THE WASSERMANN REACTION IN THE PATHOLOGY, DIAGNOSIS AND TREATMENT OF SYPHILIS *

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INTRODUCTION

Metchnikoff, in his preface to the recent treatise of Levaditi and Roché on experimental syphilis, compares the evolution of our knowledge of syphilis to the three phases of the development of human thought as established by Comte: the theological, the metaphysical, and the scientific. He sketches briefly the history of syphilis through its first period, that of superstition, in which the only advance was the discovery of the specific remedy, mercury; through the second period of empirical medicine with its thorough clinical studies of the varied manifestations of syphilis and the recognition of gonorrhea and chancroid as disease entities; and through the period represented by the past half-decade of scientific investigation, during which the experimental transmission of the disease has been demonstrated, the etiology determined and a method of serum diagnosis established.

He makes the statement, somewhat pardonable in one so largely responsible for our new knowledge of the disease, that the study of syphilis, until now purely clinical, has become so much a matter of laboratory method that the diagnosis can be made without seeing the patient by the simple examination of his blood or of the secretions from his lesions. Be this as it may, it is not my intention to laud the achievements of the laboratory or to go into detail concerning its methods as applied to syphilis. I do wish, however, to demonstrate that these methods are destined ultimately to establish the pathology of syphilis on a sound basis, to afford thereby a clear insight into many obscure conditions heretofore but imperfectly understood clinically and to result eventually in a rational therapy.

The methods at hand are (1) the recognition of the *Spirochæta pallida*, which we owe to Schaudinn and Hoffman (1905); (2) the experimental production of the disease by inoculation, as first clearly

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shown by Metchnikoff and Roux (1903); and (3) the method of serum diagnosis with which we associate especially the names of Wassermann, Neisser and Bruck (1906). The first and second of these I shall discuss briefly, as their use is practically limited to the primary and secondary manifestations of the disease. It is of the more obscure manifestations of late syphilis affecting the cardiovascular and nervous systems, the bones and joints and the organs of special sense, to which can be applied only the method of serum diagnosis that I wish especially to speak. It is to this phase of the subject that I shall give most of my time, but, in order to round out my presentation, a few words may be said concerning the results of animal inoculation and the distribution of the *Spirochæta pallida*.

It is a tribute to past generations of syphilographers that the conclusions which they reached concerning many of the problems of infection, extension of the virus, acquired immunity, etc., have been confirmed by our present knowledge of experimental syphilis and of the distribution of the spirochete, as have also, through the use of the Wassermann method, many conclusions of the pathologist concerning the chronic lesions more or less frequently found in individuals with syphilitic history. It is no mean triumph that the views concerning a disease of unknown etiology, based on clinical and pathological observations, should have been thoroughly supported when the causative agent of the disease was discovered and its distribution in the tissues and fluids of the body determined.

In the first place, a word may be said as to the importance of the experimental work in the establishment of syphilis as essentially a disease of man, and incidentally confirming man's blood-relationship to the higher apes. Although it has been asserted that lesions similar to the chancre have been produced in various animals, no disease at all comparable to syphilis was ever produced in animals until the ape was used. In view of our comparatively recent knowledge of the blood-relationship of various animals, as definitely established by the use of the biological blood test (precipitin test), this is not surprising. But even to one familiar with zoological relationships, it is interesting to note the varying susceptibility of various members of the monkey family to syphilis. As Metchnikoff and Roux clearly brought out in their first communication on experimental syphilis, success or failure depends chiefly on the species of monkey used. Neisser has shown that this depends on the position of the species in the zoological series, the higher monkeys (chimpanzee, gorilla, orang-outang), nearest to man in the animal scale, take syphilis typically and present the primary and secondary lesions as they occur in man, that

is, chancre, enlarged glands, secondary eruption and mucous patches. The lower monkeys react locally only, while the gibbon, which is intermediate in the scale, gives atypical primary and secondary lesions. It is evident, therefore, that the production of syphilis in the anthropoid apes was not merely a matter of demonstrating that an animal susceptible to the virus of syphilis had been found. Such information would have been of no more aid to us than our present knowledge that the rabbit is susceptible to infection with the pneumococcus, which organism does not produce a typical pneumonia in this animal. The experiments on apes showed not only the possibility of reproducing syphilis with its primary lesions and many of its secondary manifestations in typical form, but—and this is of greatest importance—of reproducing these lesions in an animal so closely related to the human species that conclusions reached for simian syphilis could be applied immediately to the disease in man. Man was no longer the only animal available for observations on the nature of syphilis and experiments in therapy. The anthropoids, on account of their close blood-relationship, became available for experiment, and many investigations impossible on man could be undertaken. Much has been accomplished. Among other things it has been found that only when the virus is inoculated into the skin proper, either by deep scarification or into actual pockets in the skin, could the disease be produced. Inoculation into the subcutaneous tissues, into the blood-vessels or into the peritoneal cavity all fail. It is evident that the spirochete finds conditions for initial propagation only in the skin, and that there it must undergo a certain degree of development before the general invasion of the blood occurs or the local lesion appears. On the other hand, the invasion of the blood may occur before the appearance of the initial lesion, which is in accord with our clinical experience concerning the futility of early excision of a chancre. This is demonstrated in experiments on monkeys, in which it was found that as early as the fifth and eighth days after inoculation the virus is present in the blood and can produce local lesions in other monkeys. Thus, the blood of an animal in which chancre was not evident until the twenty-second day was found to be virulent on the fifth day; in another, in which chancre developed on the twenty-eighth day, the blood was virulent on the eighth day.

Experimental syphilis also throws light on the question of the localization of the virus during the florid period of syphilis, and especially during the quiescent periods which separate the active stages. Of all organs in the infected animal capable of transmitting the disease, infection follows most frequently after inoculation with the bone-marrow, the spleen, the

lymph-nodes and the testicle, in the order named. The localization in the first three of these, all hematopoietic organs, reminds one of the localization of the malarial parasite during certain stages of its development. As Neisser has found these tissues to be capable of transmitting the disease after nearly 300 days, there can be little doubt of their importance in the preservation of the spirochete. As to the predilection of the spirochete for the testicle it is not surprising to find that this localization has been invoked as an explanation of the transmission of hereditary syphilis, it being assumed that the transmission occurs in the semen, with infection of the ovum, but no infection of the mother. In this connection it is noteworthy that Finger and Landsteiner have produced syphilis in the monkey with the sperm of a syphilitic.

As to the presence of the virus in the circulating blood of man, there is little evidence. Experimental inoculations of the monkey have given positive results in a few instances in which the blood has been taken from individuals in the first two months of the disease, but they have usually been unsuccessful. Likewise, it has been found extremely difficult to demonstrate the spirochete by direct examination of the blood. It is necessary to conclude, therefore, that although it may occasionally occur in the peripheral circulation, it is localized for the most part in the bone marrow and spleen.

Experimental syphilis also explains the relative infrequency of infection from contact with tertiary lesions. While monkeys may readily be infected with material from chancre and mucous patches, inoculation with material from tertiary lesions has seldom been successful. There is, however, some evidence at hand that the spirochete may exist in some tertiary lesions in very small numbers. This conclusion is supported by the experience of those who have made a search for the spirochete in such lesions by direct examination.

Of extreme importance, in view of the well-known involvement of the vascular structures in syphilis, is the histological observation that in all early lesions of syphilis the spirochete is found most abundantly in the cell accumulations in and about the blood-vessels and lymphatics, and is presumably directly responsible for the endothelial and perivascular changes so characteristic of the disease and which explain so much of its pathology.

THE WASSERMANN REACTION

As the diagnosis of syphilis by the recognition of the spirochete is limited to the primary and secondary lesions, the internist and the specialist interested in the late lesions of syphilis must have recourse to the

method of serum diagnosis as described by Wassermann, Neisser and Bruck. Although the literature of this diagnostic method is now enormous, its use in this country has been limited to a few medical centers and its general importance has not, I am sure, been thoroughly appreciated by the profession at large; nor have the results of its use been presented, from the clinical point of view, in comprehensive form. My interest was first stimulated by the work on this subject carried out in my laboratory at New York University during the past two years by one of my assistants, Dr. Homer F. Swift. Day by day I have followed his results, impressed by the constancy with which a positive reaction supplemented definite clinical diagnosis, now and then amazed by the marvelous success of the reaction in clearing up the diagnosis of obscure or doubtful syphilitic conditions, and finally I have been forced to the conclusion that in this method we have, at last, the means not only of clearing up the pathology of many phases of syphilis, but of establishing definite rules for treatment, and, apparently, as recent work indicates, of recognizing complete cure. I shall therefore outline the work which has been accomplished, emphasizing the importance of this method in medicine, in surgery, and in the various specialties; its relation to certain conceptions of syphilis hitherto considered fundamental, as those embraced in Colles' law, and shall conclude with a discussion of the importance of the reaction in controlling treatment.

TABLE 1.—OBSERVATIONS ON SYPHILIS IN VARIOUS STAGES

Observer.	Primary —Syphilis—		Secondary —Syphilis—		Tertiary —Syphilis—		Early Latent —Syphilis—		Late Latent —Syphilis—		Hereditary —Syphilis—	
	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +
Collected by Noguchi *	416	69.8	1605	89.4	581	78.1	1233	51	861	47	125	94.5
Noguchi †	70	92.8	197	96	177	89.9	115	75.6	150	79.3	17	100
Swift	21	81	137	97	83‡	89	79	76	94	46	14	86
							Latent					
							Cases.	79	Per	Cent.		
Kaplan	138	90	281	86	191	73			51		20	90
Collected by Bruck §	520	64.4	1301	71-100	512	63-100	1549		47.5		..	
Bruck, Stern, Merz and Grosser	111	72.1	528	94	224	73.6	867		30.5		..	

* Ten observers.

† By Noguchi modification.

‡ Cutaneous lesions of tertiary syphilis; in a second group of fifty-two cases of visceral syphilis positive results were obtained in 79 per cent.

§ Twenty-one observers.

The time at my disposal will not allow of a discussion of the principles and technic of the Wassermann reaction. For such information I refer you to the numerous communications on this subject, and more especially

to those of our own workers, Noguchi, Swift, Kaplan, Fox and Gay and Fitzgerald. I shall, however, in order to demonstrate the efficiency of the test, present a tabulation of extensive observations in primary, secondary, tertiary, latent and hereditary syphilis (Table 1):

With Table 1 may be compared Table 2, which includes the reaction in individuals in whom syphilis could be excluded by history or clinical symptoms with a fair degree of certainty.

TABLE 2.—REACTION IN NON-SYPHILITIC CASES

Observer	No. of Cases	No. +	Per Cent. +
Swift	272	3	1.1
Noguchi	333	12	3.6
Bruck's collected cases*.....	4,432	57	1.2
Bruck, Stern and Merz.....	596	2	0.3
Matson	313	1	0.3

* 33 observers.

These figures give some idea of the results in large series. Many of the individual series are, however, more striking. Thus, in primary syphilis we frequently find reports of 90 to 98 per cent. positive results; in secondary lesions, 100 per cent. (Boas in 393 cases), with never less than 80 per cent.; in tertiary syphilis the figures vary from 60 to 100 per cent., and in hereditary syphilis, they are uniformly high, 70 to 100 per cent. The highest and most constant results are obtained in secondary and hereditary syphilis; the most irregular in primary and latent. It is evident that these variations depend on many factors, as technic, the influence of treatment and, especially in primary syphilis, on the length of time which has elapsed since infection; it is noteworthy that early cases are frequently negative. Also the view is now definitely established that in late syphilis treatment causes the reaction to disappear.

In Swift's experience all cases of syphilis react by the end of the fourth week after the appearance of the chancre, so that in doubtful cases a diagnosis is possible two weeks before the appearance of the roseola. The earliest reaction is reported by Lesser, who found the blood positive eight days after exposure; fourteen days later an initial lesion appeared, and six weeks afterward a typical roseola. Experiments on apes (Bruck) indicate that a positive reaction is evidence of general invasion of the body, and with this is correlated the observation that the ape resists reinfection after a positive reaction.

If this interpretation is correct, one might assume that with the demonstration of the spirochete in the primary lesion and a negative Wassermann reaction, excision of the initial lesion might prevent or

modify the subsequent course of the disease. Theoretically, this would appear possible, but experience indicates that this result is rare.

In other diseases than syphilis, the reaction occurs in leprosy, scarlet fever, yaws (frambesia), and trypanosomiasis frequently, and, to a slighter extent, with tuberculosis, carcinoma and certain diseases of the blood, conditions which, with the exception of yaws, however, are not usually confounded with syphilis and for which we have definite diagnostic methods.¹

That the Wassermann reaction should be positive in yaws, a disease due to a spirochete and frequently confounded with syphilis, is a matter of biological interest, but not of diagnostic importance in northern countries, in that yaws is essentially a disease of the tropics. As to scarlet fever, it may be pointed out that with convalescence from scarlet fever the positive reaction disappears, whereas in syphilis it persists. The occasional positive reaction in tuberculosis, cancer and diseases of the blood appears to be dependent in some instances on a condition of profound cachexia, in others the condition may be syphilis ignorata.

With this demonstration of the diagnostic value of the Wassermann reaction, a method which should be in use in every modern clinic and in every state and municipal laboratory, we may turn to a consideration of those lesions of general interest to the internist.

THE NERVOUS SYSTEM

An early application of the Wassermann reaction was naturally made to the well-known metasyphilitic affections, tabes and general paralysis. As a result, not only has the general opinion concerning the syphilitic nature of these affections been confirmed, but many suggestive observations concerning the possible relation of syphilis to other diseases of the nervous system have been made.

The results of the more important investigations of tabes and general paralysis, covering large series of cases, are shown in Table 3.

It will be seen that in general paralysis the average of positive results obtained by the various observers is about 80 per cent., with extremes

1. Positive results in leprosy vary from 10 to 70 per cent. Noguchi has collected from the reported results eighty-six cases of leprosy, of which 72.4 per cent. gave positive results. The results for scarlet fever vary from 1 to 50 per cent. of positive or doubtful results according to various observers. The cases collected by Fuá and Koch give 12 per cent. of positive results in 353 cases, though in fifty-nine cases which they examined no positive results were obtained. Swift has analyzed 562 examinations by various observers and finds 5 per cent. of positive results.

of 49 and 100 per cent. The most remarkable results are those of Plaut, Boas and Lesser, each with 100 per cent. of positive reactions in 156, 62 and 42 cases, respectively. In tabes the percentages are lower, with, however, an average for all investigators of 65 per cent., the extremes being 41 and 83.

TABLE 3.—INVESTIGATIONS OF TABES AND GENERAL PARALYSIS

Observer.	General Paralysis				Tabes			
	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.
	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.
Lederman	23	87	...	..	68	76	..	..
Hoehne	30	80	...	..	45	60	..	..
Schütze	..	...	...	..	79	65	29	83
Boas	42	100	...	..	20	80	..	..
Lesser	62	100	...	..	61	56	..	..
Sachs	31	68	...	..	28	64	..	..
Plaut	156	100	147	95	14	79	11	64
Stertz	45	80	...	..	...	..	..	..
Marie, Levaditi and Yamanouchi	27	59	30	93	...	..	..	..
Eichelberg	..	...	61	93	...	..	49	56
Raviart, Breton and Petit..	..	...	72	93	...	..	..	..
Smith and Chandler.....	10	90	64	59	...	..	..	..
McCampbell and Rowland...	50	96	50	84	...	..	..	..
Noguchi *	..	...	...	..	22	41	..	..
Noguchi †	15	87	...	..	125	68	..	..
Swift	3	66	...	..	54	62	..	..
Kaplan	61	65	...	..	205	60	..	..
Rosanoff and Wiseman †....	75	49	57	76	...	..	..	..
Totals	630	81	424	85	721	65	89	68
		(Average)		(Average)		(Average)		(Aver.)

* Original Wassermann method used. † Noguchi's modification used.

There has been some discussion about the relative frequency of the reaction in the blood and in the cerebrospinal fluid in cases of tabes and paralysis. Table 4, taken from Noguchi's collected data, shows but slight difference, though individual workers vary somewhat in their results. (Compare Table 3).

TABLE 4.—REACTION IN BLOOD AND CEREBROSPINAL FLUID

	Blood Serum		Cerebrospinal Fluid	
	Cases	Per Cent.	Cases	Per Cent.
General paralysis	498	88.1	432	90.
Tabes	216	62.66	52	56.2

An important question is that concerning the interpretation of a negative reaction with the cerebrospinal fluid when the blood serum is positive. Some investigators insist that, as any syphilitic affection may give a positive reaction with serum, it is necessary to have the cerebrospinal fluid positive also to be sure of a diagnosis of general paralysis or tabes. This question must be considered for the present as undecided.²

The results in cerebrospinal lues vary from 16 to 88 per cent. The figures collected by Noguchi give an average of 47.6 per cent.; Swift obtained 54 per cent. of positive results in eleven cases clinically diagnosed as cerebrospinal syphilis, and in 66 per cent. of nine cases clinically termed syphilitic meningitis. The percentage of positive results obtained by all investigators is as a rule lower than in general paralysis and tabes. If, however, the figures for these three groups are compared with the series in Table 5 representing psychiatric cases in which there was no evidence of syphilis or metasyphilitic disease, the importance of the Wassermann reaction in the study of diseases of the nervous system becomes evident.

TABLE 5.—REACTIONS IN PSYCHIATRIC CASES

Observer	Character of Cases	Number	Positive	Doubtful
Plaut	Psychiatric	95	4	0
Noguchi	Psychiatric	140	20*	12*

* Twelve of the cases with positive and nine with doubtful reactions were epilepsy.

Some confusion, however, is caused by certain forms of psychiatric disease of non-syphilitic origin, which give a fair proportion of positive reactions. This is seen in Table 6, a summary abstracted from one of Noguchi's tables.

TABLE 6.—MENTAL DISEASE OF NON-SYPHILITIC ORIGIN

Clinical Diagnosis	No. Cases	Syphilis Known	Reaction Positive	Reaction Doubtful	Reaction Negative
Alcoholic psychosis.....	9	4	2	3	4
Dementia præcox.....	131	5	15	17	99
Manic-depressive insanity..	14	1	2	3	9

To what extent these positive reactions are due to unrecognized cerebrospinal or latent syphilis, it is difficult to say. The same is true of suggestive results obtained in the study of idiocy, epilepsy and various

2. For a discussion of the relative importance of the Wassermann reaction, the cytological and globulin methods, see Noguchi, McCampbell and Howland and Rosanoff and Wiseman.

dementias; thus Raviart, Breton and Petit obtained positive reactions in 76 of 246 cases of idiocy or imbecility, with and without epilepsy; in 5 of 31 cases of epilepsy alone; in 3 of 5 cases of senile dementia, and in 5 of 19 cases of dementia præcox. Roubinovitsch and Levaditi in dementia præcox obtained positive reactions in 3 of 15 cases; Noguchi, in the study of 69 cases of epilepsy, had positive results in 12 and doubtful in 9; Rosanoff and Wiseman in epileptic psychoses in 13 of 73 cases; in dementia præcox in 21 of 122 cases, and in manic depressive insanity in 4 of 21 cases. These and other reports of occasional positive results in idiots (Bergmann, Frankel-Heiden, Knoepfelmacher and Lehndorf) have led to special investigations of the Wassermann reaction in this group of diseases. The results cannot as yet be definitely stated. One investigation, however, that of Kellner, Clemenz, Brückner and Rautenberg, who have studied 216 idiots of various types, is fairly conclusive. They obtained a positive Wassermann reaction in nine cases, but all except one of these occurred in a group of sixteen cases with definite clinical evidence of hereditary syphilis. It is evident, therefore, that idiocy may be frequently associated with hereditary syphilis, but, on the other hand, syphilis is not so frequent a cause of idiocy as has been heretofore held. The same is true also of epilepsy and the dementias, which give 20 to 40 per cent. of positive results. The percentage is too low to assume that these conditions are usually of syphilitic origin, but it indicates rather that they are associated occasionally with hereditary or acquired syphilis.

Other conditions in the central nervous system giving a positive Wassermann reaction are apoplexy and hemiplegia, as observed by Marie, Levaditi, and Yamanouchi in 3 of 6, by Hoehne in 3 of 7, and Swift in 10 of 12 cases; chronic internal hemorrhagic pachymeningitis (Pick and Proskauer), multiple sclerosis (Nonne, Eichelberg, Swift) and myelitis (Citron, Swift).

It is evident from this summary that the Wassermann reaction has been of value in corroborating opinions concerning the relation of syphilis to tabes and general paralysis and that these diseases may now be regarded as metasyphilitic manifestations. It also promises to be of great value in the diagnosis of other forms of syphilis of the nervous system. As Sachs has pointed out, any method which will differentiate between disseminated sclerosis and multiple cerebrospinal syphilis, or central gliosis and syphilitic central myelitis, or between malignant tumor of the brain and gumma, is most welcome. In this connection, Sachs states that the method should be practiced in every neurological ward as a guide to therapeutics, and adds that no operation should be done in a case of sus-

pected tumor without a Wassermann test. He also speaks of the value of the test in doubtful cases of hemiplegia and in cases of mysterious epilepsy beginning late in life. A negative reaction he regards as of almost as great value as a positive reaction, and is influenced accordingly in his treatment.

THE CARDIOVASCULAR SYSTEM

It has long been recognized by the clinician and by the pathologist that certain affections of the vascular system are as constantly associated with syphilis as are the so-called metasymphilitic affections of the nervous system. Aortitis, aneurism and aortic insufficiency represent the group of conditions which clinically have been considered as frequently syphilitic. The relation of aneurism to syphilis we find emphasized in the writings of all able observers. Thus in the sixteenth century Ambroise Paré suggested the relation of syphilis to aneurism, and Osler, in his Schorstein Lecture, refers to Fernellius, a contemporary of Vesalius, who described a venereal form of aneurism; Lancisi in 1728, and Morgagni in 1761, recognized the great influence of syphilis, as did also many Italian physicians of the seventeenth and eighteenth centuries. In recent times the association of aneurism and syphilis was brought out most prominently by F. H. Welch who, in 1875, found that in fifty-six cases of fatal syphilis among English soldiers aortic disease was present in 60.7 per cent. and aneurism of varying grades in 32 per cent. In thirty-four cases of fatal aortic aneurism, there was a syphilitic history in 50 per cent., without other etiologic factors for the causation of aneurism. Welch also recognized the fact that the aortitis of syphilis was different macroscopically from ordinary arteriosclerosis.

The most definite advance, however, in our knowledge of aortic syphilis dates from 1885, and is due to the work of Heller and his associates (Doehle, Backhaus, Phillipe, Moll and Eisenberg) in Kiel. Until this time the lesions of the aorta known under the general head of arteriosclerosis or atheroma had been considered more or less as an entity and due to various causes of which syphilis was only one. It is true that Köster, in 1875, had described a chronic mesarteritis, which he considered the essential factor in aneurism, and that Heiberg, in 1877, had advanced convincing evidence of a lesion occurring in comparatively young individuals, affecting especially the arch of the aorta, limited almost entirely to the media and due to syphilis, but it is from Doehles' first publication from the Kiel laboratory that the detailed study of syphilitic aortitis dates. As described by the Heller school, it is a mesaortitis involving especially the arch of the aorta, characterized by the presence of fleshy

nodules, involving media and adventitia, with cellular infiltration about the vasavosorum and the presence in the media of focal areas of necrosis, by some (Laveran) considered to be gummatous. Later the formation of cicatricial tissue leads to scarring, with either thickening or shrinkage of the vessel wall. The intima is unchanged or involved only secondarily; calcification and atheromatous ulcers are infrequent. It is the injury of the media that predisposes to aneurism, and Heller makes the statement that syphilitic aortitis is the cause of aneurism in 90 per cent. of all cases. Numerous confirmations of these observations appeared, the most important of which are Puppe's study of sixteen aneurisms, three of which he ascribed to ordinary atheroma, one to senile atrophy and the remaining twelve, all in young people, to progressive mesarteritis; and Straub's investigation of aortitis in eighty-four persons dying of progressive paralysis, in sixty-nine of whom he found syphilitic aortitis.

In 1903 the question was thoroughly discussed by the German Pathological Society when Chiari distinguished two types of aortic diseases, one of which he termed "Form A," the usual lesion of arteriosclerosis, an endarteritis with primary changes in the intima, and the other "Form B," corresponding to Heller's "mesaortitis syphilitica," but which he termed "mesaortitis productiva." This latter he found in sixteen of twenty-seven individuals (59 per cent.) in which syphilis was established by clinical or anatomical diagnosis, or by both, and in which arterial disease was present; in the other eleven cases endarteritis ("Form A") was found. Moreover, mesaortitis was found in a further group of twenty cases of probable, but not definitely established syphilis, in fourteen of which, however, progressive paralysis was present. Chiari further states that mesaortitis was found in 47 per cent. of all cases of progressive paralysis which he examined. Aneurism occurred in four of the individuals with the medial disease and in three with the intimal form.

Chiari concludes that mesaortitis frequently accompanies syphilis and may be caused by it; that it is most frequent in younger individuals and is associated with aneurism and with narrowing of the coronary arteries. He implies, however, that syphilis may not be the sole cause of mesaortitis, and apparently for this reason uses the term "mesaortitis productiva" instead of Heller's earlier term "mesaortitis syphilitica." At the same meeting Benda brought forth evidence to indicate the syphilitic nature of the necroses (miliary gummata), in the early vascular lesions, of the transition of such lesions to the late scarring, and of the relation of this sequence of lesions to aneurism.

Since this exposition, mesaortitis has had a very definite standing as a type of aortitis, presumably due to syphilis and distinct from endarteritis deformans. This view is supported by the studies which Weisner, Bruhns and Klotz have made of congenital syphilitic aortitis, which they find is a disease of the outer layers of the media and adventitia, quite analogous to mesaortitis in acquired syphilis. The verdict, however, is not unanimous. Marchand, while admitting that mesaortitis may be associated with syphilis, is not convinced that the lesion is histologically specific and adheres to his earlier opinion that the majority of aortic aneurisms are caused by the ordinary form of arteriosclerosis. In this country also, Ophüls considers arteriosclerosis of the aorta to be a unit; the disease affecting all coats, but involving at times one coat more than the others. He does not deny the importance of syphilis as an etiologic factor, but believes in the unity of the disease, anatomically, "even if in some cases the syphilitic virus should be eventually demonstrated in the lesions."

It is of interest that, at the time of this declaration, the spirochete of syphilis had already been demonstrated in mesaortitis. Ophüls' communication was published in June, 1906; in the preceding April appeared a note by Reuter concerning the finding of the spirochete in a mesaortitis of the Heller type. This was followed by similar communications by Benda, in July of the same year, and by Schmorl in January, 1907. During the past year (1909) Wright and Richardson have found the spirochete in five cases of syphilitic aortitis. Owing to the possible error of confusing degenerated tissue fibrils with the spirochete, and also owing to numerous negative findings, the earlier reports were received with some skepticism, but it is noteworthy in this connection that Schaudinn, to whom Reuter's preparations were shown, confirmed the finding of the spirochete, and Reuter's illustrations in his second communication are very convincing. Benda found the spirochete in a cerebral artery in tertiary syphilis, the vessel lesion being characteristic of fresh arterial syphilis, spirochetes, both typical and granular, being found in a focus in the outer portion of the media. Levaditi and Roché, in their monograph on "Experimental Syphilis," state that one of them had examined Benda's preparations and was convinced of the identity of the organisms with the *Spirochaeta pallida*. Schmorl found the organisms in a mesaortitis of tertiary syphilis, as did also Dr. Oscar Klotz.³

In the five cases of Wright and Richardson the ages of the individuals varied from 30 to 43. An aortitis limited mainly to the ascending por-

3. Quoted by Osler; confirmed by personal communication.

tion and arch was common to all, as were also well-marked fibrous changes in the aortic valves, the other valves not being affected. The coronary arteries were not remarkable except in that their orifices were more or less occluded by the fibrosis in the walls of the sinuses of Valsalva. Hypertrophy and dilatation of the heart occurred in three, and aneurism in one. The aortitis was of the type usually described as syphilitic; calcification of the aorta or the aortic valves was found but once. Necrosis of the media was common to all five cases, and it was in this necrotic material that spirochetes were found. In only one instance were spirochetes found in a granulomatous area. The number of the organisms varied greatly in the different aortas and in different places in the lesions. They were not found in all necrotic areas, and when present were usually few in number, though in one case they are described as fairly numerous and in another as present in enormous numbers. In two cases atypical forms predominated, but as similar atypical forms were found not only accompanying typical spirochetes in other cases but also in the livers of congenital syphilis, they conclude that these were degenerated spirochetes. Although these investigators state that they are not thoroughly convinced of the identity of these forms with the *Spirochæta pallida*, their control observation, including a careful study of tissue fibrils, leaves no other conclusion. From their description and drawings the organisms appear as typical as any found in congenital syphilis.

Perhaps the most important observation which they make, in that it has a bearing on the etiology of mesaortitis, is that concerning the relation of the spirochetes to the necrotic areas. "The finding of the spirochetes in an area of primary necrosis in the media, as well as in association with the necrosis in the fibrous tissue, seems to justify the belief that the micro-organisms are the cause of the necrosis by their local action on the tissue and that they are to be regarded as the cause of the whole process, although the possibility that they may be merely secondary invaders cannot be denied. Their numbers and distribution in the lesions would suggest that they rapidly multiply at a given point, produce necrosis and then degenerate and disappear."

In view of such evidence, it is difficult to deny that the mesaortitis found under such circumstances is a lesion of syphilis due to the local action of the *Spirochæta pallida*. We may confidently expect further observations to confirm this view.

AORTIC INSUFFICIENCY

Although the spirochete has been demonstrated only in mesaortitis, we have other evidence, that based on the method of serum diagnosis, to indi-

cate that various lesions of the vascular system may be caused by syphilis. Most of the work by this method has had for its object the demonstration of the syphilitic origin of aortic insufficiency. That syphilis is a common cause of aortic insufficiency is a matter of common clinical knowledge, and pathologists have long been aware of its frequent association with the mesaortitis ascribed to syphilis. Indeed, recent investigation seems to show conclusively that the lesion of the valve is an extension of the disease in the aortic wall. Numerous statistics based on clinical and pathological observation are available, and of these a few may be given. Thus, Saathoof has emphasized the close relation of aneurism and aortic insufficiency to syphilis, and describes seven cases of luetic aortitis, in six of which aortic insufficiency was present. Mönckeberg analyzed thirty cases of mesaortitis, in eleven of which there was a definite history of syphilis. Narrowing or occlusion of the coronary arteries occurred in eight, aortic insufficiency in thirteen, and aneurism in ten. He further states that fully 33 per cent. of published cases of mesaortitis offer a history of syphilis, and of the remainder 44 per cent. are associated with metasymphilitic conditions. Citron has shown that in thirty-five cases of pure aortic insufficiency, a definite history of syphilis was present in 14.2 per cent. and a history of probable syphilis in 25.7 per cent. His results with the Wassermann reaction, as will be shown later, give syphilis a most prominent place in the etiology of this lesion.

The subject has recently been investigated clinically and pathologically by Longcope, who has utilized the material of the Pennsylvania Hospital. In a series of 930 autopsies, seventy-six cases of chronic aortic endocarditis were found. Twenty-one of these were unassociated with lesions of any of the other valves and constantly accompanied by mesaortitis, which was always confined to the arch of the aorta, sometimes extending only a few centimeters from the aortic cusps. The gross and histological lesions of the aorta in all cases were those of syphilitic aortitis. Aneurism was present in four; calcification in one case only. Moreover, in those cases in which the valves were studied histologically the process in the aorta could be followed to the attachment of the cusps, and in the cusps certain features of the histological lesions of mesaortitis could be found. In eleven of the individuals, all of whom were young or middle-aged, there was a definite history of syphilis or the diagnosis was established by finding gummata at autopsy. Eighteen of the twenty-one gave clinical evidence of aortic insufficiency.

In a second group of twenty-one cases with clinical evidence of aortic insufficiency but with other valves also affected, lesions of the aorta were

absent. These were, for the most part, in young persons with, as a general rule, a history of rheumatic fever.

In a third group of thirty-four cases, in which the aortic valves alone were affected, no mesaortitis existed. They were for the most part elderly individuals, and in all but nine the intimal type of arteriosclerosis or endarteritis deformans characterized by calcification, was present. In only four were signs of aortic insufficiency present during life.

These results may be expressed in tabular form (Table 7).

TABLE 7.—AORTIC ENDOCARDITIS

	Pure with Mesaortitis	Pure with Endarteritis	Other Valves and Rheumatism
Aortic insufficiency.....	18	4	21
No aortic insufficiency.....	3	30	0

Thus it is seen that a pure aortic endocarditis with insufficiency is in the great majority of cases associated with mesaortitis and is presumably of syphilitic origin.

To this anatomic evidence of the importance of syphilis in vascular disease may be added that obtained by the use of the Wassermann reaction, as presented in Table 8.

TABLE 8.—WASSERMANN REACTION IN CARDIOVASCULAR LESIONS

Observer.	Aneurism.		Aortic In-		Other Valv-		Mesaortitis.		Arteriosclero-	
	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.
Kroner	...	...	1	1	...	...	...	...	1	...
Citron	...	...	16	10	3	1	...	...	...	...
Schütze	3	3	6	5	...	...	1	1	1	1
Danielopolu	2	2	2	2	...	...	10	5	...	...
Laubry and Parvu..	6	4	6	3	14	3	9	8	7	3
Donath	3	3	23	19	...	...	1	1	...	...
Collins and Sachs..	5	5	13	10	16	3	...	...	2	1
Swift	3	1	12	6	...	...	...	...	...	...
Hoehne	3	1	2	1	...	...	5	3	1	1
Noguchi	...	...	1	1	...	...	...	...	...	...
Clough*	20	10	9	6	...	...	2	2	...	...
Bellner and Mus- catello	...	...	1	1	...	...	...	...	6	2
Beckers	...	...	2	2	...	...	...	...	...	...
Hasenfeld and Szili	...	...	...	...	...	...	...	...	188	20
Löhlein †	...	...	...	...	...	...	3	3	...	...
Fränkel and Much†	4	2	...	...	...	...	23	19	8	1
Schlimpert†	1	1	...	...	...	...	16	15	...	...
Reinhart†	7	6	3	3	1	1	...	...	...	...
Deneke	...	...	13	3	...	...	...	...	...	...
Saathoof	...	...	12	12	...	...	...	...	...	...
Totals	57	38	122	85	34	8	70	57	214	29

* Includes the 9 cases of Barker, quoted by Osler.

† Reaction with post-mortem blood.

From this table it will be seen that the general theory concerning the association of mesaortitis, aortic insufficiency and aneurism, and the relation of these conditions to syphilis is supported. In a total of fifty-

seven cases of aneurism the reaction was positive in 66.6 per cent.; also positive in 69.6 per cent. of 122 cases of aortic insufficiency and in 81.4 per cent. of seventy cases of mesaortitis.

The most striking results are those of Citron, with positive results in 62.6 per cent., Collins and Sachs 77 per cent., Clough 66 per cent., and Swift 50 per cent. in aortic insufficiency; Fraenkel and Much⁴ in 83 per cent. of cases of mesaortitis; Collins and Sachs in all of five cases of aortic aneurism, and Donath's 85 per cent. of twenty-seven cases of mesaortitis, aneurism and aortic insufficiency. If doubtful reactions were included some of these percentages would be higher.

On the other hand, it is seen that positive results in valvular lesions other than aortic insufficiency are relatively infrequent, in less than 25 per cent. of those given in the table. Also in arteriosclerosis of the intimal type it occurs infrequently; the largest series, that of Hasenfeld and Szili, giving but 10.6 per cent. in 188 cases.⁵

In view of these results it is evident that a more thorough investigation of this field may lead to a very satisfactory separation of syphilitic from non-syphilitic vascular lesions and therefore to a more rational therapy. The three important conditions described have long been treated by many practitioners as syphilitic affections, this treatment being based on a history of syphilis and the knowledge that as a result improvement was not infrequent. One cannot hope to cure an aortic lesion, but the process, be it aneurism, mesaortitis or insufficiency, may perhaps be arrested or the progress of the disease influenced by vigorous antisymphilitic treatment.

4. It must be admitted that some doubt has been raised recently concerning the accuracy of results with blood taken at autopsy. Thus Bruck points out the frequency of positive reaction with post-mortem blood from definitely non-luetic individuals. The results of Fraenkel and Much and of Schlimpert must therefore be accepted tentatively. In this connection see Löhlein, M.: *Zur Frage der Verwertbarkeit der Wassermannschen Syphilisreaktion an der Leiche*, *Folia serologica*, 1910, iv, 227.

5. In addition to the tabulated cases it may be noted that Lenhartz has recently commented on the frequency of a positive Wassermann in aneurism, early aortic disease and sclerosis of the coronary arteries. Saathoof reports positive results in cases of aneurism and angina pectoris, but gives no figures. Øignard made the test on twenty-five patients with cardiac disease and obtained a positive reaction in all of those suffering from aneurism or uncomplicated aortic insufficiency and negative results in the cases of mitral disease. Sonnenberg reports nine cases of aneurism with aortic insufficiency, in five of which a positive Wassermann was obtained, as it also was in half of sixteen cases of arteriosclerosis in young individuals. M'Intosh reports a positive Wassermann in one case of aneurism as do Coenen and Wolfsohn in one each of aortic insufficiency. More recently, Krefling has reported positive results in eight of nine cases of aortic insufficiency.

This view is supported by Longcope and also by Cabot, who states that since the discovery by Wright and Richardson of the spirochete in mesoarteritis it has been his practice to "push antisyphilitic treatment in all cases of non-rheumatic cardiac disease in which there is a history of syphilitic infection, especially if the Wassermann reaction is obtained." Such patients, he thinks, respond to this treatment better than would be expected under the ordinary treatment of rest, purgation and cardiac stimulation. Collins and Sachs definitely recommend antisyphilitic medication in cardiovascular conditions giving a positive Wassermann, and state that marked improvement has followed such treatment. Laubry and Parvu report improvement in certain cases of aortic lesions giving a positive Wassermann reaction and placed under antisyphilitic treatment.

There is some evidence that the Wassermann reaction may also lead to the recognition of the syphilitic nature of various vascular conditions not included in the group just discussed, and also of disease of the myocardium. The view that a primary interstitial myocarditis associated with panarteritis may be due to syphilis is held by many writers, and in this country has been emphasized, especially by Adler, who reports very satisfactory results from antisyphilitic treatment. It is not surprising therefore to find that Schlimpert reports a positive Wassermann reaction in two cases and Schütze in one case of coronary sclerosis; Reinhart in three of six cases and Citron in one case of myocarditis. Positive reactions have also been obtained in individuals with sclerosis of the pulmonary artery and cerebral aneurism (Schlimpert), and by Clough in one case, and by Laubry and Parvu in three cases of obliterating endarteritis with gangrene, and by the latter also in one of diffuse endarteritis of the extremities.⁶

Much work must be done before definite conclusions can be reached concerning the more obscure vascular lesions. We may hope, however, in view of what has already been accomplished, for results which may be utilized to shape therapeutics.

I have been especially impressed, in studying the statistics of syphilis, by the frequent association of cardiovascular lesions with the so-called parasyphilitic affections of the nervous system and their relative infrequency in syphilis without paralysis. Thus Straub found mesoarteritis in sixty-nine of eighty-four paralytics (82.1 per cent.) with syphilis, but,

6. Kaliski and Buerger have failed to get a positive reaction in sixteen cases of thrombo-angiitis obliterans. This statement is made by Noguchi in reporting two cases of Raynaud's disease with negative reaction.

on the other hand, aortitis was present in only seven of seventy-one syphilitics (9.9 per cent.) without paralysis. It was present in 47 per cent. of the cases of progressive paralysis examined by Chiari and in 63 per cent. of twenty-four cases of tabes described by Müller and Rogge (Strümpell's clinic), and Mönckeberg states that an analysis of the published cases of mesaortitis shows that 44 per cent. are associated with metasyphilitic affections.

Such vascular lesions are, apparently, as truly parasymphilitic as are tabes and progressive paralysis; and this view, suggested by pathological studies, is supported by the results of the Wassermann reaction. One wonders whether the individuals with parasymphilitic vascular and nervous lesions are those in which active virus persists, while those without such lesions represent individuals in which the spirochete has been destroyed by proper treatment. If the former, one may advance a second hypothesis, that based on the finding of the spirochete in mesaortitis, to the effect that the nervous lesions may be due to the poison of the spirochete persisting in the chronic vascular lesions.

CIRRHOSIS OF THE LIVER

Aside from affections of the cardiovascular system, the only disease of interest to the internist concerning which we have much data is cirrhosis of the liver. Of the reports⁷ which I have been able to collect, twenty-two of thirty cases have given a positive Wassermann reaction. Of these, about half were in individuals with a history of syphilis; in the others, a history of antecedent syphilis was absent or doubtful. Of special interest is the negative result in a case of Banti's cirrhosis (Pick and Proskauer), a lesion which has been considered as possibly syphilitic. Esmein and Parvu report a positive reaction in a case of cirrhosis with hypertrophy; under mercurial treatment rapid improvement was noted. Clough found five alcoholic cirrheses negative and one, clinically syphilitic, positive. It is possible, therefore, that further work may show that the etiology of various cirrheses may be determined by this method, thus adding to our knowledge of the pathology of the liver and aiding in the establishment of a satisfactory treatment. It is also possible that the ascitic fluid of cirrhosis may be utilized for the test, as demonstrated by Esmein and Parvu, by Swift and by Cheney.

7. Citron, 2 cases; Hoehne, 2; Fraenkel and Much, 2; Ballner and Muscatello, 1; Noguchi, 7; Esmein and Parvu, 1; Pick and Proskauer, 1; Clough, 6; Swift, 7; Cheney, 1.

SURGERY

Among the first to recognize the importance of the Wassermann reaction in the practice of surgery were Karewski and Coenen. Karewski, early in 1908, emphasized the value of the method in the differential diagnosis of gumma and tumor, of tuberculous and syphilitic affections of bone, and as an additional means of establishing the diagnosis in those cases in which, although the presence of syphilis is probable, an absolute diagnosis could not otherwise be made. On the basis of his experience with twenty-eight tests, he emphasizes the value of the reaction in the recognition of syphilis of bone and in the determination of treatment, and comments on the advisability of replacing the therapeutic test by the serum reaction.

Coenen, later in the same year, published the results of seventy observations. His cases include a great variety of surgical affections which may be grouped in three classes, diseases of bones and joints, tumors and diseases of blood-vessels. Of the seventy individuals tested, thirty presented clinical evidence of syphilis and twenty-six gave a positive Wassermann reaction. Of these latter, mainly individuals with disease of bone, a history of syphilis was lacking in nine. Coenen also emphasizes the importance of the reaction in the differentiation of syphilitic bone disease from tumors, especially sarcoma. He points out the difficulty of making a histological diagnosis between an inflammatory condition of bone, syphilis and sarcoma on the small piece of tissue removed at operation and hastily examined. The Wassermann reaction under many circumstances may therefore be preferable to a histological examination. He also considers it important in the diagnosis between syphilitic leukoplakia and early cancer of the tongue. Here, however, one must interpret with caution, for cancer frequently develops in the lesion of leukoplakia.

Baetzner, after a study of 120 cases, urges the use of the reaction in the differentiation between chancre and peculiar localized inflammatory conditions and between gummata and necrotic tumor-like masses, a positive reaction assuring early treatment. He has also found it of assistance in joint and bone disease. He concludes that the method ranks in importance with those of histology, bacteriology and radiography in the diagnosis of syphilitic disease. Pick and Proskauer likewise emphasize the importance of the method in certain lesions, as sarcoma, infectious granuloma and chronic inflammation, which are not readily differentiated from syphilis by histological examination.

Clough refers to two patients with tumors of the chest wall clinically resembling sarcoma. Each gave a positive Wassermann and on exploratory excision and histological examination evidence of lues was found.

Swift, who has obtained positive results in three of four cases of gumma of the testicle, makes an interesting observation on this subject. In one patient a testicle was removed because of a diagnosis of tuberculosis; subsequently the other testicle became involved. A positive Wassermann reaction at this time led to antisyphilitic treatment and marked improvement.

Several references to the use of the reaction in the recognition of syphilitic strictures of the rectum are also at hand (Wolfsohn, Clough), and Wolfsohn, who details some observations on its use in surgery, classes it with the tuberculin reaction in importance.

Several observers (Citron, Reinhart, Noguchi, Clough) have obtained positive reactions in chronic bone and joint disease, as chronic arthritis and spondylitis. Donath and Heckman have called special attention to these conditions. In Donath's twenty-seven cases of vascular disease, of which 88 per cent. gave a positive reaction, polyarthritis occurred in three. Although these cases all gave a history of articular rheumatism, he believes that certain special features of the joint affection show the lesion to be of a syphilitic nature rather than a true rheumatic polyarthritis.

Swift also emphasizes the value of the test in disease of bone; he has obtained sixteen positive results in seventeen cases of osteomyelitis, periostitis, and gumma of bone. Four of these were confirmed by *x*-ray and all improved under treatment with potassium iodid.

Heckman gives a detailed study of four cases of arthritis deformans of the mono-articular type and eleven of the polyarticular type. A fairly definite history of syphilis was obtained in all of the first group, without evidence of tertiary lesions, and all of these gave a positive Wassermann reaction. In six of the second group (polyarticular type), definite evidence of syphilis was present and less definite evidence in one. In seven cases the Wassermann reaction was definitely positive and in four weak or doubtful. On this evidence of the frequently positive Wassermann reaction, the fairly constant history of syphilis, and the improvement under antisyphilitic treatment, Heckman comes to the conclusion that not only the mono-articular, but also to a large degree the polyarticular form of arthritis deformans, has a luetic basis. Swift reports positive results in two cases of mono-articular and one of polyarticular chronic arthritis, with cure under antiluetic treatment.

It is evident from this summary that in surgery the Wassermann method for the diagnosis of syphilis is at least of equal importance with the tuberculin reaction. Although, as Baetzner points out, a positive reac-

tion is an indication of general disease and not of local lesion, nevertheless, with a doubtful local lesion, a positive reaction supplementing other methods of examination, is of great value. The reaction has not thus far been extensively employed in surgery, but if the reported results are confirmed we may confidently expect it to become one of the common procedures of the surgical clinic.

LARYNGOLOGY

Specialists treating the throat, nose and ear have utilized the Wassermann reaction in the diagnosis of obscure ulcerative lesions, in the study of ozena and for the purpose of determining the relation of syphilis to certain forms of deafness.

Ozena, on account of its frequent association with congenital syphilis, has been especially studied. It has long been a disputed point as to what percentage of cases of ozena was to be ascribed to syphilis. Investigations to determine this point by demonstrating the presence of the spirochete have been uniformly unsuccessful, and it is but natural that the assistance of the Wassermann method should be invoked. Alexander has examined twenty-six cases of ozena, free of clinical evidence of syphilis, with negative results in all, but takes the stand that a negative reaction is of no value and does not exclude the syphilitic origin of the disease.

Sobernheim obtained similar results in seventeen cases and concludes, in the light of the frequently positive Wassermann in tertiary and latent syphilis and in tabes and general paralysis, that ozena is not necessarily a metasyphilitic disease. In a later communication he reports a positive reaction in two cases of ozena with evidence of syphilis.

Scheier reports negative results in eight cases of simple ozena and a positive result in one case in an individual with tertiary syphilis. Negative results have also been reported by Weinstein, who examined eight cases.⁸ Eisenlohr, one of the first investigators in this field, also obtained negative results in fifteen cases. It is as yet a little difficult to decide as to the exact importance of these negative results. It is certain that a negative Wassermann reaction is uncommon, as a constant result, in any large series of cases representing acquired, inherited or latent syphilis. The conclusion, therefore, seems justified that ozena may occur independently of syphilis.

8. These cases are reported from Scheier's clinic and apparently are the same observations presented above under Scheier's name in the discussion of Sobernheim's work.

Sobernheim has also called attention to the value of the Wassermann reaction in the differential diagnosis of Vincent's angina and of early syphilitic ulceration of the tonsil, a negative as well as a positive reaction being of aid both in diagnosis and treatment.

Weinstein called especial attention to the importance of the reaction in the differential diagnosis between syphilis and tuberculosis of the respiratory mucous membranes, both as an adjunct to the histological examination of excised tissue and as a substitute for the therapeutic test. He gives instances in which a positive serum reaction led to the clearing up of a diagnosis which lay between syphilis and tuberculosis, but which could not be determined by history, clinical appearance, histology or bacteriology. In all the cases in which the diagnosis of syphilis was established by the serum reaction, appropriate treatment led to rapid improvement.

Weinstein also speaks of the use of this method in connection with the diagnosis of primary syphilitic lesions of the mouth, of leukoplakia, and in the differential diagnosis of Vincent's angina. While a negative result should be considered cautiously, he believes it strong evidence against syphilis.

My own experience has been such as to indicate that the Wassermann reaction promises to be of great value in the diagnosis of affections of the respiratory passages.

The following experience is illustrative. A laryngologist sent me a small piece of tissue from an extensive ulcerative lesion of the post-pharynx, with a request for histological examination. He was inclined to a diagnosis of syphilis, but as one of the two dermatologists who were consulted concerning an associated lesion of the skin had made a diagnosis of tuberculosis and the other of syphilis, he was in doubt. On examining the sections, I could not make a diagnosis between syphilis and tuberculosis, and in this found myself in agreement with three other pathologists. The serum test was tried, and a strongly positive reaction was taken as definite evidence of syphilis and appropriate treatment instituted.

I have been able to find only one reference to the use of the Wassermann reaction in the study of diseases of the ear. Busch has examined twenty-nine cases of nervous deafness and seventeen of otosclerosis. Positive reactions were obtained in 52 per cent. of the former and in 23.5 per cent. of the latter. He concludes that the method is of value in establishing the proper treatment of these conditions and suggests that it also

may be of value in clearing up the etiology of some of the as yet little understood chronic affections of the ear.

OPHTHALMOLOGY

Leber appears to have been the first to use the Wassermann reaction in the diagnosis of diseases of the eye. In a series of 160 examinations he found sixteen certainly syphilitic affections, in 93.7 per cent. of which a positive reaction was obtained, and ninety-five doubtful cases with a positive serum test in 42.1 per cent. He emphasizes the importance of the test, not only for diagnosis and treatment, but also as a means of establishing more exactly the etiology of many diseases of the eye. In this connection, he states that a positive reaction was obtained in 83.9 per cent. of thirty-one cases of keratitis, exclusive of the suppurative form, in iritis in 33 per cent., in retinitis and chorioiditis in 26 per cent., and, finally, in eye lesions accompanied by cerebral symptoms in 59.3 per cent. He especially refers to the importance of the test in the differentiation of tuberculous and syphilitic disease.

Gutmann comments on the value of the Wassermann for early diagnosis and early treatment, for the differential diagnosis of tuberculosis and tumor from syphilitic disease, as a substitute for the removal of pieces of tissue for diagnosis, and for the recognition of the cause of muscle paralysis. He quotes cases illustrating early diagnosis in which patients were successfully treated by mercury who, ordinarily, would have been operated on.

Cohen has examined sixty-four cases; positive reactions being obtained in cases of iritis, keratitis, chorioiditis, cataract, optic atrophy, optic neuritis, and muscle paralysis, in 61 per cent. of known syphilis and in 29 per cent. of suspected or doubtful syphilis. Cohen concludes that a negative reaction is of some diagnostic aid and a positive reaction of direct value both in diagnosis and treatment.

Schumacher reports 215 examinations, with positive results in 40 of 58 cases of syphilis and in 24 of 73 cases of suspected syphilis, his positive results occurring in much the same group of cases as those reported by Cohen, and he supports the latter in the belief that a negative reaction in ophthalmic cases is of considerable diagnostic value. In the doubtful cases he considers the reaction to be of the greatest value, although in hereditary syphilis free from recent acute symptoms a positive reaction is rare. He presents observations concerning the development of tuberculosis secondary to changes due to syphilis in the internal eye, such cases giving both the Wassermann and tuberculin reactions, and for this

reason recommends the tuberculin treatment as well as anti-syphilitic treatment.

Best has made observations which lead him to think that the Wassermann reaction may be useful in distinguishing between hereditary syphilitic chorioidoretinitis and clinically similar forms of non-syphilitic origin.

Other studies are those of keratitis by Hoehne, Pisani and Silbersiepe. Pisani obtained positive results in all of seven cases of parenchymatous keratitis, and regards these results as definitely establishing the syphilitic nature of the disease.

Silbersiepe has examined 100 cases of keratitis parenchymatosa with the aid of the Wassermann reaction, and finds that it supports the theory of the great importance of syphilis, especially hereditary syphilis, in the etiology of the disease.

Noguchi gives a table of twenty-nine cases of eye diseases, in fourteen of which a positive Wassermann reaction was obtained; in eight of twelve cases of interstitial keratitis, four of six cases of iritis, one of optic neuritis, and in one of two cases of acromegaly with ocular symptoms. Negative results were obtained in optic atrophy (five), scleritis, chorioiditis, and paralysis of the external rectus. Swift has obtained positive results in uveitis, central amaurosis and optic atrophy.

DERMATOLOGY

The use of the reaction as an aid in the diagnosis of the common skin lesions of syphilis need not be discussed. Its use in this field has been definitely established. Of other diseases of the skin of doubtful etiology, one that has been especially investigated is scleroderma. Castelli reports positive results in two, Noguchi in one of four and Whitehouse in four of five cases. Whitehouse's investigation was suggested by a positive result obtained by Lustgarten. His cases were those of diffuse scleroderma; three gave a strong and one a faint positive reaction, and one was negative. The two latter patients had been under anti-syphilitic treatment, one for over a year and the other for six months. In addition to these five cases of the diffuse type, two cases of the band-like morphea type gave negative reactions. Whitehouse considers it not improbable, in view of the histological resemblance between the changes in scleroderma and syphilis, that syphilis may be an etiological factor in the diffuse form of scleroderma. Swift,⁹ however, has examined three cases of sclerodactylia and one of the diffuse form with negative results.

9. Personal communication.

Another condition especially studied is leukoplakia of the tongue. The status of leukoplakia has never been quite clear. That it may occur independently of syphilis is known. But its frequency in well-defined syphilis renders doubtful the diagnosis when leukoplakia occurs in the absence of other symptoms of syphilis, that is, in those conditions in which it is the only manifestation of an otherwise latent syphilis. Under such circumstances the question of treatment is doubtful and for that reason the help of the Wassermann reaction has been invoked. Pürckhauer has examined twelve cases, with positive results in ten. Positive results have also been reported by Coenen in three cases, by Schlimpert in seven of ten cases, by Swift in six of seven cases and by Joseph. It would seem that, as a rule, leukoplakia is to be regarded as evidence of syphilis and often the only manifestation of a latent syphilis. If so regarded and treated as such, it is possible that cancer of the tongue, of which leukoplakia is frequently a forerunner, may in many instances be prevented.

Neisser has emphasized the importance of the reaction in the differentiation between lupus and tertiary syphilis and between early round-celled sarcoma and chancre. He presents illustrative cases, one of which had been wrongly diagnosed as lupus of the nose and treated as such, with the result that extensive destruction of the nose, pharynx, gums and both eyes resulted. A positive Wassermann reaction led to anti-syphilitic treatment and improvement, but too late to save the eyes and prevent extreme disfiguration of the face.

The literature contains numerous reports of isolated instances in which the Wassermann reaction has led to the recognition of the syphilitic nature of ulcerative lesions at first supposed to be tuberculous (Clough). In all such cases improvement has followed antisyphilitic treatment. Another use of the Wassermann reaction, as pointed out by Swift, is in those cases in which a syphilitic roseola is marked by other eruptions, as for example, scabies.

GYNECOLOGY, OBSTETRICS, AND COLLES' LAW

The Wassermann reaction in gynecology is in part a matter of diagnosis, but to a greater extent—and this is particularly true of its relation to obstetrics—it is of importance in the interpretation of those general principles embraced under Colles' and Profeta's laws. The significance of the results obtained concerning this latter aspect of the problem overshadow the use of the method in the diagnosis of local lesions. The

results may be said to render necessary a revision of Colles' and Profeta's laws and to constitute practically a new biological law.

One of the first investigators in this field was Opitz, who concluded that the reaction merited the earnest consideration of the gynecologist and obstetrician. It became at once not only a means of recognizing syphilis in women and the new-born in which the diagnosis was doubtful, but also a means of clearing up the etiology of stillbirths and habitual abortion. Such observations (Knöpfelmacher and Lehdorf, Bauer, Bab, Ledermann) led to a thorough investigation, with the aid of the reaction, of the principles embraced in the laws of Colles and Profeta.

It may perhaps be unnecessary to observe that Colles' law covers those instances in which the mother of a syphilitic child is herself immune to infection and cannot be infected, even though she presents no signs of the disease. It has always been a question whether the immunity is real or whether the mother is so lightly infected as to present none of the actual manifestations of the disease. Profeta's law refers to the reverse condition, that in which an apparently healthy child, born of a mother suffering from active syphilis, can suckle its mother without contracting the disease from her. Here again the question is that of immunity versus latent infection.

The Wassermann reaction has been used to determine whether in the first instance the mother and in the second the child actually has syphilis, or, on the other hand, is really immune to the disease. The use of the test for this purpose is based on the assumption that a positive Wassermann reaction means active syphilis, if not, indeed, the actual presence of the spirochete. All recent work, especially that with latent acquired syphilis, indicates that this assumption is correct. Positive reactions in the mothers of syphilitic children and in the apparently healthy children of syphilitic mothers have therefore been considered as evidence of actual syphilis in each instance, thus removing any interpretation of Colles' or Profeta's law based on the principles of immunity. The results all hold together. Thus Knöpfelmacher and Lehdorf obtained a positive reaction in 56 per cent. of thirty-two women apparently healthy, but mothers of syphilitic children; Buer obtained similar results in all his cases, as did also Ledermann and Engelman and Bergmann. Such results in small groups of cases led to the conclusion that these apparently healthy mothers were really affected with latent syphilis, and led to numerous other investigations (Bunzel, Reinhart, Frankl), one of the most extensive of which, that of Baisch, may be quoted in detail. It includes a study of 140 cases, with a search for spirochetes in the fetus and pla-

centa and the use of the Wassermann method on the mother. Of these, 102 were mothers with positive Wassermann reaction whose children had syphilis, evident macroscopically, or shown by the finding of the spirochete in the tissues. Seventy-five of these mothers were without clinical evidence of syphilis. On the basis of finding spirochetes (Trinchese) in the spaces between the villi in the maternal portion of the placenta in selected cases Baisch concludes that the spirochetes are present in the blood of the mother and that therefore the positive Wassermann reaction is not an evidence of immunity of the mother, but rather of latent syphilis, or, as he puts it, the mother is refractory to infection with syphilis because she is already infected. He further shows that in twelve mothers giving a negative reaction, spirochetes were present in the maternal portion of the placenta, thus indicating that all such mothers are syphilitic and that there are no exceptions to the principle of Colles' law. As to Profeta's law, much the same conclusion has been reached. The children of syphilitic mothers are not immune to syphilis but are either syphilitic, that is, have latent syphilis, or are healthy, and in the latter case may later become infected.

Aside from the light thrown on the problems of congenital syphilis,¹⁰ the demonstration of latent syphilis under these circumstances is of great importance in that it points to the necessity of treatment, in order that active manifestations of the disease may be prevented.

Frankl, who has studied in detail eighty-seven cases, states that a woman who has given birth to a syphilitic child and has a positive Wasserman reaction is to be considered as having latent syphilis and should be given specific treatment without waiting for further manifestations of the disease. Also a positive reaction in the child of a syphilitic mother, though the child be apparently healthy, demands specific treatment for the child. McDonagh urges that all apparently healthy pregnant women giving a positive reaction should receive specific treatment through the entire pregnancy, for, as the result of such treatment, women habitually aborting may have healthy children.

10. The reaction has added little of special interest to the diagnostic methods of the gynecologist, though some casuistic reports are of interest, as in the case of Neisser, in which the uterus was extirpated for what appeared on histological examination to be a round-celled sarcoma of the cervix. The later development of the secondary lesions of syphilis and a positive Wassermann indicated the lesion to be a chancre, from which experience was drawn the lesson that if the serum diagnosis had been attempted first the operation might have been avoided. It is also worthy of note that Bunzel found six of seven cases of eclampsia positive at the height of the disease, but negative after the disappearance of the symptoms. Under such conditions, therefore, the reaction is to be considered with caution.

A closely analogous investigation is that of wet-nurses. Physicians have long sought to rule out two infections, tuberculosis and syphilis, without, however, in the latter having any definite criterion in the absence of symptoms. Bergmann has examined seventy-five wet-nurses, only two of whom presented evidence of syphilis, and found a positive Wassermann reaction in seven (9.3 per cent.). Rietschel found a positive reaction in 10 per cent. of the wet-nurses whom he examined. Both Bergmann and Pust state emphatically that every physician or clinic seeking a wet-nurse should have a Wassermann reaction done, irrespective of clinical findings. This statement is supported by Bruck and is in accord with the observations of Opitz and Rietschel.

LATENT SYPHILIS

It has been seen that the study of the principles of Colles' law has furnished valuable evidence in support of the theory of latent syphilis. Of the greatest importance, however, in this regard, as well as from the point of view of public health, are the results of the use of the Wassermann reaction on the prostitutes of foreign cities. Such investigations have been made by Beckers, Hoehne, Jundell, Almkvist and Sandman, and by Dreyer and Meirowsky. Beckers examined eighty prostitutes, of whom thirty-three, or 41.25 per cent., gave a positive reaction and five, or 6.25 per cent., a doubtful reaction. Of those reacting positively only eleven, or one-third, presented clinical evidence of syphilis. Of fifty who had had syphilis but presented no symptoms twenty, or 40 per cent., gave positive reactions. Jundell and his associates obtained 23 per cent. of positive results in thirty-two prostitutes without clinical evidence of syphilis. Hoehne examined 107 *puella publica* with no manifest syphilis, and obtained a positive reaction in 21.5 per cent.

The investigation of 100 women by Dreyer and Meirowsky is most complete. They found two with active syphilis and fifty-five with a history of syphilis and earlier treatment but no manifestations. Of these fifty-seven, thirty-nine, or 68.4 per cent., gave a positive reaction. In the remaining forty-three with no history or manifest lesions of syphilis, a positive reaction was obtained in twenty-six, or 60.5 per cent. It is seen, therefore, that if the cases with a positive Wassermann reaction only are added to those with a history of syphilis, or with the lesions of the disease, we have 83 per cent.¹¹ of 100 women presenting evidence of

11. The figures given are those obtained by the original Wassermann method. The investigators used also Stern's modification, and by this means obtained a somewhat higher number of positive reactions, that is, 78 per cent. for the first group, 74.4 for the second group, and 89 per cent. for the combined groups.

infection. Or, to put it another way, we have 2 per cent. with active lesions and 81 per cent. with either a history of syphilis or a positive Wassermann reaction as evidence of the frequency of infection in this class. Moreover, of those giving a negative reaction all but three had been registered less than a year and none for more than three years. Few, therefore, would appear to escape; all apparently become infected within three or four years of exposure. Syphilis occurred in those between 21 and 25 years of age in thirty-four of the total number as compared with seven of the same period free of the disease. In the next age period of 25 or 30, thirty-one were infected, as compared with two free of syphilis. Of the total of 100, only one of twenty-four women over 30 years of age was non-syphilitic. These figures, if we accept the Wassermann reaction as evidence of active syphilis, would appear to throw grave doubt on the possibility of a natural immunity to syphilis.

When one considers that in the past the presence of syphilis could be demonstrated by history and examination in only about 50 per cent.¹² of these women, the value of the Wassermann method as presumptive evidence of syphilis becomes apparent. It is evident that in European cities, in which cases of this class are registered and carefully watched, many problems of syphilis may be studied; as (1) the question of the infectivity of individuals with a positive Wassermann reaction as the only symptom of the disease; (2) the control of this mode of infection; (3) the study of the frequency of the development of tertiary and quaternary lesions in individuals presenting only a positive Wassermann reaction; (4) the influence of treatment on the Wassermann reaction, and (5) other general problems concerning individuals who are, essentially, spirochete-carriers without evidence of disease.

SPECIAL APPLICATION OF THE REACTION

The experience with prostitutes, wet-nurses, and especially the information brought out by the study of the laws of Colles and Profeta have thrown an interesting light on the question of so-called latent syphilis, or, as it is now frequently termed, "syphilis without manifestations." Many authors are of the opinion that in so-called latent syphilis we have to do with visceral syphilis giving no outward (clinical) manifestations of disease and recognizable only by a positive Wassermann reaction. If this can be substantiated—and this is a view already supported by many investigators—and if we are to regard a positive Wassermann reaction as

12. Bruhns and Lumme's statistics give 3,179 as treated for syphilis and 3,118 as not treated for syphilis. The figures are for fifteen years (1892 to 1907).

evidence of active syphilis, the reaction has many other practical applications which are suggested by what has been said in the discussion of Colles' law, of wet-nurses, and of prostitutes. One of these is the use of the test in the examination of applicants for life-insurance. Ledermann has suggested that it would be of value in those cases in which the examiner suspects syphilis but cannot establish a diagnosis by history or symptoms. This is of particular interest in view of the fact that the vital statistics of all life-insurance companies indicate that individuals with syphilis are not as good risks as those who are non-syphilitic. Recently Brockbank, who has investigated the subject most thoroughly, made the statement that "no syphilitic proposer who cannot bring forward satisfactory evidence of having undergone proper treatment should be accepted." The difficulty naturally is to decide on what is "satisfactory treatment." Swift prophesies that for this the Wassermann method will eventually be the test, and that the evidence required will be repeated negative reactions over a period of time sufficient to show that the individual is free from the disease. He also believes that a positive reaction, even when clinical symptoms are absent, should be considered as sufficient evidence for rejection or for acceptance at an advanced premium. McDonagh holds that a candidate giving a positive reaction, even though years have elapsed since the original infection, should be considered ineligible on the ground that the positive reaction is an indication of a visceral lesion which will ultimately shorten life. On the other hand, he recommends the acceptance of a candidate who after two years of treatment gives a negative reaction after intervals of three, six and nine months. Certainly, if we are to accept a positive Wassermann reaction as a sign of active syphilis and also accept Brockbank's rule that "no proposer showing signs of the disease in any one of its stages should be accepted," these conclusions are logical.

Another question is that of marriage. The infectious stage of syphilitics is generally considered to be three or four years. If lues ignorata is as common as the Wassermann reaction in the hands of Dreyer and Meirowsky indicates, and if those without manifest lesions but with a positive Wassermann are truly spirochete-carriers, whether treated or not, our views concerning the control of those exposed to syphilis must be altered. It seems probable that the reaction will be an aid in deciding the question of marriage, and that to the rule which demands thorough treatment and a lapse of years will be added successive negative Wassermann reactions.

Also it may be used to set at rest the mind of the syphilophobiac by convincing him after the repeated negative tests of the non-existence of the disease; in those instances in which the disease really is present a positive reaction allows proper treatment to be instituted before symptoms appear and the fears of the patient are allayed by assurances of a satisfactory outcome. Bruck has especially emphasized the value of the reaction in syphilophobia and Marcus has used it for this purpose with satisfactory results in two cases.

On the other hand, it is of decided value in those instances in which a patient with a doubtful lesion denies, intentionally or otherwise, the possibility of infection.

Finally, it would appear that the Wassermann reaction will eventually replace the therapeutic test. The latter has frequently been of doubtful value, for it is well known that many neoplasms as well as chronic inflammatory and proliferative conditions improve for a time under iodids. If further work supports our provisional view of the accuracy of the serum test we have a more certain means of diagnosis. A negative reaction will save much valuable time which may be applied to other methods of diagnosis and treatment, while a positive reaction will allow thorough treatment and perhaps not infrequently prevent operative interference.¹³

EFFECT OF TREATMENT

Finally, we have the question of the effect of treatment on the reaction and the correlated problem of whether the disappearance of the reaction is to be considered as an indication of cure.

Practically all observers have found that positive results are more frequent in untreated than in treated individuals. In Citron's statistics these two groups are represented by 81 and 65 per cent. respectively; in Bruck's by 82 and 29 per cent. So also in cases which have been carefully followed, it is seen that the number of positive reactions diminishes with the lapse of time and bears also a definite relation to the number of courses of treatment. This is best shown in the table of Jesionek and Meirowsky, illustrating the treatment of latent syphilis:

13. Many other phases of the work with the Wassermann reaction might be discussed, as its use by the pathologist to demonstrate the origin, syphilitic or otherwise, of various chronic lesions, as for example, fibrous orchitis (Reinhart, Fraenkel and Much, Schlimpert). Also the positive reactions which have been obtained in myxedema (Castelli), infantilism (Pisani), and gigantism (Pisani), and various other conditions of disturbed nutrition are of interest. Much work must be done, however, before any definite conclusion can be reached concerning the significance of occasional positive reactions in these conditions.

Number of courses....	0	1	2	3	4 and 5	6 and 7	8 or more
Number of cases.....	76	85	76	55	76	38	16
Per cent. positive.....	97	64	75	47	42	34	31

Swift states that he obtained positive reactions in 74 per cent. of cases treated six months or less, with a steady fall to 37 per cent. in those treated three years. Blaschko, who has examined his cases repeatedly during treatment, finds a gradual disappearance of the reaction in seventy-six of ninety cases. Boas, who has shown very clearly the effect of treatment in causing a disappearance of the reaction, points out that in the late stages of the disease relapses are usually preceded by a return of the positive reaction,¹⁴ and that it is possible by treatment at such times to prevent the return of clinical manifestations of the disease.

Lesser, who has studied 525 cases with the Wassermann reaction from the point of view of ultimate cure, finds 49 per cent. of properly treated cases negative on repeated examination. Even a single course of treatment greatly reduced the positive results, and the percentage of negative results increased constantly with the number of courses of treatment. Contrary to the experience of Jesionek and Meirowsky, he finds the maximum number of negative reactions, 55 to 65 per cent., to occur after four courses. After this the percentage is not increased. He believes that a positive reaction indicates the presence of active spirochetes and that the Wassermann reaction is a reliable index for treatment both as to dose and length of course. Repeatedly negative reactions in later stages indicate the probability of a final cure, but he lays little stress on negative tests early in the disease. He places the period of cure, as indicated by repeated negative tests, at not less than five years, and considers the peace of mind that comes with repeated negative reactions as one of the greatest benefits of the reaction. Butler recommends that a serum test should be made every three months in the early period and every six months in the late period of chronic intermittent treatment. Such a precaution will, he believes, prevent many of the serious and fatal consequences of syphilis.

Much might be added to this discussion of treatment, but it must be sufficiently evident from what has been said that the reaction promises to be a most satisfactory guide to treatment in all its aspects.

14. Donath has described what he calls "provocatory treatment;" that is, in persons with syphilis but a negative Wassermann the administration of mercury causes the reaction to become positive. Donath compares it to the influence of quinin on a latent malaria. The observation has not been generally confirmed and its significance is not clear.

Seldom has a new method, either of diagnosis or treatment, promised as much as does the Wassermann reaction, and if future work tends to the fulfilment of this promise, we have in the Wassermann reaction one of the greatest advances in the history of medicine. The knowledge which it yields, coupled with that resulting from the study of the etiology and from experimental inoculation should eventually place syphilis in the group of subjugated diseases—diseases of which the etiology and pathology is known, for which there exist an absolute diagnostic method and a rational specific treatment.

[Since the preparation of this manuscript there has appeared an interesting communication by Delbet on the syphilitic origin of certain malformations. He obtained positive Wassermann reactions in seven children with congenital affections of the nervous system, Little's syndrome or contractures and in a case of cleft palate. In none was clinical evidence of syphilis present. Delbet is convinced that syphilis is responsible for these conditions more frequently than is generally supposed. (Delbet, P.: *La syphilis dysplasique*, Presse médicale, 1910, xviii, 273.)]

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