react in a manner similar to the cutaneous. The gummatous formations become swollen, may ulcerate, and are capable of producing considerable exudation. This is particularly important to the neurologist, who may have to consider such a reaction in a cerebral gumma before advising salvarsan therapy.

The viscera involved in the syphilitic process react in a manner similar to the cutaneous manifestations; if the liver is affected an angiocholitis sets in, and bile-products appear in the urine. The author has observed that in cases where the patient had an alcoholic history as well as lues of the nervous system, the injection of salvarsan would give an intense reaction with Ehrlich's dimethyl-amido-benzaldehyd solution. In some instances the reaction is quite severe, and is to be regarded as a toxic manifestation of the salvarsan injection. The symptoms are more pronounced, there being pains in the limbs, depression, restlessness, lassitude, and rapid pulse. Three or four days later the face becomes congested and red, the redness being not of the usual febrile color or of the scarlet red previously spoken of, but of a brick-like hue, somewhat resembling the red paint used by Indians. At the same time the conjunctivæ become very much injected, and pinhead-sized extravasations may occur in the sclera. The urine is high colored, and shows a marked albumin reaction. On the following day the urine becomes almost green in color, and at times even black, and gives the reaction for bile-pigments. The temperature is usually very high, and the general condition of the patient is very poor. On the sixth day the redness of the face is replaced by a true icteric color, the conjunctivæ also becoming yellow.

The liver is small; the spleen is large; the feces are of an ashen hue. The patient becomes extremely emaciated and very weak. The symptoms gradually abate, and a crisis occurs at the end of about two weeks, when the patient begins to void large quantities of urine.

The Nervous System.—The nervous system is more lastingly involved in a Herxheimer reaction than is any other portion of the body affected by such a process. This is particularly

the case where the cranial nerve traverses a rigid bony canal, and where opportunities for compression are greatest. The facial paralyses that follow a salvarsan injection are due to a Herxheimer reaction that manifests itself in the Fallopian aqueduct. The vestibular and cochlear branches of the eighth nerve are affected for a similar reason. The involvement of the vestibular branch is frequently the cause of the vomiting and vertigo that sometimes occur. A Ménière phenomenon may occur after a salvarsan injection.

In cases of cerebral lues the reaction usually manifests itself in the form of severe headaches. In other cases, where focal signs exist, the reaction assumes an exudative character, producing irritative manifestations and paralyses. These, as a rule, are transient in character, and usually appear after the second injection. In patients with tabes the intravenous injection of salvarsan or neosalvarsan produces a Herxheimer reaction characterized by severe pains, which appear in from one-half to one hour after the injection is given. The pains may last for forty-eight hours and may not disappear entirely for three or four days. These painful reactions require vigorous morphin therapy until the pinching exudation affecting the posterior roots disappears. These pains may at times be checked by giving another smaller injection of salvarsan. The so-called provocative positive Wassermann reaction must also be considered as a Herxheimer phenomenon.

For purposes of differentiation between a Herxheimer reaction and a reaction due to arsenic intolerance, the following table of Milian is offered:

Herxheimer Reaction.	Reaction Due to Intolerance.
1. Reaction becomes less marked with repeated injections. This may in some cases require more than two or three injections.	1. Whether the same dose is given or a larger or a smaller one, the subsequent injection produces a more marked toxic effect.
2. As the syphilis improves the reactions become less marked.	2. Irrespective of the improvement in the syphilis, the toxic manifestations remain the same.
3. The reaction is observed most frequently in syphilis of the nervous system.	3. Occurs regardless of the nature of syphilitic involvement.

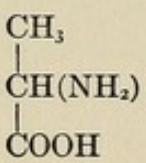
4. The reaction is usually accompanied by a pleocytosis. Where a cellular increase was present before the injection, this is markedly augmented after.	4. Is not accompanied by a pleocytosis, nor is the cell count changed if it was present before the injection.
5. The Wassermann reaction remains unchanged or becomes more intensely positive.	5. The Wassermann reaction becomes negative or disappears.
6. The injection of adrenalin has no effect whatever on the reaction.	6. An injection of a sufficient quantity of adrenalin is capable of diminishing the intensity in a large number of cases due to intolerance.
7. The phenomena attending the reaction possess to a certain degree the characteristics of syphilitic manifestations.	7. The reaction differs from any symptom usually found in syphilitic phenomena.

THE AMINO (NH_2) NITROGEN CONTENT OF SERA

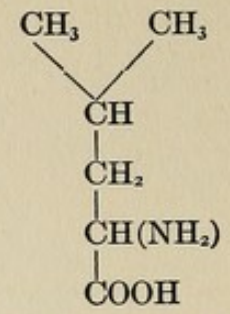
The results obtained with the quantitative estimation of the alpha NH_2 nitrogen of the aliphatic acid group of sera from syphilitic and non-syphilitic patients make it desirable to insert here a brief description of this chemical test:

Rationale.—On a previous page the spirillotropism of salvarsan and neosalvarsan was spoken of. It was demonstrated that there are certain chemical groups that act as haptophores (anchoring or prehensile), which render the two drugs of great therapeutic importance. These groups may be the OH or the NH_2 or the $(CH_2)OSNa$ side-chains of salvarsan or neosalvarsan. The fact that the Treponema pallidum anchors these drugs through these chemical side-chains led the author to seek to ascertain the effect, if any occurred, of the sojourn of the treponema in the human body upon the chemical constituents of the serum having similar side-chains. The many chemical substances forming the blood-serum molecule are chiefly amino-acids, of which the simpler ones are the following:

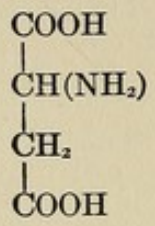
Alanin, or alpha-amino-propionic acid:



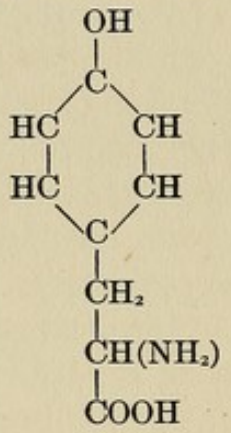
Leucin, or alpha-amino-isobutyl-acetic acid:



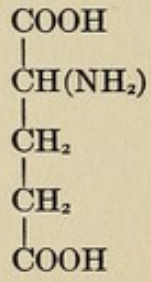
Asparaginic acid, or amino-succinic acid:



Tyrosin, or para-oxyphenyl-alpha-amino-propionic acid:



Glutaminic acid, or alpha-amino-glutaric acid:



The tropism that exists between a certain drug and a given microörganism was extensively studied by Ehrlich and his pupils, and resulted in the formulation of a hypothesis, previously referred to; *i. e.*, "*Corpora non agunt nisi fixata.*" The possibility of analyzing quantitatively the

alpha-amino-nitrogen of the aliphatic acid radicle of the amino-acids composing the serum molecule was introduced by Donald van Slyke, whose method will here be given:

Technic.—

(*a*) *Reagents:* (1) Glacial acetic acid.
(2) 300 grams sodium nitrite in 1000 c.c. of distilled water.
(3) Potassium permanganate, 50 grams; potassium hydoxid, 25 grams, dissolved in 1000 c.c. of distilled water.

(*b*) *Apparatus:* This consists of a special receptacle for the liberation of the amino-nitrogen from the serum to be analyzed, and is provided with four stop-cocks.

A measuring buret with the top $1\frac{1}{2}$ c.c. graduated into hundredths.

A 200 c.c. leveling water bulb, pear shaped.

A Hempel pipet, and a connecting glass tube.

Preparation of Apparatus for Use.—Having joined the various parts of the apparatus, as shown in the accompanying illustration (Fig. 31), fill the Hempel pipet with the potassium permanganate solution so that the lower bulb will be entirely full and the upper one only half-full.

Fill the pear-shaped water reservoir with distilled water; turn stop-cock 2 so that it communicates with the waste and with the measuring buret only; in other words, with the short limb of the bore in the stop-cock pointing to the buret.

Turn stop-cock 3 so that it communicates with the cross tube of the nitrogen-separating receptacle *b*. Raise the water bulb slightly higher than the buret, pour in sufficient water to fill the buret, and leave the water bulb about half-full. Turn cock 3 neutral. Lower the water bulb.

Now turn cock 3 so that it communicates with the Hempel pipet. The permanganate will flow into the buret. Turn cock 3 neutral. Quickly communicate cock 3 with the waste, raise the water bulb, and rid the buret of the permanganate. Turn cock 3 neutral again, and cock 2 so that it communicates with the waste, but not with the buret, *i. e.*, with the

short limb of the bore to the left, pointing to the nitrogen-liberating receptacle *b*. The apparatus is now ready for use.

As the sodium nitrite is rarely absolutely pure, it is therefore necessary to perform a preliminary test to ascertain the amount of non-absorbable gas present in the chemical.

Turn stop-cock 1 neutral and pour into *a* glacial acetic acid up to mark 10. Turn cock 1 so that the acid will flow

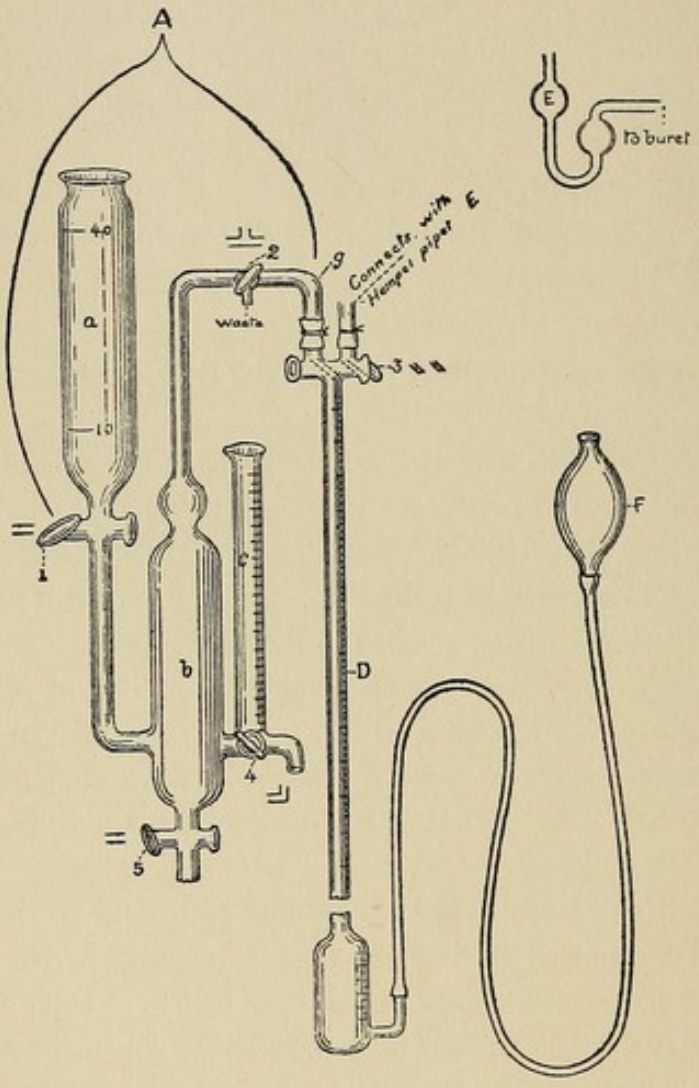


Fig. 31.—Schematic diagram of the apparatus.

into *b*, and turn stop-cock 1 again neutral. Pour into *a* enough of the nitrite solution to fill it up to mark 40, and permit it to flow into *b* by turning the cock 1. During this operation cocks 4 and 5 must be in the neutral position. As soon as all the sodium nitrite solution is out of part *a* cock 1 is turned neutral and the motor started. The com-

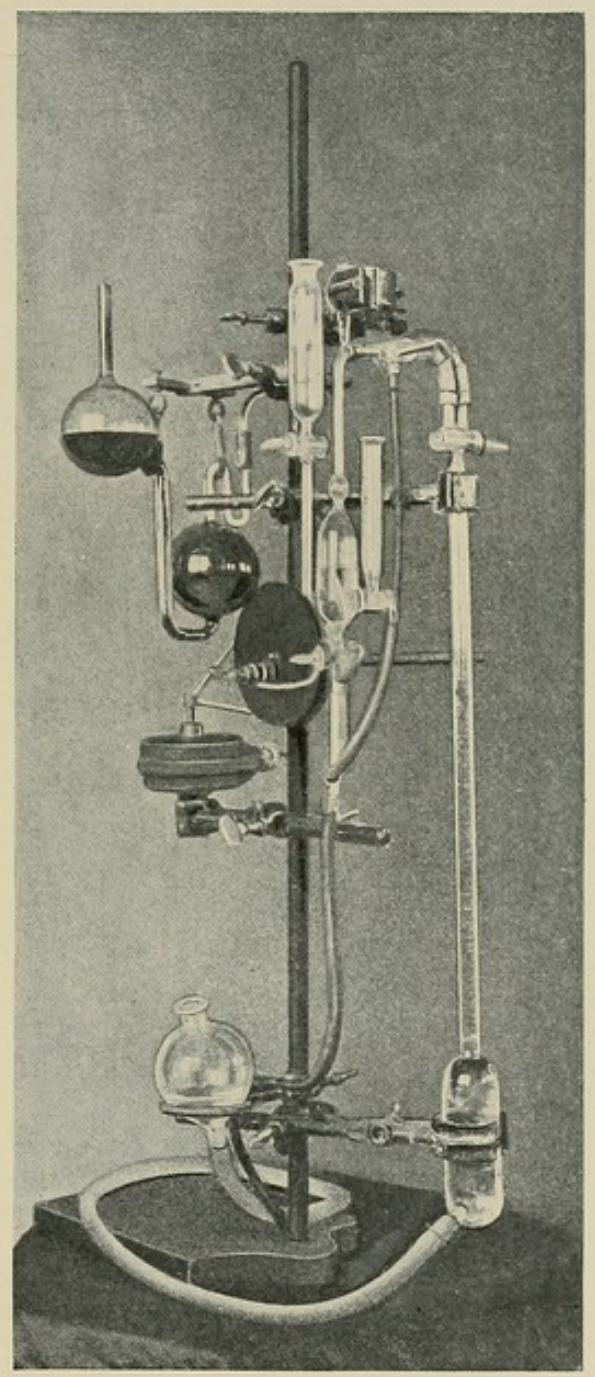


Fig. 32.—Entire apparatus assembled for permanent use.

bination of glacial acetic acid and the nitrite solution causes a rapid formation of NO gas, which forms the brownish fumes that escape through the waste. The motor shakes the gas-separating receptacle and fills the entire apparatus with NO gas, driving off the air present in the apparatus. Having effected the filling of the apparatus with NO gas, the motor is stopped, and stop-cock 1 is opened again. Now turn stop-cock 2 in the neutral position, pointing with the short limb of the bore upward, and start the motor again. This causes the liquid to rise gradually into part *a*, and when it reaches mark 40 the motor is stopped and cock 1 turned neutral. The stop-cock 3 is turned so that it communicates with the cross tube from the gas-liberating part; this causes the water in the buret to fall 4 or 5 inches, which is caused by the NO in *b*.

The apparatus is now ready either for the determination of the amount of amino-nitrogen in the serum or for the correction of the nitrite solution.

Correction of the Nitrite Solution.—With the apparatus in the position just outlined, pour 10 c.c. of slightly warmed distilled water into part *c* of the apparatus, and, by gently turning stop-cock 4, allow the water to flow into *b*, being careful not to permit the least amount of air to enter compartment *b*. Stop-cock 4 is turned neutral, and the motor started. The shaking is continued for exactly five minutes, during which time the gases formed lower the water column in the buret. At the end of five minutes' shaking stop the motor, and after waiting two minutes open stop-cock 1, permitting the fluid in *a* to empty into *b*, thus driving all the gas into the buret, *d*. Do not permit any of the fluid to flow into the buret. Having driven over all the gas, turn cock 3 into the neutral position. Raise the water bulb above the buret, and turn cock 3 so that it communicates with the Hempel pipet. This causes the gas to flow into the Hempel pipet, during which the apparatus must be watched closely, as the NO gas may not be absorbed as rapidly as it flows into the permanganate solution; it is, therefore, necessary to shake the pipet occasionally, a proceeding that is required more often as the permanganate solution ages. The solution

may be used for about a dozen tests, when it ought to be replaced with fresh solution.

Having driven over all the gas as well as a little distilled water (about 0.5 c.c.), stop-cock 3 is turned neutral and the water bulb lowered. Shake the Hempel pipet vigorously for two minutes, and then open cock 3 again, so that the permanganate will flow over to the buret. Having collected the gas over the water, cock 3 is turned neutral again, and the amount of gas present is ascertained. Some samples of nitrite solution give as much as 0.4 c.c. of unabsorbable gas, a fact which must be taken into consideration when determining the amount of amino-nitrogen present in sera. The amount of impurity in the nitrite is known as the correction number.

Testing Sera for the Amino-nitrogen.—To perform this test 2.5 c.c. of the patient's serum is placed in an Erlenmeyer flask and precipitated with 25 c.c. of 95 per cent. alcohol. This is allowed to remain at room temperature overnight, and the next morning it is filtered. The filtrate is collected in a porcelain dish, and evaporated over a water-bath, being careful not to secure complete dryness. Dissolve the mass in about 10 c.c. of boiling distilled water, when it is ready for the determination in the van Slyke apparatus.

The process of determining the amino-nitrogen in the serum is the same as that followed for the determination of the impure gas in the nitrite solution, the dissolved evaporated filtrate taking the place of the water poured into *c*. The calculation is made according to the table compiled by Gattermann, in his book, "Praxis des organischen Chemikers," ninth edition. The entire reaction depends upon the chemical fact that aliphatic amino-groups react with nitrous acid according to the following equation:

$$RNH_2 + HNO_2 = ROH + H_2O + N_2$$

The nitrous acid decomposes with the formation of NO. This NO is made use of in this reaction to drive off all the air from the apparatus. Later it is completely absorbed by the permanganate solution, and the gas obtained in the buret is the correction number together with the amino-nitrogen in the patient's serum.

GATTERMANN'S TABLE FOR AMINO-NITROGEN CALCULATION

T.	b.728	730	732	734	736	738	740	742	744	746	748	750*mm*	b.752	754	756	758	760	762	764	766	768	770	772*mm*
11°	.5680	.5695	.5710	.5725	.5745	.5760	.5775	.5790	.5805	.5820	.5840	.5885	.5870	.5885	.5900	.5915	.5935	.5950	.5965	.5980	.5995	.6010	.6030
12°	.5655	.5670	.5685	.5700	.5720	.5735	.5750	.5765	.5780	.5795	.5815	.5830	.5845	.5860	.5875	.5590	.5905	.5925	.5940	.5959	.5970	.5985	.6000
13°	.5630	.5645	.5660	.5675	.5695	.5710	.5725	.5740	.5755	.5770	.5785	.5805	.5820	.5835	.5850	.5865	.5880	.5895	.5910	.5930	.5945	.5960	.5975
14°	.5605	.5620	.5635	.5650	.5665	.5680	.5700	.5715	.5730	.5745	.5760	.5775	.5790	.5805	.5825	.5840	.5855	.5870	.5885	.5900	.5915	.5935	.5950
15°	.5580	.5595	.5610	.5625	.5640	.5655	.5670	.5685	.5705	.5720	.5735	.5750	.5765	.5780	.5795	.5810	.5830	.5845	.5860	.5875	.5890	.5905	.5920
16°	.5555	.5570	.5585	.5600	.5615	.5630	.5645	.5660	.5675	.5690	.5710	.5725	.5740	.5755	.5770	.5785	.5800	.5815	.5830	.5850	.5865	.5880	.5895
17°	.5525	.5540	.5555	.5575	.5590	.5605	.5620	.5635	.5650	.5665	.5680	.5695	.5710	.5730	.5745	.5760	.5775	.5790	.5805	.5820	.5835	.5850	.5865
18°	.5500	.5515	.5530	.5545	.5560	.5580	.5595	.5610	.5625	.5640	.5655	.5670	.5685	.5700	.5715	.5730	.5745	.5765	.5780	.5795	.5810	.5825	.5840
19°	.5475	.5490	.5505	.5520	.5535	.5550	.5565	.5580	.5595	.5610	.5630	.5645	.5660	.5675	.5690	.5705	.5720	.5735	.5750	.5765	.5780	.5795	.5810
20°	.5445	.5460	.5475	.5495	.5510	.5525	.5540	.5555	.5570	.5585	.5600	.5615	.5630	.5645	.5660	.5675	.5690	.5705	.5725	.5740	.5755	.5770	.5785
21°	.5420	.5435	.5450	.5465	.5480	.5495	.5510	.5525	.5540	.5555	.5575	.5590	.5605	.5620	.5635	.5650	.5665	.5680	.5695	.5710	.5725	.5740	.5755
22°	.5395	.5410	.5425	.5440	.5455	.5470	.5485	.5500	.5515	.5530	.5545	.5560	.5575	.5590	.5605	.5620	.5635	.5650	.5665	.5680	.5695	.5715	.5730
23°	.5365	.5380	.5395	.5410	.5425	.5440	.5455	.5470	.5485	.5500	.5515	.5530	.5545	.5560	.5575	.5595	.5610	.5625	.5640	.5655	.5670	.5685	.5700
24°	.5335	.5350	.5365	.5380	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520	.5535	.5550	.5565	.5580	.5595	.5610	.5625	.5640	.5655	.5670
25°	.5310	.5325	.5340	.5355	.5370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520	.5535	.5550	.5565	.5580	.5595	.5610	.5625	.5640
26°	.5280	.5295	.5310	.5325	.5340	.5355	.4370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520	.5535	.5550	.5565	.5580	.5595	.5610
27°	.5250	.5255	.5280	.5295	.5310	.5325	.5340	.5355	.5370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520	.5535	.5550	.5565	.5580
28°	.5220	.5235	.5250	.5265	.5280	.5295	.5310	.5325	.5340	.5355	.5370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520	.5535	.5550
29°	.6195	.5210	.5220	.5235	.5250	.5265	.5280	.5295	.5310	.5325	.5340	.5355	.5370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490	.5505	.5520
30°	.6160	.5175	.5190	.5205	.5220	.5235	.5250	.5265	.5280	.5295	.5310	.5325	.5340	.5355	.5370	.5385	.5400	.5415	.5430	.5445	.5460	.5475	.5490

The amount of gas obtained in the buret, minus the correction for the nitrite solution, is multiplied by the figure corresponding to the temperature and pressure. This is divided by 5 and multiplied by 100, to give the result for that quantity of serum; or to diminish calculations the number obtained may be multiplied by 20.

In the determination of the quantity of nitrogen gas the temperature and barometric pressure must be taken into consideration, and for this purpose the table of Gattermann, on p. 259, is utilized. The figures in that table represent the weight of amino-nitrogen in milligrams, which corresponds to 1 cm. of nitrogen gas as obtained by the action of nitrous acid, and measuring the gas over water at the given temperature and pressure. As the result obtained is that for moist nitrogen, the figures obtained must consequently be divided by two.

From an analysis of over 1000 sera from various clinical conditions, the author reached the conclusion that when the amino-content in 100 c.c. of serum is 2.8 milligrams or more, it is then to be regarded as normal; when it is more than 2.3 and less than 2.8, it is to be considered as doubtful, and any amount less than 2.3 milligrams is to be regarded as suggestive of syphilis.

This reaction was not devised as an additional test for syphilis, but was established as a means of weeding out occasional conflicting positive Wassermann reactions obtained in patients who denied and who did not present any clinical evidence of the existence of syphilis.

In giving the results obtained with this quantitative chemical method, the findings obtained in the third communication, together with Dr. J. E. McClelland, will be tabulated, N. Y. Med. Jour., Nov. 22, 1913. The material was divided into six groups:

Group 1: Patients who did not present clinical evidence of syphilis, who were not treated, and who gave a negative Wassermann in the serum—in all, 117 cases.

Amino-nitrogen diminished in 20 cases, or 17.6 per cent.
Amino-nitrogen normal in 94 cases, or 80.3 per cent.
Amino-nitrogen doubtful in 3 cases, or 2.1 per cent.

Group 2: Patients who showed no clinical evidence of lues were not treated, and gave a positive Wassermann in the serum—12 cases.

Amino-nitrogen diminished in 3 cases, or 25.0 per cent.
Amino-nitrogen normal in 9 cases, or 75.0 per cent.

Group 3: Lues clinically present; patients were not treated and gave a positive Wassermann in the serum—40 cases.

Amino-nitrogen diminished in 36 cases, or 90.0 per cent.
Amino-nitrogen normal in 3 cases, or 7.5 per cent.
Amino-nitrogen doubtful in 1 case, or 2.5 per cent.

Group 4: Lues clinically present; patients were not treated recently, and showed a negative Wassermann serum—32 cases.

Amino-nitrogen diminished in 26 cases, or 77.0 per cent.
Amino-nitrogen normal in 6 cases, or 23.0 per cent.

Group 5: Lues clinically present, treated, showed a positive serum Wassermann—7 cases.

Amino-nitrogen diminished in 3 cases, or 42.87 per cent.
Amino-nitrogen normal in 2 cases, or 28.65 per cent.
Amino-nitrogen doubtful in 2 cases, or 28.65 per cent.

Group 6: Lues clinically present, treated, Wassermann reaction in serum negative—21 cases.

Amino-nitrogen diminished in 8 cases, or 38.0 per cent.
Amino-nitrogen normal in 13 cases, or 62.0 per cent.

From the foregoing exposition it is clearly evident that a positive Wassermann reaction in a patient exhibiting no clinical evidence of lues can be checked if an estimation of the amount of amino-nitrogen in the patient's serum is made. This is shown by the results obtained in Group 2. It may be stated that such occurrences are very few, and, as a rule, a positive serum Wassermann when present means lues; it cannot be denied, nevertheless, that a certain percentage of errors, as in Group 2, cannot be entirely avoided. The author would suggest, therefore, the adoption of the foregoing chemical analysis for the entire weeding-out of unexpected positive serum Wassermann reactions.

The Amino-nitrogen Content of Luetic Sera.—The vast majority of syphilitic material that came under the observation of the author showed a diminished amount of amino-nitrogen. This is, perhaps, dependent upon a hypothesis, suggested elsewhere, that in order to live and propagate, the treponema requires a certain amount of this

nitrogen as food. The NH_2 side-chain in the serum molecule is taken up in a manner similar to that by which the NH_2 is probably anchored from the salvarsan or neosalvarsan, and when one stops to consider the structure of these amino-acids and the drugs used to introduce arsenic into the economy of the treponema, one can readily observe the similarity of structure. The NH_2 molecule in both is a side-chain, and not an essential part of the real nucleus of the substance.

The amino-nitrogen of syphilitic sera is diminished in over 90 per cent. of untreated syphilitic patients, and as the system is more or less freed from the treponema there is a tendency for the amino-nitrogen to increase in amount. If a given serum does not show a normal content of amino-nitrogen, regardless of the negative serum Wassermann, it may be taken as a sign that the microörganisms are still present in large numbers. It must also be remembered that this reaction has nothing in common with the Wassermann test, the latter being purely biologic, whereas the former is a chemical test, easily controllable, and having a definite chemical basis.

The Amino-nitrogen Content of Non-luetic Sera.—From a review of the entire material on the subject, it became apparent that only 7 per cent. of the clinical and biologic non-luetic cases gave a diminished amino-content in the serum. Regardless of the negative history and absence of signs, a number of cases that showed diminished amino-nitrogen subsequently returned with unmistakable symptoms of syphilis. Among the 1142 sera analyzed, 12 gave a positive Wassermann in the absence of clinical evidence of syphilis. Of these 12, 3 showed a diminished amino-nitrogen content, and of these 3 patients, 2 returned with luetic skin lesions. The positive Wassermann error is reduced to less than 1 per cent., which is the degree of inaccuracy secured in the author's hands for the year 1912–13. The last seven months of 1913 gave a percentage of error estimated at 0.5 per cent. With amino-control this error was reduced to 0.1 per cent.

Further studies with this reaction are being made, and will cover a larger range of clinical entities, the material here considered having been gathered largely from neurologic cases, as the original communications will show.

General Conclusions

The technology of the subject of nervous and mental diseases as here discussed includes the methods pursued by the author and those that have proved of distinct value in the progress of this subject.

The serology of the negative types (non-luetic diseases) is very instructive, showing that a pleocytosis may occur even without syphilis, and helping to differentiate those that are caused by syphilis. The most benefit will be gained from a study of the serology of the syphilogenous diseases of the nervous system, where diagnostic, therapeutic, and prognostic information may be secured.

The section on Salvarsan is a practical exposition of the subject, giving, besides the ordinary methods as gathered from the literature, also such new methods as have proved of utility in the treatment of nervous diseases due to syphilis. It may be repeated here that the treatment of syphilitic nervous diseases by salvarsan and neosalvarsan is still in the experimental stage. We are advancing gradually to that stage of therapy where a retrospect will show how far we are from possessing a therapia sterilisans magna. To guarantee a cure to the patient suffering from a syphilitic nervous disease, and even to state a time when this will be accomplished, will not be the practice of a conscientious physician: all that can be accomplished today is to effect an amelioration of the active and painful manifestations. Occasionally a fixed pupil will become mobile or the memory defect may disappear, but no promise of these things can as yet be held out by physicians to their patients.

Syphilis itself and its active manifestations will be influenced by salvarsan, but the outcome of syphilis, whatever this may be, still remains *sub judice*. Our chief efforts today are directed toward removing active manifestations, and thereby minimizing the formation of permanent tissue changes. These manifestations in syphilitic diseases of the nervous system can be determined by proper serologic investigation.

LITERATURE

THE literature of salvarsan and neosalvarsan is so extensive that to attempt to give even a partial review of the treatment of syphilis with this remedy would require a volume larger than the one here offered. Very instructive reading is to be had in Ehrlich's Abhandlungen ueber Salvarsan, 3 volumes, J. F. Lehmann, Munich.

Benario, J.: Ueber Neurorezidive, J. F. Lehmann, Munich.

Ehrlich-Hata: Die experimentelle Chemotherapie der Spirillosen, Julius Springer, Berlin.

Gennerich, W.: Die Liquorveränderungen in den einzelnen Stadien der Syphilis, August Hirschwald, publishers, Berlin, 1913.

Lenzmann, R.: Salvarsan, Jena, Gustav Fischer.

Milian, G.: Traitement de la syphilis, by J. B. Bailliere et fils, Paris, 1912.

Pinkus, Felix: Ueber den Stand unserer Kenntnisse vom Salvarsan, Urban and Schwarzenberg, Berlin.

Schmitt, A.: Wirkliche und angebliche Schädigungen durch Salvarsan, Curt Kabitzsch, Würzburg.

Stokar, Kurt von: Die Syphilis-Behandlung mit Salvarsan, Lehmann, Munich.

Tomasczewski, E.: Die Technik der Salvarsanbehandlung, Thieme, Leipzig, 1911.

Wechselmann, W.:

Die Behandlung der Syphilis mit Dioxydiamidoarsenobenzol, Oscar Coblentz, Berlin.

Ueber die Pathogenese der Salvarsantodesfälle, Urban and Schwarzenberg, Berlin.

A

ENGLISH LITERATURE

Ager: Urotropin, Medical Annual, p. 503, 1908.

Allen: Cholin. A New Method of Testing for its Presence in the Blood in Cerebrospinal Fluid, Proc. of the Phys. Soc., July 29, 1904.

Allen and French: Some Observations Upon the Test for Cholin in Human Blood, Proc. of the Phys. Soc., Nov. 14; Jour. of Phys., p. 30, 1903.

Amsden: Report of Certain Lumbar Punctures at Bloomingdale Hospital, N. Y. Med. Jour., 1910, 438.

Atwood, C. E.: Idiocy and Hereditary Syphilis, Jour. Amer. Med. Assoc., 1910, p. 464.

GERMAN LITERATURE

Abraham and Ziegenhagen: Ueber cytodiagnostische Untersuchungen bei Dementia paralytica, Cent. f. Nervenh. u. Psy., 1904, xxvii, 323.

Abramof, S.: Ueber den Einfluss der Reaktion auf die Komplementbindungs phänomene und die sie vermittelnden Komponenten, Zeitschr. f. Immunit., 1910, 145.

Alexander, A.: Serodiagnostische Untersuchungen zur Frage der Beziehungen zwischen Ozæna und Syphilis, Zeitschr. f. Laryng., 1910, p. 669.

Allaria: Ueber die Natur der haemolytischen Erscheinung der cerebrospinalfluessigkeit, Revista di Clinica pediatrica, No. 6, 1907.

Alt: Das neue Ehrlich-Hata Präparat gegen syphilis, Münch. med. Woch., 1910, No. 11, 561.

Alzheimer: Einige Methoden zur fixierung der zelligen Elemente der Cerebrospinalflüssigkeit, Centr. f. Nervenh. u. Psy., 1907, No. 239.

Andernach: Beiträge zur Untersuchung des Liquor cerobrospinalis mit besonderer Beruecksichtigung der zelligen Elemente, Arch. f. Psy. u. Nervenheilk., 47, 2, 1910.

Angerer, C.: Ueber Amboceptorwirkung in Salzlösung verschiedener Konzentration, Zeitschr. Immunitätsf., 1910, p. 243.

Apel: Beiträge zur Frage der Berechtigung der spinalen und cerebralen Punktion, Berl. klin. Woch., 1910, p. 1540.

Apelt:

Die Bedeutung cytologischer Untersuchungen der Cerebrospinalfluessigkeit fuer die Neurologie, Monatschr. f. Psy., 20, Erg. H. I, 1906.

Untersuchungsergebnisse am Liquor von Trypanosomen infizierten Hunden, Cent. f. Nervenh. u. Psy., 1908, xxxi, 975.

Untersuchungen des Liquor cerebrospinalis auf Vermehrung der zelligen Elemente und Eiweisskoerper bei Trypanosomiasis der Hunde, Münch. med. Woch., 1909, No. 44.

Zum Wert der Phase I fuer die diagnose in der Neurologie, Arch. f. Psy., 46, 1, 1909.

Apelt and Schumm: Untersuchungen ueber Phosphorsäuregehalt der Spinalflüssigkeit., Arch. f. Psy., 1908, xliv, p. 2.

Arzt and Boese: Ueber Paratyphus Meningitis im Kindesalter, Wien. klin. Woch., No. 7, 1908.

Aschenheim, Erich:

Ueber die natürlichen hæmolytischen Zwischenkörper des menschlichen Blutes, Cent. f. Bact., 1909, xlix, I. Abt., Orig., 124.

Serumkomplementbestimmung im homologem System, Centralbl. f. Bakt., 1909, p. 424.

Assman, H.:

Diagnostische Ergebnisse aus der Lumbalpunction von 150 Faellen mit besonderer Beruecksichtigung der Nonne-Apeltschen Reaction, Duet. Zeits. f. Nervenh., 1910, xl, No. 131.

Assman, H.: Erfahrungen ueber Salvarsan-Behandlung luetischer und metaluetischer Erkrankungen des Nervensystems unter Contro durch die Lumbalpunction, Deut. med. Woch., 1911

FRENCH LITERATURE

Abadie: Resultats de l'examen cytologique de quelques liquides céphalo-rachidiens, Compt. rend. de la Soc. de Biol., 25, 946, 1902.

Abundo: Sulle vie linfatiche del Sistema nervosa centrale, Ann. di Neurologia, 1896.

Acchiote: Poliomyelite anterieure aigue et lymphocytose, Revue Neurol., 19, 1911.

Achard:

Microbes dans cellule dans le liquide de la ponction lombaire, Soc. Med. des Hôp., Nov. 13, 1908.

Examen du liquide cephalorachidien, Gaz. hebd. de med. et chir., July 21, 1901.

Achard and Landry: Contribution a la cryoscopie du liquide céphalo-rachidien, Arch. de med. experim., 1901, 567.

Achard and Loeper: Deux cas de fièvre zoster aved examen microbiologique du liquide céphalo-rachidien, Bull. Soc. med. des hôp., July 26, 1901.

Variations comparatives de la composition du sang et des serosites, C. R. Soc. Biologie, 18 juin, p. 645 et Presse Med., No. 73, 1901.

Passage du ferrocyanure de potassium dans l'humeur aqueuse an cas d'obstacle a l'élimination rénale, C. R. Soc. Biol., 15 M, 1902.

Allaria:

Action du liquid céphalo-rachidien sur quelques bactéries, 11 Morgagni 47, No. 11, 1905.

La reazione attuale e la reazione potenziale del liquido cerebrospinale a meningi sane e nelle meningiti, Archivi delle scienze medicale, 32, 3, 1908.

Anfinoff (1907): Hemorragies menues sur la surface cerebrale comme phenomene constant dans le l'epilepsie et leur signification, Revue Russe de Psychiatrie de Neurologie et de Psychologie expérimentale, No. 5, p. 257; Revue Neurologique, 1908, p. 243.

Anglada:

Le liquide céphalo-rachidien; bilan actuel du diagnostic par la ponction lombaire, Thèse de Montpellier, 1909.

Le liquide céphalo-rachidien; sur ces proprietés physiques, physiologiques et biochemiques, chemiques, microbiologiques, cytologiques, Revue generale in Gaz. des Hôp., March 26, No. 36, 1910.

Le liquide céphalo-rachidien, Paris, 1910 (literature).

Le liquide céphalo-rachidien; sur ces proprietés physiques, physiologiques et biochimeques, chemiques, microbiologiques, cytologiques, Gaz. des Hôp., March 26, 1910.

Anglada and Jacquin (1906): A propos des quelques resultas pratiques et immediates obtenues par la ponction lombaire, Soc. de Médicine et de Chirurgie de Bordeaux, April 6th; Gaz. hebdom. des Sciences méd. de Bordeaux, No. 25, June 24th.

Ardin-Delteil:

Indications diagnostiques fournies par la coloration du liquide, C. R. Montpellier Médicale, 16, p. 25, 1903.

Le liquide céphalo-rachidien des Paral., Gen. Rev. Neurol., p. 1212, Dec. 3, 1903.

Le liquide céphalo-rachidien des paralytiques généreaux, Revue Neurol., Dec., 1903.

Ardin-Delteil and Monfrin (1903): Toxicité du liquide céphalo-rachidien des Paral., Gen. C. R. Soc. Biol., November, p. 1512.

Armand-Delille:

Toxicité du liquide céph. rach. et la mening. tubercul., C. R. Soc. Biol., p. 1010, 1902.

Rôle des poison du bacille de Koch dans la méningite tuberculeuse, Thèse de Paris, No. 449, 1903.

Réaction de Wassermann dans le liquide céphalo-rachidien des paralytiques généreaux, Soc. med. des Hôp., 1907, xxiv, 1570.

Aubry: Le syndrome de coagulation massive du liquide, Thèse de Paris, 1909.

B

ENGLISH LITERATURE

Bailey:

Cryoscopy of the Cerebrospinal Fluid in Epidemic Cerebrospinal Meningitis, N. Y. Medical Record, No. 6, 1905.

The Serum Diagnosis of Syphilis; an Analysis of Two Hundred Consecutive Sera Examined for the Wassermann Reaction in which a Modified Neisser Technic was Used, Lancet, p. 1523, 1909.

Ball, C. R.: The Value of the Four Reactions in the Diagnosis and Treatment of Syphilitic Diseases of the Nervous System, Jour. Amer. Med. Assoc., Oct. 5, 1912.

Battersby : Congenital and Acquired Hydrocephalus, Medical and Surgical Journal, Edinb., July, 1850.

Bolduan:

Immune Sera, John Wiley & Sons, N. Y., 1908.

Collected Studies on Immunity, by Prof. Paul Ehrlich, John Wiley & Sons, N. Y., 1908.

Boyd: Cerebrospinal Fluid in Mental Conditions, Jour. of Mental Sciences, 1912, 58.

Browning and McKenzie:

Modifications of Serum and Organ Extract Due to Physical Agencies, and their Effect on the Wassermann Syphilis Reaction, Jour. of Path. and Bact., 1909, xiii, 325.

Browning and McKenzie:
The Biological Syphilis Reaction, its Significance and Method of Application, Lancet, 1909, i, 1521.
On the Wassermann Reaction and Especially its Significance in Reaction to General Paresis, Jour. of Mental Science, 1909.
On the Complement Containing Serum as a Variable Factor in the Wassermann Reaction, Z. f. Immunitaetsforsch, 1909, i, 459.
Bury and Ransbottom: On Lymphocytosis of the Cerebrospinal Fluid in Relation to Tabes, The Quarterly of Medicine, Oct. 9, 1909.
Butler: Serum Diagnosis of Syphilis, Jour. Amer. Med. Assoc., 1908, li, 824.

GERMAN LITERATURE

Bab: Kurze Mittheilung zu dem Aufsatz von Wassermann und Plant ueber syphilitische Antistoffe in der Cerebrospinalfluessigkeit von Paralytikern, Deut. med. Woch., 1906, 1895.
Baetzner: Die Bedeutung der Wassermannschen Reaction fuer die Differentialdiagnose der chirurgischen Syphilis, Münch. med. Woch., 1909, 330.
Baginsky, A.: Pathologie der Parasyphilis im Kindesalter, Arch. f. Kinderheilk., 1910, p. 133.
Baisch: Die Vererbung der Syphilis auf Grund serelogischer und bakteriologischer Untersuchungen, Münch. med. Woch., 1909, p. 1920.
Ballner and Decastello: Ueber die klinische Verwertbarkeit der komplementbindungsreaction fuer die Serodiagnostic der Syphilis, Deut. med. Woch., 1908, xxxiv, 1923.
Balogh: Beiträge zur Bestimmung des Cytodiagnostischen Wertes der Liquor cerebrospinalis, Orvosi Hetelap, 8, 1905.
Bang, Ivar: Biochemie der Zellipoide, II, Asher Spiro's Ergebnisse der Physiologie, 1909, viii, 466–517.
Baron: Das Eiweisgehalt und die Lymphocytose der Liquor cerebrospinalis bei Saeuglingen mit Lues congenita, Jahrbuch f. Kinderheilkunde, 1909, 69, i.
Bauer, J.:
Zur Methodik des serologischen Luesnachweises, Duet. med. Woch., 1908, 698.
Wassermannsche Luesreaction, Berl. klin. Woch., 1908, 834.
Ueber die Wassermannsche Luesreaction wirksamen Koerper, und ueber die haemolytischen Eigenschaften der Organextracte, Biochemische Zeitschr., 1908, x, 304.
Das Colle'sche und Profeta'sche Gesetz im Lichte der modernen Serumforschung, Wien. klin. Woch., 1908, xxi, 1259.
Bauer, R., and Hirsch, A.: Beiträge zum Wesen der W. R., Wien. klin. Woch., 1910, xxiii.
Bauer and Meyer: Zur Technick und klinischen Bedeutung der Wassermannschen Reaction, Wiener klin. Woch., 1908, No. 51.

Beck, K.: Ueber die Verwendbarkeit der W. R. in der Otiatrie, Zeitschr. f. Ohrenheilk., 1910, 218.

Beckers: Zur Serodiagnostik der Syphilis, Münch. med. Woch., 1909, 551.

Beltz: Ueber Liquoruntersuchungen mit besonderer Beruecksichtigung der Nonne-Apelt'schen Reaction, Deut. Zeitschr. f. Nervenheilk., 1911, 43, 1 and 2.

Bendixson: Psychiatrische Erfahrungen mit der Wassermannschen Reaction, Zeitschr. f. Immunitätsf., vol. iv, No .3, pp. 349–356.

Beneke: Die Wassermannsche Syphilis Reaction, Berl. klin. Woch., 1908, 730.

Berdach: Bericht ueber die Meningitis Epidemie in Trifail im Jahre 1898, Arch. f. klin. Med., 65, 449, 1900.

Bergl and Klausner: Ueber das Verhalten des Liquor cerebrospinalis bei Luetikern, Prager med. Woch., 37, 1912.

Bering, Fr.:

Die praktische Bedeutung der Serodiagnostik bei Lues, Münch. med. Woch., 1908, 2476.

Was leistet die Seroreaction fuer die Diagnose, Prognose, und Therapie der Syphilis, Arch. f. Dermat. u. Syph., 1909, p. 301

Welche Aufschluesse liefert die Seroreaktion ueber das Colles-Baumesche und das Profetasche Gesetz, Deut. med. Woch., 1910, 219.

Berneheim and Moser: Ueber diagnostische Bedeutung der Lumbalpunction, Wiener klin. Woch., 1897, 20 and 21.

Bertels and Schwarz: Ueber "Meningitis" carcinomatosa, Deut. Zeit. f. Nervenh., 1911, 42.

Bertelsen and Bisgaard: Resultate objectiver Ausmessung der biologischen, cytologischen und chemischen Reactionen in der Cerebrospinalfluessigkeit, besonders bei Paralytikern, sowie Beschreibung einer neuen chemischen Reaction in der Spinalfluessigkeit, Zeitschrift f. d. ges. Neur. u. Psych., 1911, 4.

Biach, M.: Psoriasis vulgaris und W. R., Wien. med. Woch., 1910, No. 20.

Binswanger and Berger: Beiträge zur Kenntniss der Lymphzirculation in der Grosshirnrinde, Virchow's Arch., 1898, 152.

Bisgaard:

Zur Differentialdiagnose zwischen Dementia Paralytika und Lues des zentralnervensystems, Arch. f. d. ges. Neurol. and Psych., 1912, 381.

Ueber ein regelmaessiges Verhaeltniss zwischen Eiweis und Wassermann Reaction in der Cerebrospinalfluessigkeit der Paralytiker, Zeitschrift. f. die gesammte Neurol. and Psych., 1912, 10, 4 and 5, 660.

Bizzozero, Enzo: Ueber den Einfluss der Jodkali Behandlung auf die W. R., Med. Klin., 1901, No. 31.

Blaschko:

Die Bedeutung der Serodiagnostik fuer die Pathologie und Therapie der Syphilis, Berl. klin. Woch., 1908, 694.

Blaschko: Ueber die klinische Verwertung der Wassermannschen Reaction, Deut. med. Woch., 1909, xxxv, 383.

Blumenthal:

Serodiagnose der Syphilis, Dermat. Zeits., 1910, vol. xvii.

Ueber Cerebrospinalfluessigkeit, Ergebnisse der Phys., 1902, i.

Blumenthal and Roscher: Die Bedeutung der Wassermannschen Reaction bei der Syphilis, wehrend ersten, der Infection folgenden Jahre, Med. Klin., 1909, 241.

Blumenthal and Wile: Ueber Komplementbindende Stoffe im Harn Syphilitischer, Berl. klin. Woch., 1908, 1050.

Boas, Harold:

Die Wassermannsche Reaction mit besonderer Beruecksichtigung ihrer klinischen Verwertbarkeit, Karger, Berlin, 1911.

Die Bedeutung der Wassermannschen Reaction fuer die Therapie der Syphilis, Berl. klin. Woch., 1909, 588.

Die W. R. bei aktiven und inaktiven Sera., Ibid., 1909, p. 400.

Die W. R., Berlin, S. Karger, 1911.

Boas and Hauge: Komplementablenkung bei Scharlach, Berl. klin. Woch., 1908, 1566.

Boas and Lind: Untersuchungen der Spinalfluessigkeit bei Syphilis ohne Nervensymptome, Zeits. f. d. ges. Neur. und Psych., 1911, Orig. 4, 689.

Boas and Neve:

Die W. R. bei Dementia paralytika, Berlin. klin. Woch., 1910, p. 1368.

Untersuchungen ueber die Weil-Kafkasche Haemolysin-Reaction in der Spinalfluessigkeit, Zeit. f. d. Neur. and Psych., 1912, 4 and 5.

Boehm: Malaria and Wassermann Reaction, Arch. f. Schiffs und Tropenhyg., 1909, xiii, Beiheft 6.

Bonfiglio: Die Wassermannsche Reaction bei Geistes und Nervenkrankheiten, insbesondere bei Tabes Dorsalis, Lecture at the Psychiatric Congress in Perugia, 1911.

Bonhoeffer: Bemerkungen zur Behandlung und Diagnose der Progressiven Paralyse, Berl. klin. Woch., 1910, 47.

Bonhoff: Ueber das Vorkommen von virulenten Diphtherie Bacillen im Blute und in der Cerebrospinalfluessigkeit des Menschen, Zeitschrift f. Hygiene, 1910, 67.

Brauer: In welcher Weise wirkt das Hg. bei der antiluetischen Behandlung auf den Ausfall der Seroreaktion, Münch. med. Woch., 1910, 905.

Braun: Ueber die Lumbalpunction und ihre Bedeutung fuer die Chirurgie, Arch. f. klin. Chir., 1897, 54.

Braun, A.: Ueber den Nachweis der Antigene mittels der komplementfixationsmethode, Berl. klin. Woch., 1907, 1535.

Braun and Husler: Eine Neue Methode zur Untersuchung der Lumbalpunctate, Deut. med. Woch., 1912, 3825.

Browning, Cruikshank, and Mackenzie: Gewebskomponenten, die bei der W. R. beteiligt sind, insbesondere Lecithin und Cholesterin, Biochem. Zeitschr., 1910, 85.

Bruck, C :

Die Serodiagnose der Syphilis, Springer, Berlin, 1909.

Zur forensischen Verwertbarkeit und Kenntniss des Wesens der Komplementbindung., Berl. klin. Woch., 1907, 1510.

Ueber die klinische Verwertbarkeit der Komplementbindungsreaction fuer die Serodiagnostic der Syphilis., Deut. med. Woch., 1908, 2178.

Zur biologischen diagnose von Infectionskrankheiten, Deut. med. Woch., 1906.

Ueber das angebliche Vorkommen der Syphilisreaktion bei Psoriasis vulgaris, Wien. klin. Woch., 1910, 704.

Ueber das angebliche, etc. (same title as above), Bemerkungen zu der Arbeit von G. Gjorgjevic und Paul Savnik., Wien. klin. Woch., 1910, 778.

Bruck and Cohn: Scharlach und Serumreaktion auf Syphilis, Berl. klin. Woch., 1908, 2268.

Bruck and Gessner: Ueber Serum Untersuchung bei Lepra, Berl. klin. Woch., 1909, 589.

Bruck and Stern:

Die Wassermann-Neisser-Brucksche Reaction bei Syphilis, Deut. med. Woch., 1908, 401, 459, 504.

Hg. Wirkung und Syphilisreaktion, Wien. klin. Woch., 1910, 534.

Ueber das Wesen der Syphilisreaktion, Zeitschr. f. Immunitätsf., 1910, 592.

Brueckner: Ueber die Beziehungen der Syphilis zur Idiotie, Münch. med. Woch., 1910, 37.

Bruhns and Halberstaedter: Zur praktischen Bedeutung der Serodiagnostik der Syphilis, Berl. klin. Woch., 1909, 149.

Buschke: Diagnose und Therapie der Syphilis, auf Grund der neueren Forschungsergebnisse, Berl. klin. Woch., 1910, 869.

Buschke and Harder: Ueber die Provokatorische Wirkung von Sublimat Injektionen und deren Beziehungen zur W. R. bei Syphilis, Duet. med. Woch., 1909, 1139.

FRENCH LITERATURE

Babinski: Meningite hémorragique fibrineuse. Paraplégie spasmodique lombaire. Traitement mercuriel. Guérison, Soc. med. d. Hôp., Oct. 23, 1903.

Babinski and Nageotte: Contribution a l'etude du cytodiagnostic du liquid cephalorachidien dans les affections nerveuses, Bull. Soc. med. des Hôp., 1901, 18.

Backman and Jacobaeus: Sur la quantite de complement et d'ambocepteur et la qualite hemolytique du serum humain physiologique, C. R. Soc. Biol., 1909, 415.

Banque: Réaction du liquide C. R. au cours de la Pachyméningite pottique, Thèse de Paris, July 12, 1911.

Bar and Daunay: Valeur de la réaction de Wassermann au point de vue du diagnostic de la syphilis latente chez le neuveau-né, C. R. Soc. Biol., 1908, 1085.

Bard:

Méthode de détermination de la tonicite du liquide C. R. par son action sur le globules rouge du porteur, C. R. Soc. Biol., Feb. 16, 1901.

Procédé clinique de détermination de l'isotonicité du liquide céphalo rachidien, Bull. Med., Jan. 5, 1901.

Du variations pathologiques du pouvoir hemolytique du liquide cephalo-rachidien, La Semaine med., Jan. 13, 1903.

Des colorations du liquide C. R. d'origine hémorragique, Semaine méd., Oct. 14, 1903.

De la coloration biliare du liquide C. R. d'origine hémorragique, C. R. Soc. Biologie, Nov. 28, 1903.

Barie and Lian: Convulsions épileptiformes et hémiplégie au cours d'une fièvre typhoide, Soc. med. d. Hôp., Oct. 25, 1907.

Barthe: Analyse d'un liquide céphalo rachidien, Bull. des travaux de la Soc. de Pharmacie de Bordeaux, 1898, p. 246.

Baudoin and Français: La réaction butyrique de Noguchi et Moore dans le Diagnostic des Affections Syphulitiques du Névraxe, Revue Neurologique, May 1910, p. 620.

Bauer and Maubān: Méningite, cérébro-spinale hémorragique aigue Archives générales de Médicine, Nov. 3, 1903.

Beaussart: Etude du liquide C. R. des Syphulitiques et Parasyphilitiques: Cyto-diagnostic, Albumo-diagnostic, Précipito-diagnostic, Réaction butyrique de Noguchi et Moore, La Clinique, January, 27, 1911.

Beletre: La ponction lombaire chez les syphilis, Thèse de Paris, 1912.

Belletrud: Etude bacteriologique "postmortem" du liquide céphalo-rachidien des aliénés, Revue de Psych., 1908.

Belliisari: Toxicité du liquide céphalo-rachidien dans la paralysie générale, Riv. med., 1899.

Bernard and Troisier: Sur un cas d'intoxication saturnine avec Méningite ancienne et Ictère, Soc. med. d. Hôp., May 22, 1908.

Beryon and Cade: Liquide céphalo-rachidien et méningite dans un cas de maladie de Friedreich, C. R. de la Soc. de Biol., 1901, p. 247.

Bierry and Lalou: Variations du Glucose du Sang et du liquide céphalo-rachidien, C. R. Soc. Biol., February 13, 1904.

Blanchetiere and Lejonne:

Syndrome de coagulation massive et de xanthochromie du liquide C. R. sans éléments cellulaires, dans un cas de Sarcome de la dure-mère, C. R. Soc. Biol., May 15, 1909, and Gazette des Hôpitaux, Sept. 14, No. 104.

Blum: Acétone et corps acétoniques rachidiens dans le coma diabétique, Congrès Français de medicine, Lyons, 1911, p. 70.

Boidin and Weil: Meningite syphilitique secondaire aigue, Presse med., 1907, p. 661.

Bonnotte: Contribution a l'étude des variations du taux de l'urée dans le liquide C. R. a l'état pathologique et principalement au cours de l'urémie, Thèse de Lyons, Dec. 16, 1909, No. 23.

Bordet:

La méthode de mise en évidence des sensibilisatrices et ses applications recentes, Bull. de l'Académie Royale de Belgique, 1906, xx, 454.

La fixation de l'alexine et sa signification pour l'immunite, Z. f. Immunitätsforschung, 1909.

Bordet and Gay: Sur les rélations des sensibilisatrices avec l'aléxine, Ann. Inst. Pasteur, 1906, xx, 467.

Bordet and Gengou: Sur l'existence des substances sensibilisatrices dans la plupart de serums antimicrobiens, Ann. Inst. Pasteur, 1901, 289.

Bougault: Sur la réaction de Florence, Jour. d. Pharm. et de Chim., 1909, p. 185.

Bousquet: Le Méningisme, ses raports avec la ponction lombaire, Gazette des Hôp., June 23, 1910.

Bousquet and Derrien:

Sur la presence de composés acétoniques dans le liquide céphalo-rachidien au cours du diabète et en dehors du coma, Montpellier Médical, 1908, p. 183.

Acetonemie et acetone dans liquide céphalo-rachidien, C. R. de la Soc. Biol., 1910, 1002.

Boveri:

Tension du liquide C. R., C. R. Soc. Biol., May 20, 1911.

Le liquide C. R. dans la Pellagre, C. R. Soc. Biol., June, 10, 1911.

Braillon: Hémorragie sous-arachnoidienne curable, Gaz. d. Hôp., 1909, p. 635.

Brandeis and Mongour: Valeur comparée de l'albumo-diagnostic et du cyto-diagnostic du liquide C. R., Communication à la Societe de Méd. et de Chirurgie de Bordeaux, April 22, 1906.

Breton: Cyto-diagnostic, Gazette des Hôp., 1901, p. 949, vol. lxxiv.

Brissaud and Sicard: Cytologie du liquide C. R. au cours du zona thoracique, Soc. méd. d. Hôp., March 15, 1901.

Broden and Rodhain: Le liquide céphalo-rachidien dans la trypanosomiase humaine (maladie de sommeil), La Nevraxe, 1909.

Bruckner and Galasesco: Syphilis et insufficiance aortique, C. R. Soc. Biol., 1910, 74.

Bruneau: De la valeur de la ponction lombaire pour le diagnostic de l'hemorragie méningée, Marseille Médical, April 1, 1902.

ITALIAN LITERATURE

Bergamesco: Sul liquido cerebrospinale, Riv. crit. di clinica med., 1908, 36, 9.

Borrelli and Datta: Viscosimetria del liquido cerebrospinale, La clinica med. ital., 1906, 45.

Borrelli and Messineo: Dell'influenza della cura arsenicale e mercuriale sulla sulla reazione di Wassermann, Gior. d. r. Accad. di med. di Torino, 1910, 113.

Bravetta:

Ricerche comparative sui recenti metodi per la diagnosi della sifilide nelle malattie nervose e mentali, Bollett. d. Soc. med.-chir. di Pavia, Dec. 10, 1910.

Sul alcuni metodi per la diagnosi della sifilide nelle malattie nervose e mentali, Rassegna di studi psichiatrici, 1911, i, 5.

C

ENGLISH LITERATURE

Cadwalader, W. B.: The Relation of Syphilis to Progressive Muscular Dystrophy, N. Y. Med. Jour., June 21, 1913.

Candler: Wassermann Reaction in General Paralysis, Lancet, Nov. 11, 1911.

Candler and Mann: Reliability of the Results Obtained by the Wassermann Test on Serums and Cerebrospinal Fluids Obtained Postmortem, Brit. Med. Jour., March 9, 1912.

Candler and Sydney: Ibid., Brit. Med. Jour., 1912, 2671.

Carlson and Martin: Contribution to the Physiology of Lymph. The Supposed Presence of the Secretion of the Hypophysis in the Cerebrospinal Fluid, Amer. Jour. Physiol., 1911, 29.

Casamajor, L.: An Unusual Form of Mineral Poisoning Affecting the Nervous System: Manganese, Jour. of Amer. Med. Assoc., March 1, 1913.

Caulfield: A Modification of Technic of Complement-fixation, Jour. of Med. Research, 1908, 507.

Collins and Armour: The Treatment of Syphilitic Diseases of the Nervous System by Salvarsan, Jour. of Amer. Med. Assoc., 1912, p. 1918.

Corbus, B. C.:

One Year's Experience with Salvarsan, Being a Report of 230 Injections with Special Reference to Eye and Ear Complications, Med. Record, Nov. 18, 1911.

Four Years' Experience with the Wassermann Reaction in Practice, Jour. Amer. Med. Assoc., Oct. 5, 1912.

Corbus and Harris: The Diagnosis of Syphilitic Eye Lesions by Means of the Spirochæta pallida and the Serum Reaction of Wassermann, Ophth. Record, 1909, 296.

Coriat:
The Cerebrospinal Fluid in Hydrocephalus, Amer. Jour. of Phys., 1903, xii.
Chemical Findings in the Cerebrospinal Fluid, Amer. Jour. of Insanity, 1904, vol. lx, No. 14, p. 758.
The Production of Cholin from Lecithin and Brain Tissue, Amer. Jour. of Phys., vol. xii, No. 4, p. 353, Dec. 1, 1904.
Cornell: The Cerebrospinal Fluid in Paresis with Special Reference as to its Cytology, Amer. Jour. of Insanity, 1907, vol. lxiv, p. 73.
Cotton and Ayen: The Cytological Study of the Cerebrospinal Fluid by Alzheimer's Method and its Diagnostic Value in Psychiatry, Collected Papers New Jersey State Hospital at Trenton, 1907–11.
Craig, C. F.:
Observations Upon the Noguchi Modification of the Wassermann Complement-fixation Test in the Diagnosis of Lues in the Military Service, Jour. Exper. Med., 1910, 726.
Complement-fixation with an Antigenic Crystal Obtained from Luetic Liver, Jour. Amer. Med. Assoc., 1910, 1264.
The Relation of Certain Bacteria to Non-specific Reactions with the Fixation Test for Lues, Jour. Exper. Med., 1911, 521.
The Immediate Effect on the Complement-fixation Test for Lues of Treatment with Salvarsan, Arch. Int. Med., 1911, 395.
Further Observations on the Complement-fixation Test in Lues, Jour. of Infect. Diseases, 1911, 213.
Craig and Nichols: The Effect of the Ingestion of Alcohol on the Result of the Complement-fixation Test of Syphilis, Jour. Amer. Med. Assoc., 1911, 474.
Crowe: Excretion of Hexamethylentetramin in the Cerebrospinal Fluid and its Therapeutic Value in Meningitis, Bull. Johns Hopkins Hosp., Baltimore, April, 1909.
Cushing, H.:
Some Experimental and Clinical Observations Concerning States of Increased Intracranial Pressure, Mutter Lecture, 1911, Amer. Jour. of Med. Sciences, Phila., 1902, p. 375.
The Pituitary Body and its Disorders, J. B. Lippincott Co., Philadelphia and London, 1912.

GERMAN LITERATURE

Caan: Ueber Komplementablenkung bei Hodgkinscher Krankheit, Münch. méd. Woch., 1910, 1102.
Calcar: Zur Serodiagnostic der Syphilis, Berl. klin. Woch., 1908.
Cavazzani:
Ueber die Circulation der Cerebrospinalfluessigkeit, Centralblatt f. Phys., Oct. 8, and Dec. 3, 1892.
Weiteres ueber die Cerebrospinalfluessigkeit, Centralbl. f. Phys., 1896, No. 4.

Cavazzani: Versuche ueber die Anwesenheit eines oxydations Fermentes in der Cerebrospinalfluessigkeit, Centralb. f. Phys., Dec. 22, 1900.

Chotzen: Beiträge zur Beurtheilung der differentiadiagnostischen Verwertbarkeit der Lumbalpunction, Centralbl. f. Nervenh., 1908, 19.

Cimbal: Chemische, physikalische und morphologische Untersuchungen an 240 Spinalpunktionen und deren diagnostische und therapeutische Verwertung, Ther. der. Gegenw., 1906, p. 495.

Citron:

Die practischen Ergebnisse der Serodiagnostic der Syphilis Ergeb. der inn., Med. u. Kinderheilk., vol. iv.

Ueber Komplementbindungsversuche bei infektioesen und postinfektioesen Erkrankungen (Tabes dorsalis, etc.), Deut. med. Woch., No. 29, 1907.

Die Serodiagnostic der Syphilis, Deut. med. Woch., 1907, and Berl. klin. Woch., 1907.

Die Bedeutung der Modernen Syphilisforchung fuer die Bekaempfung der Syphilis, Berl. klin. Woch., 1908, 518.

Ueber Aorteninsifficienz und Lues, Berl. klin. Woch., 1908, 2142.

Komplementbindung, Eulenberg's Realencyklop., 4th ed., 1908.

Ueber die Grundlagen der biologischen Quecksilbertherapie der Lues, Med. Klin., 1909.

Citron and Munk: Das Wesen der W. R., Deut. med. Woch., 1910, 1560.

Citron and Reicher: Intersuchungen ueber das Fettspaltungsvermoegen luetischer Sera und die Bedeutung der Lipolyse fuer die Serodiagnostic der Lues, Berl. klin. Woch., 1908, 1398.

Cohen, C.: Die Serodiagnose der Syphilis in der Ophthalmologie, Berl. klin. Woch., 1908, 877.

Csiki, Michael, and Elfer: Ueber die Wirkung des Sublimats bei der W. R., Wien. klin. Woch., 1910, 896.

Curschmann:

Ueber die therapeutische Bedeutung der Lumbalpunction, Therapie der Gegenwart, 1912, 242.

Ueber artificielle Drucksteigerung des Liquor cerebrospinalis als Hilfsmittel bei der Lumbalpunction, Therapie der Gegenwart, Aug., 1907.

Ueber einige Indicationen und contraindicationen der Lumbalpunction, Lecture ref. in Münch. med. Woch., 1910, p. 1308.

FRENCH LITERATURE

Calmette: Méthode simple de H. Noguchi pour le sero-diagnostic de la Syphilis, La presse méd., 1909, No. 26.

Carriere:

Méningisme par auto-intoxication gastro-intestinale, Nord. méd., June 15, 1902.

Polynucléose et Méningite tuberculeuse, Nord. méd., June 15, 1902.

Méningisme urecémique, Arch. Gén. de méd., 1903, p. 641.

Carriere: Le liquid C. R. dans l'urémie nerveuse, Arch. gén. de méd., Sept. 12, 1905; C. R. Soc. Biol., July 29, 1905.

Carrieu:

Les injections intra-rachidienes d'électro mercurol dans le tàbes et le méningo-myélitis chroniques, Congr. internat. de méd. de Budapesth, Aug 30, 1909.

Du traitement du tabès par la rachicentèse et les injections sous arachnoidiennes d'électro-mercurol, Leçons cliniques, premiere semestre, 1910, Montpellier médical.

Valeur diagnostique, prognostique et thérapeutique de la ponction lumbaire dans l'urémie, Livre jubilaire du Prof. Lepine, Lyons, Oct., 1911.

Carrieu and Bousquet: Le traitement du tabès par les injections sous arachnoidienne d'électro-mercurol, Montpellier méd., May 1910; Provence méd., June 11, 1910.

Cassagne: Ponction lombaire et Eclampsie, Thèse de Toulouse, 1907, p. 766.

Castaigne: Toxicité du liquide C. R. dans l'urémie nerveuse, C. R. Soc. Biol., Nov. 3, 1900; Presse méd., Nov. 7, 1900.

Castaigne and Debre: Pneumocoques abondants dans le liquide C. R. sans réaction cytologique de ce dernier, Soc. méd. des Hôp., Nov. 20, 1908.

Castaigne and Weill: Considérations pratique d'ordre clinique et thérapeutique sur le liquide C. R. des urémiques, Jour. med. Franc., Jan. 15, 1911.

Cathelin: Sur la circulation du liquide C. R., C. R. Soc. Biol., 1903, p. 1167; Presse méd., No. 90, Nov. 11, 1903.

Caussade and Vilette:

Urémie convulsive et comateuse. Liquide C. R. puriforme, Soc. méd. des Hôp., July 24, 1908.

Urémie curable, Soc. méd. des Hôp., 1909.

Cavazzani: Pression du liquide C. R. au cours de crises épileptiques, Bull. Accademia di Ferrara, Jan., 1902.

Ceconi: Etude physico-chimique du liquide C. R. normal et pathologique, Revista de clinical méd., 1905, Nos. 26 and 30.

Cesari: Recherche de la choline dans liquide cérébro-spinale chez les chiens soumis à l'épilepsie expérimentale, C. R. Soc. de Biol., Jan. 19, 1907, p. 66.

Cestan and Ravaut: Coagulation en masse et xanthochromie du liquide C. R. dans un cas de pachimeningomyelite, Gaz. des Hôp., Sept. 6, 1904.

Charrier: Les anticorps syphilitiques dans le liquide C. R. Complement a l'étude du liquide C. R. dans la Par. Gen. et le tabes, Thèse de Paris, July, 1907.

Chauffard: Urémie aiguë et polynucléose rachidienne, Semaine med., Nov. 13, 1907.

Chauffard and Froin:
Du diagnostic différentiel de l'hémorragie méningée sous-arachnoidienne et de la méningite cérébro-spinale, Soc. méd. des Hôp., Oct., 1903.
Pachymèningite hémorragique avec chromodiagnostic sans hématies: hyperthermie terminale, Soc. méd. des Hôp., March 27, 1903.
Chauffard and Vincent: Méningite urémique et infectieuse, Soc. méd. des Hôp., April 15, 1910.
Chauffard, Froin, and Boidin: Formes curables de hémorragies méningés arachnoidiennes, Presse méd., June 24, 1903.
Chauffard, LaRoche, and Grigant: Le taux de la cholestérine dans le liquide C. R. normal et pathologique, Compt. rend. de la Soc. de Biol., 1911, 855.
Claret and Lyon-Caen: Méningite a bacille d'Eberth au cours d'une dothiénentérie, Soc. méd. des Hôp., 1906.
Claude: Polynévrite alcoolique ayant débuté par un syndrome méningé avec coagulation massive du liquide C. R., Soc. de Neurol., Nov. 4, 1909.
Claude and Blanchetiere: Sur la présence de la choline dans le sang et au cours de maladies du système nerveux, Jour. de Phys. et Pathol. général, vol. ix, p. 87, 1907.
Clemenceau de la Loquerie: Liquide C. R., Glycométrie, Thèse de Paris, No. 69, 1905, 1906.
Clergier: La ponction lombaire de la Paral. Gen. Sa valeur clinique, pronostique, therapeutic, médico-légale, Thèse de Paris, No. 285, 1905.
Cohen: De l'emploi de la réaction de fixation de Bordet-Gengou pour le diagnostic de la méningite cérébro-spinale, Presse méd., Nov. 6, 1909.
Concetti: Rapport sur les méningites aiguës non tuberculeuses, Congrès de méd. section de maladies de l'enfance, vol. v, p. 345, 1900.
Conos, B., and Xantopoulos, C.: Hémorragie méningée curable, valeur diagnostique du liquide C. R., L'Encephale, July 18, 1912.
Crisafi: Recherches et considérations cliniques sur la quantité de chlorures contenue dans le liquide C. R. des enfants malades, Il Morgagni, Jan., 1904, No. 1.
Cruchet: Perméabilité méningée dans les méningitis, C. R. de la Soc. de Biol., 1904, p. 591.

ITALIAN LITERATURE

Calleja, Camilo: Alcance del Serodiagnosis con especial mencion del metodo de Wassermann-Noguchi, Rev. Med. y Cirug. pract., Madrid, April, 1909.
Cavazzani: Richerche sull' Alkalinita del liquido cerebro-spinale, Atti dell'Accademia di Ferrara.

Comba:
Sulla natura de la sustanza riducata contenuta nel liquido cefalorachideo, Clin. med. ital., 1899, No. 7.
Richerche sulla quantita de azoto contenuta nel liquido cefalorachideo, Clin. med. ital., 1899, No. 9.
Crisafi: Sul pottere ossidante del liquido cerebrospinale di Bambini malati, Revista di clinica pediatrica, No. 12, 1903.

D

ENGLISH LITERATURE

Dean: An Examination of the Blood-serum of Idiots by the Wassermann Reaction, Lancet, 1910, p. 227.
Dixon and Halliburton: The Action of the Choroid Plexuses on the Secretion of Cerebrospinal Fluid, Jour. of Phys., March 19, 1910.
Dochez: Proteolytic Enzymes and Anti-enzymes of Normal and Pathologic Cerebrospinal Fluids, Jour. of Experimental Medicine, vol. ii, p. 718, 1909.
Donaldson: Studies of the Choroid Plexus, Jour. of Nerv. and Mental Dis., 1907, p. 720.
Donath: Detection of Cholin in the Cerebrospinal Fluid by Means of the Polarising Microscope, Medical News, N. Y., 1905; also Jour. of Physiol., 1905, p. 211.
Doree and Golla: Is Trimethylamin a Normal Constituent of the Blood, Urine, and Cerebrospinal Fluid? Biochem. Jour., 1911, vol. v, p. 306.

GERMAN LITERATURE

Dembrowski: Zur Kenntniss des Ausfalls der W. R. bei Erkrankungen des Nervensystems, Duet. med. Woch., 1911, p. 1661.
Detre: Ueber den Nachweis von specifischen Syphilisantisubstanzen und deren Antigenen bei Lueitikern, Wien. klin. Woch., 1906, p. 619.
Detre and Brezovski: Serumreaktion bei Syphilis, Wien. klin. Woch., 1908, 1700.
Dohi: Ueber den Einfluss von Heilmitteln der Syphilis auf die Immunsubstanzen des Organismus, Z. f. Exp. Path. u. Ther., 1909, 171.
Donath, K.:
Ueber die W. R. bei Aortenerkrankungen und die Bedeutung der provokatorischen Hg. Behandlung fuer die serologische Diagnose der Lues, Berl. klin. Woch., 1909, 2015.
Ueber den Werth der Lumbalpunktion fuer die Diagnose und Therapie, Wien. med. Woch., 1903, No. 19.
Das Vorkommen und die Bedeutung des Cholins in der Cerebrospinalfluessigkeit bei Epilepsie und organischen Erkrankungen des Nervensystems, nebst weiteren Beiträgen zur Chemie derselben, Zeitschr. f. phys. Chem., 1913, vol. xxxix, p. 526.

Donath, K:
Der Phosphorsaueregehalt der Cerebrospinalfluessigkeit bei verschiedenen, insbesondere Nervenkrankheiten, Hoppe-Seyler, Zeitschr. f. phys. Chem., 1904, vol. xlii.
Fleischmilchsauere in der Eclampsie, Berl. klin. Woch., March 4, 1907.
Ueber Choline in der Cerebrospinalfluessigkeit, Neurologisches Centralblatt, 1908, p. 964; Zeitschr. f. phys Chem., vol. lxvi, 1908, p. 383.
Ueber die Stoffe die bei der Ausloesung des epileptischen Anfalles eine Rolle spielen, Deut. Zeitschr. f. Nervenh., 1909, p. 231.
Zur Serodiagnostic der Meningitis tuberculosa, Wien. klin. Rundsch., No. 41, 1901.
Die Bedeutung des Cholins in der Epilepsie, nebst Beiträgen zur Wirkung des Cholins und Neurins, sowie zur Chemie der Cerebrospinalfluessigkeit, Duet. Zeitschr. f. Nervenh., vol. xxvii, 1904.
Dreuw: Blutgewinnung bei der W. R., Deut. med. Woch., 1910, 221.
Dreyer and Meirowsky: Serodiagnostische Untersuchungen bei Prostituirten, Deut. med. Woch., 1909, p. 1698.
Dreyfus:
Die Bedeutung der modernen Untersuchungs und Behandlungsmethoden fuer die Beurteilung isolierter Pupillenstoerungen nach vorausgegangener Lues, Münch. med. Woch., 1912, p. 1647.
Nervoese Spaetreaktionen Syphilitischer nach Salvarsan, Münch. med. Woch., 1912, 1027.
Erfahrungen mit Salvarsan, Münch. med. Woch., 1912, 1801.
Dungern, Von: Wie kann der Arzt die Wassermannsche Reaction ohne Vorkenntnisse leicht vornehmen? Münch. med. Woch., 1911, p. 507.
Dungern and Hirschfeld: Ueber unsere Modifikation der W. R., Münch. med. Woch., 1910, 1124.

FRENCH LITERATURE

Danielopolu:
Sur une substance hémolytique contenue dans le liquide C. R., C. R. de la Soc. de Biol., vol. lxix, 28, 259.
Séróreaction de la syphilis dans les affections de l'aorte et des arteres, C. R. Soc. Biol., 1908, 971.
Delamare and Merle: Ependymites aiguës et subaigues, Revue Neurol., 1910, p. 333.
Delaunay: Contribution à l'étude du rôle des acides amines dans l'organisme animal, Thèse de Bordeaux, 1910, p. 29.
Delmas: La ponction lombaire chez le nouveau-ne, Prog. med., 1912, No. 7.
Demanche and Detre: Valeur de la réaction de fixation pour le diagnostic de la syphilis héréditaire, C. R. Soc. Biol., 1910, 696.

Demanche and Menard: Valeur de la methode de Hecht pour le séro-diagnostic de la syphilis; comparaison avec la réaction de Wassermann, C. R. Soc. Biol., 1910, 714.

Deniges:

Travaux recentes sur la réaction de Florence, Bull. de la Soc. de Pharm. de Bordeaux, 1900, p. 104.

Recherche microchimique de traces de triméthylamine. Identification de ce corps, Bull. de la Soc. Pharm. de Bordeaux, 1908, v, 48.

Deniges and Sabrazes: Sur la valeur diagnostique de la ponction lombaire. Examen comparatif au point de vue bactériologique et clinique du liquide C. R., Revue de méd., 1896, vol. xvi, p. 833.

Deval, L.: Séro-réaction dans la Syphilis. Méthode de Wassermann modifiée par Noguchi, Presse méd., 1909, 937.

Donath: Preuve de l'existence de la choline dans le liquide C. R. à l'aide du microscope polarisant, Revue Neurol., 1906, No. 4, p. 145.

Dopter:

Le liquide C. R. dans la méningite cérébrospinale épidémique, Le Prog. med., 1910, p. 53.

La méningite ourlienne, Paris méd., 1910, 35–40.

Le liquide C. R. dans le coup de chaleur, Soc. méd. des Hôp., Dec. 4, 1903,

Drouet: Méningite aiguä syphilitique, Thèse de Paris, No. 24, 1904–05.

Dubos:

Du diagnostic de la P. G., Thèse de Montpellier, No. 75, 1905.

De l'absence de glycose dans le liquide C. R., Annal. mèd. psychol., 1905, p. 393.

Ducros: Etude sur le rôle sécrétoire du liquide C. R. par le plexus choroides, Thèse de Bordeaux, No. 45, 1905.

Ducros and Gautrelet: Présence de pigments biliaires dans le liquide C. R. après suppression physiologique des Plexus choroides, C. R. de la Soc. de Biol., 1905, vol. lviii, p. 161.

Duflos: La ponction lombaire en psychiatrie, Paris, 1901.

Dufour:

Méningite sarcomateuse diffuse avec envahissement de la moelle et des racines. Cytologie positive et spéciale, Soc. Neurologique, Jan. 7, 1904.

Sucre rachidien, Soc. Méd. Hôp., June 17, 1904.

Du liquide C. R. hémorragique dans un cas d'insolation, C. R. de la Soc. de Biol., February, 1909.

Des résultats de la ponction lombaire dans l'insolation, Rev. Neurol., vol. vi, p. 317, 1909.

Cytologie du liquide C. R. dans la méningite Chronique Alcoolique, Gaz. hebdomad., 1901, p. 1015.

Dumont, J.: La nouvelle préparation arsénicale d'Ehrlich (No. 606) dans le traitement de la syphilis, Presse med., 1910, 636.

ITALIAN LITERATURE

Donzello: L'esame batteriologica del liquido cefalo-rachidiano nella puntura lombare alla Quincke, Riforma med., 1900, vol. iii, p. 350.

E

ENGLISH LITERATURE

Ellis and Swift: The Cerebrospinal Fluid in Syphilis, Jour. Exp. Med., vol. xviii, No. 2, 1913.

Eve: Some Motile Elements Seen in Certain Cerebrospinal Fluids, Brit. Med. Jour., 1907, p. 1399.

GERMAN LITERATURE

Edel: Die W. R. bei der progessiven paralyse und paralyse aehnlichen Erkrankungen, Ref. in Allg. Zeitschr. f. Psych., 1909, pp. 217–223.

Ehlers: Ehrlich's 606 gegen Lepra, Münch. med. Woch., 1910, 2141.

Ehrlich, H.: Einige Beiträge von Wassermannschen Syphilisreaktion, Wien. med. Woch., 1910, No. 22.

Ehrlich, Paul:

Gesammelte Arbeit aus dem Gebiete der Immunitaetsforschung, 1904.

Bietet die intravenoese Injektion von 606 besondere Gefahren, Münch. med. Woch., 1910, 1826.

Beiträge zur experimentellen Pathologie und Chemotherapie, Leipzig, 1909.

Chemotherapie von Infektionskrankheiten, Ztschr. f. aerzt. Fortbildung, 1909, 721.

Die Salvarsantherapie, Münch. med. Woch., 1911, lviii.

Ehrlich and Hata: Die experimentelle Chemotherapie der Spirilosen, Berlin, Julius Springer, 1910.

Ehrmann and Stern: Mittheilungen zur W. R., Berl. klin. Woch., 1910, 283.

Eichelberg:

Die Serumreaktion auf Lues mit besonderer Beruecksichtigung ihrer praktischen Verwertbarkeit fuer die Diagnostic der Nervenkrankheiten, Deut. Zetschr. f. Nervenh., 1909, pp. 319–341.

Die Bedeutung der Untersuchung der Cerebrospinalfluessigkeit, Med. Klin., 1912, p. 1187.

Die praktische Verwertbarkeit der W. R. auf Lues, und das Vorkommen derselben bei Scharlach, Münch. med. Woch., 1908, 1206.

Eichelberg and Pfoertner: Die praktische Verwertbarkeit der verschiedenen Untersuchungsmethoden des Liquor cerebrospinalis fuer die Diagnostic der Geistes und Nervenkrankheiten, Monatschr. f. Psych. u. Neurologie, 1909, pp. 486–497.

Eisler: Ueber Komplementablenkung und Lezithinausflockung, Wien. klin. Woch., 1908, p. 422.

Eitner:

Ueber den Nachweis von Antikoerpern im Serum eines Leprakranken mittels Komplementablenkung, Berl. klin. Woch., 1906, p. 1555.

Zur Frage der Anwendung der Komplementbindungsreaktion auf Lepra, Wien, klin. Woch., 1908, p. 729.

Elias, Neubauer, Porges, and Salomon:

Theoretisches ueber die Serumreaktion auf Syphilis, Wien. klin. Woch., 1908, p. 376.

Ueber die Methodik und Verwendbarkeit der Ausflockungsreaktion fuer die Serodiagnose der Syphilis, Wien. klin. Woch., 1908, p. 831.

Eliasberg: Zur Theorie und Praxis der W. R., St. Petersburger, Med. Woch., 1910, xxvii.

Engel: Ueber die Sekretionserscheinungen in den Zellen des Plexus Choroides des Menschen, Arch. f. Zellforschung, 1909.

Epstein and Pribram:

Wirkung des Sublimats auf die komplexe Haemolyse durch immunserum und die W. R., Ztschr. f. Exp. Path. and Ther., 1909–10, 549.

Zur Frage des Zusammenhanges zwischen W. R. und Hg. Behandlung, Wien. klin. Woch., 1910, 290.

Erb: Ueber die Diagnose und Fruehdiagnose der Syphilogenen Erkrankungen des Zentralnervensystems, Deut. Zeit. f. Nervenh., 1907, p. 425.

FRENCH LITERATURE

Ehlers and Bourret: La réaction de Wassermann dans la Lépre, Mitteil. und Verhandl der II. internation. wissenschaftl. Lepra-Konference, III, 368.

Enriquez and Sicard: Les oxydations de l'organisme (Oxydases), Actualités med. Balliere fils, Paris, 1902.

Esmein and Paru: Diagnostic de la nature syphilitique de certaines cirrhoses du foie par la séroreaction de Wassermann; recherche comparée des anticorps dans le sérum et l'ascite, C. R. Soc. Biol., 1909, 159.

Espinet: Polynucléose rachidienne et méningite tuberculeuse, Thèse de Paris, No. 28, Nov., 1908.

Euzier: Paralysie generale et Tabès, Montpellier Med., 1910.

Euzier, Mestrezat, and Roger: La réaction du liquide C. R. à l'acide butyrique (Reaction de Noguchi) sa valeur dans le diagnostic de syphilid du névraxe, L'Encéphale, September, 1911, No. 9.

F

ENGLISH LITERATURE.

Famulener and Alice Mann: Experimental Data Relating to Hemolytic Sera, Collected Studies from the Research Lab. Dept. of Health, City of N. Y., 1908–09, p. 161.

Farnell: The Cerebrospinal Fluid; its Cellular Elements and Globulin Content, Amer. Jour. of Insanity, 1911, p. 23.

Feiling, A.: The Blood and the Cerebrospinal Fluid in Mumps, Lancet, July 12, 1913.

Fitzgerald, J. S.: A Few Remarks on Serum Diagnosis of Syphilis, N. Y. Med. Jour., 1910, 221.

Fleischman and Butler: Serum Diagnosis of Syphilis, Jour. Amer. Med. Assoc., 1907, 934.

Fleming, A.: A Simple Method of Serum Diagnosis of Syphilis, Lancet, 1909, 1512.

Forbes: A Note on the Cerebrospinal Fluid in Acute Poliomyelitis, Lancet, Nov. 18, 1911.

Fordyce, J. A.:

Further Observations On the Use of the Ehrlich-Hata Preparation 606 in the Treatment of Syphilis, N. Y. Med. Jour., 1910, 957.

The Administration of Salvarsan in Syphilis, Jour. Amer. Med. Assoc., Oct. 5, 1912.

Foster: Sugar in the Cerebrospinal Fluid in Diabetes, Boston Med. and Surg. Jour., 1906, p. 441.

Fox, Howard:

The Principles and Technic of the Wassermann Reaction and its Modifications, Med. Rec., 1909, 421.

A Comparison of the Wassermann and Noguchi Complement-fixation Tests, Jour. of Cutan. Dis., 1909, 338.

The Relative Value of Mercury and Salvarsan from a Serologic Point of View, Jour. Amer. Med. Assoc., Oct. 5, 1912.

The Wassermann and Noguchi Complement-fixation Test in Leprosy, Amer. Jour. Med. Sciences, 1910, 724.

The Wassermann Reaction (Noguchi Modification) in Pellagra, N. Y. Med. Jour., 1909, 1206.

GERMAN LITERATURE

Facchini: Beiträge zur Technik der Wassermannschen Reaktion, Z. f. Immunitaetsforchung, 1909, 257.

Fankhauser:

Erfahrungen ueber Lumbalpunktion bei Geisteskranken, Korrespondenzblatt f. Schweizer Aerzte, 1907, p. 33.

Zur Technik der Zaehlung der zelligen Elemente des Liquor cerebrospinalis, Zeitschr. f. ges. Ner. u. Psy., 1910, p. 341.

Fauser:
Zyto und Serodiagnostic und ihre Bedeutung fuer die Neurologie, Ref. in Deut. med. Woch., 1909, p. 1460.
Ueber den heutigen Zustand der Diagnostik und differentialdiagnostik der luetischen und metaluetischen Gehirnerkrankungen, Fortschr. d. Med., 1910, xxviii, Nos. 14, 15, 16.
Favente: Ueber 156 mit Ehrlich-Hata 606 behandelte Faelle, Münch. med. Woch., 1910, 2080.
Faworsky: Zur chemischen und cytologischen Untersuchungen der Lumbalfluessigkeit bei Nervenkranken, Rousski Vratsch, 1910, p. 756.
Fischer, O:
Zur Frage der Zytodiagnose der Progressiven Paralyse, Prager med. Woch., 1904, p. 515.
Klinische und anatomische Beiträge zur Frage nach den Ursachen und der Bedeutung der cerebrospinalen Pleocytose (der Zellvermehrung im Liquor cerebrospinalis), Jahrbuch f. Psy. und Neurol., 1906, No. 27.
Die anatomische Grundlage der cerebrospinalen Pleocytose, Monatschr. f. Psy. u. Neurol., 1910, p. 512.
Flatau: Ueber Xanthochromie und Bildung eines fibrinoesen Coagulums im Liquor cerebrospinalis, Neurologia polska, 1910, No. 6.
Fischer, W.:
Klinische Betrachtungen ueber die W. R. bei Syphilis, Berl. klin. Woch., 1908, 151.
Die Wassermannsche Syphilisreaction und ihre diagnostische und therapeutische Bedeutung, Ther. d. Gegenw., 1908, 168.
Die Bewertung der Wassermannschen Reaction fuer die Fruehdiagnose und die Therapie der Syphilis, Med. Klin., 1909, 176.
Fischer and Meier: Ueber den klinischen Wert der Wassermannschen Serodiagnostik bei Syphilis, Deut. med. Woch., 1907, 2169.
Fleischer: Cytodiagnostische Untersuchungen des Liquor cerebrospinalis bei Augenkranken, Vereinsbeilage der Deut. med. Woch., 1908, p. 1615.
Fleischmann: Die Theorie, Praxis, und Resultate der Serumdiagnostik der Syphilis, Derm. Zentralbl., 1908, pp. 226–239.
Fornet and Schereschewsky: Serodiagnose bei Lues, Tabes, und Paralyse, Münch. med. Woch., 1907, 1471.
Foster and Tomasczewski: Nachweis von lebenden spirochaeten im Gehirn von paralytikern, Deut. med. Woch., 1913, xxxix, 1237.
Fraenkel, E.: Ueber das Verhalten des Gehirns bei akuten Infektionskrankheiten, Virch. Arch., Beiheft Z, 194, 1908.
Fraenkel and Much, H.:
Die W. R. an der Leiche, Münch. med. Woch., 1908, p. 2479.
Ueber die Wassermannsche Serodiagnostik der Syphilis, Münch. med. Woch., 1908, p. 662.

Fraenkel, Heiden:
Zur Cytodiagnose der Tabes, Neurol. Zentralb., 1903, p. 1135.
Zur Chemie der Cerebrospinalfluessigkeit, Biochem. Zeitschr., 1907, p. 188.
Liquor cerebrospinalis und Wassermannsche R., Neurol. Zentralb., Jan. 16, 1912.
Die Zellen der Cerebrospinalfluessigkeit in ungefaerbtem Zustande, Neurol. Zentralb., 1912, vol. xxxi.

Fraenkel, M.: Weitere Beiträge zur Bedeutung der Auswertungsmethode der Wassermannschen Reaction im Liquor cerebrospinalis an der Hand von 32 klinisch und anatomisch untersuchten Faellen. Ueber das Vorkommen der Wassermann Reaction im Liquor cerebrospinalis bei Faellen von frischer primaerer und secundaerer Syphilis, Zeitschr. f. d. gesamm. Neurol. u. Psy., 1912, vol. ii, 1 and 2.

Fraenkel and Grouven: Erfahrungen mit dem Ehrlichschen Mittel 606, Münch. med. Woch., 1910, 1771.

Frankl, O.: Beiträge zur Lehre von der Vererbung der Syphilis, XIII Kongres der deut. Gesel. f. Geburtshilfe u. Gynek., June, 1909; also Monatschr. f. Geburtshilfe u. Gynek., 1910, xxxi, 340.

Freudenberg: Eine Mahnung zur Forsicht beit der diagnostischen Verwertung der Wassermannschen Syphilisreaktion, Berl. klin. Woch., 1910, 1231.

Frey: Ueber die Wirkung des Enesol auf die metalueitischen Nervenerkrankungen und auf die W. R., Berl. klin. Woch., 1911, 1171.

Freyham: Ein Fall von Meningitis tuberculosa mit Ausgang in Heilung, Deut. med. Woch., 1896, No. 35.

Friedberger:
Ueber die Haltbarmachung der Komplemente, Berl. klin. Woch., 1907, 1299.
Ueber das Verhalten der komplemente in hypertonischen Salzloesungen, Centralb. f. Bakt., 1908, 441.
Ueber Haltbarmachung der Komplemente, Berl. klin. Woch., 1907, 1299.

Friedländer: Der wert der W. R. fuer die Diagnose der Syphilis, Arch. f. Dermatologie und Syph., 1910, 255.

Fritz and Kren: Ueber den Wert der Serumreaction bei Syphilis nach Porges, Meier and Klausner, Wien. klin. Woch., 1908, 386.

Froederstroem and Wigert: Ueber das Verhaeltniss der W. R. zu den Zytologischen und chemischen Untersuchungsmethoden der Spinalfluessigkeit, Monatschr. f. Psy., 1910, vol. xxviii.

Frugoni and Pisani: Vielfache Bindungseigenschaften des Komplementes einiger Sera (Leprakranker) und ihre Bedeutung, Berl. klin. Woch., 1909, 1530

Fua and Koch: Zur Frage der W. R. bei Scharlach? Wien. klin. Woch., 1909, 522.

Fuchs: Ueber Beobachtungen an Flimmerzellen, Anat., Heft von Merkel and Bonnet, 1904, p. 77.

Fuchs and Rosenthal: Physikalische, chemische, zytologische und anderweitige Untersuchungen der Zerebrospinalfluessigkeit, Wien. med. Presse, 1904, p. 2061.

Fuerbringer: Zur klinik der Lumbalpunktion, Kongr. f. inn. Med., 1897, p. 331.

Fumarola Tramonti: Globulinreaction, Albuminreaction, und Lymphocytose bei den organischen Erkrankungen des Nervensystems, Monatschr. f. Psy. und Neurologie, 1911, vol. xxx.

Füth and Lockemann: Ueber den Nachweis von Fleischmilchsauere in der Cerebrospinalfluessigkeit Eklamptischer, Arch. f. Gyn., 1905, 76.

FRENCH LITERATURE

Ferrier: Cytologie du liquide C. R. dans la Leucemie, C. R. de la Soc. de Biol., 1908, 803.

Feuille: Etude sur l'albumine et la cytolyse du liquide C. R., Soc. méd. des Hôp., April 27, 1906.

Fiessinger and Marie: Le ferment proteolytique des leucocytes dans les méningites aiguës et méningocoques, Compt. rend. de la Soc. Biol., 1909, 915.

Foix: Technique simplifiee de réaction de fixation, C. R. Soc. Biol., July, 1909; Semaine méd., 1909, 359.

Follet and Chevrel: Hémorragies sous-arachnoidiennes spontanées chez des jeunes gens. Nouvel example de biligénie hémolytique, Gaz. des. Hôp., April 5, 1910.

Folty, C.: Etudes sur le liquide C. R., Gaz. méd. de Paris, 1855, p. 114.

Fornaca: Coagulation et xanthochromie du liquide C. R. dans un cas de méningo-myélite de la queue de cheval, Gazzette degli Ospedale e delle Cliniche, August 4, 1906.

Francis: Le liquide céphalo-rachidien, Progrès méd., 1910, 376.

Froin:

Inflamations méningées avec réaction chromatique, fibrineuse et leucocytique du liquide céphalo-rachidien, Gaz. des Hôp., September 3, 1903.

Le liquide C. R. dans l'hémorragie cérébroméningée, Gaz. des Hôp., Nov., 1903.

Les hémorragies sous-arachnoidiennes et le méchanisme de l'Hématolyse en général, Thèse de Paris, Dec., 1904, No. 113.

Froin and Ramond: Evolution des réactions cellulaires et séro-fibrineuses dans le liquide C. R. retiré par ponction lombaire des méningites tuberculeuses, C. R. Soc. de Biol., Nov. 11, 1905.

Froment: Diagnostic et pronostic de l'urémie nerveuse par le dosage de l'urée dans le liquide C. R., Lyon méd., February 6, 1910.

ITALIAN LITERATURE

Forbes, G.: Pathologie du liquide C. R., Lavore Revista di Clinica e Microscopia Clinica, Oct. and Nov., 1908.

G

ENGLISH LITERATURE

Gay:

The Fixation of Alexins by Specific Serum Precipitates, Centralb. f. Bact., 1905, xxii, 522.

Studies in Immunity, Wiley & Sons, N. Y., 1909.

Gay and Fitzgerald: The Serum Diagnosis of Syphilis, Boston Med. and Surg. Jour., 1909, 432.

Gibbs and Wansey: Preliminary Note on the Comparative Value of the Various Methods of Antisyphilitic Treatment Estimated by the Wassermann Reaction and Clinical Observation, Lancet, 1910, 1256.

Goetsch, Cushing, and Jacobson: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Bull. Johns Hopkins Hosp., 1911, pp. 165–190.

Gottheil, W. S.: Experiences with Arsenobenzol, Med. Rec., 1910, 1174.

Gradwohl: The Luetin Test for Syphilis. A Preliminary Report of 44 Cases, Med. Rec., 1912, 973.

Gregory and Karpas: A Case of Cerebral Syphilis Occurring Six Months After the Initial Lesion; Review of Neurology and Psychiatry, May, 1913.

Groat, W. A.: The Serum Diagnosis of Syphilis, Using the Noguchi System, N. Y. Med. Jour., 1910, p. 954.

Grulee and Moody: Lange's Colloidal Gold Chlorid Test on Cerebrospinal Fluid in Congenital Syphilis, Jour. Amer. Med. Assoc., July 5, 1913.

GERMAN LITERATURE

Geissler: Eine objektive Methode zur Bestimmung pathologischer Zellvermehrung im Liquor cerebrospinalis, Münch. med. Woch., 1911, No. 36.

Gelarie, A.: Ueber die diagnostische und therapeutische Bedeutung der W. R. und die Brauchbarkeit der Modifikation Hecht, Arch. f. Dermat. u. Syph., 1910, 266.

Gennerich: Ueber Syphilisbehandlung mit Ehrlich 606, Berl. klin. Woch., 1910, 1735.

Gerhardt: Ueber die diagnostische und therapeutische Bedeutung der Lumbalpunktion, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1904, 13.

Geronne, Hr.: Ueber die Wirkung des Ehrlich-Hataschen Arsenpraeparates auf menschliche Syphilis, Berl. klin. Woch., 1910, 1338.

Ghon, Mucha, and Mueller: Zur Aetiologie der acuten Meningitis, Centralblatt fuer Bakteriologie und Parasitenkunde, vol. xli.

Gianuzzi: Beiträge zum Studium der Cytodiagnose, Wien. med. Blaetter, 1903, 47.

Gjorgjevic and Savnik: Ueber die W. R. bei Lues und bei Psoriasis vulgaris, Wien. klin. Woch., 1910, 1264.

Glaser, F.: Die Erkennung der Syphilis und ihrer aktivitaet durch probatorische Hg. Injektionen, Berl. klin. Woch., 1910, 1264.

Glaser and Wolfssohn: Klinische Beobachtungen ueber die Wassermann-Neisser-Brucksche Reaktion und deren Kontrolle durch Sektionsresultate, Med. Klin., 1909, 1731.

Glueck: Kurzer Bericht ueber 109 mit "606" behandelte Luesfaelle, Münch. med. Woch., 1910, 1638.

Goldschmidt and Pribram: Wirkung der Narkotika und Alkaloide auf das Komplement, Zeitschr. f. Exper. Path. u. Ther., 1909, 211.

Gross, S., and Volk, R.: Weitere Serodiagnostische Untersuchungen bei Syphilis, Wien. klin. Woch., 1908, 1522.

Grosz, Emil V.:

Arsenobenzol (Ehrlich 606) gegen syphilitische Augenleiden, Deut. med. Woch., 1910, 1698.

Bemerkungen zur Mitteilung von R. Bauer u. A. Hirsch. Beiträge zum Wesen der W. R., Wien. klin. Woch., 1910, 103.

Schlussbemerkung zu der Entgegnung von R. Bauer u. A. Hirsch, Wien. klin. Woch., 1910, 171.

Grouven, Karl: Beginn und Dauer der Arsenausscheidung im Urin nach Anwendung des Ehrlich-Hataschen praeparates Dioxydiamidoarsenobenzol, Münch. med. Woch., 1910, 2079.

Gruenberger: Ueber den Befund von Acetessigsauere in der Cerebrospinalfluessigkeit bei Coma Diabeticum, Zeitschr. f. Inn. med., 1905, 617.

Gulewitsch:

Ueber Choline und einige Verbindungen, Zeitschr. f. Phys. Chemie, 1898, vol. xxiv, p. 513.

Choline in der normalen und pathologischen Spinalfluessigkeit und deren physiologische Funktion, Kongress f. inn. Med., April, 1900.

Gumprecht:

Gefahren bei der Lumbalpunction, ploetzliche todesfaelle danach, Deut. med. Woch., 1900, 24.

Cholin in der normalen und pathologischen Spinalfluessigkeit und die physiologische Funktion derselben, XVIII Kongress f. innere med., 1900.

FRENCH LITERATURE

Gaston and Girauld: Séro-diagnostic (Reaction de Wassermann) chez un malade, atteint de chancre syphilitique de l'amygdale, Bull. de la Soc. Franc. de Dermat. et de Syph., 1908, 235.

Gaston and Lebert: Séro-diagnostic de la syphilis. Réflections sur la technique et la valeur des méthodes, à propos de 200 cas, Bull. de la Soc. Franc. de Dermat. et de Syph., 1910, 199.

Gaucher and Abrami: Le séro-diagnostic des formes atypiques de la lépre, Bull. de la Soc. med. des Hôp. de Paris, 1908, p. 497.

Gaucher and Merle: Constatation du tréponéma pallidum dans le liquide C. R. au cours de la syphilis acquise des centres nerveux, C. E. de l'Acad. des Sci., 148, 13, 862.

Gay: La déviation de l'alexine dans l'hémolyse, Ann. Inst. Pasteur, 1905, 539.

Gilbert and Castaigne: Le liquide C. R. dans la cholémie, Presse méd., Nov. 3, 1901.

Gillard: Le glucose dans le liquide C. R., Thèse de Lyon, 1904, No. 67.

Giraudet: Complications méningitiques de la fievre typhoide chez l'enfant, Thèse de Bordeaux, 1905, No. 27.

Greco: Sur le pouvoir reducteur du liquide C. R., Revue d'hygiene et de médicine infantiles, 1909, p. 353.

Grimbert and Coulaud: Caractérisation du glucose dans le liquide C. R., C. R. Académie des sciences, February, 1903.

Guillain and Parant: Présence d'albumine coagulable par la chaleur dans les liquides de paraplégiques spinaux, Soc. Neurol., April 2, 1903.

Guinard: La ponction lombaire et le fractures du crâne, Jour. de Méd. de Paris, 1910, No. 28.

Guinon and Paris: Paralyse infantile avec réaction méningée, C. R. de la Soc. des Hôp. de Paris, 1903, 673.

Guinon and Rist: Deux cas de poliomyélite anterieure aigue sans réaction méningée cytologique, Ibid.

ITALIAN LITERATURE

Gonzales and Verga: Nota sul liquido C. R. nei Pazzi, Archiv. delle Malattie mentali, 1890, p. 23.

H

ENGLISH LITERATURE

Halliburton:

On Cerebrospinal Fluid, Jour. of Physiol., 1889, vol. x, p. 176.

Choline, Folia Neurologica, 1907, p. 33.

Halliburton, Thompson, and Hill: Observations on the Cerebrospinal Fluid of Man, Proc. of the Royal Soc. of London, 1899, vol. lxiv, p. 343; Lancet, 1898, No. 9.

Hand:

The Diagnostic Value of Chemical and Bacteriologic Analyses of Cerebrospinal Fluids, Amer. Pediatr. Soc., May 25, 1908; Medical Record, Sept. 26, 1908, p. 544.

The Positive Diagnosis of Meningitis, Particularly Tuberculous, by Means of Lumbar Puncture, Phila. Med. Jour., 1902, p. 292.

Heiman: Lumbar Puncture in Infants; Measurement of the Cerebrospinal Pressure, New York Med. Jour., Nov. 17, 1906.

Heimann, W. J.:

A Method for the Mathematical Reading of the Original Wassermann Reaction, Jour. Amer. Med. Assoc., May 21, 1910.

The Wassermann Reaction and the Physician, N. Y. State Med. Jour., July, 1911.

Present Day Diagnosis of Acquired Cutaneous Syphilis, Amer. Jour. of Urology, March, 1912.

Hemenway: The Constant Presence of Tubercle Bacilli in the Cerebrospinal Fluid of Tuberculous Meningitis, with Observations on the Cerebrospinal Fluid in Other Forms of Acute Meningitis, Amer. Jour. of Diseases of Children, 1911, p. 37.

Hough: Remarks on the Comparative Diagnostic Value of the Noguchi Butyric Acid Reaction and the Cytologic Examination of the Cerebrospinal Fluid, Bull. No. 2, Government Hosp. for Insane, Washington, 1910, 118.

Hough and Lafora: Some Findings in the Cerebrospinal Fluid in Eleven Cases of Acute Anterior Poliomyelitis, Epidemic Form, Folia Neurobiologica, 1911, No. 5, p. 3.

GERMAN LITERATURE

Halberstaedter: Die Bedeutung der neueren Hilfsmittel fuer die Diagnostik und Therapie der Syphilis, Therap. Monatsch., 1910, xxiv, 64.

Halberstaedter, E. Mueller, and Reiche: Ueber Komplementbindung bei Syphilis hereditaria, Scharlach und anderen Infektionskrankheiten, Berl. klin. Woch., 1908, p. 1917.

Hald: Zur permeabilitaet der Leptomeningen besonders Hexamethylin tetramin gegenueber, Arch. f. exper. Pathol. u. Pharmak., 1911, Nos. 5 and 6.

Hartwich: Bacterium Coli im Liquor cerebrospinalis, Berl. klin. Woch., 1911, 795.

Hata: Chemotherapie der Spirilosen, Münch. med. Woch., 1910, 981.

Hauck: Positiver Ausfall der W. R. bei Lupus erythematoss acutus, Münch. med. Woch., 1910, lvii, 17.

Hauptmann:

Serologische Untersuchungen von Familien syphilogener Nervenkranke, Zeitschr. f. d. ges. Neurol. u. Psy., 1911, No. 8.

Eine biologische Reaktion im Liquor cerebrospinalis bei organischen Nervenkrankheiten, Med. Klin., 1910, No. 6, p. 181.

Die Vorteile der Verwendung groesserer Liquormängen (Auswertungsmethode) bei der Wassermannschen Reaktion fuer die Neurologische Diagnostik, Deut. Zeitschr. f. Nervenheilk., 1911, 240.

Hauptmann and Hoessli: Erweiterte Wassermannsche Methode zur Differentialdiagnose zwischen Lues cerebrospinalis und multipler Sklerose, Münch. med. Woch., 1910, No. 30.

Hecht:

Eine Vereinfachung der Komplementbindungsreaktion bei Syphilis, Wien. klin. Woch., 1908, p. 1742, No. 50.

Untersuchung ueber haemolytische, eigenhemmende und komplementaere Eigenschaften des menschlichen Serums, Wien. klin. Woch., 1909, 265.

Hecht, Hugo:

Eine Vereinfachung der Komplementbindungsreaktion bei Syphilis, Wien. klin. Woch., 1909, 338.

Was leistet die Serodiagnose dem praktischen Arzte? Prager med. Woch., 1910, xxxv, 166.

Zur Technik der Seroreaktion bei Syphilis, Ztschr. f. Immunitätsf., 1910, v, 572.

Hecht, V., Lateiner, M., and Wilenko, M.: Ueber Komplementbindungsreaktion bei Scharlach, Wien. klin. Woch., 1909, p. 523.

Heckmann: Zur Aetiologie der Arthritis deformans, Münch. med. Woch., 1909, lvi, 1588.

Hendel and Schultz: Beiträge zur Frage der Komplementablenkenden Wirkung der Sera von Scharlachkranken, Zeitschr. f. Immun., 1908–09.

Henkel: Untersuchungen ueber die Cerebrospinalfluessigkeit bei Geistes und Nervenkranken, Arch. f. Psy., 1907, 327.

Herxheimer: Arsenobenzol und Syphilis, Deut. med. Woch., 1910, 1517.

Herxheimer and Schoenfeld: Weitere Mitteilungen ueber die Wirkung des Ehrlichschen Arsenobenzols bei Syphilis, Med. Klin., 1910, 1400.

Hess and Poetzl: Ueber Schwankungen des Zuckergehaltes des Liquor C. R. bei psychischen Erkrankungen, Wien, klin. Woch., 1910, 1065.

Hoehne:

Was leistet zur Zeit die Wassermannsche Reaktion fuer die Praxis? Med. Klin., 1908, 1787.

Ueber das Verhalten des Serums von Scharlachkranken bei der Wassermannschen Reaktion auf Syphilis, Berl. klin. Woch., 1908, 1488.

Die W. R. und ihre Beeiflussung durch die Therapie, Berl. klin. Woch., 1909, 869.

Hoehne, Fritz: Ueber die verschiedenen Modifikationen der W. R., Berl. klin. Woch., 1910, 334.

Hoffmann and Blumenthal: Die Serodiagnostik der Syphilis und ihre Verwendbarkeit in der Praxis, Dermat. Zeitschr., 1908, xv, 23.

Hofmann: Ueber das wahrscheinliche Vorkommen von Carbaminsaeure bei Eklampsie, Centralbl. f. inn. Med., 1897, p. 725.

Holm: Der Befund der Lumbalfluessigkeit bei tuberculoeser Meningitis, Berl. klin. Woch., 1911, No. 18.

Holzmann:

Fortschritte in Bezug auf die Diagnostik der syphilitischen und metasyphilitischen Erkrankungen des Zentralnervensystems vermitttelst der vier Reaktionen, Die Heilkunde, Jahrgang, 1911.

Holzmann:
Liquor C. R. und W. R., Neurol. Centralbl., 1912, No. 2.
Scharlach und Wassermannsche Syphilisreaktion, Münch. med. Woch., 1909, 715.
Hoppe: Ueber die chemische Zusammensetzung der Cerebrospinalfluessigkeit, Virchow's Arch., 1859, vol. xvi, p. 391.
Huebner: Zur Lehre von den syphilogenen Erkrankungen des Zentralnervensystems, Jahresvers. des deutsch. Vereins f. Psy., April 23 and 24, 1909; ref. in Allgemeine Zeits. f. Psy., vol. lxvi, pp. 657, 658.

FRENCH LITERATURE

Hallion and Bauer: Sur les variations du glucose C. R. dans un cas de méningite à bacilles de Pfeiffer, Rev. Neurologique, March 2, 1911.
Haushalter and Thiry: Etudes sur l'hydrocéphalie, Revue de Méd., Aug. 10, 1897.
Hirschhorn: Méningite tuberculeuse; valeur de l'examen du liquide B. R., Thèse de Paris, No. 216, 1903.
Hugot: Un cas de méningite a bacille d'Eberth, Gaz. hebdomad., 1899, No. 20.
Hutinel: Réactions méningées dans les erythémes chez les enfants, Presse med., March 24, 1909

I

GERMAN LITERATURE

Isabolinsky: Beiträge zur klinischen Beurtheilung der Serumdiagnostik der Syphilis, Arbeiten aus dem Instit. zur Erforschung der Infektionskrankheiten, Bern, 1909.
Iversen:
Ueber die Wirkung des neuen Arsenpraeparates (606) Ehrlich's bei Rekurrens, Münch. med. Woch., 1910, 777.
Ueber die Behandlung der Syphilis mit dem Praeparate "606" Ehrlichs, Ibid., 1910, 1723.

FRENCH LITERATURE

Iscovesco:
Etudes sur les constituants colloidaux des humeurs de l'organisme; Liquide C. R. normal, C. R. de la Soc. de Biol., 1907, p. 183.
Les lipoides, La presse méd., 1908, Nos. 58, 67, 70.

J

ENGLISH LITERATURE

Jones:
A Simplified Technic for Accurate Cell Enumeration in Lumbar Puncture, Revue of Neurol. and Psych., 1907, p. 539.

Jones:
The Protein Content of Cerebrospinal Fluid in General Paralysis, Revue of Neurol. and Psych., June, 1909, p. 379.
Modern Progress in Our Knowledge of the Pathology of General Paralysis, Lancet, 1909, p. 209.
A Review of our Present Knowledge Concerning the Serodiagnosis of General Paralysis, Amer. Jour. of Insanity, 1909, p. 653.

GERMAN LITERATURE.

Jach: Technik und Ergebnisse der Lumbalpunktion, Arch. f. Psych.
Jacobsthal:
Ueber positive W. R. der Lumbalfluessigkeit bei negativer des Blutes, Münch. med. Woch., 1909, p. 2662.
Die W. R. eine Precipitationsreaktion, Münch. med. Woch., 1910, 215.
Zur Frage nach der Herkunft der die W. R. herforrufenden Substanzen, Ibid., 1036.
Jadassohn: Bedeutung der modernen Syphilisforschung, besonders der Serodiagnostik, fuer die Klinik der Syphilis, Korrespondenzbl. f. Schweizer Aerzte, 1909, No. 5.
Jaksch, R.: Ueber die Zusammensetzung der Cerebrospinalfluessigkeit, Klinische Diagnostik innerer Krankheiten, 5th edition, p. 567.
Jaworski and Lapinski: Ueber das Schwinden der W. R. bei syphilitischen Erkrankungen und einige strittige Punkte derselben, Wien. klin. Woch., 1909, 1442.
Jerusalem: Ueber ein neues Verfahren der Bestimmung der Milchsauere in organen und Tierischen Fluessigkeiten, Biochemische Zeitschr., 1909, p. 361.
Jesionek and Meirowsky: Die praktische Bedeutung der W. R., Münch. med. Woch., 1909, 2297.
Jochmann and Toepfer: Zur Frage der Spezifizitaet der Komplementbindunsmethode bei Syphilis, Münch. med. Woch., 1908, 1690.
Jolowicz: Ueber Behandlungsversuche mit Natrium nucleinicum und Salvarsan bei progessiver Paralyse, unter besonderer Berueck-sichtigung der Veraenderungen des Liquir cerebrospinalis, Neurol. Centralbl., 1913, No. 4.
Jundell, Almkvist, and Sandmann: Wassermannsche Syphilis Reaktion bei Lepra, Centralbl. f. innere. Med., 1908, 1181.
Junkermann: Die Behandlung der Syphilis mit Ehrlich-Hata 606, Med. Klin., 1910, 1350.

FRENCH LITERATURE

Jacobaeus and Backmann: Sur les differentes modifications de la réaction de Wassermann, C. R. Soc. Biol., 1909, No. 30.

Jaskowski and Rajchmann: Quelques remarques sur la réaction de Wassermann dans le tabès et la paralysie générale, C. R. de la Soc. de Biol., 66, 14, 618, 1909.

Javorski: Influence du traitement mercuriel sur la composition du liquide Ç. R. dans le maladies du systeme nerveux de nature syphilitique ou parasyphilitique, Revue neurol., 1910, p. 264.

Jeanselme and Sezary: Lymphocytose C. R. et formule sanguine chez les Syphilitiques, Compt. Rend. de la Soc. de Biologie, 64, 5, 201.

Joffroy and Mercier: De l'utilité de la ponction lombaire pour le diagnostic de la paralysie génerale, Congrés des méd. alienist, Grenoble, 1902, 12th session.

Joltrain: Nouvelles méthodes de séro-diagnostic, Paris, 1910.

Jousset: Les sérums anti-tuberculeux. Precipito-diagnostic de la tuberculose, C. R. de la Soc. Biol., Dec. 11, 1909.

Jousset and Paraskevopoulos: De la variabilité du complément et des causes d'erreur dans le syphilodiagnostic par la réaction de fixation, C. R. de la Soc. de Biol., lxvii, 22.

K

ENGLISH LITERATURE

Kakels, M. S.: Concerning the Ehrlich-Hata Preparation 606, Med. Rec., 1910, 1079.

Kaliski, D. J.: Specificity of the Noguchi Modification of the Wassermann Reaction, Arch. of Internal Med., 1910, 205.

Kaplan, D. M.:

The Conservative Utilization of the Wassermann Reaction, Jour. Amer. Med. Assoc., Dec. 3, 1910.

The Theoretical Consideration of the Wassermann Reaction and its Practical Application, Amer. Jour. Med. Sci., July, 1910.

The Principles and Technic of the Wassermann and Noguchi Reactions and their Comparative Value to the Clinician, Amer. Jour. Med. Sci., January, 1910.

The Practical Value of the Wassermann Test, Med. Rec., June, 15, 1912.

Neurological Serology, Jour. Nerv. and Mental Dis., June, 1911.

The Laboratory Findings in Neurological Manifestations, N. Y. Med. Jour., July 22, 1911.

The Wassermann Test: Some Factors of Non-specific Inhibition, N. Y. Med. Jour., Sept. 7, 1912.

Concerning the Restoration of Inhibitory Qualities in Liver Extracts, Med. Rec., Nov. 19, 1912.

Approximate Estimation of Protein (Globulin?) in the Cerebrospinal Fluid, Med. Rec., Dec. 31, 1912.

The Wassermann Fast Tabes, Jour. Amer Med. Assoc., Dec. 20, 1913.

Kaplan, D. M.:

A Quantitative Chemical Reaction for the Control of Positive Wassermann Results, N. Y. Med. Jour., June 7, 1913.

The Laboratory Differentiation Between General Paresis and Cerebrospinal Syphilis and the Serology of Spinal Cord Tumors, Amer. Jour. of Insan., October, 1912.

Amino (NH_2) Nitrogen Content of Syphilitic and Non-syphilitic Sera, N. Y. Med. Jour., July 26, 1913, 2d communication.

The Importance of Serological Analyses in Neurology, N. Y. Med. Jour., Aug., 16, 1913.

Kaplan and Casamajor, L.: The Neuroserological Findings in Tabes, Cerebrospinal Syphilis, General Paresis, and Other Nervous and Mental Diseases, Archives of Internal Med., Feb., 1912.

Kaplan and McClelland:

A Quantitatlve Chemical Reaction for the Control of Positive Wassermann Reactions, Nov. 22, 1913, 3d communication.

The Precipitation of Colloidal Gold, Jour. Amer. Med. Assoc., Feb. 14, 1914.

Karpas, M.:

Clinical Significance of the Cerebrospinal Fluid in Nervous and Mental Diseases, Jour. Amer. Med. Assoc., July 26, 1913.

The Significance of the Wassermann Reaction for Psychiatry, Bellevue Hosp. Bull., N. Y., 1911.

The Clinical Interpretations of the Serological Content of the Blood and Cerebrospinal Fluid, with Some Reference to the Cytology and Chemistry of the Latter in Mental Diseases, Amer. Jour. of Insan., 1912, vol. lxix.

Kensington: On Rhythmical Variations in the Cerebrospinal Pressure, Brit. Med. Jour., 1906, 553.

Klein, Bernhard: The Practice of the Wassermann Reaction from the Quantitative Standpoint, Lancet, 1910, 1255.

Koplik, H.: Meningitis of the Epidemic Type in Children Below Two Years of Age, Jour. Amer. Med. Assoc., June 17, 1913.

Kramer:

The Circulation of the Cerebrospinal Fluid and its Bearing on the Pathogenesis of Poliomyelitic Disease, N. Y. Med. Jour., 1912, 1532.

Cerebrospinal Fluid in General Paresis, Amer. Jour. of Insan., 1903–04.

GERMAN LITERATURE

Kaemmerer, Hugo: Diagnostische Intrakutanreaktion mit Spirochaetenextrakt, Münch. med. Woch., 1912, 1534.

Kafka:

Ueber die klinische Bedeutung der Komplementbindungsreaktion im Liquor cerebrospinalis, speciell bei der progressiven Paralyse, Monatschr. f. Psych. u. Neurol., 1909, vol. xxiv.

Kafka:

Ueber Technik und Bedeutung der cytologischen Untersuchung des Liquor cerebrospinalis, Monatschr. f. Psych. u. Neurol., 1910, vol. xxvii.

Zur Frage der Permeabilitaet der Meningen, Med. Klin., 1910, 5, 2.

Ueber die Polynucleose im Liquor cerebrospinalis bei der progressiven Paralyse, Zeitschr. f. d. ges. Neurol. u. Psych., 1910, 648.

Beiträge zur Pathologie des Liquor cerebrospinalis, Zeitschr. f. d. ges. Neurol. u. Psych., 1910, 117.

Ueber cytolyse im Liquor cerebrospinalis, Ibid., 1911, 252.

Ueber die Bedingungen und die praktische und theoretische Bedeutung des Vorkommens Hammelblutloesender Normalamboceptoren und des Komplements im Liquor cerebrospinalis, Zeitschr. f. d. ges. Neurol. u. Psych., 1912, vol. ix.

Ueber die Fermente des Liquor cerebrospinalis, Neurol. Centralb., 1912, No. 10.

Zur Biologie des Liquor cerebrospinalis; Ueber die Fermente des Liquor C. S. mit besonderer Beruecksichtigung der Psychosen, Mittheilungen aus den Hamburger Staatskrankenanstalten, 1912, 47.

Ueber Entstehung, Circulation und Funktion des Liquor cerebrospinalis, Vortrag gehalten bei Jahresversammlung des deutchen Vereins f. Psychiatrie zu Kiel, May 30, 1912.

Kalb, Richard: Ueber die Einwirkung des Ehrlichschen Arsenobenzols auf die Lues der Kinder mit besonderer Beruecksichtigung der Syphilis congenita, Wien. klin. Woch., 1910, 1378.

Kaplan, D. M.: Analyse der Spinalfluessigkeit und des Blutserums in ihrer Bedeutung fuer die Neurologie., Deut. med. Woch., 1913, No. 22.

Kauffmann:

Das Cholin des Liquor cerebrospinalis, Neurol. Centralbl., 1908, 6, p. 260. Answer to Donath, Ibid., 1908, No. 20.

Ueber das Vorkommen von Cholin in pathologischer Lumbalfluessigkeit, Zeitschr. f. phys. Chem., June, 1910, p. 343.

Kauffmann and Vorlaender: Ueber Nachweis des Cholins, Dissert., Halle, 1909.

Kellner, Clemenz, Brueckner, and Rautenberg: W. R. bei Idiotie, Deut. med. Woch., 1909, No. 42.

Kiralfy, Geza: Zur Frage des Zusammenhanges zwischen W. R. und Antiluetischer Behandlung, Wien. klin. Woch., 1910, xxiii, 162.

Kiss, J.: Experimentelle Beiträge zur Erklaerung der W. R., Zeitschr. f. Immunitaetsf., 1909, vol. iv.

Klausner, E.:

Vorläufige Mitteilung ueber eine Methode der Serodiagnostik bei Lues, Wien. klin. Woch., 1908, xxi, p. 214.

Ueber eine Methode der Serodiagnostik bei Lues, Ibid., p. 363.

Klausner, E.: Klinische Erfahrungen ueber das Praecipitationsphaenomen mit destillirtem Wasser im Serum Syphilitischer, Wien. klin. Woch., p. 940.

Kleischmidt:

Ueber die Sternsche Modifikation der W. R., Zeitschrift für Immunitaetsforschung, 1909, p. 512.

Bildung Komplementbindender Antikoerper durch Lipoidkoerper, Berl. klin. Woch., 1909, 57.

Klieneberger:

Zur Erweiterung der Wassermannschen Methode, Monatschr. für Psychiatrie, 1912, vol. xxxii, p. 76.

Ein eigenthuemlicher Liquorbefund bei Rueckenmarkstumoren (Xanthochromie, Fibringerinnung, und Zellvermehrung der cerebrospinalfluessigkeit), Monatschr. f. Psych. u. Neurol., 1910, vol. xxviii.

Zur differentialdiagnostischen Bedeutung der Lumbalpunktion und der serodiagnostik, Arch. f. Psych. u. Nervenkrankheiten, 1911, vol. xlviii.

Knopfelmacher and Lehndorff:

Komplementablenkung bei Muettern hereditaer luetischer Saueglinge, Wien. med. Woch., 1908, p. 813.

Komplementfixation bei Muettern heredo-syphilitischer Saueglinge (Zweite Mitteilung), Med. Klin., 1908, 1182.

Hydrocephalus chronicus internus congenitus und Lues, Ibid., 1908, 1863.

Die Untersuchungen heredo-luetischer Kinder Mittels der W. R., Wien. med. Woch., 1909, 2230.

Das Colle'sche Gesetz, Med. Klin., 1909, 1506.

Das Colle'sche Gesetz und die neuen Syphilisforschungen, Jahrbuch f. Kinderheilk., 1910, 156.

Koenig: Warum ist die Hecht'sche Modifikation der Wassermannschen Lues-reaktion dieser und der Stern'schen Modifikation vorzuzienen? Wien. klin. Woch., 1909, 1127.

Kopp, C.:

Ueber die Bedeutung der W. R. Serodiagnose der Syphilis fuer die Praxis, Münch. med. Woch., 1909, 1184.

Zur Frage der praktischen Bedeutung der Sero-diagnose der Syphilis, Münch. med. Woch., 1910, 1126.

Krefting:

Leichensera und die Wassermannsche Syphilisreaktion, Deut. med. Woch., 1910, 356.

Aorteninsiffizience und die Wassermannsche Luesreaktion, Berl. klin. Woch., 1910, 713.

Kretschmer: Lymphocytose des Liquor cerebrospinalis bei Lues hereditaria tarda, Deut. med. Woch., 1907, No. 46.

Kroenig:

Ueber Lumbalpunktion bei Eklampsie, Centralb. f. Gynaekol., 1904, 1153.

Kroenig: Ueber die diagnostische Bedeutung gewisser histologischer und physikalischer durch die Lumbalpunktion gewonnener Befunde, Ref. in Wien. med. Blaetter, 1899, vol. xxv.

Kromayer: Theoretische und praktische Erwaegungen ueber Ehrlich-Hata 606, Berl. klin. Woch., 1910, 1585.

Kroner: Wassermannsche Serodiagnostik bei Lues, Berl. klin. Woch., 1908, 149.

Kronfeld, A.: Beiträge zum Studium der W. R. und ihre diagnostischen Anwendung in der Psychiatrie, Zeitschr. f. d. Ges. Neurol. u. Psych., 1910, 376.

Kutner: Ueber den diagnostischen Wert der Lumbalpunktion in der Psychiatrie, Monatschr. f. Psych. u. Neurol., 1906, p. 540.

L

ENGLISH LITERATURE

Litterer: Serodiagnosis of Syphilis, Jour. Amer. Med. Assoc., 1909, 1537.

Livingood: Epidemic Cerebrospinal Meningitis, Bull. Johns Hopkins Hosp., No. 273.

Louria, Leon: The Diagnostic and Therapeutic Value of Lumbar Puncture, Med. Rec., Nov. 12, 1912.

GERMAN LITERATURE

Landau and Halpern: Beiträge zur Chemie der Cerebrospinalfluessigkeit, Biochem. Zeitschr., 1908, No. 9.

Landsteiner and Mueller: Zur Frage der Komplementbindungsreaktionen bei Syphilis, Münch. klin. Woch., 1907, No. 50, p. 1565.

Landsteiner and Stankoviz: Ueber die Bindung von Komplement durch suspendierte und kolloid-geloeste Substancen, Centralb. f. Bakt., Orig. I., 1906, Heft 4.

Landsteiner, Mueller, and Poetzl: Zur Frage der Komplementbindungsreaktion bei Syphilis, Wien. klin. Woch., 1907, 1565.

Lange, Carl:

Ergebnisse der W. R. bei Vorbehandlung der Sera mit Bariumsulphate nach Wechselmann, Deut. med. Woch., 1910, 217.

Zur Kenntniss der W. R. insbesondere bei mit Ehrlichs 606 behandelten Luesfaellen, Berl. klin. Woch., 1910, 656.

Die Ausflokkung kolloidalen Goldes durch Cerebrospinalfluessigkeit bei syphilitischen Affectionen des Centralnervensystems, Zeitschr. f. Chemotherapie, 1912, No. 1.

Langstein: Zur Kenntnis der Cerebrospinalfluessigkeit in einem Fall chronischer Hydrocephalie, Jahrb. f. Kinderheilk., 1903, p. 924.

Lateiner: Das Verhalten des Reduxionsindex nach E. Mayerhofer in der normalen und pathologischen Cerebrospinalfluessigkeit, Wien. klin. Woch., 1911, No. 22.

Ledermann:
Ueber den praktischen Wert der Serodiagnostik der Syphilis, Deut. med. Woch., 1908, p. 1760.
Ueber Beziehungen der Syphilis zu Nerven und anderen inneren Erkrankungen auf Grund von 573 serologischen Untersuchungen, Berl. klin. Woch., 1910, 1787.
Ledermann and Reinhold: Ueber die Bedeutung der Wassermannschen Serumreaktion fuer die Diagnostik und Behandlung der Syphilis, Med. klin., 1909, 419.
Leede: Bakteriologische Untersuchungen des Liquor cerebrospinalis bei Diphtherie, Zeitschr. f. Hygiene, 1911, p. 79.
Lehndorf and Baumgarten: Zur Chemie der Cerebrospinalfluessigkeit, Zeitschr. f. experim. Pathol. u. Ther., 1907, p. 330.
Lenhartz:
Ueber den diagnostischen und therapeutischen Wert der Lumbalpunktion, Münch. med. Woch., 1896, Nos. 8, 9.
Weitere Erfahrungen mit der Lumbalpunktion, Therapeut. Monat., 98, 437.
Lesser, Fritz:
Tabes und Paralyse im Lichte der neueren Syphilisforschung, Berl. klin. Woch., 1908, No. 39.
Zu welchen Schluessen berechtigt die W. R.? Med. klin., 1908, 299.
Weitere Ergebnisse der Serodiagnostik der Syphilis, Deut. med. Woch., 1909, 379.
Zur Technik und zum Wesen der W. R., Berl. klin. Woch., 1909, 974.
Die verschiedenen Modifikationen der W. R. und ihre Bewertung, Dermat. Zeitschr,, 1910, 504.
Lewandowsky: Zur Lehre von der Cerebrospinalfluessigkeit, Zeitschr. f. klin. Med., 1900, No. 40, p. 480.
Lewkowicz: Zur Aetiologie der Cerebrospinalmeningitis und zur Bedeutung der Lumbalpunktion, Przglad lekarski, 1900, 48–52.
Liebscher: Die cytologische und chemische Untersuchungen des Liquor cerebrospinalis bei Geisteskranken, insbesonderheit bei progressiver Paralyse, Wien. med. Woch., 1906, 2209.
Liefmann: Ueber den Mechanismus der Seroreaktion der Lues, Münch. med. Woch., 1909, 2097.
Lippmann, H.:
Ueber die Beziehungen der Idiotie zur Syphilis, Deut. Zeitschr. f. Nervenheilk., 1910, 81.
Ueber den Zusammenhang von Idiotie und Syphilis, Münch. med. Woch., 1909, No. 47, p. 2417.
Lockemann: Nachweis von Fleischmilchsauere im Blut, Urin, und Cerebrospinalfluessigkeit, Münch. med. Woch., 1906, No. 7.
Loehlein, M.:
Die Luesreaktion an der Leiche, Vortschritte der Med., 1909, No. 3.

Loehlein, M.:
Zur Frage der Verwertbarkeit der Wassermannschen Syphilisreaktion an der Leiche, Folia Sero., 1910, 227
Ueber die Seroreaktion auf Syphilis nach Wassermann, Fortschr. der Med., 1909, vol. xxvii, p. 97.

FRENCH LITERATURE

Labuze: Des réactions méningées dans les polynévrites, Thèse de Montpellier, No. 113.
Laignel, Lavastine, and Lasausse: Sur l'analyse chimique du liquide C. R. des paralytiques généreaux, Compt. rend. de la Soc. de Biol., 1910, vol. lxviii.
Lair: Méningite cérébro-spinale; Diagnostic et Pronostic, Thèse de Paris, No. 546.
Landowski and Claret: Polynucléose rachidienne dans 3 cas de méningite tuberculeuse, Archives générales de Medicine, Aug., 1907, p. 584; Progres méd., 1908, p. 245.
Lannois, Lesieur, and Gauthier: Action du liquide C. R. sur quelques bactéries pathogènes, C. R. de la Soc. de Biol., July, 1908, vol. lxv.
Lapersonne: Lymphocytose rachidienne et affections oculaires, Arch. d'ophthalmol., 1903, p. 337.
Laruelle:
Pression rachidienne, Ier. Congrès belge de Neurologie Liège, 1905.
Ponction lombaire et cytodiagnostic. Importance de la numeration, Jour. de Neurol., 1906, p. 576.
Lassaigne: Note sur la composition du liquide qui se trouve dans le canal rachidien, Annales de chimie et de physique, 1826; Jour. de chimie méd., vol. iv, 1828.
Laubry and Paru: La réaction de Wassermann au cours de quelquse affections cardio-vasculaires, C. R. de la Soc. de Biol., 1909, lxvii, p. 48.
Launois and Boulud: Sur la teneur en sucre du liquide C. R., Rev. Neurol., May, 1904.
Launois and Leroux: Imperméabilité méningée au mercure, au cours du traitement hydrargyrique prolongé, C. R. de la Soc. de Biol., 1902, vol. lxiv, p. 1482.
Laval: Méningite typhique, Thèse de Paris, 1903.
Legry and Duvoir: Réaction méningée au cours de 2 cas d'intoxication par l'oxyde de carbone, Soc. méd. des Hôp., Dec. 18, 1908.
Leitao d'Acunha and Vianna: Contribution à la cytologie du liquide C. R. dans les affections nerveux et mentales, Ann. méd. Psychol., 1909, 39.
Lepine, J.:
Le liquide C. R. dans le processus méningés subaigues d'origine rheumatismale, Lyon méd., Aug. 23, 1903.
A propos de la méningite spinale du tabès, Lyon méd., 1905, p. 981.
Existe-il une méningite urémique? Sem. méd., July 31, 1908.

Leri:

Sur le liquide C. R. et spécialement la perméabilité des méninges dans la méningite tuberculeuse, Arch. de Méd. des Enfants, 1902, vol. vi, p. 449.

Etude cytologique et cryoscopique. Perméabilité dans les méningites, C. R. de la Soc. de Biol., July, 1901.

Lesieur: Cytologie et virulence du liquide C. R. chez les rabiques, C. R. de la Soc. de Biol., vol. lvii, p. 615.

Letulle, Lagane, and Vincent: Precipito-diagnostic de la méningite cérebro-spinale, C. R. de la Soc. de Biol., May 15, 1909, p. 758.

Levaditi and Marie: Action de liquide C. R. de paralytiques généreaux sur le virus syphilitiques, C. R. de la Soc. de Biol., May, 1907; Sem. méd., 1907, No. 21.

Levaditi and Yamanouchi:

La sérodiagnostic de la syphilis, C. R. de la Soc. de Biol., 1907, vol. lxiii, 740.

Diagnostic de la syphilis et de la paralysie générale, C. R. de la Soc. de Biol., 1908, lxiv, 27, 349.

Levaditi, Laroche, and Yamanouchi: Le diagnostic précoce de la syphilis par la methode de Wassermann, C. R. de la Soc. de Biol., 1908, 745.

Levaditi, Ravaut, and Yamanouchi: Localisation nerveuse de la syphilis et proprietes du liquide C. R., C. R. de la Soc. de Biol., 1908, vol. lxiv.

Loederich: Leucocytose C. R. tardive dans un cas de méningite tuberculeuse, Gaz. des. Hôp., 1908, 897.

Lutier: Le nouveaux procédés d'investigations dans le diagnostic de méningite tuberculeuse, Thèse de Paris, July 16, 1903.

M

ENGLISH LITERATURE

MacCambpell: Studies On the Clinical Diagnosis of General Paralysis of the Insane, Jour. Med. Research, 1910, No. 20.

McDonagh, J. E. R.:

Wassermann's Reaction from a Practical Point of View, Lancet, 1910, 920.

Salvarsan in Syphilis and Allied Diseases, Oxford Med. Publications, London, 1912.

McIntosh: The Serodiagnosis of Syphilis, Lancet, 1909, p. 1515.

M'Intosh, J.: Observations on the Wassermann Reaction, with Special Reference to the Influence of Specific Treatment Upon It, Zeitschr. f. Immunitaets., 1910, p. 76.

M'Kenzie: The Serum Diagnosis of Syphilis, Jour. Path. and Bact., 1909, 311.

Morse: The Value of Lumbar Puncture and of the Leukocyte Count in the Diagnos isof Acute Poliomyelitis (Infantile Paralysis), Arch. of Pediat., 1911, No. 28, p. 164.

Morton: Biochemical Examination of the Cerebrospinal Fluid in Cases of Mental Disease, Jour. of Mental Sci., 1911, vol. lvii.

Mott:

Oliver-Sharpey Lectures on the Cerebrospinal Fluid, Lancet, 1910, p. 179, No. 2.

The Cerebrospinal Fluid, Lancet, July 2 and 9, 1904.

The Morrison Lectures on the Pathology of Syphilis of the Nervous System in the Light of Modern Research, Arch. of Neurol. and Psych., 1909, vol. iv.

A Lecture on the Cerebrospinal Fluid in Relation to Diseases of the Nervous System, Brit. Med. Jour., 1904.

The Diagnosis of Syphilitic Diseases of the Nervous System, Brit. Med. Jour., 1909, p. 1403.

Mott and Halliburton:

On the Physiological Action of Cholin and Neurin, Philosophical Trans. of the Royal Soc. of London, 1899, vol. cxci.

The Chemistry of Nerve Degeneration, Lancet, April 13, 1901.

Muir, R.: Studies on Immunity, London, 1909.

Muirhead:

The Occurrence of Organisms in the Blood and the Cerebrospinal Fluid in Mental Diseases, Jour. Ment. Sci., 1910, 232.

The Wassermann Reaction in the Blood and Cerebrospinal Fluid and the Examination of Cerebrospinal Fluid in General Paralysis and Other Forms of Insanity, Jour. Ment. Sci., 1910, 649.

The Wassermann Reaction in the Blood and Cerebrospinal Fluid in Insanity and Examination of the Spinal Fluid, Lancet, 1911, 515.

Myers: Cerebrospinal Fluid in Certain Forms of Insanity with Special References to the Potassium Content, Jour. of Biol. Chem., Baltimore, May, 1909.

GERMAN LITERATURE

Mansfeld, G.: Ueber den Donatschen Nachweis von Cholin in Faellen von Epilepsie, Hoppe-Seyler, Zeitschr. f. phys. Chem., 1904, vol. xlii.

Margulies: Ueber die Aktivitaet des Liquor cerebrospinalis, Monatschr. f. Psych. und Neurol., 1912, No. 31.

Marschalko, Janco, and Csiki: Der klinische Wert der Wassermannschen Syphilisreaktion, Arch. f. Dermat. und Syphil., 1910, vol. ci.

Maslakowich and Liebermann:

Theorie und Technik der Reaktion von Wassermann und die diagnostische Bedeutung derselben, Zentralb. f. Bakt., 1908, 378.

Zur Technik der W. R., Zeitschr. f. Immunitaetsf., 1909, 564.

Mayerhofer:
Zur Charakteristik und Differentialdiagnose des Liquor cerebrospinalis, Wien. klin. Woch., 1910, p. 651.
Kritische Bemerkungen zur Arbeit von G. Simon ueber meine Methode der Permanganattitration des Liquor cerebrospinalis, Wien klin. Woch., 1911.
Mayerhofer and Neubauer: Ueber Meningitis tuberculosa und Meningitis serosa, Ergebnisse der Permanganattitration des Liquor cerebrospinalis, Zeitschr. f. Kinderheilk., 1912, vol. iii.
Medizinische Klinik: Umfrage ueber die Wirkung des Ehrlichschen Arsenobenzols bei Syphilis, 1910, 1451, 1500, 1533, 1573, 1614, 1702, 1782.
Meier, George:
Technik und klinische Bedeutung der W. R. auf Syphilis, Berl. klin. Woch., 1907, 1636.
Scharlach und Serodiagnostik auf Syphilis, Med. klin., 1908, 1383.
Serologische Untersuchungen bei Lepra, Mitteilungen und Verhandlungen der zweiten Internat. wissenschaftlichen Leprakonferenz, 1909, 334.
Ueber Komplementbindung mit besonderer Beruecksichtigung ihrer praktischen Anwendung (zweiter Teil), Weichardt's Jahresbericht ueber die Ergebnisse der Immunitaetsforschung, 1909, Abt. i, 140–272.
Meirowsky:
Ueber die von Bauer vorgeschlagene Technik der Wassermann-Neisser-Bruckschen Reaktion, Berl. klin. Woch., 1909, 152.
Ueber die von M. Stern vorgeschlagene Modifikation der W. N. B. Reaktion, Berl. klin. Woch., 1909, 1310.
Ueber paradoxe Erscheinungen bei der W. R., Med. klin., 1910, 947.
Die Einwirkung des Ehrlichschen Mittels auf den syphilitischen Prozess, Ibid., 1910, 1653.
Merzbacher:
Ergebnisse der Untersuchung des Liquor cerebrospinalis, Neurol. Centralbl., 1903, 548.
Die Beziehung der Syphilis zur Lymphocytose der Cerebrospinalfluessigkeit und zur Lehre von der meningitischen Reizung, Centralblatt für Neurologie, No. 212, 1906.
Meyer, E.:
Utersuchungen des Liquor cerebrospinalis bei Geistes und Nervenkranken, Arch. f. Psych., 1907, p. 971.
Zur Untersuchung des Liquor cerebrospinalis, Neur. Centralb., 1909, 402.
Meyer, L.: Einige Beiträge zur Theorie und Technik der W. R. und zur Wertbemessung der gepruefteN Seren, Berl. klin. Woch., 1909, 829.

Michaelis, L.:
Die Wassermannsche Syphilisreaktion, Berl. klin. Woch., 1907, 1103.
110 Faelle von Syphilis, behandelt nach Ehrlich-Hata, Berl. klin. Woch., 1910, 1195.
Michaelis and Lesser: Erfahrungen mit der Serodiagnostik der Syphilis, Berl. klin. Woch., 1908, 301.
Mohr: Zur Pathologie des Liquor cerebrospinalis, Deut. Zeitschr. f. Nervenheilk., 1912, p. 417.
Morgenroth and Stertz: Ueber den Nachweis syphilitischer Antikoerper im Liquor cerebrospinalis von Paralytikern nach dem Wassermann Plautschen Verfahren der Komplementablenkung, Virch. Arch. f. path. Anat., 1907, vol. clxxxvii, p. 166.
Much:
Eine Studie ueber sogenannte Komplementbindungsreaktion, mit besonderer Beruecksichtigung der Lues, Med. klin., 1908, 1067, 1117.
Nachpruefungen der Resultate der W. R., Deut. med. Woch., 1909, 606.
Die praktische Brauchbarkeit der W. R., Münch. med. Woch., 1909.
Psychiatrie und Serologie, Berl. klin. Woch., 1910, 1492.
Much and Eichelberg: Die Komplementbindung mit waessrigem Luesextrakt bei nichtsyphilitischen Krankheiten, Med. klin., 1908, 671.
Muehlens, P.: Ueber Zuechtungsversuche der Spirochaeta pallida und Sp. refringens, sowie Tierversuche mit den kultivierten Spirochaeten, Klin. Jahrbuch, 1910, 339.
Muehsam: Klinische Leistungsfaehigkeit der Serodiagnostik bei Lues, Berl. klin. Woch., 1908, xlv.
Mueller, R.: Zur Verwertbarkeit und Bedeutung der Komplementbindungsreaktion fuer die Diagnose der Syphilis, Wien. klin. Woch., 1908, 382.
Muelzer, P.:
Praktische Anleitung zur Syphilisdiagnose auf biologischem Wege (Spirochaetennachweis, W. R.), Berlin, J. Springer, 1910.
Zur Technik und praktischen Verwertung der W. R., Zeitschr. f. Immunitaetsf., 1910, 236.
Muelzer and Michaelis: Hereditaere Lues und W. R., Berl. klin. Woch., 1910, 1402.
Muir, R.: Ueber die Hitzbestaendigkeit der Blutkoerperchenreceptoren, Biochem. Zeitschr., 1909, p. 510.

FRENCH LITERATURE

Magendie:
Mémoire sur un liquide qui se trouve dans le crâne et la colonne vertébrale de l'homme et des animaux mammifères, C. R. Acad. des Sci., Jan. 10, 1825; 2 e mémoire in Jour. de physiol. expérim. et pathol., Jan., 1827.

Magendie: Recherches physiologiques sur le liquide C. R., Paris, 1842.

Maillard: De la valeur clinique du cytodiagnostic C. R. dans les cas douteux de la paralyse générale progressive, Thèse de Bordeaux, 1901.

Maillet: Les formes frustes et larvées des méningites cérébrospinales aiguës, les réactions méningées, Thèse de Montpellier, Feb. 19, 1910.

Mancini: Pouvoir mydriatique du liquide C. R. dans un cas d'urémie aiguë, Revista critica clinica med., vol. x, p. 387.

Manicatide: Diagnostic bactériologique de la méningite tuberculeuse, C. R. de la Soc. de Biol., 1903, p. 523.

Marchand, L: Dosage d'albumine dans quelques maladies mentales et spécialement la Paral. gen., Rev. de Psych. et de Pathol. Exper., 1903, p. 196.

Margarot: Zona et Méningite, Thèse de Montpellier, 1910, No. 102.

Marie, A.: Du serodiagnostic en psychiatrie, Rev. de psych., Oct., 1908.

Marie and Crouzon: Quelque résultate du cytodiagnostic du liquide C. R., Revue Neurol., 1903, 339.

Marie and Levaditi:

La réaction des anticorps syphilitiques dans la paralysie générale et le tabés, Bull. et mem. de la Soc. méd. des Hôp., Dec. 21, 1906.

Les anticorps syphilitiques dans le liquide C. R. des paralytiques genereaux et des tabétiques, Ann. Inst. Pasteur, 1907, 673.

Marie and Violet: L'albumodiagnostic dans les maladies mentales, Congrès de Rennes, Aug., 1905.

Marie and Yamanouchi:

La réaction de Wassermann dans la paralysie générale, C. R. de la Soc. de Biol., vol. lxvi, 1908, 169.

Réaction hemolytique comparée du serum et du liquide des alienes paralytiques, Soc. méd. des Hôp., Feb. 20, 1908.

Marie, Levaditi, and Bankowski:

Presence du treponema pallidum dans trois cerveaux des paralytiques generaux, Bull. et Mem. des Hôp. de Paris, 1913, 881.

Presence du treponema pallidum dans les cerveraux des paralytiques generaux, C. R. Soc. Biol., 1913, 794, lxxiv.

Presence constante du treponema pallidum dans les cerveaux des paralitiques generaux morts en ictus, Ibid., 1009.

Marinesco: Sur le diagnostic de la paralysie générale et du tabès par les nouvelles méthodes, C. R. de la Soc. de Biol., 1909, vol. lxvi.

Marinesco and Goldstein: Deux cas de pseudo-tumeur cérébrale; méningite séreuse et hydrocéphalie acquise, Nouv. iconograph. de la Salpétriere, 1912, vol. xxv.

Marinesco and Minea:

Presence du treponema pallidum dans un cas de meningite syphilitique associee a la paralysie generale et dans la paralysie generale, Bull. De l'Acad. de med. Paris, 1913, lxix, 3^{e}, Ser. 235.

Marinesco and Minea:
A propos de la presence du treponema pallidum dans le cerveaux de paralytiques generaux, Rev. Neurol., 1913, xxi, 581.
Relation entre les treponema pallidum et les lesions de la paralysie generale, C. R. Soc. de Biol., 1913, lxxv, 231.
Mathieu:
Chromodiagnostic du liquide C. R., Thèse de Paris, 1901, No. 456.
Contribution à l'étude de la ponction lombaire dans les différents processus méningés, Thèse de Lyon, 1904, No. 101.
Mauriac, P.:
La séroreaction de Wassermann, C. R. Soc. Biol., 1909, 666.
Conclusions fournies par 300 cas de séro-réactions de Wassermann, C. R. Soc. Biol., 1909, 668.
Mery: L'examen du Liquide C. R. et le diagnostic dans les méningites, Bull. med., 1902, 458, No. 39.
Mestrezat:
Analyses chimique de liquide C. R. In Anglada, Thèse de Montpellier. (See Anglada, 1909.)
Contribution à l'étude chimique du liquide C. R. Remarques sur la nature du principe reducteur, Jour. de phys. et Path. générale, May, 1909, 408.
Analuse du liquide C. R. dans la méningite cérébrospinale à méningocoques. Composition et formule chimique; valeur diagnostiqueet pronostique de cette formule, Rev. de méd., 1910, 189.
Composition chimique du liquide C. R. normal. Vrais nature de cette humeure, Bull. de la Soc. chimique, 1911, 683.
Le liquide céphalo-rachidien normal et pathologique; valeur clinique de l'examen chimique. Syndrômes humoraux dans les diverses affections, Paris, 1912, A. Maloine.
Mestrezat and Anglada: Xanthochrômie du liquide C. R. dans un cas d'ictére par retention avec urôbilin et hyperglycose. Passage tardif des pigments biliaires dans ce liquide, Compt. rend. de la Soc. de Biol., 1909, vol. lxvi.
Mestrezat and Gaujoux:
Analyses du liquide C. R. dans la méningite cérébrospinale à méningocoques, C. R. de la Soc. de Biol., 1909, 364.
Présence de nitrates et de nitrites dans le liquide C. R. Perméabilité méningee aux nitrates, Ibid., 1909, 424.
Contribution à l'étude du liquide C. R. dans la méningite tuberceleuse. Essai d'établissement d'une formule chimique, Rev. neurol., 1909, 733.
Exagération de la perméabilité méningée aux nitrates; diagnostic de la méningite tuberculeuse, C. R. de la Soc. de Biol., 1909, 533.
Mestrezat and Roger, H.:
Syndrôme de coagulation massive, de xanthochrómie et d'hematoleucocytose du liquide C. R., Compt. rend. de la Soc. de Biol., June 7, 1909.

Mestrezat and Roger, H.: A propos du syndrôme de coagulation massive et de xanthochromie du liquide C. R. Eassi de pathogénie. Veural diagnostique, Gaz. des Hôp., No. 120, p. 1495, October 21, 1909.

Mignon: La rhinorrhee cérébro-spinale, Presse Méd., April 26, 1900.

Milian:

Le liquide C. R., Steinheil, Paris, 1904.

Le liquide C. R. hémorragique, Gaz. hebdom. de méd. et de chir., Aug. 7, 1902,

Le liquide C. R. des tabétiques, Soc. franc. de dermat. et de syphilographie, April, 1903.

La reaction de Herxheimer, Paris Medical, Nov. 15, 1913.

Milian and Chiray: Xanthochromie du liquide C. R., Bull. de la Soc. Anat., June 6, 1902.

Milliet: De la valeur diagnostique de la ponction lombaire dans les hémorragies du Nevraxe, Thèse de Paris, No. 397, 1901–02.

Moindrot: De la ponction lombaire dans les tumeurs cérébrales, Thèse de Lyon, No. 164, 1904.

Moizard and Grenet: La forme cérébro-spinale de la fièvre typhoide, Archives de médicine des enfants, 1903, No. 1.

Mollard and Froment: Urée dans le liquide C. R. et urémie nerveuse, Jour. de phys. et de pathol. générale, 1909, vol. ii, 263.

Mongour:

Sur la teneur du liquide C. R. en pigments biliaires dans les ictères choluriques, C. R. Soc. Biol. Séance de Bordeaux, 1904, 397.

Ictère cholémique et acholurique: examen du liquide C. R., C. R. Soc. Biol., 1905, p. 518.

Monod, R.:

Réactions méningées chez l'enfant, Thèse de Paris, 1902, No. 77.

Les éléments figures du liquide C. R. aux cours de tabès et de la paralyse générale progressive, Bull. soc. méd. des Hôp. de Paris, Jan., 1901.

Montagnon: Significations de la réaction albumineuse dans le liquide C. R. dans la méningite des enfants, Rev. neur., 1906, 1039.

Mosny and Javal: Récherches et dósage des pigments biliaries dans le liquide C. R. des ictèriques, C. R. Soc. Biol., May 21, 1910.

Mosny and Molloisel: Saturnisme et lymphocytose rachidienne, C. R. de la Soc. de Biol., 1904, p. 211, vol. lvii.

Muttermilch: Sur la nature des substances qui provoquent la réaction de Wassermann dans les sérums des syphilitiques et des lapins trypanosomies, C. R. Soc. Biol., 1909, 125.

ITALIAN LITERATURE

Morselli: La reazione di Wassermann raffrontata nel liquido cefalorachidiano e nel sangue dei paralytici, Pathologica, 1911, 3, p. 387.

Mya: Sulla quantita del liquido C. R., etc., Revista di patologia nervosa e mentale, 1898, vol. iii, p. 385.

N

ENGLISH LITERATURE

Newmark: The Occurence of a Positive Wassermann Reaction in 2 Cases of Non-specific Tumor of the Central Nervous System, Jour. Amer. Med. Assoc., Jan. 6, 1912.

Nichols, Henry J.:

Preliminary Note on the Action of Ehrlich's Substance (606) on Spirochæta Pertenuis in Animals, Jour. Amer. Med. Assoc., 1910, 216.

The Present Status of Salvarsan Therapy in Syphilis, Ibid., 1912, 603.

Nichols and Fordyce: The Treatment of Syphilis with Ehrlich's 606, Ibid., 1910, 1171.

Nichols and Hough:

Demonstration of Spirochæta Pallida in the Cerebrospinal Fluid From a Patient with Nervous Relapse Following Upon the Use of Salvarsan, Jour. Amer. Med. Assoc., 1913, 108.

Positive Results Following the Inoculation of Rabbit with Paretic Brain Substance, Jour. Amer. Med. Assoc., 1913, 120.

Noguchi, H.:

The Relation of Protein, Lipoids, and Salts to the Wassermann Reaction, Jour. Exper. Med., 1909, xi, 84.

A New and Simple Method for the Serum Diagnosis of Syphilis, Jour. Exper. Med., 1909, xi, 392; also in C. R. Soc. Biol., 1909, 456, and in Münch. med. Woch., 1909, 494.

Serum Diagnosis of Syphilis, Jour. Amer. Med. Assoc., 1909, 934.

The Butyric Acid Reaction for Syphilis in Man and Monkeys, Proc. Soc. for Exper. Biol. Med., 1909, vi, 51.

Some Critical Considerations on the Serum Diagnosis of Syphilis, Ibid., 1909, vi, 77.

Non-fixability of Complement, Ibid., 1909, vii, 14.

On Non-specific Complement Fixation, Ibid., vii.

Thermostabile Anticomplementary Constituents of the Blood, Jour. Exper. Med., 1906, viii, 726.

The Luetin Reaction, Jour. Amer. Med. Assoc., Oct. 5, 1912.

Identification of the Spirochæta Pallida in Culture, Ibid.

The Present Status of the Noguchi System of Serodiagnosis of Syphilis, Interstate Med. Jour., 1911, St. Louis, Mo., Medical Symposium Series, No. 1.

Pure Cultivation of Pathogenic Treponema Pallidum, Jour. Amer. Med. Assoc., 1911, 102.

Experimental Research in Syphilis with Especial Reference to Spirochæta Pallida (Treponema Pallidum), Jour. Amer. Med. Assoc., 1912, 1163.

Morphological and Pathogenic Variations in Treponema Pallidum, Jour. Exper. Med., 1912, 90.

Noguchi, H.:
A Cutaneous Reaction in Syphilis, Jour. Exper. Med., 1911, 557.
The Transmission of Treponema Pallidum from the Brains of Paretics to the Rabbit, Jour. Amer. Med. Assoc., July, 12, 1913.
Transmission of Treponema Pallidum from the Brains of Paretics to the Rabbit, Jour. Amer. Med. Assoc., 1913, lxi, 85.
Noguchi and Bronfenbrenner:
Biochemical Studies on So-called Antigen, Jour. Exper. Med., 1911, xiii, 43.
The Comparative Merits of Various Complements and Amboceptors in the Serum Diagnosis of Syphilis, Ibid., p. 78.
Biochemical Studies on the Phenomena Known as Complement Splitting, Ibid, 1912, xvi.
Sublimate and Serum Diagnosis of Syphilis, Ibid., 1911, xiii.
Barium Sulphate Absorption and Serum Diagnosis of Syphilis, Ibid., 1911, xiii, 217.
Noguchi and Moore:
The Butyric Acid Test for Syphilis in the Diagnosis of Metasyphilitic and Other Nervous Disorders, Jour. Exper. Med., 1909, 604.
A Demonstration of the Treponema Pallidum in the Brain in Cases of General Paralysis, Jour. Exp. Med., 1913, 232.
Additional Studies on the Presence of Spirochæta Pallida in General Paralysis and Tabes Dorsalis, Jour. Cutan. Dis., 1913, xxxi, 543.
Nonne: Clinical Diagnosis of the Syphilogenous Diseases of the Central Nervous System, Jour. Amer. Med. Assoc., 1909, liii, p. 289.
Norman and Rosenberger: Purulent Cerebrospinal Meningitis Produced by Eberth's Bacillus in the Course of Typhiod, etc., Amer. Jour. Med. Sci., 1908, p. 240.

GERMAN LITERATURE

Nawratzki: Zur Kenntnis der Cerebrospinalfluessigkeit, Zeitschr. f. physiol. Chemie., 1897, 532.
Neisser, A.:
Ueber die Bedeutung der Wassermannschen Serodiagnostik für die Praxis, Münch. med. Woch., 1909, p. 1076.
Ueber das neue Ehrlichsche Mittel., Deut. med. Woch., 1910, 1212.
Forschung der Syphilis. Arbeit aus der kais, Gesundheitsamte, 1911, xxxvii.
Neisser and Kuznitsky: Bedeutung des Ehrlich-Hata 606 für die Syphilis Behandlung, Berl. klin. Woch., 1910, 1485.
Neisser and Siebert: Die Bedeutung und Wertung der serodiagnostischen Luesreaktion in der Praxis, Jahreskurse f. Aerztlige Fortbildung, April, 1910.

Neisser, Bruck, and Schucht: Diagnostische Gewebs und Blutuntersuchungen bei Syphilis, Deut. med. Woch., 1906, 1937.

Neüe: Ueber die "Auswertungsmethode" des Liquor cerebrospinalis vermittels der W. R., Münch. med. Woch., 1912, 121.

Nieden: Ueber Lumbalpunktion, insbesondere die Befunde bei Kachexie, Inaug. Dissert., Bonn, 1911.

Niedner and Mamelock:

Ueber die Cytodiagnose, Wien. med. Blaetter, 1905, 327.

Die Frage der Cytodiagnose, Zeitschr. f. klin. Med., 54, p. 132.

Nissl: Die Bedeutung der Lumbalpunktion fuer die Psychiatrie, Centralbl. f. Nervenheilk. u. Psych., 1904, 225.

Nobl:

Diagnostische Bedeutung der Cerebrospinalfluessigkeit bei Syphilis und den Parasyphilitischen Affektionen, Berl. klin. Woch., 1904, 37.

Cuti-Reaktion mit waesserigen und alkoholischen Extrakten, Arch. f. Dermatol., 1910, xcix, 434.

Nobl and Arzt: Zur Serodiagnostik der Syphilis (Porges-Meier und Klausnersche Reaktion), Wien. klin. Woch., 1908, p. 287.

Noble and Fluss: Zur Intrakutanreaktion bei Syphilis, Ibid., 1912, 475.

Noguchi, H.:

Ueber gewisse chemische komplementsubstanzen, Biochem. Zeitschr., 1907, vii, 327.

Ueber chemische Inaktivierung und Regeneration der Komplemente, Biochem. Zeitschr., 1907, vi, 172.

Die W. R. und der praktische Arzt., Münch. med. Woch., 1910, 1399.

Weitere Erfahrungen mit vereinfachter Methode der Serumdiagnose der Syphilis, Zeitschr. f. Immunitaetsforsch, 1910, vii, 353.

Die quantitative Seite der W. R. mit Bemerkungen ueber den Globulin und natuerlichen antihammel Amboceptorgehalt syphilitischer Sera, sowie ueber die angebliche Gefahr von Auftreten des Neisser-Sachs'schen Phaenomens beim Verwenden des antimenschlichen Amboceptors, Ibid., 1911, x.

Ueber die Gewinnung der Reinkulturen von pathogener Spirochaeta pallida und von Spir. pertenuis, Münch. med. Woch., 1911, 1550.

Hautallergie bei Syphilis, ihre diagnostische und prognostische Bedeutung, Münch. med. Woch., 1911, 2372.

Studien ueber den Nachweis der Spirochaeta pallida im Centralnervensystem bei progressiven Paralyse und bei Tabes dorsalis, Münch. med. Woch., 1913, lv, 737.

Nonne:

Die Diagnose der Syphilis bei Erkrankungen des Zentralnervensystems, Centralbl. f. Nervenheilk. u. Psych., 1908, p. 974.

Syphilis und Nervensystem, Berlin, 1909, 2d ed., p. 631.

Nonne:

Die Diagnose der Syphilis bei Erkrankungen des zentralen Nervensystems mit besonderer Beruecksichtigung: (*a*) der cytologischen und chemischen Ergebnisse der diagnostischen Lumbalpunktion; (*b*) der serodiagnostischen Untersuchungen am Blute und an der Lumbalfluessigkeit, speziell bei der Tabes und Paralyse, Deut. Zeitschr. f. Nervenh., 1908, p. 36.

Weitere Erfahrungen (Bestaetigungen und Modifikationen) ueber die Bedeutung der "Vier Reaktionen" (Pleocytose, Phase I, der W. R., im Blut-serum und im Liquor spinalis) fuer die Diagnose der syphilogenen Hirn und Rueckenmarks Krankheiten, Deut. Zeitschr. f. Nervenheilk., 1910, 38.

Ueber das Vorkommen von starker "Phase I Reaktion" bei fehlender Lymphocytose bei 6 Faellen von Rueckenmarkstumor, Ibid., 1910, p. 161.

Der heutige Standpunkt der Lehre von der Bedeutung der "Vier Reaktionen" fuer die Diagnose und differentialdiagnose organischer Nervenkrankheiten, Ibid., 1911, p. 201.

Ueber Wert und Bedeutung der modernen Syphilistherapie fuer die Behandlung von Erkrankungen des Nervensystems, Ibid., 1912, vol. xliii.

Klinische und anatomische Untersuchung eines Falles von isolierter Pupillenstarre ohne Syphilis bei Alkoholismus Chronicus gravis, Neurol. Centralblatt, 1912, No. 1.

Nonne and Apelt:

Ueber fraktionierte Eiweissausfaellung in der Spinalfluessigkeit von Gesunden, Luetikern, funktionell und organisch-Nervenkranken und ihre Verwertung zur Differentialdiagnose der Dermentia paralytica, Tabes dorsalis, tertiaeren, und abgelaufenen Syphilis, Arch. f. Psych. u. Nervenh., 1907, vol. xliii.

Ueber Lymphocytose und Globulinuntersuchung der Spinalfluessigkeit bei organische Nervenkrankheiten, Neurol. Centralbl., 1908, 181.

Nonne and Hauptmann: Liquor cerebrospinalis und W. R., Neurol. Centralbl., 1912, No. 2.

Nonne and Holzmann:

Weitere Erfahrungen ueber den Wert der neueren cytologischen, chemischen und biologischen Untersuchungsmethoden fuer die Differentialdiagnose der syphilogenen Erkrankungen des Zentralnervensystems, gesammelt an 295 neuen Faellen von organischen Erkrankungen des Hirns und des Rueckenmarks, Deut. Zeitschr. f. Nervenheilk., 1909, p. 195, vol. xxxvii.

Ueber W. R. im Liquor spinalis bei Tabes d. sowie ueber quantitative Auswertung von Staerkegraden der W. R. bei syphilogenen Erkrankungen des Zentralnervensystems, Monatschr. f. Psych. und Neurologie, 1910, p. 128.

FRENCH LITERATURE

Nageotte: Limite de la lymphocytose physiologique, C. R. Soc. Biol., Dec. 14, 1907.

Nageotte and Levi-Valensi: Numération directe des éleménts cellulaires du liquide C. R.: limites physiologiques de la lymphocytose, Comptes rend. de la. Soc. de Biol., 1907, 603.

Nageotte, Madam: Numération directe des éléments figures du liquide C. R., Soc. Pédiatr., April 25, 1911.

Nanu-Musell and Vasiliu: La réaction de Wassermann dans la malaria, Sem. méd., 1910, No. 6.

Netter: Formes méningitiques de la fièvre typhoide; leur frequence et leur importence pronostique. Utilite de la recherche du signe de Kernig. Charactères du liquide retiré par la ponction, Soc. méd. des Hôp., April 15, 1904.

Netter and Clerc: Hémorragie des méninges médullaires, reinseignements fournis par la ponction lombaire, Ibid., July 25, 1900.

Netter and Debre: Liquide C. R. au cours des méningites cérébro-spinales (première note) Liquide clairs pendant 23 premieres heures de la maladie, C. R. Soc. Biol., 1909, 866.

Netter and Gendron:

Liquide Céphalo-rachidiens limpides au cours de méningites cérébro-spinales (Deuxieme note) Liquide clairs a une periode avancée de la maladie, Ibid., 1909, p. 1009.

Troisième note. Liquide normaux dépourvus des microbes dans les formes attenues et abortives. Pouvoir agglutinant du sang vis a vis du méningocoque, Ibid., 1909, 1252.

Modifications consécutives a l'introduction du sérum humain dans le canal rachidien, Ibid., 1910, 550.

Nicholas, Favre, and Gautier: Intra-dermo-réaction et cuti-réaction avec la syphiline chez les syphilitiques, C. R. Soc. Biol., 1910, 257.

Nicloux: Perméabilité à l'alcool, C. R. Soc. Biol., 1900, p. 621.

Noguchi:

Decouverte du treponeme pale dans les cerveaux de paralytiques generaux, C. R. Soc. Biol., 1913, lxxiv, 349.

Sérodiagnostic de la syphilis, Traité sur le sang humain, Gilbert and Weinberg, Paris, 1912.

Norman: Méningite urémique, Loire Medicale, 1911.

ITALIAN LITERATURE

Nizzi: La reazione de Wassermann in rapporto a lesioni sperimentali della sostanza nervosa centrale, Rivista sperim. de freniatria, 1910, 36.

O

GERMAN LITERATURE

Ohm: Einiges ueber die diangostische Bedeutung des Blutgehaltes und der Lymphocytose im Liquor Cerebrospinalis. (Zugleich ein Beitrag zur Kasuistik der basalen Hirnaneurysmen), Deutsche med. Woch., 1906, p. 1694.

Opitz: Ueber die Bedeutung der W. R. fuer die Geburtshilfe, Med. Klin., 1908, p. 1137.

Oppenheim: Ueber Lecithinwirkung bei Syphilis, Wien. klin. Woch., 1908, 679.

Orgelmeister: Zum diagnostischen Wert der Lumbalpunktion, Deutsch. Arch. f. klin. Med., 1903, p. 142.

Orth: Ueber die Exsudatzellen im allgemeinen und die Exsudatzellen bei verschiedenen Formen der Meningitis im besonderen, Reference in Münch. med. Woch., 1906, No. 3.

Ossipow: Ueber die pathologische Veraenderungen welche in dem Zentralnervensystem von Thieren durch die Lumbalpunktion hervorgerufen werden, Deut. Zeitschr. f. Nervenheilk., 1902, vol. xix.

FRENCH LITERATURE

Obregia: La ponction cervicale, Compt. r. Soc. Biol., 1908, vol. lxiv.

Obregia and Bruckner:

Le liquide C. R. dans la paralyse générale stationaire soumise a la reaction de Wassermann, C. R. Soc. Biol., 1909, lxvi.

Résistance à la putrefaction de l'anticorps syphilitique, C. R. Soc. Biol., 1909, lxvi, p. 482.

Olmer and Tian:

Présence de Thalium dans le liquide C. R. après l'intoxication par l'acétate de Thalium, C. R. Soc. Biol., Dec. 15, 1908.

Perméabilité de méninges normales au salicylate de lithium, C. R. Soc. Biol., May 18, 1909.

ITALIAN LITERATURE

Orefici: Sul passaggio del bromo et del iodo nel liquido C. R. dei Bambini, VIth Congres de Pediatrie Italian, Oct., 1907.

Ormea: Sulle modificazioni della pressione sub-archnoidiana e del caratteri del liquido cerebro-spinale nell'epilessia sperimentale, Revista sperimentale di Freniatria, 1902, vol. xxviii, p. 40.

P

ENGLISH LITERATURE

Parkinson: Note on the Cerebrospinal Fluid in General Paralysis of the Insane, Archives of Neurology, 1909.

Peabody, W. F., George Draper, and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph of the Rockefeller Inst. for Med. Research, New York, 1912.

Pedersen, V. C.: Serodiagnosis of Syphilis, N. Y. Med. Jour., 1910, pp. 947, 1012, 1063, 1113.

Pomroy: The Diagnostic Value of Lumbar Puncture in Psychiatry, Jour. of Nerv. and Ment. Dis., 1907, p. 225.

GERMAN LITERATURE

Pandy: Ueber eine neue Eiweissprobe fuer die Cerebrospinalfluessigkeit, Neurol. Centralbl., 1910, p. 915.

Panzer:

Zur Kenntniss der Cerebrospinalfluessigkeit, Wien. klin. Woch., 1899, 805.

Ueber die Polynukleose im Liquor cerebrospinalis, insbesondere bei der progressiven Paralyse, Zeitschr. f. die gesamte Neurol. Psych., 1911, vol. iv.

Pappenheim, M:

Ueber paroxysmale Fieberzustaende bei prog. Paralyse mit Vermehrung der polynukleaeren Leukocyten im Blute und in der Cerebrospinalfluessigkeit, nebst Bemerkungen ueber Blut und Liquor bei Exacerbationen des paralytischen Prozesses, Monatschr. f. Psych. u. Neurol., 1907, vol. xxxi, Heft 6.

Beiträge zum Zellstudium der Cerebrospinalfluessigkeit, Zeitschr. f. Nervenheilk., 1907, p. 315.

Faerbung der Zellen des Liquor cer. spin. mit und ohne Zusatz von Eiweiss, Wien. klin. Woch., 1907, vol. xx.

Zum Wesen der Komplementbindungsreaktion der Cerebrospinalfluessigkeit, Deutsche Zeitschr. f. Nervenheilk., Sept. 30, 1908.

Ueber die Polynukleose im Liquor Cerebrospinalis, insbesondere bei der progressiven Paralyse, Zeitschr. f. die gesamte Neurol. u. Psych., 1911, 267.

Peritz, G.:

Ueber das Verhaeltniss von Lues, Tabes, und Paralyse zum Lecithin, Zeitschr. f. Exper. Path. u. Ther., 1908, 9, 607.

Lues, Tabes, und Paralyse in ihren therapeutischen Beziehungen zum Lecithin, Berl. klin. Woch., 1908, vol. xlv, p. 607.

Pfaundler:

Physiologisches, Bakteriologisches, und Klinisches ueber die Lumbalpunktion, Beiträge zur klin. Med., 1899, 20.

Lumbalpunktion bei Kindern, Jahresbl. f. Kinderheilkunde, 1899, p. 264.

Pick, E. P.: Darstellung der Antigene mit chemischen und physikalischen Methoden, Handbuch der Immunitaetsfor., 1908, p. 568, vol. i.

Pick and Proskauer: Die Komplementbindung als Hilfsmittel der anatomischen Syphilisdiagnose, Med. Klin., 1908, p. 539.

Pick, W.: Bericht ueber die bisherigen Resultate der Behandlung der Syphilis mit dem Praeparate von Ehrlich-Hata (120 Faelle), Wien. klin. Woch., 1910, No. 33.

Pieper: Die Essigsauere Probe zur Unterscheidung der Exsudate und Transudate, Münch. med. Woch., Jan. 4, 1910.

Pighini:

Ueber den Cholesteringehalt der Lumbalfluessigkeit einiger Geisteskrankheiten, Zeitschr. f. phys. Chemie, 1909, p. 518.

Cholesterine und die W. R., Centralbl. f. Nervenheilk. und Psych., 1909, 775.

Chemische und biochemische Untersuchungen ueber das Nervensystem unter normalen und pathologischen Bedingungen, Drei Mittheilungen in der Biochemischen Zeitschr., 1912, 129.

Ueber die Indophenolexydase im Zentralnervensystem in der Tela choroidea und in der Cerebrospinalfluessigkeit, Ibid.

Pighini and Barberi: Untersuchungen ueber Katalase im Liquor cerebrospinalis, Ibid.

Pighini and Nizzi: Aufsuchung der Esterase und Lecithase in der normalen und pathologischen Cerebrospinalfluessigkeit, Ibid.

Pilcz: Zur diagnostischen Bedeutung der Lumbalpunktion, Wien. klin. Rundschau, 1907, 425.

Plaut, F.:

Die Wassermannsche Serodiagnostik der Syphilis in ihrer Anwendung auf die Psychiatire, 1909, Fischer, Jena.

Ueber dass Vorhandensein luetischer Antistoffe in der cerebrospinalfluessigkeit, Neurol. Centralbl., 1906, p. 1127.

Untersuchungen zur Syphilisdiagnose bei Dementia paralytika und Lues Cerebri, Monatschr. f. Psych. u. Neurol., 1907, p. 95.

Ueber den gegenwertigen Stand des serologischen Luesnachweises bei den syphilogenen Erkrankungen des Centralnervensystems, Münch. med. Woch., 1907, p. 1468.

Die Lues Paralyse Frage. Jahresversam. des Deutsch, Vereins f. Psych., Koeln und Bonn, April 23 and 24, 1909; Allgemeine Zeitschrift f. Psych., 1909, 66.

Die W. R. und der praktische Arzt, Münch. med. Woch., 1910, No. 10.

Die Bedeutung der W. R. fuer die Psychiatrie, Zeitschr. f. die gesamte Neurol. u. Psych., 1911, p. 39.

Die W. R. in der Psychiatrie und Neurologie, Ueberblick ueber die Arbeiten des Jahres 1909; Ibid., 1910, Ref. 1.

Ueber das Vorhandensein luetischer Antistoffe in der Cerebrospinalfluessigkeit von Paralytikern, Berl. klin. Woch., 1907, 144.

Serodiagnostik der Syphilis, Centralbl. f. Nervenheilk. und Psychiatrie, 1908, xxxi, p. 289.

Die Wassermannsche Serodiagnostik bei erworbener und hereditaerer Syphilis des Zentralnervensystems, Ibid., 1908, 975.

Plaut and Goering: Untersuchungen an Kindern und Ehegatten von Paralytikern, Münch. med. Woch., 1911, No. xxxvii.

Plaut and Heuck: Zur Fornetschen Praecipitaetreaktion bei Lues und Paralyse, Berl. klin. Woch., 1908, p. 1141.

Plaut, Rehm, O., and Schottmueller: Leitfaden zur Untersuchung der Cerebrospinalfluessigkeit, 1913, Fischer, Jena.

Poetzl, Eppinger, and Hess: Ueber Funktionspruefungen des vegetativen Nervensystems bei einigen Gruppen von Psychosen, Wien. klin. Woch., 1910, 1831.

Popper and Zak: Ueber die klinische Bedeutung des Essigsauerenachweis in seroesen Fluessigkeiten, Wien. klin. Woch., 1910, No. 21.

Porges, Otto:

Technik und Methodik der Serodiagnostik der Lues mit Hilfe der Ausflockungsmethode, Kraus and Levaditi, Handbuch der Immunitaetsforsch, 1909, 1182.

Die Beziehungen der Lipoide zur Immunitaetslehre, Ibid., 1909, pp. 1162, 1181.

Porges and Meier: Rolle der Lipoide bei der Wassermannschen Syphilisreaktion, Berl. klin. Woch., 1908, p. 731.

FRENCH LITERATURE

Parisot:

La pression du liquide C. R. chez l'homme à l'etat normal et pathologique, XIX Congres des médicins alienistes et neurologistes de France et des pays de langue française, Nantes, April 2, 1909.

Le rôle de modifications de pression du liquide C. R. dans la symptomatologie de diverses affections, Revue méd. de l'Est, Feb. 15, 1910, p. 97.

Pauly: Méningite tuberculeuse sans reaction leucocytaire du liquide C. R., Lyon med., 1906.

Pavy: Les hémorragies méningées à forme méningitique, Thèse de Montpellier, No. 51, 1905.

Percheron: Le diagnostic de la méningite tuberculeuse chez l'enfant. Valeur de la ponction lombaire, Thèse de Paris, 1903, No. 442.

Petit, A., and Girard, J.: Sur la fonction sécrétoire des plexus choroides, Archives d'anatomie microscopique, Sept., 1902, p. 224.

Pitres: Lymphocytose du liquide C. R. dans trois cas de névralgie trijumeau, C. R. Soc. Biol., 1904, p. 270.

Pust: Contribution à l'étude de la valeur de la ponction lombaire et du signe de Kernig dans le diagnostic des méninges tuberculeuses de l'enfance, Thèse de Toulouse, 1907, No. 67.

ITALIAN LITERATURE

Paegna: L'examen cytologique du liquide C. R. dans les maladies mentales, Annali di Neurologia, xxiv, 1906.

Pende, N.: Meningite syphilitique, Accademia italiana di Roma, 1906.
Pighini: La colesterina nel liquido cefalo-rachidiano dei paralitici, e sua partecipiazione alla reazione di Wassermann, Rif. medica, xxv, 1909.

Q

GERMAN LITERATURE

Quincke:
Ueber Lumbalpunktion, Berl. klin. Woch., 1895, No. 41.
Zur Physiologie der cerebrospinalfluessigkeit, Arch. f. Anat. u. Physiol., 1878, 153.
Die Lumbalpunktion des Hydrocephalus, Berl. klin. Woch., 1891, No. 38.
Ueber Meningitis serosa und verwandte Zustaende, Deutsche Zeitschrift f. Nervenheilk., 1896.
Zur Pathologie der Meningen, Ibid., 1910, No. 40.
Diagnostische und therapeutische Bedeutung der Lumbalpunktion, Deut. med. Woch., 1905.

R

ENGLISH LITERATURE

Rae: The Diagnostic Value of Rachicentesis, Brit. Med. Jour., June 17, 1911.
Robertson and Brown: The Bacteriology of the Cerebrospinal Fluid in General Paralysis of the Insane, Jour. of Mental Sci., 1909, 56.
Robinson, D. M., and Orleman:
The Noguchi Method of Serum Diagnosis of Syphilis, its Practical Value, Med. Rec., July 23, 1910.
Diagnostic Value of the Noguchi Luetin Reaction in Dermatology, Jour. of Cutan. Dis., July, 1912.
Rosanoff and Wiseman: Syphilis and Insanity, Amer. Jour. of Insan., 1910, 419.
Rosenheim:
New Tests for Cholin in Physiological Fluids, Jour. of Physiol., 1905, p. 220.
Cholin in the Cerebrospinal Fluid, Jour. of Physiol., 1906–7, 405.
Ross: The Application of Certain New Chemical Tests to the Diagnosis of General Paralysis and Tabes, Brit. Med. Jour., May 8, 1909.
Ross and Jones: On the Use of Certain New Chemical Tests in the Diagnosis of General Paralysis and Tabes, Brit. Med. Jour., 1909, 1111.
Rous, P. F.: Clinical Studies of the Cerebrospinal Fluid with Especial Reference to Pressure, and the Number and Character of the Cells, Amer. Jour. Med. Sci., April, 1907, 567.

GERMAN LITERATURE

Ranke: Die Lumbalpunktion bei der tuberkuloesen Gehirnhautentzuendung des Kindesalters, Münch. med. Woch., 1897, 38.

Ranzi: Ueber Komplementablenkung durch Serum und Organe, Wien. klin. Woch., 1906, 1552.

Raven:

Die Bedeutung der isolierten Eiweisvermehrung und der Xanthochromie im Liquor cerebrospinalis fuer die Diagnose von Kompression des Rueckenmarks. Erfahrungen an 15 durch Operation oder Sektion diagnostisch sichergestellten Faellen, Deut. Zeitschr. f. Nervenheilk., 1912, 380.

Die Bedeutung der isolierten Eiweisvermehrung und der Xanthochromie im Liquor Cerebrospinalis, Ibid., Band 44, Seite 380.

Redlich, Poetzl, and Hess: Untersuchungen ueber das Verhalten des Liquor cerebrospinalis bei Epilepsie, Zeitschr. f. d. ges. Neur. u. Psych., 1910, 715, 492.

Rehm:

Die Zerebrospinalfluessigkeit. Physikalische, chemische, und cytologische Eigenschaften und ihre klinische Verwertung, Histologische und Histopathologische Arbeiten, v. Nissl und Alzheimer, vol. iii, p. 2, 1909 (Literature).

Weitere Erfahrungen in dem Gebiete der Lumbalpunktion, Centralbl. f. Neurol. u. Psych., 1905, No. 119.

Ueber den Wert cytologischer Untersuchung der Cerebrospinalfluessigkeit fuer die Differentialdiagnose, Ref. Centralbl. f. Nervenheilk. u. Psych., 1907.

Ergebnisse der cytologischen Untersuchung der Cerebrospinalfluessigkeit und deren Aussichten, Münch. med. Woch., 1908, 31.

Cytologie der Cerebrospinalfluessigkeit und deren diagnostische Verwertbarkeit, Ref. Zeitschr. f. d. Ges. Neurol. u. Psych., 1912, p. 481.

Reicher: Ueber W. R. und Narkose, Deut. med. Woch., 1910, 617.

Reichmann:

Zur Technik der Lumbalpunktion und der Untersuchung des Liquor cerebrospinalis, Münch. med. Woch., 1912, 468.

Zur Physiologie und Pathologie des Liquor cerebrospinalis, Deut. Zeitschr. f. Nervenheilk., 1911, No. 42.

Reinhardt:

Ueber positive W. R. bei Lepra, Framoesie und Scharlach, Münch. med. Woch., 1909, 2197.

Erfahrungen mit der W. R., Münch. med. Woch., 1909, 2092.

Richter: Beiträge zur diagnostischen Verwertung der Cerebrospinalfluessigkeit in der Psychiatrie, Zeitschr. f. d. ges. Neur. u. Psych., 1910, 318.

Rieken: Ueber Lumbalpunktion, Deut. f. klin. Med., 1895, Bd. 56.

Rindfleisch: Ueber diffuse Sarkomatose der Meningen mit charakteristischer Veraenderung des Liquor cerebrospinalis, Deut. Zeitschr. f. Nervenheilk., 1904, p. 144.

Roemheld: Zur Klinik postdiphtherischer Laehmungen und Liquorbefund bei postdiphtherischer Pseudotabes, Ref. Neur. Zentralbl., 1908, 1007.

Rolly: Die Wassermannsche Seroreaktion bei Lues und anderen Infektions krankheiten, Münch. med. Woch., 1909, 62.

Rosenfeld: Ueber das Cholin, Neurol. Centralbl., 1904, 632.

Rossi, O.: Beiträge zur Kenntniss der in der Cerebrospinalfluessigkeit enthaltenen reduzierenden Substance, Zeitschr. f. phys. Chemie, July, 1903, p. 183.

Rotstadt: Ueber die Cerebrospinalfluessigkeit unter normalen und pathologischen Verhaeltnissen, Ref. Zeitschr. f. d. ges. Neur. u. Psych., 1912, 483.

FRENCH LITERATURE

Rabinivitch and Levaditi: Rôle de la syphilis dans l'étiologie de la démence précoce, C. R. Soc. Biol., 1909, 889.

Ramond, L.: Pleuro-tuberculose primitive et méningite tuberculeuse. Etude comparée du liquide pleurale et C. R., Thèse de Paris, Jan., 1907, No. 132.

Ravaut:

Le liquide C. R. de syphilitiques en périod secondaire, Ann. de dermat. et de Syph., 1903, 537.

Etudes cytologiques de liquide C. R. chez les syphilitiques, Ibid., 1903, p. 1; Lyon médicale, 1903.

Le liquide C. R. au course de la syphilis acquise et héréditaire, Rev. mens. de méd. int. et de therap., 1909, 273.

Les indications cliniques et thérapeutiques fournies par la ponction lombaire au course de la syphilis acquise et héréditaire, Mond. méd., Oct. 5, 1911, No. 428.

Ravaut and Darre:

Contribution à l'étude des Herpès géniteaux. Etudes du liquide C. R., Gaz. des Hôp., Oct. 15, 1903, No. 119.

Etudes des réactions méningées dans un cas de syphilis héréditaire, Ibid., 1907 207.

Ravaut, Gastinel, and Velter: La rachicentèse, Monograph, Critzman, May 31, 1910, Masson, Paris.

Raviart, Breton, and Petit: Récherches sur la réaction de Wassermann chez 400 alienes, C. R. Soc. Biol., Feb. 29, 1908.

Raymond and Sicard: Liquide C. R. au course de l'hydrargyrisme chronique, Présence de Hg. Revue neurologique, 1902, T. 10, p. 467.

Renard, Rene, Joltrain, E.: Résultats comparés de la méthode de Wassermann et d'une méthode de simplification pratique pour le diagnostic de la syphilis, C. R. Soc. Biol., 1910, 241.

Renon and Monier, Villard: Paralysie ascendente de Landry; Guerison. Modifications chimiques du liquide C. R., Soc. méd. des Hôp., July, 1899, No. 24.

Renon and Tixier:

Examen cytologique dans un cas de méningite tuberculeuse, presence d'une notable quantité d'albumine dans le liquide C. R., Soc. méd. des Hôp., June 8, 1906, p. 579.

Sur les albumines du liquide C. R. pathologique, C. R. Soc. Biol., 1906, 639.

Riedel: Contribution à l'étude du liquide C. R. et sang dans l'épilepsie, Archivos brasilieros di Psychiatria, Neurologia, Medicina legal, 1908, pp. 235–287.

Robert: La ponction lombaire. Deux ans de pratique dans un service de maladies mentales, Thèse de Bordeaux, No. 101, 1905.

Robinson, D. M., and Orleman: La méthode de Noguchi dans le serodiagnostic de la syphilis, avec quelques considerations pratiques et sérologiques, Ann. de maladies vener., 1910, 881.

Rocaz: Du diagnostic de la méningite tuberculeuse chez l'enfant: Méningites et pseudo-méningites de l'enfance: Valeur diagnostique de la ponction lombaire, Gaz. hebd. des sciences méd. de Bordeaux, Jan., 1902, No. 2, p. 3.

Rombach and De Josselin de Jong: Meningitis gonorrhoica, Ned. Tijdschr. v. Geneesk., 1907, 1262.

Roubinovitch and Paillard:

Le liquide C. R. dans diverses maladies mentales, C. R. Soc. Biol., 1910, p. 582.

Le liquide C. R. dans les maladies mentales, Revue gener. en Gaz. des Hôp., Feb. 11 and 18, 1911, Nos. 17 and 20.

S

ENGLISH LITERATURE

Sabrazes, J., Eckstein, and Kenneth: Note on a Simple Method of Fixation of the Complement in Syphilis, Lancet, 1910, 232.

Sawyer: The Value of Cytodiagnosis in Practical Medicine, Lancet, 1908, 283.

Schaller, W. F.: A Report of Analysis of the Cerebrospinal Fluid with Clinical Notes in 109 Cases of Disease of the Nervous System, Not Including the Acute Meningeal Affections, Jour. of Nerv. and Ment. Dis., Aug., 1913.

Schoelberg and Goodall: On the Wassermann Reaction in 172 Cases of Mental Disorder and 66 Control Cases, Syphilitic and Other, with Historical Survey for the Years 1906–10, inclusive; Comments and Conclusions, Jour. of Ment. Sci., 1911, 237.

Simon: Complement Fixation in Malignant Diseases, Jour. Amer. Med. Assoc., 1909, 1090.

Simon and Thomas: Complement Fixation in Malignant Diseases, Jour. Amer. Med. Assoc., 1908, 673.

Slyke, Van, and Meyer, G. M.: The Amino-acid Nitrogen of the Blood. Preliminary Experiments on Protein Assimilation, Jour. Biol. Chem., vol. xii, Sept., 1912.

Smith and Candler: On the Wassermann Reaction in General Paralysis of the Insane, Brit. Med. Jour., 1909, 199.

Soltmann: The Chemistry of Cerebrospinal Fluid, Jour. Amer. Med. Assoc., June 6, 1903.

Stern, Samuel: The Value of the Noguchi Butyric Acid Reaction in Syphilis and Parasyphilitic Affections, Proc. Path. Soc., Phila., 1910, 39.

Swift, Homer:

A Comparative Study of Serum Diagnosis in Syphilis, Arch. of Int. Med., 1909, 376.

The Use of Active and Inactive Serum in Complement Deviation Tests for Syphilis, Arch. of Int. Med., 1909, 494.

Anaphylaxis to Salvarsan, Jour. Amer. Med. Assoc., Oct. 5, 1912.

The Intensive Treatment of Syphilis, Ibid.

GERMAN LITERATURE

Sachs, Hans:

Antigene tierischen Ursprunges, Kraus-Levaditi, Handbuch der Immunitaetsf., 1908, 244–293.

Spezifische Bindung und Antikörper, Oppenheimer's Handbuch der Biochemie des Menschen und der Tiere, G. Fischer, 1909, 275.

Sachs and Altmann:

Ueber die Wirkung des Oleinsaueren Natrons bei W. R. auf Syphilis, Berl. klin. Woch., 1908, 494

Einfluss der Reaktion auf das Zustandekommen der Wassermannschen Komplementbindung bei Syphilis, Berl. klin. Woch., 1908, 699.

Sachs and Bolkowska: Beiträge zur Kenntnis der komplexen Konstitution der Komplemente, Zeitschr. f. Immunitaetsf., 1910, 776.

Sachs and Rondoni:

Theorie und Praxis der Wassermannschen Syphilisreaktion, Berl. klin. Woch., 1908, xlv.

Same title, Zeitschr. f. Immunitaetsf., 1908–9, p. 132.

Salomon, Oscar: Beiträge zur Behandlung der Syphilis mit Ehrlich-Hata 606, Med. Klin., 1910, 1652.

Samele: Beiträge zur Kenntniss der Cytologie der Cerebrospinalfluessigkeit bei Nervenkrankheiten, Zeitschr. f. klin. Med., 1906, p. 262.

Sarbo: Ueber atypischen Ausfall der W. R. bei einem Fall von anatomisch sicherer Paralyse, Monatschr. u. Neurol., 22.

Satta and Donati:
Ueber das Verhalten von verschiedenen Extrakten bei der W. R. mit Beruecksichtigung ihrer antikomplementaeren und hemolytischen Wirkung, Wien. klin. Woch., 1910, 659.
Ueber die Hemmung der W. R. durch Sublimat und ueber die Moeglichkeit dieselbe aufzuheben, Münch. med. Woch., 1910, 567.
Hat das Sublimat eine Wirkung auf die W. R., Wien. klin. Woch., 1910, 739.
Ueber den Einfluss des Alkohols auf luetische Sera bei der Komplementbindungsreaktion, Ibid., 1910, 1074.

Schaefer: Ueber das Verhalten der Cerebrospinalfluessigkeit bei gewissen Geisteskrankheiten, Neurol. Centralbl., 1901, p. 1066.

Schatiloff and Isabolinsky: Untersuchungen ueber die Wassermann-Neisser-Brucksche Reaktion bei Syphilis, Zeitschr. f. Immunitaetsf., 1909, 316.

Scheidemantel: Erfahrungen ueber die Spezificitaet der W. R.: Die Bewertung und Entstehung inkompletter Hemmungen, Deut. Arch. f. klin. Med., 1911, Bd. 101.

Schereschewsky: Ueber Serumreaktion bei Scharlach und Masern, Münch. med. Woch., 1908, 794.

Schleier, F.:
Zur Frage der Komplementbindung, Deut. med. Woch., 1908, p. 1373.
Zur Frage der Komplementbindung bei Scharlach, Wien. klin. Woch., 1908, p. 1373.

Schlesinger: Cytologische Untersuchungen des Liquor cerebrospinalis, Deut. med. Woch., 1904.

Schnitzler: Zur differentialdiagnostischen Beurteilung der isolierten "Phase I" reaction in der Spinalfluessigkeit, Zeitschr. f. d. ges. Neur. u. Psych., 1911, p. 210.

Schoenborn: Bericht ueber Lumbalpunktionen an 230 Nervenkranken, mit besonderer Beruecksichtigung der Cytodiagnose, Med. Klinik, 1906, Nos. 23 and 24.

Schoo, H. T. M.: Ueber positive Reaktion von Wassermann bei Malaria, Nederl. Tydschr. v. Geneeskunde, 1910, No. 5.

Schottmueller:
Der Liquor cerebrospinalis insbesondere im Zusammenhange mit der W. R. bei Poliomyelitis acuta epidemica, Münch. med. Woch., 1912, p. 1988.
Meningitis cerebrospinalis epidemica (Weichselbaum), Münch. med. Woch., 1905.

Schottmueller and Schumm: Nachweis von Alkohol in der Spinalfluessigkeit von Saeufern, Neurol. Centralbl., 1912, No. 31.

Schreiber and Hoppe: Ueber die Behandlung der Syphilis mit dem neuen Ehrlich-Hataschen Arsenpraeparat, No. 606, Münch. med. Woch., 1910, 1430.

Schuermann: Luesnachweis durch Farbenreaktion, Deut. med. Woch., 1909, 616.

Schuermann, W.: Ein kuenstlicher Extrakt zur Anstellung der Luesreaktion, Med. Klin., 1909, 627.

Schuetze: Tabes und Lues, Zeitschr. f. klin. Med., 1908, pp. 397–424.

Schuetze, A.: Experimentelle Beiträge zur Wassermannschen Serodiagnostik bei Lues, Berl. klin. Woch., 1907, 126.

Schultz-Zehden: Erfahrungen ueber die Dungernsche Methode der Syphilisreaktion in der Sprechstunde, Med. Klin., 1910, 1058.

Schwartz, W., and Flemming: Ueber das Verhalten des Ehrlich-Hataschen Praeparates, des Arsenophenylglycin, des Jodkali und des Sublimats zur W. R., Münch. med. Woch., 1910, 1933.

Schwarz: Ueber Tabes und Lues Cerebri und ihre Beeinflussung durch Salvarsan, Petersburger med. Woch., 1911, 49.

Seligmann, E.: Zur Kenntnis der W. R., Zeitschr. f. Immunitaetsf., 1909, 340.

Seligmann and Blume: Die Luesreaktion an der Leiche, Berl. klin. Woch., 1909, 1116.

Seligmann and Klopstock: Serumreaktion bei Scharlach, Berl. klin. Woch., 1908, 1719.

Seligmann and Pinkus: Beiträge zur Theorie und Praxis der W. R., Zeitschr. f. Immunitaetsforschung, 1910, 377.

Siemerling: Ueber den Wert der Untersuchung des Liquor cerebrospinalis fuer die Diagnose der Nerven un Geisteskrankheiten, Berl. klin. Woch., 1904, No. 21; 1909, No. 21.

Silberberg: Ueber Befunde der Eberth-Gaffkyschen Bacillen in der Cerebrospinalfluessigkeit bei Typhus abdominalis, Berl. klin. Woch., 1908, 1354.

Simon: Zur Untersuchung des Liquor cerebrospinalis, Wien. klin. Woch., 1911, No. 24.

Skoczynski: Chemische Untersuchung der Cerebrospinalfluessigkeit, Ref. Neurol. Centralbl., 1905, No. 1.

Slawyk: Ein Fall von Allgemeininfektion und Influenzabacillen, Zeitschr. f. Hyg., 1899, No. 32.

Sleeswijk, J. G.: Die Serodiagnostik der Syphilis nach Noguchi, Deut. med. Woch., 1910, 1213.

Slyke, Van: Die gasometrische Bestimmung von primaerem aliphatischen Aminostickstoff und ihre Anwendung auf physiologisch-chemischem Gebiete, Handbuch der biochemischen Arbeitsmethoden Urban and Schwarzenberg, Berlin, 1912.

Smidt: Ueber Eiweissreaktion in der Cerebrospinalfluessigkeit Gesunder, Geistes und Nervenkranker, Thèse, June, 1909.

Sobernheim, W.:

Wassermannschekomplementbindungsmethode und Ozaena, Arch. f. Laryngol., 1909, xxii, 1.

Ozaena und Syphilis, Zeitschr. f. Laryngol., 1909, 430.

Sobernheim, W.: Zur Organisation der Serodiagnostik nach Wassermann, Berl. klin. Woch., 1910, 1365.

Spaet, W.: Ueber den Mechanismus der W. R., Folia Serol., 1910, v.

Spielmeyer: Schlafkrankheit und progressive Paralyse, Münch. med. Woch., 1907, No. 22.

Spiethoff: Salvarsan und Nervensystem, Münch. med. Woch., 1912, p. 1087.

Spiethoff, Bodo: Arsenobenzol bei Syphilis, Münch. med. Woch., 1910, 1822.

Spina:

Experimentelle Untersuchungen ueber die Bildung des Liquor cerebrospinalis, Arch. f. d. ges. Physiol., 1899, p. 204.

Ueber den Einfluss des hohen Blutdruckes auf die Neubildung der Cerebrospinalfluessigkeit, Ibid., 1900, p. 80.

Staeubil: Meningismus typhosus und meningotyphus, Duet. Arch. f. klin. Med., 1905, Bd. 82.

Stanek: Ueber die Cholin Salze, Zeitschr. f. phys. Chem., 1905, p. 448.

Steffenhagen: Ueber Komplementbindungsreaktion bei Lepra, Berl. klin. Woch., 1910, 1363.

Stern, Carl:

Ueber die sogenannte "Verfeinerungën" der W. R., Deut. med. Woch., 1910, 1118.

Ueber den Einfluss der Zittmannschen Kur auf den Ausfall der W. R., Med. klin., 1910, 898.

Stern, Margar:

Zur Technik der Serodiagnostik der Syphilis, Berl. klin. Woch., 1908, 1489.

Eine Vereinfachung und Verfeinerung der serodiagnostischen Syphilisreaktion, Zeitschr. f. Immunitaetsf., 1909, 422.

Ueber die Bewertung der unsicheren und paradoxen Reaktionen bei der serodiagnostischen Untersuchung der Syphilis, Ibid., 1910, 201.

Stertz:

Die Serumdiagnostik in der Psychiatrie und Neurologie, Allgemeine Zeitschr. f. Psych. u. psych. gericht. Med., 1908, 565.

Die Serodiagnostik in der Psychiatrie und Neurologie, Allgemeine Zeitschrift f. Psychiatrie, 1908, p. 665.

Die Bedeutung der Lumbalpunktion fuer die Diagnose von Gehirn und Rueckenmarkskrankheiten, Med. Klin., 1912, p. 133.

Strauss: Die diagnostische Bedeutung der Punktion des Wirbelkanals, Deut. Arch. f. klin. Med., 1896, Bd. 57.

Stuehmer:

Typhusbacillen in der Cerebrospinalfluessigkeit, Münch. med. Woch., 1911, No. 7.

Zur Technik der Untersuchung der Lumbalfluessigkeit auf W. R., Zentralbl. f. Bacter., 1911, p. 171.

Stuemer, A.: Ueber die Verwendung autolisierter Lebern zu Organextrakten fuer die W. R., Zentralbl. inn. Med., 1910, No. 14.

Stuempke, G.: Welche Beziehungen bestehen zwischen Jod (Jodkali) und dem Ausfall der Seroreaktion, Münch. med. Woch., 1910, 1532.

Sugai: Zur klinisch-diagnostischen Verwertung der Komplementbindunsmethode bei lepra, Arch. f. Dermat. u. Syph., 1909, 313–319.

Swift, Homer, and Ellis, W. M.: Die kombinierte lokal und Allgemeinbehandlung der Syphilis des Zentralnervensystems, Münch. med. Woch., Nos. 36 and 37, 1913.

Szesci:

Beiträge zur Differentialdiagnose der Dementia paralytica, Sclerosis multiplex und Lues cerebrospinalis, Monatschr. f. Psychiatrie, Sept., 1910, No. 26.

Neue Beiträge zur Cytologie des Liquor cerebrospinalis, Ueber Art und Herkunft der Zellen, Zeitschr. f. d. ges. Psych. u. Neurol., 1911, No. 6.

Weitere Beiträge zur Cytologie des Liquor cerebrospinalis. Ueber die sogenannte Degeneration der Zellen, Ibid., 1912, No. 9.

Ueber das Vorkommen von peptolytischen Fermenten in der Lumbalfluessigkeit, Wien. klin. Woch., 1911, No. 33.

Zur Technik der chemischen und cytologischen Untersuchung der Lumbalfluessigkeit, Monatschr. f. Psych. u. Neurol., 1910, p. 152.

FRENCH LITERATURE

Sabrazes:

Note sur le point de congélation. Examen cytologique des liquides du d'hydrorrhée nasale, Gaz. des sciences méd. de Bordeaux, Jan. 25, 1903.

Présence de sérine dans le liquide C. R. normal, Gaz. hebd. de sciences med. de Bordeaux, Aug. 2, 1903, p. 376.

La ponction lombaire, Gaz. hebd. des Scien. méd. de Bordeaux, July 22, 1906, p. 339.

Salebert and Louis: Cytologie du liquide C. R. dans la méningite cérébrospinale. Role phagocytaire cellules endothéliales, C. R. Soc. Biol., 1909, p. 770.

Sappey: Les thérapeutiques rachidiennes du tabès; L'Electro-mercurol. Considerations sur son mode d'action, Thèse Montpellier, 1910.

Schaeffer, G.: La choline. Etude chimique et physiologique de cette substance, Biologie méd. (F. Billon), Oct., 1909, p. 309.

Schmiergeld: Etude sur la poliomyelite anterieure de l'adulte, Paris, Jules Rousset, 1907.

Sezary and Palliard: Constatation de tréponéme dans le liquide C. R., C. R. Soc. Biol., 1910, p. 295.

Sicard:

Le liquide C. R., Masson & Co., Paris, 1902.

Les injections sous-arachnoidiennes et le liquide C. R. Récherches expérimentales et cliniques, Thèse de Paris, 1899, No. 124.

Sicard:

Perméabilité méningée, C. R. Soc. Biol., 1902, p. 1356.

Chromodiagnostic du liquide C. R. Hémorragies du névraxe, méningites, ictère, Presse méd., Jan. 25, 1902.

Glycométrie du liquide C. R., Acad. de Médecine, Oct. 18, 1904.

Nevralgie du trijumeau et ponction lombarie, C. R. Soc. Biol., 1904, p. 357.

Traitement par les injections arachnoidiennes lombaires de certains symptomes du tabès inférieur, C. R. Soc. Biol., 1910, p. 1105.

Sicard and Bloch:

Perméabilité méningée a l'arsenobenzol, C. R. Soc. Biol., 1910, p. 624; Soc. méd. des Hôp., Nov. 18, p. 479.

Variations quantitatives de la lymphocytose rachidienne chez les tabétiques non traités. Influènce de la statique. Déductions pathogéniques, Soc. méd. des Hôp., July 7, 1911.

Sicard and Brecy:

Méningite cérebro-spinale ambulatoire curable. Cytologie, Soc. med. Hôp., April, 1901, p. 369.

Chromodiagnostic dans l'hémorragie méningée, C. R. Soc. Biol., Nov., 1901, p. 1050.

Sicard and Descomps: Syndrome de coagulation massive de xanthochromie et d'hémato-lymphocytose du liquide C. R., Gaz. des Hôp., Oct., 1908.

Sicard and Foix:

Les réactions du liquide C. R. au cours des pachyméningites rachidiennes, Soc. de Neurol. de Paris, No. 10, p. 636, 1910.

Glucose rachidien et septicite, Soc. de Neurol., March, 1911.

Sicard and Gy: Méningite sarcomateuse à predominance bulbo-protubérantielle. Cytodiagnostic. Réaction néoplastique, Revue Neurologique, Dec. 15, 1908.

Sicard and Rousseau Langwelt: Glycométrie du liquide C. R. chez l'enfant. Sa valeur dans le diagnostic des méninges aiguës, Soc. méd. des Hôp., Oct. 14, 1904.

Sicard and Salin: Réactions méningées consécutives aux injections sous-arachnoidiennes lombaires du sérum du cheval et de sérum artificiel, C. R. Soc. Biol., 1910, 523.

Sicard, Guillain, and Ravaut: Chimie du liquide C. R., Archives de Neurologie, 1903, p. 472.

Slatineanu and Danielopolu:

Fixation de l'alexine essayée avec le sérum et le liquide céphalo-rachidien des lépreux, en présence de la lécithine comme antigene, C. R. Soc. Biol., 1909, 332.

Réaction de fixation avec le sérum et le liquide céphalo-rachidien des malades de lepre en présence de l'antigéne syphilitique, Centralbl. f. Bakt., etc., Orig. 1, Abteil, 1909, 289.

Slatineanu and Galesesco: Récherches cytologiques sur le liquide C. R. dans le typhus exanthématique, C. R. Soc. Biol., No. 61, p. 230.

Souques and Aynaud: Passage de l'acétone dans le liquide C. R. au cours du coma diabetique chez l'homme et à l'état normal chez les animaux, Soc. med. des Hôp., Jan. 25, 1907.

Subsol: Etude de liquide C. R. dans l'épilepsie essentielle, Thèse de Paris, 1903, No. 308.

ITALIAN LITERATURE

Serra, Alberto: La sierodiagnosi di Wassermann nella lepra, Policlin. Sez. med., 1909, 545.

Sorrentino: Sull' importanza della citoscopia cefalo-rachidiana nei sifilitici, Rif. med., 1911, p. 49.

T

ENGLISH LITERATURE

Thomson, Hill, and Halliburton: Observations on the Cerebrospinal Fluid in the Human Subject, Lancet, 1899, No. 9.

Turner: Examination of the Cerebrospinal Fluid as an Aid to Diagnosis in Certain Cases of Insanity, etc., Jour. of Ment. Sci., 1910, 485.

GERMAN LITERATURE

Taege: Die Technik der Wassermannschen Serodiagnostik der Syphilis, Münch. Med. Woch., 1908, 1730.

Tedeschi: Ueber Cuti und Ophthalmoreaktion bei Syphilis, Münch. med. Woch., 1908, 2200.

Thomsen, O.: Die Bedeutung der positiven W. R. mit Frauenmilch fuer die Wahl einer Amme, Berl. klin. Woch., 1910, 1748.

Thomsen and Boas, Ismar: Die W. R. bei congenitaler Syphilis, Berl. klin. Woch., 1909, 539.

Tobler: Ueber die Lymphocytose der Cerebrospinalfluessigkeit bei kongenitaler Syphilis und ihre diagnostische Bedeutung, Jahrbuch f. Kinderheilkunde, 1906, p. 64.

Tomasczewski:

Ueber eine einfache Methode bei Kanienchen Primaeraffekte zu erzeugen, Deut. med. Woch., 1910, 1025.

Untersuchungen ueber die Wirkung des Hg. und Jods bei der experimentellen Syphilis, Ibid., 1910, 653.

Torday, A. von: Bericht ueber die Ehrlich-Hatasche Behandlung, Wien. klin. Woch., 1910, 1381.

Toyosumi:

Welche Antikoerper spielen bei der Komplementbindung eine Rolle, Arch. f. Hyg., 1909, No. 1.

Toyosumi:
Ueber die Natur der Komplementbindenden Stoffe bei Lues, Wien. klin. Woch., 1909, 747.
Komplementabsorption durch Bakterienextrakte, Zentralbl. f. Bakt., Abteil 1, 1909, 325.
Ueber die Komplementbindenden Stoffe Luetischer Sera, Ibid., 1909, 601.
Trembur: Die Quinckesche Lumbalpunktion bei der Erkennung der Meningitis tuberculosa, etc., Klin. Jahrbuch, 1911, p. 360.
Treupel, G.: Weitere Erfahrungen bei syphilitischen para und meta syphilitischen Erkrankungen mit Ehrlich-Hata Injektionen, Deut. med. Woch., 1910, 1787.
Tschernogubof:
Einfache Methode der Serumdiagnose bei Syphilis, Berl. klin. Woch., 1908, 2107.
Zur Frage der Herstellung von syphilitischen Antigenen, Wien. klin. Woch., 1906, 336.
Ein vereinfachtes Verfahren der Serumdiagnose bei Syphilis, Deut. med. Woch., 1909, 668.

FRENCH LITERATURE

Tedeschi: Syndrome de la queue de cheval, Gazetta degli Ospedali e delle Cliniche, Aug., 1906.
Tesson: Contribution à l'étude de la ponction lombaire dans les fractures du crâne, Gaz. des Hôp., April 22, 1901, p. 921.
Thiery, P.: De la présence du sucre dans le liquide hydrocéphalique, Prog. méd., 1886, p. 286.
Tuffier and Milian:
Pronostic des fractures du crâne par la ponction lombaire, C. R. Soc. Anat., June 5, 1901.
La ponction lombaire dans les fractures du crâne, C. R. Soc. Biol., May, 25, 1901; Soc. méd. des Hop., July 12, 1901.
Diagnostic des fractures du crâne par la ponction lombaire, Soc. méd. des Hôp., July 12, 1902.
Hémorragies intra-crâniennes, Presse méd., March 5, 1902.
La xanthochromie du liquide C. R. Fracture du crâne chez un alcoolique, Bull. de la Soc. Anat., May 16, 1902, p. 489.

U

GERMAN LITERATURE

Uhlenhuth: Komplementbindung und Bluteiweisdifferenzierung, Deut. med. Woch., 1906, p. 1244.
Uhlenhuth and Muelzer: Die experimentellen Grundlagen chemotherapeutischer Versuche mit neueren Arsenpraeparaten bei Spirochaetenkrankheiten mit besonderer Beruecksichtigung der Syphilis, Deut. med. Woch., 1910, 1262.

V

FRENCH LITERATURE

Vigneras: Hemorragie méningo-spinale, Thèse de Paris, 1908.

Villaret and Tixier:

Dissociation des réactions cliniques, cytologiques, bactériologiques et anatomo-pathologiques dans certains formes de méningite tuberculeuse, C. R. Soc. Biol., Nov., 1905.

Eclampsie puerpérale et leucocytose du liquide C. R., C. R. Soc. Biol., 1907, p. 1042.

Vincent: Deux cas de méningite chronique syphilitique, Rev. neurol., 1908, p. 1050.

Vincent and Combe: Contribution au diagnostic de la méningite tuberculeuse, C. R. Soc. Biol., 1909, p. 465.

Viteman: Le régime déchloruré dans l'épilepsie, Thèse de Paris, June 14, 1906, No. 315.

Voisin, J. and R.: Le liquide C. R. dans l'épilepsie essentielle, Soc. méd. des Hôp., March 18, 1910, p. 282.

Voisin, R.: Les méninges au cours des infections aiguës de l'appareil respitatoire; broncho-pneumonie et pneumonie, Thèse de Paris, Feb., 1904, No. 203.

Voisin and Paisseau: Les réactions méningees au cours des encéphalopathies chroniques de l'enfant, Arch. de Méd. des enfants, No. 4, 1910.

Voulcoff: Contribution a l'étude du liquide C. R. dans les P. G., Thèse de Montpellier, March, 1904, No. 6.

W

ENGLISH LITERATURE

Walker and Swift: A Study of the Addition of Cholesterin to the Alcoholic Extracts of Tissues Used for Antigens in the Wassermann Reaction, Jour. Exp. Med., vol. xviii, No. 1, 1913.

Waugh, J. F.: Results of Experience with Noguchi Modification of the Wassermann Serodiagnosis Test for Syphilis, Jour. Amer. Med. Assoc., 1919, 844.

Weil, Richard: On the Resistance of Human Erythrocytes to Cobra Venom, Jour. Infect. Dis., 1909, 688.

Wieder and L'Engle: Some Studies of the Precipitin Tests for Syphilis, Jour. Amer. Med. Assoc., 1909, 1535.

Williamson:

The Cerebrospinal Fluid in General Paralysis and in Nervous Lues, Lancet, 1909, 1047.

The Bacillus Paralyticus, Jour. of Ment. Sci., 1909, 642.

Williamson and Phillips: Further Investigation on the Cerebrospinal Fluid in Insanity, Jour. of Ment. Sci., 1912, p. 240.

Wolbarst, Abr.: Contradictory Findings in the Wassermann Test, N. Y. Med. Jour., Feb. 22, 1913.

Wolfsohn: The Cutaneous Reaction of Syphilis, Bull. Johns Hop. Hosp., 1912, p. 223.

Wollstein: Influenza Meningitis and its Experimental Production, Amer. Jour. Dis. of Children, 1911, p. 42.

Wollstein and Lamar: The Presence of Antagonistic Substances in the Blood-serum in Early and Late Syphilis, Paralysis, and Tabes, Arch. of Int. Med., 1908, 341.

Wright, H. W.: A Consideration of Constitutional Inferiority, N. Y. Med. Jour., Dec. 26, 1908.

GERMAN LITERATURE

Wada and Matsumoto: Liquor cerebrospinalis bei Geisteskrankehiten, Jahrbuch f. Psych., 1910, p. 153.

Wagner: Einige Beobachtungen ueber den Druck im Lumbalkanal, insbesondere bei Tabes dorsalis, Charite-Annalen, 1909, No. 33.

Walter: Studien ueber den Liquor cerebro-spinalis, Monatschr. f. Psych. und Neurol., Sept., 1910, No. 28.

Wassermaeyer and Bering: Die W. R. in der Psychiatrie und Neurologie mit besonderer Beruecksichtigung, etc., Arch. f. Psych., 1910, p. 822.

Wassermann, A.:

Ueber die Entwicklung und den gegenwertigen Stand der Serodiagnostik gegenueber Syphilis, Berl. klin. Woch., 1907, 1599, 1634.

Ueber die Serodianostik der Syphilis und ihre praktische Bedeutung fuer die Medizin, Wien. klin. Woch., 1908, 745.

Die Diagnose der Syphilis bei Erkrankungen des Zentralnervensystems, Zentralbl. f. Nervenheilk. u. Psych., 1908, 975.

Wassermann and Meier: Die Serodiagnostik der Syphilis, Münch. med. Woch., 1910, No. 24.

Wassermann and Plaut: Ueber das Vorhandensein syphilitischer Antistoffe in der Cerebrospinalfluessigkeit vqn Paralytikern, Deut. med. Woch., 1906, 1769.

Wassermann and Schucht: Nachweis specifisch-luetischer Substanzen durch Komplementverankerung, Zeitschr. f. Hyg. u. infektionskr., 1906, 451.

Wassermann, Neisser, and Bruck: Eine Serodiagnostische Reaktion bei Syphilis, Deut. med. Woch., 1906, 745.

Wassermann, M., and Meier: Zur klinischen Verwertung der Serodiagnostik bei Lues, Deut. med. Woch., 1907, 1287.

Wechselmann:

Postkonzeptionelle Syphilis und W. R., Deut. med. Woch., 1909, 665.

Beobachtungen an 503 mit Dioxy-diamido-arseno-benzol behandelten Krankheitsfaellen, Deut. med. Woch., 1910, 1478.

Wechselmann:
Ueber die Behandlung der Syphilis mit 606, Berl. klin. Woch., 1910, 126.
Ueber intravenoese Injection von Neosalvarsan, Berl. klin. Woch., 1912, p. 1446.
Ueber die Wirkung des Salvarsans auf die Cerebrospinalfluessigkeit, Berl. klin. Woch., 1912, p. 688.
Wechselmann and Meier: W. R. in einem Fall von Lepra, Deut. med. Woch., 1908, 1314.
Weidanz: Die W. R. bei Anwendung kleinster Blutmengen, Berl. klin. Woch., 1908, 2440.
Weil, E., and Braun, H.:
Ueber die Entwicklung der Serodiagnostik bei Lues, Wien. klin. Woch., 1908, 624.
Ueber Antikoerper Befunde bei Lues, Tabes dorsalis, und Paralyse, Berl. klin. Woch., 1907, pp. 1517, 1570.
Ueber die Rolle der Lipoide bei der Reaktion auf Lues, Wien. klin. Woch., 1908, 151.
Ueber positive W. R. bei nicht-luetischen Erkrankungen, Wien. klin. Woch., 1908, 938.
Weil and Kafka:
Ueber die Durchgaengigkeit der Meningen besonders bei der progressiven Paralyse, Wien. klin. Woch., 1911, No. 26.
Weitere Untersuchungen ueber den Haemolysingehalt der Cerebrospinalfluessigkeit bei akuter Meningitis und progressiver Paralyse, Med. klin., 1911, No. 34.
Werther: Ueber das Wesen und den Wert der W. R. und 500 eigene Untersuchungen mit der Hechtschen Modifikation, Monatschr. f. prakt. Dermat., 1910, 147.
Werther and Koenig: Ueber die Hechtsche Modifikation der W. R. ueber die Erfahrungen bei 500 Untersuchungen und ueber den Wert der Reaktion fuer die Praxis, Münch. med. Woch., 1910, 161.
Weygandt: Ueber die Frage syphilitischer Antistoffe in der Cerebrospinalfluessigkeit bei Tabes dorsalis, Ref. Münch. med. Woch., 1907, p. 1557.
Wolff, Arthur: Vergleichende Untersuchungen ueber W. R., Lymphocytose und Globulinreaktion bei Erkrankungen des Nervensystems, Deut. med. Woch., 1910, 748.
Wolfssohn, G.: Ueber W. R. und Narkose, Deut. med. Woch., 1910, 505.

FRENCH LITERATURE

Widal and Abrami: Ictère grave infectieux avec rétention et urémie sèche par azotémie; perméabilité des voies biliaires. Hyperplasie des cellules hépatiques, Bull. de la Soc. med. des Hôp. de Paris, Feb., 1908.

Widal and Foin: Urée dans le liquide C. R., C. R. Soc. Biol., Oct., 1904, p. 282.

Widal and Froin: L'urée dans le liquide C. R. des brightiques, Gaz. des Hôp., Oct. 26, 1904, p. 1182.

Widal and Joltrain: Biligenie hémolytique local dans l'hémorragie méningée, C. R. Soc. Biol., June 5, 1909, p. 917.

Widal and Sicard: Etude sur le séro-diagnostic de la fièvre typhoid, Annales de l'Institute Pasteur, 1897.

Widal, Lemierre, and Boidin: Liquide C. R., puriforme au cours de la syphilis des centres nerveux; intégrite des polynucleares, Soc. méd. des Hôp., June 22, 1906, p. 645.

Widal, Sicard, and Ravaut:

Cryoscopie du liquide C. R. Application al 'étude des méningites, C. R. Soc. Biol., Nov. 2, 1900.

Les albumines de liquide C. R. au cours de certains processus méningés chroniques, Rev. neurol., April 2, 1903, 437.

Cytologie du liquide C. R. au cours de quelques processus méningées chroniques, Gaz. hebdom. des méd., 1901, 77.

A propos de cytodiagnostic de tabès, Rev. neurol., 1903, p. 289.

Présence d'un pigment dérive dans le liquide C. R. au cours des ictères chroniques, C. R. Soc. Biol., Feb. 8, 1902, p. 159.

Wilson: Choline signe de dégénérescence nerveuse, son importance clinique, Soc. Neurol., 1904, p. 401.

Wolf: Des éléments de diagnostic tirés de la ponction lombaire, Thèse de Paris, July 20, 1901, No. 669.

Z

GERMAN LITERATURE

Zaloziecki:

Zur klinischen Bewertung der serodiagnostischen Luesreaktion nach Wassermann in der Psychiatrie, Monatschr. f. Psych. u. Neurol., Sept., 1900.

Liquor Cerebrospinalis und Salvarsan, Berl. klin. Woch., 1912, No. 49.

Ueber den Antikoerpernachweis im Liquor cerebrospinalis, seine theoretische und praktische Bedeutung, Münch. Arch. f. Hygiene, 1913, Bd. 80.

Zur Frage der Permeabilitaet der Meningen, Leipzig, Vogel, 1913.

Bemerkungen zu J. Portmann's Notiz; Eine neue Modifikation der W. R., Berl. klin. Woch., 1913, No. 5.

Ueber den Eiweisgehalt der Cerebrospinalfluessigkeit, Deut. Zeitschr. f. Nervenheilk., 1913, Bd. 47, 48.

Ueber "Eigenloesende" Eigenschaften des Meerschweinchenserums und dadurch bedingte Fehlerquellen der W. R., Deut. med. Woch., 1913, No. 17.

Zeissl: Meine bisherigen Erfarungen mit Ehrlich 606, Wien. med. Woch., 1910, 1865.

Zeissler:

W. R. bei Scharlach, Berl. klin. Woch., 1908, 1887.

Komplementschaedigung durch Schuetteln, Ibid., 1909, 2340.

Quantitative Hemmungskoerperbestimmung bei der W. R., Ibid., 1909, 1968; 1910, 968.

Zradek: Einige Beiträge zur Kenntnis der Cerebrospinalfluessigkeit, Zeitschr. f. Phys. Chem., 1902, No. 291.

Zuelchaur: Die Serodiagnose der Dementia paralytika, Inaug. Diss., Leipzig, 1910.

Zweifel: Zur Aufklaerung der Eklampsie, Arch. f. Gynaekol., 1905, 76.

ITALIAN, GREEK, AND FRENCH LITERATURE

Zaccaria: Ricerche sulla quantita di calcio contenuta nel liquido C. R. di bambibi ammalati, Clinica Ital. med., 1906, p. 813, No. 12.

Zilanakis:

Intoxication par l'atropine, Rev. Neurol., 1907, p. 20.

Contribution a l'étude du liquide C. R. chez les alienes. Statistique et conclusions de 160 ponctions, Rev. Neur., 1907, p. 20.

Ziveri, A.: Modification de la méthode de recherche de la choline et nouvelles investigations sur sa présence et la présence de la léci-thine dans le liquide C. R., Revista de pathologia nervosa e mentale, vol. xiv, p. 134, March, 1909.

INDEX

The New Keen's Surgery

Surgery: Its Principles and Practice. Written by 81 eminent specialists. Edited by W. W. Keen, M. D., LL.D., Hon. F.R.C.S., Eng. and Edin., Emeritus Professor of the Principles of Surgery and of Clinical Surgery at the Jefferson Medical College. Six octavos of 1050 pages each, containing 3100 original illustrations, 157 in colors. Per volume: Cloth, $7.00 net; Half Morocco, $8.00 net.

VOLUME VI GIVES YOU THE NEWEST SURGERY

ALL THE ADVANTAGES OF A REVISION AT ONE-FIFTH THE COST

We have issued a Volume VI of "Keen"—the volume of the newest surgery. In this way you get all the advantages of a complete and thorough revision at but *one-fifth the cost.* It makes Keen's Surgery the best, the most up-to-date surgery on the market.

In this sixth volume you get the newest surgery—both general and special—from the pens of those same international authorities who have made the success of Keen's Surgery world-wide. Each man has searched for the new, the *really useful,* in his particular field, and he gives it to you here. Here you get the newest surgery, and fully illustrated. Then, further, you get a *complete index* to the entire six volumes, covering 125 pages, but so arranged that reference to it is extremely easy. If you want the newest surgery, you must turn to the new "Keen" for it.

SOME OF THE NEW MATTER IN VOLUME VI

Vaccine serum, opsonic index, etc.
Antiferment and trypsin treatments
Beck's bismuth paste
Postoperative and catgut tetanus
Murphy's formalin-glycerin injections
W. L. Clark's desiccation method
DeKeating-Hart fulguration
Anoci-association (its *practical* use)
New extension treatments for fractures
Lane's bone-plates
Differential pressure cabinets
Carbon-dioxid snow
Laminectomy
Bone-grafting and transplantation
Nitrous oxid, intratracheal and intravenous anesthesia
Pituitary surgery
Kocher's horizontal ("normal") incision
Thyroid and parathyroid surgery
Tracheal grafts
Pulmonary emphysema
Ochsner's peritonitis treatment
Jejunal and gastrojejunal ulcers
Lane's kink
Murphy's five diagnostic methods
Subphrenic abscess
Unilateral suppurative nephritis
New gynecologic operations (90 pages)

Hornsby and Schmidt's The Modern Hospital

The Modern Hospital. Its Inspiration; Its Construction; Its Equipment; Its Mangement. By JOHN A. HORNSBY, M. D., Secretary, Hospital Section, American Medical Association; and RICHARD E. SCHMIDT, Architect. Large octavo of 644 pages, with 207 illustrations. Cloth, $7.00 net; Half Morocco, $8.50 net.

HOSPITAL EFFICIENCY

"Hornsby and Schmidt" tells you just exactly how to plan, construct, equip, and manage a hospital in all its departments, giving you every detail. It gives you exact data regarding heating, ventilating, plumbing, refrigerating, etc.—*and the costs.* It tells you how to equip a modern hospital with modern appliances. It tells you what you need in the operating room, the wards, the private rooms, the dining room, the kitchen—every division of hospital housekeeping. It gives you the duties of the directors, the superintendent, the various staffs, their relations to each other. It tells you all about nurses' training-schools—their management, curriculum, rules, regulations, etc. It gives you definite diets for the patients and the hospital household. It gives you hundreds of valuable points on the business management of hospitals—large and small. In fact, it tells you how to plan, construct, equip, and maintain a hospital with the greatest economy compatible with the highest efficiency.

Campbell's Surgical Anatomy

A Text-Book of Surgical Anatomy. By WILLIAM FRANCIS CAMPBELL, M. D., Professor of Anatomy, Long Island College Hospital. Octavo of 675 pages, with 319 original illustrations. Cloth, $5.00 net; Half Morocco, $6.50 net.

THE NEW (2d) EDITION

The first aim in the preparation of this original work was to emphasize the practical. It is in the fullest sense an applied anatomy—an anatomy that will be of inestimable value to the surgeon because only those facts are discussed and only those structures and regions emphasized that have a peculiar interest to him. Dr. Campbell has treated his subject in a very systematic way. The magnificent original illustrations will be found extremely practical.

Boston Medical and Surgical Journal

"The author has an excellent command of his subject, and treats it with the freedom and the conviction of the experienced anatomist. He is also an admirable clinician."

Cotton's
Dislocations and Joint Fractures

Dislocations and Joint Fractures. By FREDERIC JAY COTTON, M. D., First Assistant Surgeon to the Boston City Hospital. Octavo of 654 pages, with 1201 original illustrations. Cloth, $6.00 net; Half Morocco, $7.50 net.

TWO PRINTINGS IN EIGHT MONTHS

Dr. Cotton's clinical and teaching experience in this field has especially fitted him to write a practical work on this subject. He has written a book clear and definite in style, systematic in presentation, and accurate in statement. The illustrations possess the feature of showing just those points the author wishes to emphasize. This is made possible because the author is himself the artist.

Boston Medical and Surgical Journal

"The work is delightful, spirited, scholarly, and original, and is not only a book of reference, but a book for casual reading. It brings the subject up to date, a feat long neglected."

Murphy's Famous Clinics

Surgical Clinics of John B. Murphy, M. D., at Mercy Hospital, Chicago. Issued serially, one number every other month (six numbers a year). Each issue about 150 octavo pages, illustrated. Per year: $8.00; Cloth, $12.00. Sold only by the year.

DOWN-TO-THE-MINUTE SURGERY

This is just the work you have been waiting for—a permanent record of the teachings of this great surgeon. These are *not* students' clinics, but delivered at Mercy Hospital, Chicago, *for physicians only*. They are *postgraduate clinics*. These CLINICS are published *just as delivered* by Dr. Murphy, an expert stenographer taking down everything Dr. Murphy says and does. In this way these CLINICS retain all that individual force and charm so characteristic of the clinical teaching of this distinguished surgeon. But the most vital point about *these* CLINICS is that they are *absolutely fresh*. They are surgery—practical, *applied* surgery—right down to the minute, published practically as soon as delivered. There is no stale matter. Everything is *new, never having appeared in print before*. It is all *live* clinical material.

Crandon and Ehrenfried's Surgical After-treatment

Surgical After-treatment. A Manual of the Conduct of Surgical Convalescence. By L. R. G. CRANDON, M. D., Assistant in Surgery, and ALBERT EHRENFRIED, M. D., Assistant in Anatomy, Harvard Medical School. Octavo of 831 pages, with 265 original illustrations. Cloth, $6.00 net; Half Morocco, $7.50 net.

THE NEW (2d) EDITION, PRACTICALLY REWRITTEN

This work tells how best to manage all problems and emergencies of surgical convalescence from recovery-room to discharge. It gives *all the details* completely, definitely, yet concisely, and does not refer the reader to some other work perhaps not then available. The post-operative conduct of all operations is given, arranged alphabetically by regions. A special feature is the elaborate chapter on *Vaccine Therapy, Immunization by Inoculation and Specific Sera*, by Dr. George P. Sanborn, a disciple of Sir A. E. Wright. The text is illustrated.

The Therapeutic Gazette

"The book is one which can be read with much profit by the active surgeon and will be generally commended by him."

Papers from the Mayo Clinic

Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic. By WILLIAM J. MAYO, M. D., CHARLES H. MAYO, M. D., and their ASSOCIATES at St. Mary's Hospital, Rochester, Minn. Papers of 1905–1909, Papers of 1910, Papers of 1911, Papers of 1912. Each an octavo of about 600 pages, well illustrated. Per volume: Cloth, $5.50 net.

PAPERS OF 1912 NOW READY

Many of these papers have been read before medical societies and all of them have been published in current medical literature. The chief reason for bringing them together in the present form is for convenience of reference. The original plan was to have the papers printed for private distribution only, but at the instance of numerous members of the medical profession, the authors have consented to having the book placed on the market. The text is profusely illustrated with original illustrations.

Bulletin Medical and Chirurgical Faculty of Maryland

"Much of the work done at the Mayo Clinic and recorded in these papers has been epoch-making in character. * * * Represents a most substantial block of modern surgical progress."

A Collection of Papers (published previous to 1909). By WILLIAM J. MAYO, M. D., and CHARLES H. MAYO, M. D. Two octavos of 525 pages each, illustrated. Per set: Cloth, $10.00 net.

Mumford's Practice of Surgery

The Practice of Surgery. By JAMES G. MUMFORD, M. D., Instructor in Surgery, Harvard Medical School. Octavo of 1015 pages, with 682 illustrations. Cloth, $7.00 net; Half Morocco, $8.50 net.

DIFFERENT FROM OTHER SURGERIES

This, as its title implies, is a work on the *clinical* side of surgery—surgery as it is seen at the bedside, in the accident ward, and in the operating room. It expresses the matured outgrowth of twenty years of active hospital and private surgical practice, together with the experience gained from clinical teaching, classroom discussions, and lectures.

John B. Murphy, M.D., *Professor of Surgery, Northwestern Medical School, Chicago.*

"This work truly represents Dr. Mumford's intellectual capacity and scope, and presents in a terse, forceful, yet pleasing manner, the live surgical topics of the day. It is in every particular up to date, and shows that rare quality of accentuating the essential and omitting the unnecessary."

DaCosta's Modern Surgery

Modern Surgery—GENERAL AND OPERATIVE. By JOHN CHALMERS DACOSTA, M. D., Samuel D. Gross Professor of Surgery, Jefferson Medical College, Philadelphia. Octavo of 1525 pages, with 1085 illustrations.

JUST READY—NEW (7th) EDITION

A surgery, to be of the maximum value, must be up to date, must be complete, must have behind its statements the sure authority of experience, must be so arranged that it can be consulted quickly; in a word, it must be practical and dependable. Such a surgery is DaCosta's. Always an excellent work, for this edition it has been very materially improved by the addition of new matter to the extent of over 200 pages and by a most thorough revision of the old matter. Many old cuts have been replaced by new ones, and nearly 150 additional illustrations have been added. Notwithstanding this large addition of matter, the *price has not been increased.*

Rudolph Matas, M. D., *Professor of Surgery, Tulane University of Louisiana.*

"This edition is destined to rank as high as its predecessors, which have placed the learned author in the fore of text-book writers. The more I scrutinize its pages the more I admire the marvelous capacity of the author to compress so much knowledge in so small a space."

Scudder's Treatment of Fractures

WITH NOTES ON DISLOCATIONS

The Treatment of Fractures: with Notes on a few Common Dislocations. By CHARLES L. SCUDDER, M.D., Surgeon to the Massachusetts General Hospital, Boston. Octavo of 708 pages, with 994 original illustrations. Polished Buckram, $6.00 net; Half Morocco, $7.50 net.

THE NEW (7th) EDITION, ENLARGED
OVER 33,500 COPIES

The fact that this work has attained a seventh edition indicates its practical value. In this edition Dr. Scudder has made numerous additions throughout the text, and has added many new illustrations, greatly enhancing the value of the work. In every way this new edition reflects the very latest advances in the treatment of fractures.

J. F. Binnie, M.D., University of Kansas

"Scudder's Fractures is the most successful book on the subject that has ever been published. I keep it at hand regularly."

Scudder's Tumors of the Jaws

Tumors of the Jaws. By CHARLES L. SCUDDER, M.D., Surgeon to the Massachusetts General Hospital, Boston. Octavo of 395 pages, with 353 illustrations, 6 in colors. Cloth, $6.00 net; Half Morocco, $7.50 net.

WITH NEW ILLUSTRATIONS

Dr. Scudder in this book tells you how to determine in each case the *form* of new growth present and then points out the best treatment. As the tendency of malignant disease of the jaws is to grow into the accessory sinuses and toward the base of the skull, an intimate knowledge of the anatomy of these sinuses is essential. Dr. Scudder has included, therefore, sufficient anatomy and a number of illustrations of an anatomic nature. Whether general practitioner or surgeon, you need this new book because it gives you just the information you want.

Sisson's Veterinary Anatomy

Text-Book of Veterinary Anatomy. By SEPTIMUS SISSON, S. B., V. S., Professor of Comparative Anatomy in Ohio State University. Octavo volume of 826 pages, with 588 illustrations, mostly original and many in colors. Cloth, $7.00 net; Half Morocco, $8.50 net.

WITH SUPERB ILLUSTRATIONS

This is a clear and concise statement of the essential facts regarding the structure of the principal domesticated animals, containing many hitherto unpublished data resulting from the detailed study of formalin-hardened subjects and frozen sections. Nearly all of the illustrations are original, the majority being reproduced from photographs, and colors frequently used. The terminology has been carefully revised with reference to the B. N. A. and the nomenclature adopted by European comparative anatomists.

Boston Medical and Surgical Journal

"It is not amiss to say that the work ranks with the best. A marked advance in English veterinary literature, upon which student and practitioner may well congratulate themselves and no medical school can afford to be without. It is an exhaustive gross anatomy of the horse, ox, pig, and dog, including the splanchnology of the sheep."

Gant on Constipation and Intestinal Obstruction

Constipation and Intestinal Obstruction. By SAMUEL G. GANT, M. D., Professor of Diseases of the Rectum and Anus, New York Post-Graduate Medical School and Hospital. Octavo of 559 pages, with 250 original illustrations. Cloth, $6.00 net; Half Morocco, $7.50 net.

INCLUDING RECTUM AND ANUS

In this work the consideration given to the medical treatment of constipation is unusually extensive. The practitioner will find of great assistance the chapter devoted to formulas. The descriptions of the operative procedures are concise, yet fully explicit.

The Proctologist

"Were the profession better posted on the contents of this book there would be less suffering from the ill effects of constipation. We congratulate the author on this most complete book."

Kelly & Noble's Gynecology and Abdominal Surgery

Gynecology and Abdominal Surgery. Edited by HOWARD A. KELLY, M.D., Professor of Gynecology in Johns Hopkins University; and CHARLES P. NOBLE, M.D., formerly Clinical Professor of Gynecology in the Woman's Medical College, Philadelphia. Two imperial octavo volumes of 950 pages each, containing 880 original illustrations, some in colors. Per volume: Cloth, $8.00 net; Half Morocco, $9.50 net.

WITH 880 ILLUSTRATIONS—TRANSLATED INTO SPANISH

This work possesses a number of valuable features not to be found in any other publication covering the same fields. It contains a chapter upon the bacteriology and one upon the pathology of gynecology, and a large chapter devoted entirely to *medical gynecology*, written especially for the physician engaged in general practice. *Abdominal surgery* proper, as distinct from gynecology, is fully treated, embracing operations upon the stomach, intestines, liver, bile-ducts, pancreas, spleen, kidneys, ureter, bladder, and peritoneum.

American Journal of Medical Sciences

"It is needless to say that the work has been thoroughly done; the names of the authors and editors would guarantee this, but much may be said in praise of the method of presentation, and attention may be called to the inclusion of matter not to be found elsewhere."

Bickham's Operative Surgery

A Text-Book of Operative Surgery. By WARREN STONE BICKHAM, M.D., of New York. Octavo of 1200 pages, with 854 original illustrations. Cloth, $6.50 net; Half Morocco, $8.00 net.

THE NEW (3d) EDITION

This work completely covers the surgical anatomy and operative technic involved in the operations of general surgery. The practicability of the work is particularly emphasized in the 854 magnificent illustrations.

Boston Medical and Surgical Journal

"The book is a valuable contribution to the literature of operative surgery. It represents a vast amount of careful work and technical knowledge on the part of the author. For the surgeon in active practice or the instructor of surgery it is an unusually good review of the subject."

Eisendrath's Surgical Diagnosis

A Text-Book of Surgical Diagnosis. By DANIEL N. EISENDRATH, M.D., Professor of Surgery in the College of Physicians and Surgeons, Chicago. Octavo of 885 pages, with 574 entirely new and original text-illustrations and some colored plates. Cloth, $6.50 net; Half Morocco, $8.00 net.

THE NEW (2d) EDITION

Of first importance in every surgical condition is a correct diagnosis, for upon this depends the treatment to be pursued; and the two—diagnosis and treatment—constitute the most practical part of practical surgery. Dr. Eisendrath takes up each disease and injury amenable to surgical treatment, and sets forth the means of correct diagnosis in a systematic and comprehensive way. Definite directions as to methods of examination are presented clearly and concisely, providing for all contingencies that might arise in any given case. Each illustration indicates precisely how to diagnose the condition considered.

Surgery, Gynecology, and Obstetrics

"The book is one which is well adapted to the uses of the practising surgeon who desires information concisely and accurately given. . . . Nothing of diagnostic importance is omitted, yet the author does not run into endless detail."

Eisendrath's Clinical Anatomy

A Text-Book of Clinical Anatomy. By DANIEL N. EISENDRATH, A.B., M.D., Professor of Surgery in the College of Physicians and Surgeons, Chicago. Octavo of 535 pages, illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

THE NEW (2d) EDITION

This new anatomy discusses the subject from the clinical standpoint. A portion of each chapter is devoted to the examination of the living through palpation and marking of surface outlines of landmarks, vessels, nerves, thoracic and abdominal viscera. The illustrations are from new and original drawings and photographs. This edition has been carefully revised.

Medical Record, New York

"A special recommendation for the figures is that they are mostly original and were made for the purpose in view. The sections of joints and trunks are those of formalinized cadavers and are unimpeachable in accuracy."

Fenger Memorial Volumes

Fenger Memorial Volumes. Edited by LUDVIG HEKTOEN, M. D., Professor of Pathology, Rush Medical College, Chicago. Two octavos of 525 pages each. Per set: Cloth, $15.00 net; Half Morocco, $18.00 net.

LIMITED EDITION

These handsome volumes consist of all the important papers written by the late Christian Fenger, for many years professor of surgery at Rush Medical College, Chicago. Not only the papers published in English are included, but also those which originally appeared in Danish, German, and French.

The name of Christian Fenger typifies thoroughness, extreme care, deep research, and sound judgment. His contributions to the advancement of the world's surgical knowledge are indeed as valuable and interesting reading to-day as at the time of their original publication. They are pregnant with suggestions. Fenger's literary prolificacy may be judged from this memorial volume—over 1000 pages.

Sobotta *and* McMurrich's Human Anatomy

Atlas and Text-Book of Human Anatomy. In Three Volumes. By J. SOBOTTA, M.D., of Würzburg. Edited, with additions, by J. PLAYFAIR MCMURRICH, A. M., PH. D., Professor of Anatomy, University of Toronto, Canada. Three large quartos, each containing about 250 pages of text and over 300 illustrations, mostly in colors. Per volume: Cloth, $6.00 net; Half Morocco, $7.50 net.

VOLUME III NOW READY—COMPLETING THE WORK

The great advantage of this over other similar works lies in the large number of magnificent lithographic plates which it contains, without question the best that have ever been produced in this field. They are accurate and beautiful reproductions of the various anatomic parts represented.

Edward Martin, M.D., *Professor of Clinical Surgery, University of Pennsylvania.*

"This is a piece of bookmaking which is truly admirable, with plates and text so well chosen and so clear that the work is most useful to the practising surgeon."

Morris' Dawn of the Fourth Era in Surgery

DAWN OF THE FOURTH ERA IN SURGERY AND OTHER ARTICLES. By ROBERT T. MORRIS, M. D., Professor of Surgery, New York Post-Graduate Medical School and Hospital. 12mo of 145 pages, illustrated. $1.25 net.

Moynihan's Duodenal Ulcer

Duodenal Ulcer. By B. G. A. MOYNIHAN, M.S. (LONDON), F.R.C.S., Leeds, England. Octavo of 486 pages, illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

THE NEW (2d) EDITION

For this edition the work has been entirely reset and brought up to date. All the cases operated upon since the appearance of the first edition have been included and a new chapter added on Jejunal and Gastro-jejunal Ulcers.

Moynihan's Abdominal Operations

Abdominal Operations. By B. G. A. MOYNIHAN, M. S. (LONDON), F. R. C. S., Leeds, England. Octavo, beautifully illustrated.

THE NEW (3d) EDITION—PREPARING

Edward Martin, M. D., *University of Pennsylvania.*

"It is a wonderfully good book. He has achieved complete success in illustrating, both by words and pictures, the best technic of the abdominal operations now commonly performed."

Moynihan on Gall-stones

Gall-Stones and Their Surgical Treatment.—By B. G. A. MOYNIHAN, M. S. (LONDON), F. R. C. S., Leeds, England. Octavo of 458 pages, illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

THE NEW (2d) EDITION

Mr. Moynihan, in revising his book, has made many additions to the text, so as to include the most recent advances. Especial attention has been given to a detailed description of the early symptoms in cholelithiasis, enabling a diagnosis to be made in the stage in which surgical treatment can be most safely adopted.

British Medical Journal

"He expresses his views with admirable clearness, and he supports them by a large number of clinical examples, which will be much prized by those who know the difficult problems and tasks which gall-stone surgery not infrequently presents."

Dannreuther's Minor and Emergency Surgery

Minor and Emergency Surgery. By WALTER T. DANNREUTHER, M.D., Surgeon to St. Elizabeth's Hospital and to St. Bartholomew's Clinic, New York City. 12mo of 225 pages, illustrated. Cloth, $1.25 net.

ILLUSTRATED

Dr. Dannreuther emphasizes just those points most necessary in emergency work, giving numerous hints and suggestions that cannot help but be of great value to you in emergency work and in minor operations.

Schultze and Stewart's Topographic Anatomy

Atlas and Text-Book of Topographic and Applied Anatomy. By PROF. DR. O. SCHULTZE, of Würzburg. Edited, with additions, by GEORGE D. STEWART, M. D., Professor of Anatomy and Clinical Surgery, University and Bellevue Hospital Medical College, N. Y. Large quarto of 189 pages, with 25 colored figures on 22 colored lithographic plates, and 89 text-cuts, 60 in colors. Cloth, $5.50 net.

Griffith's Hand-Book of Surgery

A Manual of Surgery. By FREDERIC R. GRIFFITH, M. D., Surgeon to the Bellevue Dispensary, New York City. 12mo of 579 pages, with 417 illustrations. Flexible leather, $2.00 net.

Keen's Addresses and Other Papers

Addresses and Other Papers. Delivered by WILLIAM W. KEEN, M. D., LL.D., F. R. C. S. (Hon.), Professor of the Principles of Surgery and of Clinical Surgery, Jefferson Medical College, Philadelphia. Octavo volume of 441 pages, illustrated. Cloth, $3.75 net.

Keen on the Surgery of Typhoid

The Surgical Complications and Sequels of Typhoid Fever. By WM. W. KEEN, M.D., LL.D., F.R.C.S. (Hon.), Professor of the Principles of Surgery and of Clinical Surgery, Jefferson Medical College, Philadelphia, etc. Octavo volume of 386 pages, illustrated. Cloth, $3.00 net.

Gould's Operations on Intestines and Stomach

The Technic of Operations Upon the Intestines and Stomach. By ALFRED H. GOULD, M. D., of Boston. Large octavo, with 190 original illustrations, some in colors. Cloth, $5.00 net; Half Morocco, $6.50 net.

Bier's Hyperemia

Second Edition

Bier's Hyperemic Treatment in Surgery, Medicine, and the Specialties: A Manual of its Practical Application. By WILLY MEYER, M. D., Professor of Surgery at the New York Post-Graduate Medical School and Hospital; and PROF. DR. VICTOR SCHMIEDEN, Assistant to Prof. Bier, University of Berlin, Germany. Octavo of 280 pages, with original illustrations. Cloth, $3.00 net.

"We commend this work to all those who are interested in the treatment of infections, either acute or chonic, for it is the only authoritative treatise we have in the English language."—*New York State Journal of Medicine.*

Haynes' Anatomy

A Manual of Anatomy. By IRVING S. HAYNES, M.D., Professor of Practical Anatomy, Cornell University Medical College. Octavo, 680 pages, with 42 diagrams and 134 full-page half-tones. Cloth, $2.50 net.

American Pocket Dictionary

New (8th) Edition

The American Pocket Medical Dictionary. Edited by W. A. NEWMAN DORLAND, A. M., M. D., Editor "American Illustrated Medical Dictionary." 677 pages. Full leather, limp, with gold edges, $1.00 net; with patent thumb index, $1.25 net.

McClellan's Art Anatomy

Anatomy in its Relation to Art. By GEORGE MCCLELLAN, M. D., Professor of Anatomy, Pennsylvania Academy of the Fine Arts. Quarto volume, 9 by 12½ inches, with 338 original drawings and photographs, and 260 pages of text. Dark blue vellum, $10.00 net; Half Russia, $12.50 net.

Fowler's Surgery

In Two Volumes

A Treatise on Surgery. By GEORGE R. FOWLER, M. D., Emeritus Professor of Surgery, New York Polyclinic. Two imperial octavos of 725 pages each, with 888 original text-illustrations and 4 colored plates. Per set: Cloth, $15.00 net; Half Morocco, $18.00 net.

International Text-Book of Surgery

Second Edition

The International Text-Book of Surgery. In two volumes. By American and British authors. Edited by J. COLLINS WARREN, M. D., LL. D., F. R. C. S. (Hon.), Professor of Surgery, Harvard Medical School; and A. PEARCE GOULD, M. S., F. R. C. S., of London, England. Vol. I.: *General and Operative Surgery.* Royal octavo, 975 pages, 461 illustrations, 9 full-page colored plates. Vol. II.: *Special or Regional Surgery.* Royal octavo, 1122 pages, 499 illustrations, and 8 full-page colored plates. Per volume: Cloth, $5.00 net; Half Morocco, $6.50 net.

American Text-Book of Surgery

Fourth Edition

American Text-Book of Surgery. Edited by W. W. KEEN, M. D., LL. D., HON. F. R. C. S., ENG. and EDIN., and J. WILLIAM WHITE, M. D., PH. D. Octavo, 1363 pages, 551 text-cuts and 39 colored and half-tone plates. Cloth, $7.00 net; Half Morocco, $8.50 net.

Robson and Cammidge on the Pancreas

The Pancreas: Its Surgery and Pathology. By A. W. MAYO ROBSON, F. R. C. S., of London, England; and P. J. CAMMIDGE, F. R. C. S., of London, England. Octavo of 546 pages, illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

American Illustrated Dictionary

The New (7th) Edition

The American Illustrated Medical Dictionary. With tables of Arteries, Muscles, Nerves, Veins, etc.; of Bacilli, Bacteria, etc.; Eponymic Tables of Diseases, Operations, Stains, Tests, etc. By W. A. NEWMAN DORLAND, M.D. Large octavo, 1107 pages. Flexible leather, $4.50 net; with thumb index, $5.00 net.

Howard A. Kelly, M.D., *Professor of Gynecology, Johns Hopkins University, Baltimore.*

"Dr. Dorland's dictionary is admirable. It is so well gotten up and of such convenient size. No errors have been found in my use of it."

Golebiewski and Bailey's Accident Diseases

Atlas and Epitome of Diseases Caused by Accidents. By DR. ED. GOLEBIEWSKI, of Berlin. Edited, with additions, by PEARCE BAILEY, M.D. Consulting Neurologist to St. Luke's Hospital, New York City. With 71 colored figures on 40 plates, 143 text-cuts, and 549 pages of text. Cloth, $4.00 net. *In Saunders' Hand-Atlas Series.*

Helferich and Bloodgood on Fractures

Atlas and Epitome of Traumatic Fractures and Dislocations By PROF. DR. H. HELFERICH, of Greifswald, Prussia. Edited, with additions, by JOSEPH C. BLOODGOOD, M. D., Associate in Surgery, Johns Hopkins University, Baltimore. 216 colored figures on 64 lithographic plates, 190 text-cuts, and 353 pages of text. Cloth, $3.00 net. *In Saunders' Atlas Series.*

Sultan and Coley on Abdominal Hernias

Atlas and Epitome of Abdominal Hernias. By PR. DR. G. SULTAN, of Gottingen. Edited, with additions, by WM. B. COLEY, M. D., Clinical Lecturer and Instructor in Surgery, Columbia University, New York. 119 illustrations, 36 in colors, and 277 pages of text. Cloth, $3.00 net. *In Saunders' Hand-Atlas Series.*

Warren's Surgical Pathology

Second Edition

Surgical Pathology and Therapeutics. By J. COLLINS WARREN, M.D., LL.D., F.R.C.S. (HON.), Professor of Surgery, Harvard Medical School. Octavo, 873 pages; 136 illustrations, 33 in colors. Cloth, $5.00 net; Half Morocco, $6.50 net.

Zuckerkandl and DaCosta's Surgery

Second Edition

Atlas and Epitome of Operative Surgery. By DR. O. ZUCKERKANDL, of Vienna. Edited, with additions, by J. CHALMERS DACOSTA, M.D., Samuel D. Gross Professor of Surgery, Jefferson Medical College, Philadelphia. 40 colored plates, 278 text-cuts, and 410 pages of text. Cloth, $3.50 net. *In Saunders' Atlas Series.*

Moore's Orthopedic Surgery

A Manual of Orthopedic Surgery. By JAMES E. MOORE, M.D., Professor of Clinical Surgery, University of Minnesota, College of Medicine and Surgery. Octavo of 356 pages, handsomely illustrated. Cloth, $2.50 net.

"The book is eminently practical. It is a safe guide in the understanding and treatment of orthopedic cases. Should be owned by every surgeon and practitioner."—*Annals of Surgery.*

Fowler's Operating Room

New (3d) Edition, Reset

The Operating Room and the Patient. By RUSSELL S. FOWLER, M. D., Surgeon to the German Hospital, Brooklyn, New York. Octavo of 611 pages, illustrated. Cloth, $3.50 net.

Dr. Fowler has written his book for surgeons, nurses assisting at an operation, internes, and all others whose duties bring them into the operating room. It contains explicit directions for the preparation of material, instruments needed, position of patient, etc., all beautifully illustrated.

Nancrede's Principles of Surgery

New (2d) Edition

Lectures on the Principles of Surgery. By CHAS. B. NANCREDE, M.D., LL.D., Professor of Surgery and of Clinical Surgery, University of Michigan, Ann Arbor. Octavo, 407 pages, illustrated. Cloth, $2.50 net.

"We can strongly recommend this book to all students and those who would see something of the scientific foundation upon which the art of surgery is built."—*Quarterly Medical Journal, Sheffield, England.*

Nancrede's Essentials of Anatomy.

Seventh Edition

Essentials of Anatomy, including the Anatomy of the Viscera. By CHAS. B. NANCREDE, M.D., Professor of Surgery and of Clinical Surgery, University of Michigan, Ann Arbor. Crown octavo, 388 pages; 180 cuts. With an Appendix containing over 60 illustrations of the osteology of the body. Based on *Gray's Anatomy.* Cloth, $1.00 net. *In Saunders' Question Compends.*

"The questions have been wisely selected, and the answers accurately and concisely given."—*University Medical Magazine.*

Martin's Essentials of Surgery.

Seventh Edition Revised

Essentials of Surgery. Containing also Venereal Diseases, Surgical Landmarks, Minor and Operative Surgery, and a complete description, with illustrations, of the Handkerchief and Roller Bandages. By EDWARD MARTIN, A.M., M.D., Professor of Clinical Surgery, University of Pennsylvania, etc. Crown octavo, 338 pages, illustrated. With an Appendix on Antiseptic Surgery, etc. Cloth, $1.00 net. *In Saunders' Question Compends.*

"Written to assist the student, it will be of undoubted value to the practitioner, containing as it does the essence of surgical work."—*Boston Medical and Surgical Journal.*

Martin's Essentials of Minor Surgery, Bandaging, and Venereal Diseases.

Second Revised Edition

Essentials of Minor Surgery, Bandaging, and Venereal Diseases. By EDWARD MARTIN, A.M., M.D., Professor of Clinical Surgery, University of Pennsylvania, etc. Crown octavo, 166 pages, with 78 illustrations. Cloth, $1.00 net. *In Saunders' Question Compends.*

"The best condensation of the subjects of which it treats yet placed before the profession."—*The Medical News, Philadelphia.*