

THE DIAGNOSIS AND TREATMENT OF "LATE" HEREDITARY SYPHILIS *

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RELATION OF "EARLY" TO "LATE" SYPHILIS

During the past two years we have seen 123 cases of manifest hereditary syphilis at the St. Louis Children's Hospital. Of these seventy-four, or 60 per cent., belonged to the group commonly described as "late" hereditary syphilis while only forty-nine, or 40 per cent., were infants under 1 year of age with the classical symptoms of rash, coryza, and enlarged spleen which characterize the "early" type. The division into "early" and "late" is arbitrary and only a matter of convenience, as these "early" symptoms may first develop after infancy, while "late" lesions may develop early in infancy. The "late" lesions may also develop primarily in older children without any "early" lesion having occurred or been recognized. Thus lesions comparable with the secondary (eruptive), tertiary (gummatous), and quaternary or para-syphilitic (vascular and nervous lesions), stages of acquired syphilis, are included among the clinical manifestations of "late" hereditary lues.

In only twelve of our cases were we able to obtain a positive history of an "early" lesion in infancy, while in twenty-five cases the history was definitely negative in regard to this point. In the remainder the history was indefinite or could not be obtained. It is highly probable that some of our forty-nine "early" cases will later develop other symptoms and thus ultimately belong to the group under consideration. In connection with the large group of cases without early lesions it is interesting to note a study¹ of the Wassermann reaction in 101 infants in St. Louis (thirty-three of whom were from this clinic) who showed no clinical evidences of syphilis. But two positive and one doubtful reactions were obtained. Although this series is small, it would tend to show that the latent infections in infancy are not so extremely common in St. Louis as might be imagined from our figures.

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1. Blackfan, Nicholson and White: AM. JOUR. DIS. CHILD., 1913, vi, 162.

We are now making a study of latent infection in older children by testing the blood and examining the brothers and sisters of the patients in our series. A large percentage of such children have given positive Wassermann reactions although they have never shown clinical evidences of luetic infection. Many items of interest have occurred in these familial studies which will be reported later.

GENERAL STATISTICS

The ages of the seventy-four patients were as follows:

Years of age.....	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12
No. of cases.....	6	4	6	4	6	4	10	7	5	5	11
Years of age.....	12-13	13-14	14								
No. of cases.....	2	2	2								

Eighty-three per cent. of the patients were white and 17 per cent. colored, while of the total clinic attendance 92 per cent. are white and 8 per cent. colored. Thirty-three were males and forty-one were females.

We were able to obtain a definite history of the feeding in infancy in twenty-seven cases. Twenty-three had been breast-fed and only four artificially fed. This may be looked on as an illustration of the better chances for life of the breast-fed syphilitic infant over the artificially fed, as the ratio is much different from the ratio of the breast to bottle-fed infants in general.

CLINICAL LESIONS

The following list of clinical diagnoses shows the wide variety of lesions encountered. In many cases there were multiple lesions, and the following figures give the number of cases in which each lesion occurred. In every case there was a positive Wassermann reaction which was checked in practically every instance by a second test.

Bones—		Central nervous system †—	
Periostitis tibia	3	Mental deficiency	14
Periostitis skull	1	Cerebrospinal syphilis	8
Joints—		Hemiplegia	5
Acute arthritis knee	7	Epilepsy	4
Acute arthritis ankle	1	Paralysis	3
Skin—		Chorea	2
Macular eruption	1	Hydrocephalus	2
Alopecia	2	Ulcerations—	
Condyloma anus	3	Nasal	2
Gummata	3	Laryngeal	1
Eye—		Pharyngeal	1
Interstitial keratitis	17*	Ozena	1
Choroiditis	1	Enlarged spleen (only lesion)...	1
		Torticollis	1
		Aortitis	1
		Obscure abdominal pain.....	1
		Obscure pain in legs.....	2

* 23 per cent.

† Thirty-two patients in all or 43 per cent.

The large number (43 per cent.) of our patients with lesions of the central nervous symptoms is one of the most interesting features from the standpoint of diagnosis. During the past two years we have tested the blood of thirteen patients with hemiplegia admitted to the wards of the hospital of which five reacted positively. In one case—a girl of 5 years—admitted at the onset of the trouble, we were able to limit the extent of the lesion by a vigorous treatment. Some of these cases had been previously looked on as poliomyelitis. Two of the eight cases reacting negatively were unquestionably birth injuries. Of eight cases of chorea tested (following and including the first positive case whose history is given later), two gave positive Wassermann reactions. In three of the negative cases there was a definite history of rheumatism, while no history or evidence of rheumatism was noted in the two positive cases and in the three remaining negatively-reacting cases.

Mental deficiency was usually associated with some other condition as epilepsy or cerebrospinal syphilis. During the period covered by our cases there were thirty-three cases of mental deficiency admitted to the wards of the hospital of whom fourteen were syphilitic. This is a very much higher percentage than is usually found and does not express the true relation of mental deficiency due to syphilis to mental deficiency in general, but is the result of admitting cases for this particular study.

Among the more unusual lesions were an aotitis and a torticollis. Three patients with indefinite pain of obscure origin—once in the abdomen and twice in the legs—which had persisted irregularly for some time and for which no cause could be found, gave positive Wassermann reactions and the pain disappeared under specific treatment. The cases of acute arthritis were very interesting. Some patients were sent to us for tuberculosis and others for acute articular rheumatism. One case (knee) developed in a child with a tuberculous hip who had been under observation and treatment in the orthopedic department for several years.

The absence of Hutchinson's teeth which is so generally described as a common symptom of syphilis was very noticeable in our cases. In forty-eight patients who were old enough to have permanent incisors the teeth were notched in but three instances. Ill-shaped and deformed teeth were very common. They were usually small and peg-shaped with broken, irregular surfaces, and were separated widely from one another and without good alignment. We have also observed typical Hutchinson's teeth in a non-syphilitic patient.

It will be noted that most of our cases fall into one of three large groups. The first of these is made up of eye conditions (24 per

cent.) and is so well recognized that it needs no discussion. The second comprises lesions of the central nervous system (43 per cent.). So many of these cases have given positive Wassermann reactions when there has been nothing to suggest lues in the early or family history that we now make the test as a part of the routine examination of nervous cases. The third group is in many ways the most interesting as it contains a group of cases less frequently recognized as of a possible syphilitic origin. It is made up of cases of chorea, acute arthritis, torticollis, and obscure muscular pain—in other words clinical conditions which are often grouped together as “rheumatic”—and amounts to about 20 per cent. of our cases. It has long been recognized that these acute “rheumatic” conditions are the result of bacterial toxins, and our cases would indicate that syphilitic infection of an hereditary nature is one of the common causes of these cases developing in childhood. We have checked the diagnosis of these cases by repeated blood tests and by Wassermann reactions on the parents. The strongest proof that they are the result of syphilis and not an accidental association lies in the rapidity with which the lesions improve under antisyphilitic treatment.

TREATMENT

The treatment we have gradually evolved consists of a combination of neosalvarsan and mercury. We prefer neosalvarsan to salvarsan because of the simplicity of the technic, which is an essential factor in dealing with children. The neosalvarsan is dissolved in 1 c.c. of freshly distilled water for each decigram and injected intravenously into any available vein with an ordinary glass hypodermic syringe. The entire preparation of the drug and syringe and the administration can be accomplished in from twelve to fifteen minutes. We made a number of intramuscular injections earlier but soon gave them up because of the pain and discomfort to the patient and the objections of the parents. The dose of the neosalvarsan varies according to the age and clinical condition of the patient—as a whole we give larger doses than are usually advised and have had no unpleasant or bad results. At first the injections were followed in a few instances by nausea and vomiting which we are inclined to attribute to the use of a “sterile” water instead of a freshly distilled water, as we have not observed such sequelae in the last year and a half. Although it is claimed by competent observers that neosalvarsan is less effective than salvarsan, we prefer neosalvarsan because it is effective and fulfills certain essential requirements for use with children which salvarsan does not. For the mercurial part of the treatment we have come to use gray powder exclusively in the late cases and to a very large extent

in the early cases. For the treatment of acute lesions (eruptions, ulcers, arthritides, etc.) the neosalvarsan is far more effective than inunctions of mercury, while the gray powder gives very good results and can be given over longer periods of time with less disturbance than mercury in any other form. We have had no experience with the mercurial injections which are so effective in the acquired forms of syphilis, as intramuscular injections are not practical with children, at least in the class of patients that we are treating.

The course of treatment we use varies somewhat, but with the usual case presenting an acute lesion is in general as follows: Three or four intravenous injections of neosalvarsan are given with a gradually increasing dosage two or three days apart. Then mercury is started, with small doses, which are gradually increased until the patient is taking a fairly large dose. In a few weeks this is interrupted for a short time and then repeated. In a number of cases a second and a third series of neosalvarsan injections are given alternating with the mercury. The mercurial treatment is continued for an indefinite period of time according to the requirements of the individual case and in general until a negative Wassermann reaction is obtained, if this is possible.

Forty of the seventy-four cases have been treated in this way and observed for a period of from three months to two years. As the cases differ so much in the types of lesions and length of treatment, they cannot be summarized to any advantage and the results of treatment are best seen by abstracting a few typical cases illustrating different points. We have given over two hundred intravenous injections of neosalvarsan and have never observed any bad or unpleasant effects besides those mentioned above.

EFFECT OF TREATMENT ON ACUTE LESIONS

There can be no question as to the value of neosalvarsan in acute syphilitic lesions with the exception of interstitial keratitis. In the acute joint lesions, ulcerations, general convulsions, torticollis, etc., the effects seem immediately to follow the first intravenous injection.

L. B., No. 3725, a girl of 17 months, was admitted for backward development. She had been normal until two months previously when she had an attack of convulsions. At the time of admission she was unable to stand alone and was apparently blind, not even noticing the milk bottle or a light. Attacks of general convulsions were frequent. Wassermann reactions on the blood and spinal fluid were positive. Neosalvarsan was given 1-14-13, 0.5; 1-17-13, 0.3; 1-22-13, 0.2 intramuscularly. The child was much better by this time and was beginning to notice objects. No attacks of convulsions since first injection. 1-31-13, 0.2, intravenously; 2-4-13, Wassermann positive; 2-12-13, 0.15, intravenously; 2-20-13, 0.2, intravenously.

Beginning about the first of February, 1913, there was rapid improvement and by the middle of the month the child was playing almost as a normal

infant. She was put on gray powder and on March 27 was discharged with a negative Wassermann. On April 24, one month later, there was a sudden return of symptoms and two days later she was readmitted. Between 12 o'clock noon and 9 p. m. there were ten attacks of general convulsions. She was then given 0.2 neosalvarsan intravenously which immediately stopped the convulsions. Inunctions of mercury were pushed for a month but no more neosalvarsan was used as the patient remained free from convulsive attacks. On May 17 the Wassermann reaction was negative and the patient was again discharged. In March, 1914 (fifteen months later), she was apparently normal although there have been "slight attacks of convulsions at times." She has taken gray powder intermittently.

R. C., No. 5043, a girl of 12 years, was admitted with a maniacal type of chorea about three weeks after the onset. She was unable to stand or walk and could not sit on a chair unless supported. Restraint was even necessary when she was in bed. Speech had been lost for several days. A family history of syphilis together with Hutchinson's teeth in the patient gave the idea of an underlying luetic infection. A dose of 0.4 gm. neosalvarsan was given a few hours after admission and a marked effect was noted within forty-eight hours. It was repeated two days later when a Wassermann reaction was strongly positive. Inside of a week the patient was up and about the ward and had lost most of the choreic symptoms. Neosalvarsan and mercury were continued for some time.

L. D., No. 4072, a 14-year-old girl, was admitted for acute pain and swelling of the right knee. One week later the ankle became swollen. A Wassermann taken two days previous to the involvement of the ankle was strongly positive. Neosalvarsan, 0.5, was given and in two days the swelling and pain had disappeared.

N. D., No. 3715, was admitted for an interstitial keratitis of five weeks' duration and an acute arthritis of the knee of two weeks. Wassermann, three plus positive. On Dec. 29, 1912, an injection of 0.9 neosalvarsan was followed by rapid improvement of the knee, but in a few days it became swollen and painful again. On Jan. 1, 1913, 0.9 neosalvarsan was given and followed by rapid relief. Treatment was continued with no return of the arthritis, but the interstitial keratitis showed but little improvement.

E. G., No. 6489, 8 years, admitted March 2, 1914, for acute arthritis of the right knee. Wassermann on March 5 was four plus positive. Neosalvarsan was given on March 7 and by March 11 all pain was gone from the knee and motion was good. She was given more neosalvarsan and discharged. Six weeks later the patient returned with an acutely swollen and painful left knee and the Wassermann was still four plus positive.

T. B., No. 3791, a boy of 6 years, was admitted with an extensive laryngeal ulcer of three weeks' duration. He was given five injections of neosalvarsan and within two weeks the ulcer had healed.

From these few reports the rapid action of neosalvarsan may be seen when the lesion is acute. The exception is apparently an acutely developing interstitial keratitis. In this condition it has an influence in some cases, but in our experience a long and extensive course of mercury is necessary in order to obtain much improvement.

TREATMENT AND CHRONIC LESIONS

We have been able to secure but little permanent effect from neosalvarsan nor have we observed any advantage from its use in chronic cases of the late type; that is, where a lesion such as a cerebrospinal syphilis or an interstitial keratitis has been present for

some time. As a matter of fact the most intensive treatment with combined neosalvarsan and mercury has been of little avail in these cases.

H. W., No. 3492, a boy of 14, was admitted for cerebrospinal syphilis (fixed unequal pupils, staggering gait, dementia, etc.), which was said to have first shown itself three years previously. Wasserman four plus positive. He was given 0.5 neosalvarsan in October, 1912, which was followed by inunctions of mercury. An injection of 0.9 neosalvarsan was given in December and the inunctions continued. In February, 1913, he was given two injections of neosalvarsan of 0.5 each and then gray powder was continued for several months. It was without effect on either the clinical condition or the Wassermann reaction. From time to time he has taken gray powder in large doses, but his condition to-day is worse than when treatment was started over twenty months ago.

In this same group must be placed the cases of hemiplegia following vascular changes and other conditions where structural changes have occurred. The only possible result of treatment in such cases is the prevention of further lesions.

TREATMENT AND THE WASSERMANN REACTION

It is not within the scope of this paper to enter into a theoretical discussion of the Wassermann reaction. For clinical purposes we look on the Wassermann reaction as a symptom of syphilis, comparable to an arthritis, a keratitis, a periostitis, etc. It is the most common symptom and present in such a large percentage of all clinically positive cases that we are inclined to be skeptical about the diagnosis of late syphilis in any untreated patient who has a negative Wassermann reaction. For example, we have had a case of interstitial keratitis in a boy who had marked Hutchinson's teeth. The Wassermann was repeatedly negative but because of the two classical symptoms of hereditary lues he was given a thorough antisymphilitic treatment which, however, was without effect. Later a rapid and marked improvement of the eye condition followed the use of tuberculin and in our opinion there is no reason for looking on this case as one of syphilis. A positive Wassermann reaction may be the only symptom of syphilis for many months or years (latent hereditary lues) and then other symptoms develop, as is shown both by the early history of some of our cases and the tests we have made on brothers and sisters of patients with manifest lues. It is quite difficult to get these patients with latent cases to take a course of treatment, but there is no reason why this symptom should be treated any less vigorously than a manifest lesion. Nothing definite is known of the future of these latent cases with a positive Wassermann and we are attempting to follow some which have not been treated.

The Wassermann reaction is stronger in hereditary lues than in any other form of syphilis and hence is correspondingly more difficult to make negative. Not only is this so but it is very apt to become positive again if treatment is stopped when it has been made negative as the result of treatment. We have not determined quantitative effects of the treatment on the Wassermann reaction.

N. D., No. 3715, a girl of 8 years, was admitted in December, 1912, for interstitial keratitis and acute arthritis. Wassermann four plus positive. The arthritis improved rapidly following two injections of neosalvarsan of 0.9 each followed by one of 0.5 and another 0.4. Gray powder, gr. 1 three times a day, was then given for three months when inunctions were started and continued for several weeks as the eyes did not improve. In May, 1913, the Wassermann was still four plus positive. Gray powder has been taken almost continuously since at the limit of tolerance and at times potassium iodid has been given. On Jan. 16, 1914, the Wassermann was still four plus positive and again on May 19, although the child has been given an intensive and uninterrupted anti-syphilitic treatment for eighteen months and the eyes have improved considerably.

C. M., No. 53166, aged 13 years, was first seen on July 16, 1913, for an interstitial keratitis which began one month previously. Wassermann four plus positive. He was given 0.5 neosalvarsan intravenously every other day for three doses and then put on gray powder. Three months later the Wassermann was still positive and the gray powder was continued. On March 6, 1914, the Wassermann was still four plus positive, although the eyes had improved very much with eight months' continuous treatment.

K. V., No. 4081, a boy of 7 years, with an acute keratitis, had a positive Wassermann on Sept. 23, 1912, at which time he could not distinguish fingers at 5 feet. He was given neosalvarsan 0.3 and inside of a week was able to make out pictures across a room. Two more doses of neosalvarsan were given, but as on March 14, 1913, the Wassermann was still strongly positive, three more injections of 0.4 each were given. A Wassermann taken five weeks later, or May 2, 1913, was still four plus positive. Gray powder—1 grain three times a day—was then given for three months but was without effect on the Wassermann. Eyes almost entirely well. This Wassermann, Aug. 1, 1913, was ten months after beginning treatment. The gray powder was then pushed to a point of salivation and kept up almost continuously until a *negative* Wassermann was obtained on Jan. 5, 1914, after fifteen months of vigorous treatment. Treatment was discontinued for two months and then a course of mercury given for one month. On May 19, 1914, six weeks after this was finished, the Wassermann reaction had again become *positive*.

At times it is not difficult to obtain a negative Wassermann reaction as in the following case.

G. G., No. 3443, an infant of 18 months, who was admitted for ulcers of the face and fingers (gummata) had a positive Wassermann Oct. 15, 1912. There was extremely rapid improvement following an injection of 0.22 neosalvarsan into the buttocks. This was repeated in fifteen days and the infant discharged one month later with a small nodule in the cheek the size of a pea. No other treatment was given. Five months later a Wassermann was taken which was strongly positive and the patient was given three intravenous injections of neosalvarsan of 0.25 each and discharged as there were no clinical lesions. Eight months later—fourteen months after first admission—the Wassermann was negative and in April of this year there had been no return of symptoms. This was one of the few cases with a permanent result following neosalvarsan alone and is decidedly exceptional in our experience.

In a treated case or a case under treatment in which the Wassermann has become negative, other symptoms of syphilis may develop, showing that the disease cannot be regarded as cured or quiescent from a negative Wassermann reaction alone.

E. P., No. 3995, a boy of 4½ years, was admitted for paronychia and malnutrition. No history obtainable, but the Wassermann was three plus positive on March 7, 1913. He was given seven intravenous injections of neosalvarsan (2 gm. in all) between this date and April 23, 1913. Inunctions of mercury were given to the point of salivation. There was marked improvement following the first few injections of neosalvarsan. In June and again in September he was given a course of mercury and on Oct. 24, 1913, (seven and one-half months after the first Wassermann) the Wassermann reaction was negative. In March of the present year he developed an alopecia which has become quite extensive. A Wassermann reaction on April 11, however, was negative, and again a few weeks later after a provocative dose of neosalvarsan.

SUMMARY

We have found the incidence of manifest hereditary lues of the "late" type much greater in proportion to the incidence of "early" syphilis than previous figures would indicate. The largest group of our cases (43 per cent.) exhibited lesions of the central nervous system, but we particularly wish to call attention to a group of cases with lesions associated as "rheumatic"—chorea, acute arthritis, torticollis, myalgia. By Wassermann reactions and the "therapeutic test" we have found that such lesions are not infrequently due to an hereditary syphilitic infection.

It has been our experience that acutely developing lesions respond promptly to intravenous injections of neosalvarsan, but that in order to obtain any permanent results and prevent the recurrence of symptoms an intensive and long continued mercurial treatment must be given in addition. The syphilitic infection—as measured by the Wassermann reaction—is most persistent, and although an intensive and uninterrupted antisyphilitic treatment has been given for nearly two years we have not been able to obtain a negative Wassermann reaction in some of our cases. Moreover, the Wassermann reaction has usually returned when treatment has been interrupted in those cases in which it has become negative as the result of treatment. We do not feel that it has been demonstrated as yet that an hereditary syphilitic infection of the "late" type can be eradicated.

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