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EXPERIMENTAL RESEARCH IN SYPHILIS

WITH ESPECIAL REFERENCE TO SPIROCHÆTA PALLIDA (TREPONEMA PALLIDUM)

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According to history, syphilis was not known, or, at least, was not recognized in Europe, until toward the end of the fifteenth century. It is considered probable that it was first introduced into Europe from America by the sailors of Columbus. The epidemic form with which this disease ravaged Europe in those early days has suggested that it is caused by a transmissible virus. No definite search, however, for such an infectious agent was possible until the discovery of the microscope. The first one to describe an organism in syphilitic lesions was Donné, who, in 1837, found a spiral organism to which Müller gave the name of *Vibrio lineola*. As no sharp differentiation between the non-syphilitic and syphilitic lesions had been yet established at that time, the finding of a spiral organism was inadequate to prove that it had any etiologic relation to syphilis. Bassereau, in 1852, rendered a great service by separating definitely the venereal sore from the true chancre, thus giving the basis for accurate investigations.

Research in syphilis became henceforth increasingly active, and the discoveries of the causative organism were announced year after year from different quarters, only to be disproved after a shorter or longer period of refutation and controversy among the investigators at the time. Hallier, in 1869, found in the syphilitic blood his *Coniothecium syphiliticum* and held it as the cause. Lostorfers, in 1872, announced his discovery of minute sparkling granules in the syphilitic blood which was kept for a few days in a moist chamber, but his finding was discredited by Neumann, Biesiadecki, Vajda and others. Then came, in 1878-9, Klebs' discovery in chancre-juice of numerous actively mobile granules and rods which he called *Helicomonades*. In 1882, Birch-Hirschfeld stained in the tissues from gumma, papules and chancres, minute bacteria which others considered as mast-cell granules, while Martineau and Hamonic reported in the same year their alleged success in reproducing the syphilitic lesions in pigs and monkeys with their bouillon cultures of cocci and bacteria. In 1884, the well-known discovery of Lustgarten was heralded from Weigert's laboratory. He demonstrated the presence of a bacillus in certain syphilitic products which resembled the tubercle bacillus discovered by Koch in 1882. The finding was confirmed by a number of reputable bacteriologists, among whom were Doutrelepont, Schütze, Giletti, de Giacomi, Gottstein, Babes and Baumgarten. It soon met with severe criticism, however, by Alvarez, Tavel, Klemperer, Matterstock, Bitter and many others, who not only failed to find this bacillus in the sections of the syphilitic tissues, but found it in other diseases as well as in normal smegma. Thus the discovery of Lustgarten gradually passed from general interest. In spite of Lustgarten's mistake, a great many investigators went further on to find the real organism of syphilis. Most of them described the cocci-like granules in the blood or lesions of syphilities and claimed to have obtained pure cultures of so-called syphilis bacillus or syphilis coccus from the blood or glands. Van Niessen still asserts that a polymorphous bacillus which he obtained from the syphilitic blood and named *syphilomyces* is the cause of syphilis. He maintains that *Spirochæta pallida* is only one of the life cycles of this bacillus, although Hoffmann points out that there is absolutely no resemblance between the *pallida* and Van Niessen's bacillus in any stage of development. Similar bacilli were reported to be present in the syphilitic blood, by de Lisle and Jullien, Paulsen, Joseph and Piorkowski, but they are now considered to be due to external contamination. There are also certain investigators who claim to have found protozoa in syphilitic products, but their findings were soon disproved as mostly due to the artefact or decomposition products.

THE DISCOVERY OF SPIROCHÆTA PALLIDA

The new era in the experimental research in syphilis began with the successful transmission of syphilitic lesions to higher apes by Metchnikoff and Roux in 1903. This opened up the field by furnishing a means of studying the nature of the causative agent of syphilis outside of human subjects. Thus Klingmüller and Baermann determined that the virus of syphilis does not pass through filters and does not, therefore, belong to an ultramicroscopic organism. The finding was confirmed by Metchnikoff. These two findings, the transmissibility to certain animals, and non-filtrability through porcelain bougies of the syphilitic virus, have exerted a great influence in enticing competent microscopists and biologists to attempt anew a thorough search for the virus, for they have learned that the organism lies within the limit of visibility.

It was not, however, until 1905 that an organism which was destined to gain universal recognition as the long-sought virus of syphilis, was viewed for the first time by Fritz Schaudinn in a joint investigation with Erich Hoffmann. Schaudinn found in the aspirated juice from the swollen inguinal glands of a syphilitic a faintly visible, extremely delicate small spirochete in fresh preparations. The organism, stained faintly with Giemsa's solution, was paler than any spirochete known

* From the Laboratory of The Rockefeller Institute for Medical Research.

* Fenger-Senn Memorial Address, delivered before the Chicago Medical Society, March 13, 1912.

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to him at that time; hence he gave it the name of *Spirochæta pallida*,* renaming it *Treponema pallidum* in the same year. Schaudinn and Hoffmann examined a series of syphilitic and non-syphilitic patients and found that the *pallida* was almost always present in syphilitic lesions, but never in other diseases. They have described at the same time another, quite larger, irregularly and less curved spirochete which was found in non-syphilitic as well as syphilitic lesions on genitals. The name of *Spirochæta refringens* was given to this form. The discovery was soon confirmed with amazing rapidity by different investigators who demonstrated the *pallida* in various lesions, blood-vessels, internal organs, blood, spermatozoa, ova, and other body-fluids of syphilitic patients. Through the investigations of Buschke, Fischer, Levaditi, Salmon, Hoffmann, Paschen, Bertarelli, Volpino, Babes, Panea, Flexner, and many others, the *pallida* was demonstrated in abundant number in different organs and tissues of syphilitic children and fetuses. The organism was also found by Metchnikoff and Roux in the lesions in monkeys produced directly with human virus or indirectly through transmission of the virus from animal to animal. Soon afterward Truffi, Bertarelli, E. Hoffmann, Uhlenhuth, Mulzer, Nichols and others succeeded in infecting rabbits, guinea-pigs and lower monkeys, and have constantly found the *pallida* in the lesions. The transmissions of the *pallida* from man to monkey, monkey to rabbit, and rabbit to monkey, for many generations, has been carried on by Hoffmann and Nichols. The testicles of rabbits were especially suitable for purifying the *pallida* from the associating organisms, as the latter disappear completely after passing one generation, through the rabbit's testicle. Uhlenhuth and Mulzer were able to produce generalized syphilis in young rabbits by the intracardial inoculation with testicular strains of the *pallida*.

Thus *Spirochæta pallida*, Schaudinn, fulfilled almost all the requirements laid down by Koch before being accepted as the causative agent of syphilis. The only missing link was that a pure culture of this organism should be able to produce the pathologic changes in experimental animals similar to those found in human syphilis.

CULTIVATION OF SPIROCHÆTA PALLIDA

1. *Mixed Cultures.*—Many investigators failed to obtain any growth of the *pallida* outside of the animal body. In 1907, Levaditi, Yamanouchi and others, found that the *pallida* remain motile in a colloidin sac filled with monkey serum and kept for many weeks in the peritoneal cavity of a monkey. The impure cultures thus obtained were non-virulent for any animal. In 1909, Schereschewsky reported that an impure culture of *pallida* may be obtained by inserting a piece of chancre into a high-layer tube of gelatinized horse serum. The success was not uniform, and he says that when the original material contained a virulent strain for rabbits or monkeys no growth in his horse serum was observed. Inversely, an impure growth may take place when the material used was non-virulent. All his cultures were non-pathogenic for monkeys and rabbits. It is difficult to decide whether his impure cultures contained an avirulent *pallida* or a certain spirochete indistinguishable from the *pallida*, because in a culture, morphology alone is no criterion for identifying the *pallida*. In 1910, Bruckner and Galasesco reported a successful production of syphilitic orchitis in rabbits by means of an impure culture in gelatinized ascitic fluid in which the original syphilitic tissue was still present. Sowade, in 1911, reported a successful generalization of syphilis in a rabbit through the intracardiac inoculation of an impure culture in gelatinized horse serum. In this case the rabbit showed scattered lesions over the body in which the *pallida* were found.

2. *Pure Cultures.*—There are up to the present date three investigators who claim to have succeeded in cultivating *Spirochæta pallida* in pure state, Mühlens, W. H. Hoffmann, and myself. Mühlens published his first article in 1909 and the second in 1910, asserting that he obtained one strain of the *pallida* in pure culture. W. H. Hoffmann, who has assisted Mühlens, continued to work alone a little longer and reported, in 1911, that he was able to isolate five more strains of the same organism as Mühlens. The method of cultivation consisted of the use of Schereschewsky's horse serum for obtaining an impure culture and then purifying it in a horse-serum agar (deep layer). The claim of Mühlens that his spirochete was a *pallida* was based entirely on the similarity of the morphology between the cultivated organism and the *pallida*, because no pathogenicity whatever was possessed by his culture. In his first report, W. H. Hoffmann mentions, also, that none of the strains of the organism cultivated by him was pathogenic. Later, in a brief report, this investigator claims to have produced an orchitis in rabbit by means of one of his cultures. He ascribes his earlier failure to accomplish this to the use of an insufficient quantity of culture. The pathologic changes produced by his culture as described by him were by no means convincing as a syphilitic nature. He succeeded in cultivating back his spirochete which, like all the other cultures of these two workers, developed a penetrating putrefactive odor. In regard to the differentiation of the organism isolated by them, both authors make very little mention, saying that the general characteristics of the culture are indistinguishable from those of *Spirochæta dentium* cultivated by Mühlens in 1906. Like the *dentium*, the spirochete of Mühlens and W. H. Hoffmann grows in a horse-serum agar without the addition of any fresh tissue, and produces a strong putrefactive odor. The differences which their spirochete presents in contrast to the *pallida* isolated by me, as will be presently described, are striking. Furthermore, as will be seen later on, there is absolutely no difference between *Treponema microdentium* isolated by me and the so-called *pallida* of these two authors.

Since 1910 I have been working on the cultivation of *Spirochæta pallida* and have succeeded in isolating six different strains from the orchitis material of rabbits and seven directly from chancres, condylomata and skin papules of human subjects. The methods used are different, according to whether the *pallida* is to be cultivated from the orchitis of rabbits or directly from man. For the former, which contains the *pallida* in almost pure state, a fluid medium is preferred. A serum-water containing a piece of sterile fresh tissue is inoculated with the emulsion of the spirochete and cultivated under most strictly anaerobic conditions. After the first generation of the growth is obtained, it is more and more acclimated to the artificial cultural conditions by passing repeated subcultures in the fluid media. Then the *pallida* is transferred to a solid medium containing the suitable nutriments and fresh tissues. If the culture is impure, it can be purified in solid media by a special technic.

* For the mere traditional reason I have employed this designation in the present article. When the subject is considered from the systematic or zoologic point of view, the term *Treponema pallidum* is preferred, as has been my custom in other papers.

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On the other hand, a fluid medium is unsuitable for obtaining a growth of the spirochete when the human material is utilized, because the medium undergoes, through the growth of the accompanying bacteria, such changes that it renders the medium unfit for the growth of *pallida*. For this reason, I have resorted to the use of a solid medium consisting of one part of ascitic fluid and two parts of weakly alkaline agar with a piece of sterile fresh tissue at the bottom. The percentage of success depends on the suitableness of the medium which can vary considerably with different specimens of ascitic fluids used, and also on the adaptability on the part of the strains of the *pallida*. The method of purification and other minor technical points will be found in my previous papers.

The six orchitis strains and seven human strains of the *pallida* thus obtained are identical in morphologic and cultural characteristics. They grow slowly and steadily around the tissues and form very faint diffuse undefined colonies extending gradually. The spirochete is strictly anaerobic and requires the presence of a fresh sterile tissue for development. It does not attack the protein constituents of the tissue or serum, nor does it produce an odor in growth in any medium. The cultivated *pallida* is less actively motile, but the variety of the movements is characteristic. Under unfavorable cultural conditions its morphology becomes less typical. The growth continues for several weeks. It has been noticed that the *pallida* strains isolated from the rabbit's orchitis grow more luxuriantly in a medium containing rabbit serum, while those from human chancres prefer the ascitic fluid agar. It appears as if the passage of the *pallida* through the rabbit's body modified the biologic property of this organism.

In regard to the pathogenicity, I have succeeded in producing typical orchitis in several rabbits by means of pure cultures of the orchitis strains. With the human strains I was able to produce the initial lesions on the skin of *Macacus rhesus* and *Cercopithecus callitrichus*. The Wassermann reaction developed in these monkeys after the appearance of the induration, several weeks after the inoculation.

The above identification of my cultivated *pallida* strains seems to amply justify my assertion, but I am now in the position to offer further evidences of its identity by means of the immunity and allergic reactions. For a fuller discussion, I will return to this topic later, but a brief statement is made here.

Several series of experiments[1] on rabbits were conducted with the purpose of producing the specific antibodies for the cultivated *pallida* and the tissue *pallida* (rabbit's orchitis). After a prolonged immunization, the serums of these rabbits were tested for the antibodies by means of a specific complement fixation test using the spirochete extract as antigen. It was found that the immune serums prepared with the cultivated *pallida* fix the complement with the antigen derived from the *pallida* of rabbit's orchitis as well as from the culture. The immune serums prepared with the orchitis tissue *pallida* reacted also with both antigens. On the other hand, both sets of the immune serums gave negative reactions with the antigens made of the pure cultures of mouth spirochetes or *Spirochæta refringens*. The mutually interchangeable reaction between the cultivated *pallida* and the tissue *pallida* establishes completely the identity of the two. It is also found that the rabbits sensitized with the orchitis *pallida* by repeated inoculation show the allergic skin reaction to the cultivated *pallida* extract (luetin) as well as to the tissue *pallida* extract. They do not react to the extracts of the *dentium* or *refringens*. This phenomenon adds further evidence that the spirochete cultivated and claimed by me to be the *pallida* is identical with the *pallida* found in the syphilitic tissues.

1. Partly aided by Dr. J. Bronfenbrenner.

DIFFERENTIATION OF SPIROCHÆTA PALLIDA AND CERTAIN MORPHOLOGICALLY AND CULTURALLY ALLIED SPECIES

The identification of a microorganism depends on a series of characteristics possessed by each organism. As the deviation of one member from the closely related members of the same family is only gradual and partial, it becomes important to discover as many individual characteristics as possible of each of them. The differentiation may thus become possible by pointing out one or more differences between the two, in spite of the presence of numerous other properties in common. It may happen that two organisms possess almost indistinguishable morphology, but grow differently, while their morphology may be quite different, yet present similar appearance in growth. Every pathologist knows that the morphologic variations can exist to a considerable extent among different strains of the same organism and offer confusion when one attempts to differentiate it from the morphologic side. Fortunately, we are now in possession of certain indirect methods of identification in such cases, and this often carries more conviction than the most of the other evidences. These indirect methods are the phenomena of immunity and anaphylaxis. While the immunity phenomena are liable to be deprived of their value of identification through occasional group reactions among allied species, yet when it occurs that there is none, it brings identification beyond any dispute. The same is true of the allergy. Another method of identification is applicable only when the organism is pathogenic for certain animals. By the nature of pathogenicity, an organism can be differentiated from the others. But, there is also a difficulty in utilizing this procedure for a definite differentiation, as certain strains of the same pathogenic organism may become attenuated or even avirulent during the cultivation. Hence the absence of pathogenicity in this instance constitutes no evidence that the organism is another species.

For the identification of the *pallida* cultivated by me, the above were taken into consideration.

It may be mentioned that I have succeeded in cultivating *Spirochæta macrodentium*, *Spirochæta microdentium* and *Spirochæta refringens* in pure state and employed them for comparative studies with *Spirochæta pallida*.

Spirochæta pallida is indistinguishable from *Spirochæta microdentium* by the morphologic characteristics, but is well differentiated from the latter by the requirement of tissue for growth, the absence of a putrefactive odor, the pathogenic property, the positive complement fixation with the antiserum produced in animals by immunizing them with pure *pallida* extract (such as the syphilitic orchitis of rabbit), and its capability of inciting an allergic reaction in syphilitic patients. The *macrodentium* and *refringens* can be easily differentiated from the *pallida* by their morphology alone, although they behave quite differently in other respects as well.

Now, turning our attention to the spirochetes cultivated and claimed by Mühlens and W. H. Hoffmann to be the *pallida*, it becomes clear that their spirochete corresponds with *Spirochæta microdentium* in every

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principal characteristic, and disagrees with the *pallida* obtained by me. It appears quite strange that neither Mühlens nor W. H. Hoffmann has isolated even once a spirochete identical with my strains of the *pallida*, while W. H. Hoffmann states that he obtained his variety, which doubtless belongs to the *microdentium*, from five different lesions. Mühlens, it may be recalled, obtained this variety only once out of nearly eighty different specimens of syphilitic tissues. Whether the *microdentium* is more frequently associated in syphilitic lesions in Germany, it is difficult to say, but so far as my personal experience with numerous chancres and condylomata is concerned, I have never isolated a single strain of the *microdentium* from a syphilitic lesion outside of the oral cavity. It was for the purpose of avoiding such a confusion between the *microdentium* and the *pallida* that I had taken the trouble to use the rabbit's orchitis for cultivation in my first series of work, and later when cultivating the *pallida* directly from human syphilitic tissues, I never utilized the lesions in the mouth.

In identifying a cultivated spirochete with *Spirochæta pallida* the following points must be fulfilled:

1. The spirochete must be morphologically correct.
2. It must not produce a putrefactive odor.

tures. I was fortunate in obtaining ten different strains of the *pallida* in the testicles of rabbits and in studying them side by side. During my observations, extending over a period of over one year, I was struck with certain variations in their morphology and pathogenicity. Seven out of ten strains had the typical morphologic features and produced the diffuse orchitis in rabbits within three to four weeks, and progressed for about six to seven weeks. Then the orchitis usually retrogressed. Two strains were somewhat heavier than the average, and produced very hard nodules of cartilaginous consistency within eight weeks. The lesions increased in size very slowly, and remained for many weeks. The lesions on section showed much mucin and were difficult to crush. One strain, derived from a case of malignant syphilis, was somewhat thinner and attained a greater length than the average. It produced a soft diffuse swelling of the testicle within ten to fourteen days, progressing for several weeks. These characteristics were maintained unchanged for the entire period of observation.

Among the pure cultures I have observed similar variations in morphology. Of thirteen strains, eight show the typical morphologic features, two thicker and three thinner forms. The morphology of the thinner

TABLE 1.—POINTS OF DIFFERENTIATION OF SPIROCHETES

Varieties of Spirochetes	Requirement for Tissue	Production of Putrefaction Odor	Appearance of Growth	Pathogenicity	Dimension (Av.)	Curves (Average)	Movements	Complement Fixation with the Pallida Immune Serum	Allergic Reaction on Syphilitic Patients
Spirochæta pallida*	+	—	Diffuse, faint.	+	0.2-0.3 μ x 6-18 μ	Regular, deep. 4-16	Rotation.	+	+
Spirochæta microdentium*	—	+	Denser, more discrete.	—	0.2-0.25 μ x 5-18 μ	Regular, fairly deep. 4-20	Rotation.	—	—
Spirochæta macrodentium*	+	—	Diffuse, faint.	—	0.25-0.4 μ x 6-18 μ	Less regular. 3-14	Vibratory and rotation.	—	—
Spirochæta refringens*	—	—	Fairly well defined, faint.	—	0.5-0.75 μ x 6-20 μ	Irregular. 3-8	Wavy and serpentine.	—	—

* They all belong to genus *Treponema*.

3. It requires the addition of fresh tissue for growth.
4. Its extractor emulsion must bind complement with the immune serum (rabbit is preferred) produced by means of repeated injections of the tissue *pallida* (to be obtained from syphilitic orchitis of rabbits).
5. Its extract or emulsion must give an allergic reaction in certain cases of syphilis.
6. It should be pathogenic. The last requirement is highly important, but one cannot exclude the possibility of the organism still being the *pallida*, even if it is avirulent, as long as it fulfils the other five points, because it is not impossible that a strain of *pallida* may become attenuated in cultivation.

MORPHOLOGIC AND PATHOGENIC VARIATIONS IN SPIROCHÆTA PALLIDA

Hitherto but little attention has been paid to certain morphologic and pathogenic variations that exist among different strains of *Spirochæta pallida*. It is true that such variations can hardly be brought out through the usual microscopic examinations of different specimens of syphilitic material. It requires a careful comparative study on a large number of strains either carried through the animal body for many generations, or in pure cul-

type resembles that of *Spirochæta microdentium*, and it is almost impossible to differentiate under the microscope. Nevertheless, the other characteristics identify it as the *pallida*. It may be mentioned that different types of the *pallida* can be present together in one lesion, as I was able to obtain a thicker and a thinner form with the average strain.

The above seems to be a highly important distinction, and, if in the study of a still larger number of specimens of the *pallida*, it is maintained, it will throw light on certain important clinical features of the human syphilitic disease.

ALLERGY IN SYPHILIS

The peculiar change of reactivity in the system of individuals infected for some time with certain pathogenic microorganisms, as characterized by a hypersensitiveness to the incorporation of the constituents of the latter in a specific sense, has been recognized for a long time. Thus Koch's tuberculin test, von Pirquet's cutaneous test, Calmette-Wolff-Eisner's ophthalmic test in tuberculosis, the malein test in glanders, and similar reactions in various chronic or acute infectious diseases, have been discovered and become useful aids in diag-

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nosis. Recent studies on anaphylaxis with various proteids, as inaugurated by Theobald Smith and thoroughly investigated by Richet, Otto, Besredka, Rosenau, Anderson, von Pirquet, Shick, Friedberger, Kraus, Dörr, Auer, Lewis, Gay, Southard, Pfeiffer, Wells, and others, clearly established the specific nature of the phenomenon. The most interesting feature of the anaphylactic phenomenon lies in the fact that the hypersensitiveness to a foreign protein develops only when a certain period of cessation of the introduction of the substance is allowed to elapse before the next injection, which then produces the well-known symptoms. The continuation of inoculation at regular short intervals does not confer on the recipient of the foreign substance any anaphylaxis during this period. It is, therefore, more likely to develop an anaphylactic condition in those patients who are infected with certain organisms which remain in their body for a long period, during which their activity undergoes fluctuations either spontaneously, possibly partly owing to the production of certain antagonistic substances by the infected hosts, and partly owing to the nature of the infecting microorganism, or fluctuations through the usual therapeutic interference. The clinical course of syphilis indicates that the infecting agent, *Spirochæta pallida,* fulfils all the requirements that lead to the development of an anaphylactic condition in syphilitic patients. Theoretically one should not expect this condition to appear as long as the activity of the *pallida* is maintained at its maximum, as is the case with the early period of infection. But one can reasonably expect the appearance of this phenomenon when the activity of the organism is abated through the gradually acquired defensive power of the hosts, or under an effective therapeutic control. Thus we may find this condition to be present in later stages of the disease. Likewise, the cases of late hereditary syphilis would behave similarly. It will be seen later that the above theoretical points are well borne out by the practical results to be reported.

Syphilis is a chronic infectious disease, and presents many difficulties in diagnosis. During its very early period, it is principally a disease of dermatologic, genitourinary, and laryngologic fields. There the clinical appearance, demonstration of *Spirochæta pallida* and the Wassermann reaction usually settle the diagnosis. On the other hand, as soon as it enters its chronic course, it manifests most diverse and often obscure symptoms. The direct demonstration of the *pallida* becomes laborious and often impossible, the serum reaction less frequent, and the clinical aspect less decisive. A great many cases of the disease at this period now pass into the fields of medicine, surgery, ophthalmology, neurology, and psychiatry. Here the detection of the allergic condition will doubtless aid in deciding the diagnosis of dubious cases.

Since the discovery of *Spirochæta pallida,* various investigators have attempted to introduce a specific cutaneous reaction based on the allergy in syphilis. Thus, Meirosky, Wolff-Eisner, Munk, Tedeschi, Nobl, Ciuffo, Nicolas-Favre-Gauthier, Neisser-Bruck, Jadassohn and Fontana carried out a series of experiments by means of an extract obtained from syphilitic tissues containing the *pallida.* They were much handicapped by not having a pure *pallida* extract for such purposes. One can imagine the way in which an extract containing various bacteria besides the *pallida* would react. With such an impure antigen, some of them obtained quite favorable results, while others were unable to come to any conclusive result.

After obtaining the pure cultures of several strains of the *pallida,* in 1910-11, I commenced my experimental work on rabbits with the purpose of ascertaining if these animals could not be made allergic to the extract of pure *pallida.* By repeated intravenous injections of the *pallida* antigen into the rabbits for several months and then giving them a month's rest, I tested them with the extract, which was termed "luetin," given intradermally. A proper control was provided. They all reacted to the luetin with marked inflammation, some leading to pustulation in several days. No normal rabbit reacted. While I was still working with the animals, Professor Welch suggested that I make the test on human subjects. Through his encouragement, I commenced the work at once at different dispensaries and hospitals with the cooperation of the physicians in charge.

My series comprised several hundred cases, including syphilis, parasyphilis, non-syphilitic diseases, and normal individuals.

In the series just referred to, the luetin was made from only two strains of pure cultures of the *pallida.* Since then, I have been preparing it with at least six different strains, thus securing a polyvalent antigen. The luetin has been recently distributed to certain hospitals in this country and Europe and their results are not reported as yet. The first report on this subject published is by Cohen, who is applying the test to the

TABLE 2.—LUETIN REACTION IN VARIOUS SYPHILITIC CONDITIONS AND IN CONTROLS

	Primary Syphilis		Secondary Syphilis				Tertiary Syphilis				Congenital Syphilis				Cerebrospinal Syphilis		Latent Syphilis		Controls			
	Symptoms Present		Symptoms Present		Symptoms Absent		Symptoms Present		Symptoms Absent		Under 1 Year		Late Cases		Symptoms Present				Normal Individuals		Non-Syphilitic Cases	
Luetin reaction	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—
No antisyphilitic treatment.	..	13	..	..	..	..	..	..	..	..	..	..	..	..	..	..	24	6	..	50	..	200
Slight mercurial treatment.	1	12	2	25	..	..	12	..	..	..	5	18	..	..	..	..	..	..	..	..	..	...
Regular mercurial treatment.	..	..	..	..	14	3	31	..	29	1	1	3	15	1	5	5	..	..	..	..	..	...
Salvarsan and mercurial treatment.	..	..	1	..	42	12	..	..	22	3	..	..	9	..	..	..	..	..	..	..	..	...
	1	25	3	25	56	15	43	0	51	4	6	21	24	1	5	5	24	6	0	50	0	200
	26		99				98				52				10		30		250			
	315																					

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ophthalmologic conditions. His results show that the reaction is specific and offers much aid in diagnosis where either the seroreaction or the clinical symptoms are indecisive. The second report is by Orleman-Robinson, who applied the reaction to dermatologic conditions at several skin clinics in New York. The results of this investigator also confirm the specificity. The reaction was positive in all tertiary and hereditary cases, and absent in the primary and untreated secondary syphilis. It was not present in a large number of skin cases, including psoriasis, epithelioma, acne vulgaris, erythema multiformis, urticaria, alopecia areata, trichophytosis, erythema toxicum, bromid eruption, sycosis, scabies, pityriasis rosea, tinea versicolor, eczema, ulcus cruris, Darier's disease, eczema seborrheicum, and also pulmonary tuberculosis. Both investigators did their work at their clinics under the joint observations of their colleagues.

In certain cases of tertiary and hereditary syphilis, they have observed the so-called *Umstimmung* of Neisser, in which the control injection also reacted more or less markedly. This confirms my earlier observations.

Regarding the varieties of the luetin reaction, I have made the following types:

DESCRIPTION OF THE REACTIONS

Normal or Negative Reactions.—After applying the emulsions, both luetin and control, to about fifty normal individuals, I was able to determine the variations and limitations of the reactions that follow intradermic administration in the normal skin of a man. In the majority of normal persons, there appears, after twenty-four hours, a small erythematous area at and around the point of injection. No pain or itching sensation is experienced. This reaction gradually recedes within forty-eight hours and leaves no induration. In certain individuals, the reaction may reach a stage of small papule formation after twenty-four to forty-eight hours, after which and within seventy-two hours it commences to subside. No induration is left behind, although occasionally slight yellowish pigmentation may result from mild ecchymosis.

Positive Reactions.—According to the manner and intensity with which the skin of syphilitics responds to the introduction of luetin, one may distinguish the following varieties of effects:

A. Papular Form: A large, raised, reddish, indurated papule, usually from 5 to 10 mm. in diameter, makes its appearance in twenty-four to forty-eight hours. The papule may be surrounded by a diffuse zone of redness and show marked telangiectasis. The dimensions and the degree of induration slowly increase during the following three or four days, after which the inflammatory processes begin to recede. The color of the papule gradually becomes dark bluish-red. The induration disappears within one week, except in certain instances in which a trace of the reaction may persist for a longer period. This latter effect is usually seen among patients with secondary syphilis under regular mercurial treatment in whom there are no manifest lesions at the time of making the skin test. Patients with congenital syphilis also show this reaction in early period of life.

B. Pustular Form: The beginning and course of this reaction resemble the papular form until about the fourth day, when the inflammatory processes commence to progress. The surface of the indurated, round papule becomes mildly edematous, and multiple miliary vesicles occasionally form. At the same time, a beginning central softening of the papule can be seen. Within the next twenty-four hours, the papule changes into a vesicle filled at first with a semi-opaque serum that later becomes definitely purulent. Soon after this, the pustule ruptures spontaneously or after slight friction or pressure. The margin of the broken pustule remains indurated, while the defect caused by the escape of the pustular content becomes quickly covered by a crust that falls off within a few days. About this time the induration usually disappears, leaving almost no scar after healing. There is a wide range of variation in the degree of intensity of the reaction described in different cases, as some show rather small pustules, while in others the pustule is much larger. This reaction was found almost constantly in patients with tertiary or late hereditary syphilis.

C. Torpid Form: In rare instances, the injection-sites fade away to almost invisible points within three or four days, so that they may be passed over as negative reactions. But sometimes these spots suddenly light up again after ten days, or even longer, and progress to small pustular formation. The course of this pustule is similar to that described for the preceding form.

This form of reaction has been observed in a case of primary syphilis, in one of hereditary syphilis, and in two cases of secondary syphilis, all being under mercurial treatment.

Neither in syphilities nor in parasyphilities did a marked constitutional effect follow the intradermic inoculation of the luetin. In most positive cases, a slight rise in temperature took place lasting for one day. In three tertiary cases and in one hereditary case, however, general malaise, loss of appetite and diarrhea were noted.

The final estimation of the luetin test awaits future investigations by a large number of observers. In the meanwhile, I consider it fairly accurate to state that in this reaction one has a specific test for syphilis. Its more constant presence in the late stage of syphilis than the serum reaction may be of special advantage to those who have to deal with this class of cases.

From my limited observations, it appears that the allergic condition of skin in syphilitic patients persists as long as the infecting agent still survives somewhere in the body, and it requires a most energetic treatment to remove it. Should the destruction of the *pallida* be complete, the allergy must also cease to exist beyond a certain length of time. In animal experiments the luetin reaction no longer appeared after a period of several months. In several instances of human syphilis, in which the symptoms and serum reaction had disappeared under the treatment with salvarsan, the subjects failed to respond to luetin reaction after from eight to twelve months, and the patients still remain in excellent health. It will be of great importance if the luetin reaction can be employed for determining a cure. I have, however, seen cases in which the disease persists in spite of the treatment, and the patients do not give a positive luetin reaction. This class of cases shows undoubtedly an unfavorable prognosis.

SPIROCHÆTA PALLIDA AND THE WASSERMANN REACTION

Although the discovery of the Wassermann reaction was due to the assumption that a syphilitic serum containing the specific antibodies fixes the complement when mixed with an extract containing *Spirochæta pallida*, the real cause of this interesting phenomenon is now generally known not to be of the nature of a specific complement fixation brought about through the com-

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bination of the syphilitic antigen (*Spirochæta pallida*) and antibodies, in the strict sense of the term. The discovery of Landsteiner, Müller and Pötzl and Porges and Meier, that an alcoholic extract of syphilitic as well as normal tissues yields practically the same results as an aqueous extract of a syphilitic organ, originally recommended by Wassermann and Bruck, and the fact that the Wassermann reaction occurs also in non-syphilitic diseases (leprosy, frambesia, malaria, etc.) as observed and confirmed by later investigators, made the original antigen-antibody view untenable. Further, the extensive series of experiments of myself, later with Bronfenbrenner, conclusively proved that the active principles of

In order to settle the above question, several series of experiments were carried out on repeated occasions in regard to the following points:

1. Can syphilitic serums giving the positive Wassermann reaction by means of the lipoidal "antigen" also bind complement when the lipoids are replaced by the extract or emulsion of *Spirochæta pallida?*

2. Is it possible to intensify the ordinary Wassermann reaction in syphilitic serums by adding the extract or emulsion of the *pallida?*

The second problem was set up through the supposition that certain syphilitic serums giving weak or negative reactions with the lipoidal "antigen," may nevertheless contain sufficient antibodies which, while on account of the absence or insufficiency of the *pallida* substance are only partially detected or remain unrevealed, may be brought into evidence by the addition of the real antigen. This assumption originates from the conception of Citron, who considers that the lipoidal "antigen" is merely an intermediator to bring about the combination of the antibody and real antigen in the syphilitic serums where they are supposed to be existing side by side without entering combination until the lipoids are added.

In deciding the first point, I have prepared the aqueous extract and emulsion of *Spirochæta pallida* derived from two different modes of cultivation, namely,

TABLE 3.—THE ANTIGENS USED FOR THE FIXATION TESTS

	Syphilitic and Non-Syphilitic Serums Used for the Complement Fixation Tests	I Acetone-Insoluble Tissue Lipoids (Wassermann Reaction or Lipotropic Fixation) ("Antibody")	II Pallida Emulsion from Rabbit's Syphilitic Orchitis	III Control Emulsion from Normal Rabbits' Testicles.	IV Pallida Emulsion from Pure Cultures	V Control Emulsion from Uninoculated Culture Media	VI No Antigen
Syphilitic Cases	Primary syphilis, untreated	± 1 unit	—	—	—	—	—
	Primary syphilis, untreated	± 3 units	—	—	—	—	—
	Primary syphilis, untreated	± 2 units	—	—	—	—	—
	Primary syphilis, untreated	+ 1 unit	—	—	—	—	—
	Primary syphilis, untreated	+ 5 units	+	+	—	—	—
	Secondary syphilis, slight treatment, general rash	+ 2 units	‹ +	‹ +	—	—	—
	Secondary syphilis, slight treatment, general rash, fading	+ 10 units	+	+	—	—	—
	Secondary syphilis, moderate treatment, manifest	± 3 units	±	±	+	—	—
	Secondary syphilis, moderate treatment, manifest	± 2 units	±	±	+	—	—
	Secondary syphilis, salvarsan, no symptoms	‹ + ‹ 1 unit	±	±	+	—	—
	Secondary syphilis, salvarsan, no symptoms	± ‹ 0.5 unit	—	—	—	—	—
	Tertiary syphilis, no recent treatment, manifest	+ 4 units	+	±	‹ +	—	—
	Tertiary syphilis, salvarsan and Hg, no symptoms	±	—	—	—	—	—
	Tertiary syphilis, salvarsan and Hg, symptoms clearing	± 2 units	±	—	‹ +	—	—
	Tertiary syphilis, Hg treatment, manifest	+ 1 unit	—	—	—	—	—
	Tertiary syphilis, Hg treatment, manifest	± ‹ 0.5 unit	—	—	—	—	—
	Late hereditary syphilis, Hg treatment, manifest	+ 2 units	±	‹	‹	—	—
	Late hereditary syphilis, Hg treatment, manifest	+	+	+	+	—	—
	Late hereditary syphilis, Hg treatment, manifest	+ 8 units	±	±	±	—	—
	Late hereditary syphilis, Hg treatment, manifest	—	—	—	—	—	—
Non-Syphilitic Cases	Gonorrhea	—	—	—	—	—	—
	Tuberculosis	—	—	—	—	—	—
	Chancroid	—	—	—	—	—	—
	Carcinoma	—	—	—	—	—	—
	Dementia præcox	—	—	—	—	—	—
	Leprosy (tuberose type)	+ 5 units	+	+	—	—	—
	Leprosy (mixed type)	+ 3 units	+	+	—	—	—
Experimental Syphilis and Controls	Rabbit, syphilitic orchitis, six weeks' duration	+ 1 unit	—	—	—	—	—
	Rabbit, syphilitic orchitis, six weeks' duration	+ 1 unit	—	—	—	—	—
	Rabbit, syphilitic orchitis, six weeks' duration	+ 2 units	‹ +	‹ +	—	—	—
	Rabbit, syphilitic orchitis, six weeks' duration	+ 1 unit	—	—	—	—	—
	Rabbit, syphilitic orchitis, six weeks' duration	+ 1 unit	—	—	—	—	—
	Rabbit, normal	—	—	—	—	—	—
	Rabbit, normal	—	—	—	—	—	—
	Rabbit, normal	—	—	—	—	—	—
	Rabbit, normal	—	—	—	—	—	—
	Rabbit, normal	—	—	—	—	—	—

Explanation: + = positive; ‹ + = weakly positive; ± = doubtful; — = negative reaction.

the so-called antigens in the Wassermann reaction are present in the lipoidal substances of the tissues, irrespective of whether they are derived from syphilitic or non-syphilitic human subjects or animals.

In spite of these facts, certain investigators still adhere to the original view without, however, any definite evidence in favor of such an assumption. Since the causative organism, *Spirochæta pallida*, has now been cultivated in pure state and identified through its pathogenicity and other biologic properties, such as the capability of inciting the Wassermann reaction in experimental animals, it is now possible to find out by exact experiments to what extent *Spirochæta pallida* plays the rôle of the so-called antigen in the Wassermann reaction.

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one in the testicles of rabbits and the other in artificial culture media. Both materials were pure and contained an enormous quantity of *Spirochæta pallida*. In making up the extract I have employed several strains of the *pallida* in order to obtain a polyvalent antigen. In case of syphilitic orchitis of rabbits, the indurated testicles of each strain were removed from the animals (under usual aseptic precaution), and these different strains were put together in a sealable porcelain jar for grinding by means of marbles in a shaking-machine. An adequate quantity of sterile physiologic salt solution was added before the grinding. The disintegration of the *pallida* was almost complete after six hours. The emulsion thus obtained was then carefully transferred to a sterile bottle, heated to 60 C for thirty minutes and 0.4 per cent. phenol (carbolic acid) was added. This was used as the antigen. For the control a similar extract with normal rabbit's testicles was prepared.

For making the antigen from pure cultures of the *pallida*, the technic used was identical with the foregoing. The control extract was prepared with inoculated media. The culture medium consisted of one part of ascitic fluid and two parts of a weakly alkaline agar to which a piece of fresh sterile rabbit's kidney was added. For the antigen only the colonies of the *pallida* were employed, the tissue (kidney) being previously removed.

After determining the anticomplementary titer of each emulsion, I have tested a large number of syphilitic serums from human subjects and also from rabbits with syphilitic orchitis. Non-syphilitic serums both of man and rabbits were used as controls. Throughout the entire series of experiments, the antihuman hemolytic system (Noguchi) was used. The serums were inactivated at 55 C. for thirty minutes. This precaution is absolutely necessary as the antigens contain various proteids capable of causing a proteotropic fixation with unheated serums.

In order to know the relation quantitatively between the Wassermann reaction produced by the lipoidal "antigen" and the fixation by the *pallida* extract as antigen, I have titrated the positive serums for their fixing-power simultaneously with the lipoidal and *pallida* antigens.

The Wassermann reaction is present in most of the syphilitic cases here studied and also in two cases of tuberous and mixed type of leprosy. It is more pronounced in untreated early cases and in hereditary cases than in the treated cases. It is present in tertiary cases in a lower percentage. On the other hand, a positive reaction was obtained with the *pallida* extracts in certain cases with weak or negative Wassermann reactions. These occurred, however, only when the patients were under treatment or had been syphilized many years ago without being cured. It is also remarkable to notice that in many cases of tertiary syphilis and later hereditary cases, there was a partial fixation, irrespective of the absence or presence of fixation as indicated by the lipoidal antigen. No fixation was obtained with the *pallida* antigen made from pure culture in the case of leprosy, while the extract from syphilitic as well as normal rabbit's testicles gave a positive reaction, due, doubtless, to the lipoidal content of the latter.

These facts may be considered as deciding (1) that the Wassermann reaction is caused by the lipotropic substances, but not by the antibodies which combine specifically with the *pallida* antigen; (2) that the fixation produced by the culture *pallida* antigen with certain syphilitic serums is caused by the specific antibodies contained in the latter and may constitute a specific diagnostic method for syphilis; (3) that the fixation caused by the testicular extracts behaves like the culture *pallida* extract in the majority of cases, but when the serums (syphilitic or leprous) contain abundant lipotropic substances, it may give a Wassermann reaction as well, which is not the case with the culture *pallida* antigen; and finally (4), that in the serum of rabbits with active syphilitic orchitis there is no indication of the presence of a sufficient amount of the antibodies for the *pallida* antigen, although it gives a strong Wassermann reaction. It remains to be seen when and under what conditions the specific antibodies for the *pallida* will most abundantly be formed in syphilitic patients. At all events it is rather remarkable that the amount of the antibodies detectable by the *pallida* antigen in these cases was so small as compared with certain other infectious diseases, in this respect. It is not improbable that those who come under our care belong to a class of individuals with comparatively less resistance to the *pallida* and are incapable of producing sufficient antibodies, while there are many who respond to the infection with more vigorous formation of the antibodies and reduce the infection to a harmless latency or even destroy the *pallida* completely. This latter class of infected persons do not, of course, frequent our clinics. If this is the case, it would be of immense prognostic importance to check a patient from the beginning of infection by the complement fixation test with the *pallida* antigen, thereby determining the resistance of the patient against the disease.

We have in the Wassermann reaction a fair measure of activity of the infecting agent, and now we will have in the *pallida* fixation reaction a gauge for the defensive activity of the infected host.

DEMONSTRATIONS

In order to illustrate the foregoing address with practical demonstrations, I have exhibited the macroscopic and microscopic (dark field) specimens of *Spirocharta pallida*, *microdentium*, *macrodentium* and *refringens* in pure cultures. For the assistance and necessary arrangements for the occasion, I express sincere thanks to Professor Zeit and his assistants.

For the demonstration of the luetin reaction, I am under deep obligation to Dr. W. L. Baum, Dr. B. C. Corbus, Dr. O. Stein and Dr. J. Grinker, who placed a series of syphilitic, parasyphilitic and non-syphilitic cases at my disposal. For the privilege of using the clinic of the Chicago Post-Graduate Medical School during the preparation for the demonstration, my thanks are due to its president, Dr. Emil Ries. It is my pleasant duty to express my gratitude to Dr. Corbus, who has also given me a series of syphilitic cases (private), for which he has been keeping all important data for a number of years. The most important feature of his private cases lies in the fact that the patients were treated by him according to a biologic measure, namely, in regard to the Wassermann reaction. The patients selected by him were those who had been or are still being treated with salvarsan and mercury, and had lost the Wassermann reaction a long or short time ago. As will be seen in the following records, some of the cases with negative Wassermann showed a positive luetin reaction, while others were negative. It seems to be highly important to keep track of the latter group of cases for many years to come, since, in my opinion, these patients with negative, clinical, serologic and allergic findings may belong among the cured patients. This assumption may not, however, apply to those patients who had been treated energetically before the allergic state of the skin was developed (such as cases of primary syphilis), because in these instances the luetin reaction may never be manifest. The prognostic value of the luetin reaction would, therefore, become obvious only in those who had had a generalized syphilis before the treatment.

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Below I present brief records of the cases used for the demonstration. The Wassermann reaction in these cases was made by Dr. Corbus.

CASE 1.—N. M., American woman, aged 29, clinic patient of Drs. Baum and Corbus. Present condition: Early secondary lues. Treatment: Mercury rubbings. Wassermann reaction not taken. Luetin mild positive.

CASE 2.—F. B., white man, aged 44, clinic patient of Drs. Baum and Corbus. Present condition: Latent secondaries. Chancre in October, 1910. Treatment: Mercury rubbings and internal. Wassermann positive. Luetin papular distinct (positive).

CASE 3.—J. D., American man, aged 34, clinic patient of Drs. Baum and Corbus. Present condition: Latent secondaries. Infected two years ago. Treatment: Mercury rubbings. Salvarsan injected in oil suspension 0.6 gm. Wassermann positive. Luetin mild positive.

CASE 4.—S. B., American man, aged 26, clinic patient of Drs. Baum and Corbus. Present condition: Recurrent secondaries. Treatment: Mercury rubbings intermittent. Wassermann positive. Luetin distinct papular (positive).

CASE 5.—W. H. W., American man, aged 23, clinic patient of Drs. Baum and Corbus. Present condition: Marked secondaries. Treatment: Salvarsan in oil suspension, February, 1912. Mercury intermittent. Wassermann not made. Luetin distinct papular (positive).

CASE 6.—L. J., colored man, aged 23, clinic patient of Drs. Baum and Corbus. Present condition: Secondaries. Eighteen months since treatment. Treatment: Intravenous injection of salvarsan eight months ago. Mercury rubbings. Wassermann positive. Luetin suppuration on both arms. No difference between control and luetin (*Umstimmung?*).

CASE 7.—C. K., German man, aged 22, clinic patient of Drs. Baum and Corbus. Present condition: Secondary period. No symptoms. Chancre four years ago. Treatment: Mercury rubbings. Salvarsan—intravenous injection May 20, 1911; June 7, 1911; October, 1911; November, 1911. Wassermann not taken. Luetin papular reaction distinct (positive).

CASE 8.—H. K., American man, aged 46, clinic patient of Drs. Baum and Corbus. Present condition: Cerebral gumma. Treatment: Mercury intermittent. Wassermann positive. Luetin large full indurated papule. Typical positive reaction.

CASE 9.—J. S., colored man, aged 34, clinic patient of Drs. Baum and Corbus. Present condition: Probable tertiary. No history. Treatment: Internal about one year. Wassermann positive. Luetin secondary infection. All reactions, both control and luetin.

CASE 10.—A. M., American woman, aged 21, clinic patient of Dr. Stein. Present condition: Congenital lues. Treatment: None at any time. Wassermann negative. Luetin distinct papular (positive).

CASE 11.—C. H., American man, aged 16, clinic patient of Drs. Baum and Corbus. Present condition: Congenital lues. Treatment: Mercury intermittent. Wassermann positive. Luetin pustular reaction (positive). Slight *Umstimmung.*

CASE 12.—W. J. H., American man, aged 42, clinic patient of Dr. Grinker. Present condition: Paresis. Probably infected twenty years ago. Treatment: Neglected. Salvarsan injected intravenously by Dr. Corbus Dec. 1, 1911, and Feb. 5, 1912. Vigorous mercury rubbings between salvarsan injections. Wassermann positive, Nov. 28, 1911. Luetin distinct papular (positive).

CASE 13.—Control case. S. C., colored man, aged 37, clinic patient of Drs. Baum and Corbus. Present condition: No history of initial lesion. No secondaries. Believed to be infected twenty years ago. Treatment: Mercury intermittent. Wassermann negative. Luetin negative.

CASE 14.—C. D., American man, aged 26, private patient of Dr. Corbus, treated after the biologic method. Present condition: Probably cured. Tonsillar chancre, November, 1910. Treatment: Salvarsan injected intramuscularly, Nov. 7, 1910, and Dec. 15, 1910. Wassermann positive, Nov. 28, 1910; negative, Jan. 23, 1911; negative, May 9, 1911; negative, March 12, 1912. Luetin negative.

CASE 15.—F. S., American man, aged 22, private patient of Dr. Corbus, treated after the biologic method. Present condition: Early secondaries. Last symptoms, Sept. 4, 1911. Treatment: Injected salvarsan in oil suspension, Sept. 4, 1911; intravenously, Feb. 6, 1912. Vigorous mercury rubbings between salvarsan injections. Wassermann negative, Jan. 16, 1912. Luetin distinct papular (positive).

CASE 16.—C. L., American man, aged 38, private patient of Dr. Corbus, treated after the biologic method. Present condition: Incipient tabes. Infected eleven years ago. Treatment: Salvarsan injected intramuscularly, Jan. 9, 1911, and March 5, 1911; intravenously, Oct. 6, 1911, and Jan. 13, 1912. Vigorous mercury rubbings between injections. Wassermann positive, Nov. 28, 1910; positive, Feb. 23, 1911; negative, July 7, 1911; negative, Oct. 6, 1911; negative, Jan. 9, 1912. Luetin negative.

CASE 17.—M. A., American man, aged 36, private patient of Dr. Corbus, treated after the biologic method. Present condition: Secondaries. Last appearance of palmar syphilid, seven months ago. Treatment: Injected salvarsan intramuscularly, Jan. 28, 1911; intravenously, March 18, 1911; intramuscularly, August, 1911. Vigorous mercury rubbings between salvarsan injections. Wassermann negative, Aug. 22, 1911; negative, Jan. 16, 1912. Luetin distinct papular (positive).

CASE 18.—P. S., American man, aged 22, private patient of Dr. Corbus, treated after the biologic method. Present condition: Cured. Primary lesion, Jan. 21, 1909. Treatment: Vigorous mercury rubbings. Cure obtained before salvarsan was administered. Injected salvarsan intramuscularly, Jan. 17, 1911. Wassermann negative, Dec. 10, 1910; Feb. 15, 1911; April 15, 1911; Aug. 1, 1911, and Dec. 15, 1911. Luetin negative.

CASE 19.—O. J. G., American man, aged 31, private patient of Dr. Corbus, treated after the biologic method. Present condition: Latent secondaries. Chancre, September, 1905. Last symptoms, Oct. 20, 1910. Treatment: Neglected at first. Injected salvarsan intramuscularly, Oct. 20, 1910, and Dec. 11, 1910; intravenously, Sept. 2, 1911, and March 9, 1912. Vigorous mercury rubbings between salvarsan injections. Wassermann positive, Nov. 11, 1910; negative, Jan. 1, 1910; positive, March 8, 1912. Luetin distinct papular (positive).

CASE 20.—A. G., American man, aged 20, private patient of Dr. Corbus, treated after the biologic method. Present condition: Secondaries. Infected Jan. 1, 1911. Last symptoms May 6, 1911. Treatment: Internal. Salvarsan injected in oil suspension, 0.6 gm., May 6, 1911; intravenously, 0.4 gm., Feb. 24, 1911. Vigorous mercury rubbings between injections of salvarsan. Wassermann positive, April 20, 1911, and March 4, 1912. Luetin distinct papular (positive).

Two patients with acne vulgaris, both adults, were also tested with the luetin and gave a negative reaction.

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THE PSEUDOMALARIAL TYPES OF PYELITIS*

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The diagnosis of pyelitis (non-calculous and non-tuberculous) appears forty-seven times in the histories of 2,500 private patients examined by me during the past five years, an incidence of approximately 2 per cent. Of these forty-seven patients, twenty-one had been treated for malaria.

In most cases of infection of the pelvis of the kidney, constitutional symptoms arise that may closely simulate malarial fever. About one-half of the cases present local signs on the part of the kidney or bladder, or urinary disturbances manifest themselves in such a way as to direct attention to the existing lesion. In the other 50 per cent. of the cases, however, neither the history of the illness nor a thorough physical examination reveal any clues suggestive of an infection of the genito-urinary tract. As a result, pyelitis may remain unrecognized for long periods of time. Furthermore, the insidious onset without pain or local symptoms, the characteristic intermittent or remittent temperature curve, and chills occurring with peculiar regularity, all suggest malaria very strongly. The rigors in such cases are probably associated with a temporary blocking of the ureter-drain with inflammatory products, as the urine during the fever may be clear and free from pus, while at the termination of the paroxysm turbid urine loaded with pus is voided. Pyelitis in early childhood is much more common than is usually supposed, and is the cause of many unexplained fevers. One such instance is included in the report of cases below (Case 2).

Instances of pyelitis of the pseudomalarial type can be divided roughly into two groups, acute and chronic. The acute cases may be of very short duration and subside with sudden alacrity (Cases 3 and 4), or may last for weeks while the patient continues to be dosed with quinin. The chronic cases are not so frankly septic, but give rise to lesser symptoms, such as periodic aching in the extremities, chilly feelings, night sweats, etc. In one such case, reported below (Case 6) these symptoms had recurred every summer for fifteen years. The urinary findings in these chronic cases may be almost insignificant, and in women it is absolutely necessary to secure a catheterized specimen for microscopic examination, in order to exclude contaminating cellular elements from the external genitalia. The real difficulty in these chronic cases of pyelitis does not lie in disproving the diagnosis of malaria, as that can be readily accomplished by careful search through a stained blood-smear, but consists in excluding pulmonary tuberculosis, as the clinical history always suggests this latter possibility.

The diagnosis of pyelitis depends on the interpretation of the microscopic cellular elements present in the urinary sediment, correlated with the constitutional symptoms. Urethritis and cystitis, in the absence of local disturbances, can only be excluded by endoscopic or cystoscopic examination. It is not the purpose of this article to discuss the differential diagnosis of pyelitis from other pyogenic infections of the genito-urinary tract, but simply to emphasize the close clinical resemblance of pyelitis to malarial fever. In acute pyelitis the paroxysms may be identical with those of malaria, presenting hot, cold and sweating stages, with fever-free intervals. Chronic pyelitis gives rise to general symptoms that are commonly attributed to chronic malaria, although, as a matter of fact, the malarial parasite is so susceptible to the action of quinin that actual chronic malaria is an extremely rare condition and only arises in individuals who harbor the parasite and remain untreated. A great number of conditions masquerade under the name of chronic malaria, and not the least of these is a chronic low-grade infection of the genito-urinary tract.

The following six cases are reported in brief abstract from my histories of patients suffering from pyelitis.

CASE 1.—*Patient.*—A professional man, aged 53, who had always enjoyed excellent health, with the significant exception of an attack of acute prostatitis one year previously, developed chills and fever in September, 1906, while on a vacation at Hot Springs, Va.

Clinical History.—After having two shaking chills at an interval of forty-eight hours, he was told that he had malaria and returned to his home in Richmond. For over three weeks he continued to have hard chills followed by high fever and profuse sweating. The chills occurred every day, although on a few occasions he went two days without a rigor. After the chill his temperature often reached 104 F. Except for the chills, fever and sweats, he was free from symptoms, complained of no pain in any part of the body and had no symptoms on the part of the bladder or kidneys. Quinin was administered in full doses from the beginning of the illness and at the time this note was made he had been taking 40 grains of quinin daily for a week.

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