

On the Influence of Pregnancy on the Wassermann Reaction and on the Clinical Manifestations of Syphilis.*

By FRANCIS J. BROWNE, M.D. (Aberd.), F.R.C.S. (Edin.),
Assistant Physician, Edinburgh Royal Maternity Hospital.

IT is well known to workers upon the pathology of Still-birth that, unlike the obstetric history, the history of syphilitic infection of the mother frequently proves of singularly little value as an aid to diagnosis of syphilis in the foetus. If such a history is present it is of course of the greatest importance, but its absence must by no means be relied upon as evidence of the absence of syphilis, for it is not uncommon to find that mothers of syphilitic infants themselves show no clinical signs, and give absolutely no history of syphilitic infection. At an early period of my work I thought that this was a discovery of my own, but on looking into the literature on the subject I found that the fact was well known and had been noted by almost every writer on syphilis in its relation to obstetrics. Unfortunately, its importance is not yet appreciated by obstetricians who are often content confidently to exclude syphilis when a history of infection is absent. As we shall see afterwards the Wassermann reaction in these cases is also frequently negative at least during pregnancy. This combination of a negative Wassermann reaction with a negative history must not be allowed to mislead, and expert examination of the product of conception, especially if dead, will prove of the greatest assistance in the future management of the case. Even in the absence of this, the therapeutic test, viz., treatment of both parents by the arsenical preparations, may result in the birth of a healthy child after other remedies have failed (for example, potassium chlorate) and thus reveal the true nature of the disease.

Abraham Colles, writing in 1837, says: "There are cases in which the foetus *in utero* has been infected under circumstances so strange and so difficult to explain that nothing short of actual observation could induce us to allow the fact. The circumstances to which I allude are these: The father of the child has had primary symptoms six or eight months before his marriage; for these he has been treated by mercury; has undergone a full course of this medicine under which his symptoms have been removed.

* Read at the British Congress of Obstetrics and Gynæcology, Edinburgh, April, 1923.

In six or eight months after this treatment he marries. In the ordinary time his wife becomes pregnant and carries the child until the 7th or 8th month when abortion takes place, and that without being preceded by any of these circumstances which in ordinary contribute to its occurrence. The same fatality attends on the second, third and perhaps fourth pregnancy. . . . At length suspicion arises in the mind of the accoucheur; he examines the product of the next abortion, and finds that the cuticle is loose and that it readily peels off in patches of greater or less extent. . . . Until these repeated abortions shall have attracted the attention of the accoucheur there has not been any one circumstance which could have raised suspicion as to the true cause of them; for both parents continue all this time to live in the enjoyment of perfect health, no trace of disease is to be discovered in either. When the husband is questioned he candidly avows that he had before marriage been affected with primary symptoms; that he had been, as he thought, cured of them; and that having allowed six or eight months to pass over before his marriage, without perceiving any sign of a return of the disease he had concluded that it had been perfectly eradicated from his system. *On further enquiry it is ascertained that his wife had never complained of any sensations which might lead even to a suspicion of her having had primary symptoms; nor has any appearance taken place in her which can even bear a resemblance to secondary symptoms.*"¹

Jonathan Hutchinson,³ in commenting upon the law of Colles, writes: "Is it not the fact that women bear syphilitic children without having ever themselves, either before or during pregnancy, had any symptoms, either primary or secondary of that disease? If this happened only once or twice we might reasonably doubt the histories given us. But it is not so; it is in hundreds of cases." He believed, however, that the mother gained immunity without herself suffering from the disease in its developed form.

McDonagh² believes that if a woman contracts syphilis after she has conceived, the Wassermann reaction will be positive because the disease becomes generalized and behaves in the ordinary way, but that in all cases of conceptional syphilis (*i.e.*, syphilis acquired at the time of conception) symptoms are absent and the Wassermann reaction negative until after the child-bearing period is over. He holds that the sporozoites which he believes to be the first stage in the life history of the leucocytozoon syphilidis and only potentially harmful, while they may develop into gametes in the embryo and kill it, are prevented from developing in the mother's blood by means of a chemical substance derived from the chorionic cells and there remain dormant for a time. McDonagh concludes that the serum of women contains more natural protective substances than

that of men and that these protective substances are increased during pregnancy. He believes that after the menopause these protective substances are to a large extent lost, and that this accounts for the alleged frequency with which tertiary symptoms, especially gummata, together with a positive Wassermann reaction, may occur in women at this period.

Hendry⁴ has had a similar experience in so far as the clinical history is concerned. "A history of primary or secondary syphilis," he says, "is difficult and rarely possible to obtain; its absence is of no value."

Nor is this absence of syphilitic history due to the fact that the mother is healthy, for there is no doubt that the mother of a syphilitic child is always herself syphilitic. The "law of Colles" was based upon the assumption that the mother of a syphilitic child might be healthy though the wording of the "law" might lead one to suppose that Colles was doubtful whether she might not really be suffering from syphilis. It is as follows; "A child born of a mother who is without any obvious venereal symptoms, and which, without being exposed to any infection subsequent to its birth, shows this disease when a few weeks old; this child will infect the most healthy nurse, whether she suckle it or merely handle and dress it; and yet this child is never known to infect its own mother, even though she suckle it while it has venereal ulcers of the lips and tongue." Since the introduction of the Wassermann test, however, it has been demonstrated that such women are in reality syphilitic.

With regard to my own experience in this matter, I have found that in 75 per cent. of cases in which a definitely syphilitic foetus was born there was no history of infection in the mother and no signs of the presence of syphilis (not including amongst signs for the moment the Wassermann reaction). All were cases of probable old standing infection, and it is possible that in them evidence of secondary syphilis had been present really at one time but had been forgotten by the patient. It is somewhat significant that a history of infection and clinical evidence of it are generally found in primigravidae, who give birth to a syphilitic infant, while in multiparæ such a history is usually absent.

With a view to obtaining some fresh light upon the significance of the frequent absence of a history or of signs of syphilis I studied the histories of all the syphilitic patients who had passed through the indoor department of the Venereal Diseases Clinic at the Edinburgh Royal Maternity Hospital since its opening three years ago. The patients numbered exactly 100, and the results obtained are summarized in the following table:—

Parity.	No. showing history or signs of infection.		Percentage showing history or signs.		Remarks on cases showing signs or giving history of syphilis.
	No. of cases.	No. showing no such history.	70	30	
1	31	22	9	30	All 22 suffered from primary or secondary syphilis at time of examination.
2	29	13	16	56	In nine secondaries were present at time of examination. One primary sore at time of examination. In six of these cases the first child was alive and well; in the others no record; in one was history of secondaries 12 years before, in one specific keratitis and W.R. + + + (no other history), and in one tertiary ulcer of the leg with no other signs or history. W.R. + + +.
3	11	3	8	73	Two of the three showed tertiary ulceration without other signs or history except W.R. + + +; the third had sores on vulva with W.R. + + +, and was probably a case of recent infection.
4	9	6	3	25	All six were cases of recent infection with evidence of primary or secondary syphilis.
5	6	1	5	84	During the fourth pregnancy this patient had come under observation at the eighth month, and then had vulval sores from which Sp. P. were obtained.
6	4	2	2	50	One showed signs of secondary syphilis, and another osteomyelitis fibrosa cystica with three spontaneous fractures of femur. W.R. + + +. No other history of infection.
7	4	3	1	25	All three cases of recent infection with secondaries.
10	2	—	2	100	
11	2	—	2	100	
12	2	—	2	100	

A study of this table shows :—

- (1) That in a general way evidence of infection is present more frequently in primigravidæ; that except for cases of recent infection the presence of a history or of signs of syphilis is less likely to be found the farther we ascend in the scale of multiparity.
- (2) In only one of the multiparæ with old infection was a history of syphilis given on questioning; in all the others in whom clinical evidence of it was found the diagnosis was made not from the history, which was negative, but from the presence of definite signs of tertiary syphilis combined with a strongly positive Wassermann reaction.
- (3) Out of 100 cases there were 31 primigravidæ, and 60 multiparæ. Twenty-two of the latter were cases of recent infection, which, in all but two, had occurred since the birth of the last child, and therefore in this connexion these should really be classified as primigravidæ. Of the remaining 47 cases, 41 gave no history and showed no evidence of infection, while of the remaining six, one admitted secondaries 12 years before, one had specific keratitis with a strongly positive Wasserman reaction, one had tertiary leg ulcer, W.R. ditto, one had ulceration of the palate, and one of the nose and upper lip, and one suffered from osteomyelitis fibrosa cystica, with three successive spontaneous fractures of the femur and a strongly positive Wassermann reaction; but none of these five gave a history of secondaries. Of the 31 primigravidæ 70 per cent. showed well-marked evidence of syphilis. *In none of these cases was it necessary to depend upon a history; probably if it had been necessary none would have been obtained.* In only one multipara out of 47, excluding those 22 who showed secondary or primary signs at time of examination, was a history of syphilitic infection given (that is, slightly over 2 per cent.); 46 failed to give any history of infection, although all revealed it by their products of conception, Wassermann reactions, or evidence of tertiary syphilis, or by all combined. Are we, therefore, to suppose that only one of these 47 multiparæ had ever any signs of secondary syphilis while such was demonstrated to be present in at least 70 per cent. of primigravidæ? Every multipara has been a primigravida at some time, and according to the above findings 70 per cent. of primigravidæ show well-marked evidence of primary or secondary syphilis. It is reasonable to suppose that at least 70 per cent. of the 47 multiparæ also at one time showed similar evidences of syphilis, but that this had been forgotten or purposely concealed.

- (4) Thirty per cent. of primigravidæ (nine cases in all) have no history (none recorded) and showed no signs of syphilis.

Details of these cases are as follows:—

No. 80, æt. 21. Husband under treatment for syphilis during present pregnancy; mother gave no history and showed no signs (closely questioned by myself). W.R. negative; but doubtfully positive after provocative Nov Arseno Billon. Has received five intravenous injections N.A.B. (1.5 grms.) during pregnancy. Infant premature, lived two days, spirochæte negative, massive hæmorrhages in lateral ventricles, and in lungs; histological and naked eye examination inconclusive as regards syphilis; cord blood negative; mother's blood negative on three occasions, viz., one day, 10 days, and nine weeks after delivery. She came again under observation in second pregnancy, having received no treatment in the interval. Her W.R. was weakly positive three days before delivery. She gave birth to a healthy full-time infant. Cord blood negative. Infant's blood also negative at 10 days old. Mother's blood negative 10 days after delivery.

It is therefore doubtful whether this woman ever has had syphilis, the only sign of it being a weakly positive W.R. shortly before delivery in both pregnancies, as well as the premature infant. It should, however, be noted that after her last injection jaundice set in with epigastric pain and sickness, after which, and possibly as a result of which, she went into labour.

No. 215, æt. 19. Admitted in labour. No previous supervision. Macerated foetus (not examined). Mother's W.R. + + + three days after delivery. No history of venereal disease recorded.

No. 232, æt. 25. Came to antenatal clinic at two weeks before term; no history of infection obtained; no signs of syphilis. Suffering from yellow discharge. Admitted to wards on account of this. W.R. + + + 10 days before delivery. Cord blood negative. Child born apparently healthy.

Note this patient's age. There was possibly old infection in this case; on the other hand, it is possible the positive W.R. was an error, for note the negative cord blood.

No. 359, æt. 31, single, had been attending a treatment centre and treated for gonorrhœa for six months before W.R. taken, then found strongly positive one year before pregnancy. W.R. strongly positive again three months later in spite of treatment. The following month contracted acute gonorrhœa, and probably about that time became pregnant. W.R. strongly positive at fourth month, and also, four days before delivery, cord blood strongly positive. Child full-time and apparently healthy. Treatment with sulpharsenal and intermittent only, on account of albuminuria.

In this case there was no doubt about the presence of syphilis.

In deciding, however, regarding possible absence of history the age should be taken into consideration, the habits of the patient making it probable that the infection had been contracted many years prior to her coming under observation. There is therefore a strong case for there having been clinical evidences of syphilis present at some time.

No. 388, æt. 27. Admitted three weeks before term on account of albuminuria. W.R. strongly positive. One injection N.A.B. given before delivery. Cord blood weakly positive. Infant's blood negative at 10 days old. Child apparently healthy; weight at birth 4,120 grms.; placenta 720.

The presence of syphilis in this case is doubtful, and if present is probably of old standing; note age.

No. 655, æt. 19. Admitted in labour; no previous supervision. Macerated foetus; organs spirochæte positive. *Cord blood negative.* Mother's W.R. + + + three days after delivery. *Questioned by myself* absolutely no history of infection could be obtained.

No. 675, æt. 30. Admitted in labour; no history of syphilis noted. Mother apparently healthy, but W.R. + + +. Child post-mature, healthy, 4,340 grms. Placenta 973 grms. The presence of syphilis in this case is doubtful; no evidence except W.R. If present is probably of old standing; note age, the patient may have forgotten she had symptoms.

No. 765, æt. 18. Admitted three days before delivery; no note of history of infection or of cord blood. Mother's W.R. + + + three days before delivery. Child three weeks premature; healthy. No further history.

No. 816, æt. 24. Admitted in labour; macerated foetus born. W.R. + + + one week after delivery. No history of infection noted.

In four of these cases, namely, 80, 232, 388 and 675, the presence of syphilis seems doubtful. In one, 359, the disease was probably of old standing, and signs had at one time been present. There remain four cases, 215, 655, 765 and 816, in which there was no history of syphilis obtained. In only one of these, however, *viz.*, 655, was the presence of syphilis proved. In the other three the diagnosis rests upon a strongly positive Wassermann reaction in the mother. How is absence of history in this case to be accounted for? (1) Signs of infection may have been present and purposely concealed or forgotten. (2) Signs of infection may have been altogether absent. (3) A primary sore may have been present where its presence passed unnoticed, *e.g.*, cervix or vagina and secondary symptoms of a mild nature.

But even if we admit that all these nine patients were syphilitic without there ever having been evidence of the presence of syphilis,

there still remain the 70 per cent. of primigravidæ who gave signs of syphilitic infection. It is reasonable, therefore, to conclude that at least 70 per cent. of the 47 multiparæ who gave a negative history had at one time suffered from secondary syphilis and that the history was forgotten or purposely concealed.

How many men with syphilis of some years standing give or do not give a history of infection?

The above-mentioned facts are suggestive; the number of cases is, however, too small to enable one to base upon them any dogmatic pronouncement, and the subject must await further clinical investigation.

THE WASSERMANN REACTION.

There has been for long a general consensus of opinion that the Wassermann reaction is considerably modified by the occurrence of pregnancy and that the occurrence of a negative reaction is therefore of little value in the exclusion of syphilis. In order to understand the reasons for the alleged frequency of a negative Wassermann during pregnancy it is necessary to have clear ideas regarding the various theories as to the methods of foetal infection. This is explained in one of the following ways:—

(1) That paternal infection of the ovum occurs at the time of conception, the mother being healthy and only infected at the time of separation of the placenta. Although the spirochæte has been demonstrated in the spermatozoon infection could not have taken place by the organism in its usual spirillar form, as it is much too large to be contained in the head which alone enters the ovum at the time of fertilization. The theory of paternal infection therefore involves acceptance of the statement that the spirochæta pallida can exist in the form of chromidian granules, or alternatively that the spirochætes present in the semen in the genital canal may gain entrance to the developing embryo whose tissues may be supposed to be highly susceptible and to form a highly favourable medium for their growth. The mother may be saved from infection by the barrier action of the placenta preventing the organisms from passing over into the tissues of the mother. If, however, the infection be a virulent one, that is, if the spirochætes in the embryonic tissues are very numerous, or belong to an unusually virulent strain, the protective action of the placenta may fail and the mother become infected during the course of pregnancy.

Routh⁵ suggests that the chorionic ferments prevent the spirochætes from developing beyond the granule stage, and that even if the latter are allowed to pass the placental barrier into the maternal tissues they are there maintained in the granular phase in which they are unable to give rise to the tissue destruction which results in the liberation of proteins, the presence of which in the

serum is the probable basis of the Wassermann reaction. In such cases the infant would be born apparently healthy with a negative Wassermann reaction, but as the inhibitive action of the chorionic ferments passed off the spirochætes would mature, the reaction would become positive and other evidences of syphilis develop. Spirochætes in the granular stage left in the decidua after expulsion of the foetal part of the placenta would then develop into mature organisms, and invading the maternal tissues no longer protected by the presence of chorionic ferments, would in due course give rise to a positive Wassermann reaction in the mother.

If this theory of paternal infection be correct it would explain not only the absence of a positive Wassermann reaction in the child at birth, but also the alleged presence of a negative reaction in the mother throughout pregnancy and its becoming positive shortly after its termination.

It seems, however, that if such intra-natal infection of the mother occurred, the development of the positive reaction in the blood would be preceded and accompanied by clinical evidences of secondary syphilis. But in this connexion it is interesting to observe that Neisser,⁶ in a case of successful intravenous inoculation of a monkey, found that this was followed not by the ordinary signs of syphilis but by a general infection. This would probably be the method of transmission in intra-natal infection, placental separation laying bare the mouths of the blood sinuses as they open on the inner surface of the uterus.

A certain amount of support for Routh's theory of the protective action of the chorionic ferments is obtained from the fact that spirochætes are but seldom found in the placentas of syphilitic foetuses. It would also explain the fact, which is one of the most remarkable in the biology of syphilis, that spirochætes are never found in abortions below the fourth month, even when such are undoubtedly syphilitic. According to Abderhalden, the chorionic ferments are most active between the 6th and 14th weeks.

Manouélian,⁷ however, explains the absence of the spirochæte from the placental tissues in another way. He claims to have demonstrated that in the foetal placenta a very active phagocytosis by means of mobile elements of the blood—macrophages, polynuclear neutrophiles and eosinophiles—as well as by the fixed cells, especially the endothelium lining the capillaries, takes place. This occurs only in the smallest vessels and capillaries and never in the vessels of larger calibre.

Routh believes that a negative Wassermann reaction in the mother during her pregnancy can only occur when the ovum has been infected by the father's seminal fluid, either at the time of fertilization or after the fertilized ovum has reached the uterine

mucosa. It would seem, however, that this position is untenable as he elsewhere admits that the ferments may also have the power of granulating the mature spirochætes and thus rendering them inactive. A negative reaction might thus be produced during pregnancy in a woman who was already syphilitic.

While it is difficult to deny the possibility of a purely paternal infection of the ovum by a spermatozoon infected by chromidian granules or of the embryo from infected semen, it seems probable that such a method of infection alone must be extremely infrequent. I myself have not met with a single instance, omitting cases of so-called latent syphilis, in which the mother of a syphilitic child had not a strongly positive Wassermann reaction either during her pregnancy or at the time of confinement. Further, it is rare in my experience for a child that is itself syphilitic to give a negative reaction in the blood from the umbilical cord. One would expect the child in a case of paternal transmission to show a high degree of infection.

(2) That the foetus is infected from the mother, who has herself been infected by the syphilitic father prior to, or at the time of, conception. It is probable that this is by far the most common method of infection. Spirochætes existing in the mother's tissues will then only be prevented from infecting the foetus by the "barrier action" of the placenta. That this may be effective is shown by the fact that a syphilitic mother may give rise to a non-syphilitic child. I have examined the child of a woman who had a repeatedly strongly positive reaction, and a leg ulcer presumably specific. The child had died of asphyxia and the organs showed no trace of disease either on naked-eye or histological examination. Probably such a favourable result only occurs when the infection is an old-standing one or when the mother is infected late in pregnancy.

Nattan-Larrier and Brindeau⁸ have, however, proved that the spirilla of relapsing fever can pass from the maternal to the foetal circulation through the epithelial coverings of the villi and the endothelial walls of the foetal capillaries. Clearly the earlier the period in pregnancy at which infection occurs the greater will be the chance of infection of the foetus. If it occurs in the last month or two the foetus may escape altogether.

Rietschel believes that the placental barrier may be completely effective until its separation commences during labour, when the tearing of villi allows the entrance of spirochætes to the foetal circulation. Thus, according to him, the infection of the foetus may be intra-natal only, and he believes that this explains the absence of a positive Wassermann reaction so often found in congenital syphilis. In my experience the Wassermann reaction in congenital

syphilis is usually positive, so that such an explanation is unnecessary.

Further, as spirochaetes have been demonstrated in the ova⁹ it is at least theoretically possible that infection of the ovum may be transmitted from the mother, although, as Von Reuss¹⁰ points out, it is doubtful whether such ova are capable of development.

(3) That infection may be both paternal and maternal— from an infected spermatozoid or embryo infected from the semen, as well as by organisms from the maternal tissues. In such cases the infection should be a more virulent one than when the mother, or even the father alone is responsible, the developing embryo being as it were attacked from two sides. It is impossible to demonstrate this clinically as spirochaetes are but seldom capable of being demonstrated in either the spermatozoid or in the semen even when active secondary syphilis is present. We cannot, therefore, definitely assert that infection is certainly directly paternal as well as maternal, even when both parents are manifestly suffering from florid syphilis. In my experience, however, when both parents show signs of florid syphilis the child more frequently displays evidence of virulent infection than is usual when one or other parent manifests no active symptoms. It is not unreasonable to suppose that in some of these cases the infection may have been derived from both sources.

I must confess that I have failed to find definite evidence that the Wassermann reaction is modified by pregnancy to any marked extent. At the beginning of my work on still-birth I thought that the reaction was frequently negative in mothers of syphilitic children, and that a negative reaction therefore during pregnancy or immediately after delivery was of little or no value in excluding syphilis. The reaction was, I found repeatedly, negative in the mothers of infants who had died from what I supposed to be syphilis. These infants displayed at post-mortem examination the so-called secondary evidences of syphilis, namely, enlarged liver, enlarged spleen, more or less well-marked, or entirely absent, chondroepiphysitis, and fibrosis in various organs, such as thyroid, thymus, lungs, liver and pancreas. *In all cases, however, in which the Wasserman reaction was negative spirochaetes were absent from the foetal tissues.* I have never yet met with a foetus the organs of which were spirochaete positive while the mother had a negative Wassermann reaction. This raises the question whether we are ever justified in diagnosing foetal syphilis from the merely secondary signs. It is probably impossible, in the present state of our knowledge to give to this question a definite answer; each case must be judged upon its merits, but it may be said that in the absence of the spirochaeta pallida we are never justified in diagnosing syphilis *with certainty*. It is impossible to assert, with

our present scanty knowledge of antenatal pathology, that no other morbid condition than syphilis can give rise to enlargement of the liver and spleen, and to interstitial fibrosis in the foetal organs. This being so, I do not consider that we are justified in building upon such an insecure foundation any elaborate theories regarding the influence of pregnancy upon the Wassermann reaction.

In order to confirm or refute the conclusions at which I had gradually been arriving in the course of my examination of still-born infants, I examined the records of the Wassermann tests of the 100 cases referred to above (p. .). In the Edinburgh Maternity Hospital the Wassermann reactions are carried out at the Royal Infirmary by three serologists, who employ a modification of the Harrison technique. The tests are carried out by each serologist in turn, namely, by Dr. W. R. Logan on one day; next day by Dr. P. McCallum; and on the third day by Dr. Buchanan. By this means the personal element of error in carrying out the test is, as far as possible, eliminated.

A study of the 100 cases with reference to the apparent influence of pregnancy in modifying the Wassermann reaction shows that of the cases of old infection (55 in number) the reaction was strongly positive during pregnancy in 41 (75 per cent.). Of these 41 it was strongly positive at one month in one case, in one case at two months, in four at three months, in one at four months, in two at six months, in 10 at seven months, in four at eight months, and in eight at nine months, while there were 10 others admitted in labour and not seen before, so that the Wassermann reaction during pregnancy was unknown, but during the puerperium it was strongly positive, *i.e.*, in four cases on the day after delivery, in one on the second day, in three on the third day, in one on the sixth day, and in one on the seventh day, so that all these were probably strongly positive during pregnancy also.

The Wassermann reaction was weakly positive (+ +) in eight of the 54 cases. Analysis of these cases gives the following result:—

Case No. 32. W.R. doubtfully positive at three months. No other evidence of syphilis; admitted with incomplete abortion; presence of syphilis doubtful.

Case No. 88. Three-para. W.R. moderately strongly positive at fifth month; history of two previous neo-natal deaths after course of treatment, during present pregnancy W.R. became negative.

Case No. 299. Two-para. W.R. doubtfully positive at ninth month; husband's negative; previous child apparently healthy. No sign or history of syphilis. Syphilis doubtful.

Case No. 232. Primigravida. W.R. weakly positive at seven months. No sign or history of syphilis. Full-time healthy child

born, only one injection N.A.B. (0.15 grm.) had been given. Cord blood negative. No further record. Syphilis doubtful.

Case No. 256. Two-para; pre-eclamptic. W.R. doubtful positive. First child healthy. No signs or history of syphilis. Syphilis almost certainly not present.

Case No. 282. Treated for syphilis during last pregnancy (see case No. 80, page *vide supra*). W.R. weakly positive three days before delivery. Cord blood negative. Child healthy and negative at 10 days old. Mother negative at 10 days after delivery.

Case No. 454. Two-para. First child dead-born at six months. W.R. moderately strongly positive at end of eighth month. The child seemed healthy at birth, but cord blood + + + also at 12 days old; mother's W.R. + + + at 12th day of puerperium.

Case No. 528. Four-para. First child alive and well. Second three months abortion. Third born at eight months—lived four days. W.R. moderately strongly positive at six months. Received six intravenous N.A.B. (2.25 grm.) from then till term; child healthy; cord blood negative.

In four of these eight cases, therefore, syphilis was probably not present. In the others the conditions of the Wassermann reaction was not known previous to pregnancy, and therefore it is impossible to say whether the present pregnancy was the cause of the modification of the reaction. There is, however, no evidence whatever that it was.

CASES OF OLD INFECTION WITH NEGATIVE WASSERMAN REACTION.

These were five in number: four of these were cases of very old standing. In none except one was there any history of infection or evidence of syphilis, excepting that found in the products of conception. Their negative reactions were not due to the pregnancies during which they were under observation as not even between these pregnancies had a positive reaction ever been obtained. They were typical cases of so-called latent syphilis. The exception mentioned above was a primigravida (No. 721) who had come under observation one year before her pregnancy suffering from interstitial keratitis; her W.R. was strongly positive and she received a course of anti-syphilitic treatment, 15 injections altogether (6.15 gr.), so that at the fifth month of pregnancy the W.R. was negative. This was obviously the result not of the pregnancy but of the treatment.

Another very important problem arises in connexion with these cases of syphilis in which the Wassermann reaction is persistently negative. The problem is this: Are these cases syphilitic at all? In none of them was a spirochæte-positive foetus found, but syphilis was diagnosed from the obstetrical history and from the findings

in the products of conception—the so-called secondary signs of syphilis. Antenatal pathologists well know that there is no more difficult problem in connexion with their work than this: By what criteria are we to diagnose syphilis in the absence of the spirochæte? The history and pathological findings in three of the above five cases will illustrate this difficulty.

Mrs. D., æt. 40; twice married. First marriage 1899.

First child born 1900, normal pregnancy and labour, child alive and well now.

Second child born 1903, normal pregnancy and labour, child alive and well now.

Third child, born 1905, normal pregnancy and labour, died with jaundice, æt. 11 days.

Fourth child, born 1907, normal pregnancy and labour, died with jaundice, æt. 11 days.

Fifth child born 1909, normal pregnancy and labour, still born.

Sixth child, born 1910, normal pregnancy and labour, died with jaundice, æt. two days.

Second marriage occurred after this.

Seventh pregnancy 1912, abortion at two months.

Eighth child born 1913, pregnancy normal, child alive and well, æt. seven.

Ninth child born 1915, pregnancy normal, still born.

Tenth child born 1917, pregnancy normal, still born.

Eleventh child born 1918, pregnancy normal, still born.

Her first husband developed "creeping paralysis" two years after marriage and died in ten years. The seventh to the twelfth pregnancies inclusive were by the second husband.

The mother, anxious to have another living healthy child, came under supervision at the third month of pregnancy. The Wassermann reaction was negative, and she was put upon calcium chloride and advised to have labour induced at 8½ months on account of previous "habitual death" of the foetus. The pregnancy during the ensuing month appeared to be normal, and at 8½ months labour was induced; a living child was born which developed jaundice immediately after birth and died in 12 hours. The spleen weighed 55 grms., and its weight ratio was 42. In my experience a spleen with a weight ratio over 150 is always syphilitic except possibly in some cases of general foetal dropsy. The liver was not enlarged but was very markedly hæmopoietic, the sinusoids containing large numbers of lymphocytes. There seemed to be also a rather well marked amount of periportal cirrhosis, but this feature was too indefinite to be diagnostic of syphilis. The same remark applies to the lung. Spirochaetes were not found in any foetal organ in Levaditi stained sections. The mother's W.R. six

days after delivery was negative, and a third test in the sixth week after delivery was again negative. The woman looks perfectly healthy, denies any history or possibility of specific infection, and points to her three perfectly healthy children as proof of her contention. The husband having emigrated to America prior to her confinement was not available for examination. Mrs. D. afterwards joined him and a letter was given her on her departure giving details of the case. She afterwards turned up at a well-known hospital in New York and was attended there for a three months' abortion. Her W.R. was again negative. In my early work I was satisfied to classify this case as syphilitic; at present I am not at all sure that it is, and think it possible that it represents some obscure familial blood disease allied to that met with in general foetal oedema. At any rate the absence of spirochaetes precludes any dogmatic assertion regarding the presence of syphilis.

Mrs. L., æt. 26, first came under observation during her fifth pregnancy. No history or signs of syphilitic infection. Her obstetrical history was as follows:—

First child born 1913, full-time, born alive, died at 15 months of German measles.

Second child born 1915, full-time, born alive, died at one year of kidney disease.

Third child born 1916, full-time, born alive, alive now but "not strong."

Fourth child born 1917, full-time, dead one month before.

Fifth child born 1919, full-time. Hydramnios during pregnancy; died at two days old. Slightly jaundiced at birth and abdomen enlarged and tense. Full-time male 3,370 grms. Liver 260 grms., W.R. 12.9. Periportal cirrhosis present. Spleen 25 grms. Weight ratio 134. Levaditi negative. The mother's W.R. was negative. Cord blood not obtained.

Sixth child born 1921, 8½ months, macerated. During this pregnancy she had been under observation at the ante-natal clinic of the Edinburgh Royal Maternity Hospital from the fourth month of her pregnancy. Her W.R. was negative at the fifth month, and again at the sixth month, and the cord blood was also negative. The urine throughout the pregnancy was normal excepting just before delivery when a trace of albumen was detected. No treatment by the arsenical preparations was given but potassium iodide and mercury were administered in mixture.

Three weeks before delivery she ceased to feel foetal movements; delivery was spontaneous and a macerated foetus was born. It weighed 2,290 grms.; length 48 cm.; liver 85 grms.; weight ratio 27. Spleen 16 grms.; weight ratio 143. Placenta 800 grms.;

weight ratio 2.8; pale and non-vascular, thickened from maternal to foetal surface; foetal organs spirochaete negative.

Seventh child. Never felt well during pregnancy. Only came under observation at eighth month. W.R. then negative; had ceased to feel life two weeks before; urine normal. Received two intravenous injections of N.A.B. (.6gr. in all). Labour spontaneous. Foetus macerated, slightly premature. Weight 2655 gr.; length 48 cm., from appearance had been dead only about 10 days; liver 110 grms., weight ratio 24, was pale yellow in colour and tough and greenish on section from bile staining. The section was pervaded by fine branching and tree-like wavy lines and greyish-white spots. This was thought to be due to lymphocytes in the sinusoids or to early cirrhosis. The surface was quite smooth and showed no granularity or unevenness. The spleen weighed 18 grms., weight ratio 147. Placenta 565, weight ratio 4.7, pale, non-vascular and thickened; foetal organs spirochaete-negative.

This case has therefore been under observation in three successive labours, and each time the child has been obtained for examination. There are certain interesting correspondences between the foetal findings in each case. Thus the spirochaeta pallida was never found. In all cases except possibly the first the liver showed no enlargement; in all the spleen was enlarged but never very much exceeded normal limits. This I have elsewhere fixed somewhat arbitrarily at 150. In these three cases it was 134, 143 and 147. The placenta was not obtained in the first, but in the two last showed what are generally described as the typical appearances of syphilis, and its weight ratio was 2.8 (certainly abnormally high) and 4.7 (not abnormally high) respectively. The Wassermann reaction has been consistently negative. It is difficult to decide whether we are really dealing with a case of syphilis. Certainly absolute signs are absent.

Mrs. F., æt. 36. No history of syphilitic infection. Has bronchitis and emphysema. Urine normal. Came under observation at fourth month for yellow discharge. W.R. negative then and at fifth and seventh month, and again six weeks after delivery.

Obstetric history.

First child born 1905 at six and a half months, still-born.

Second child born 1906 at nine months, alive now but hand and foot have been paralyzed for two years.

Third child born 1907 at six months, still-born.

Fourth child born 1908 at seven months, still-born.

Fifth child born 1909 at seven months, still-born.

Sixth child born 1911 at seven months, still-born.

Seventh, eighth, ninth 10th and 11th were all miscarriages.

Twelfth pregnancy delivered spontaneously of a premature ($7\frac{1}{2}$ to 8 months) macerated foetus. Weight 1,400 grms., length 43 cm. about four or five days. Liver 70 grms., weight ratio 20. Spleen 12, weight ratio 116 (higher than normal). Organs spirochæte-negative.

The placenta weighed 170 grms., weight ratio 8.2, was small and fairly vascular looking, thin from foetal to decidual surface and contained a few old hæmorrhages here and there but no white infarcts.

This case was almost certainly not syphilitic.

In all these cases, therefore, of supposed latent syphilis with negative Wassermann reaction the diagnosis of syphilis rested entirely upon such facts as the pathological findings in the foetus and placenta and upon a bad obstetrical history in the mother. In no cases were spirochætes found in the foetus. The presence of syphilis has not therefore been proved, for the presence of the spirochæta pallida is the only absolute sign of syphilis. Further, as stated above, I have never yet found a case in which there was a spirochæte-positive foetus born of a mother whose W.R. was negative. Indeed in every case in which the foetus was spirochæte-positive the mother had not merely a positive Wassermann but a *strongly* positive Wassermann. Further investigation is needed upon this subject. This can be carried out by observing the W.R. before pregnancy, at intervals *during* pregnancy and again at intervals after pregnancy. It is obvious, however, that such an investigation is likely to be attended by a certain amount of difficulty because cases that come under observation are almost without exception treated at once either before, during or after the termination of the pregnancy, and this will of course modify the reaction.

In the meantime I have found no convincing evidence that the Wassermann reaction is modified to any important extent by the occurrence of pregnancy.

It may be that the spirochætes are present in some modified form as suggested by McDonagh, and that, as suggested by Routh, this is caused by the chorionic ferments, and that the latter may lead to a modification of the W.R. at the same time as or indeed because they granulose the spirochætes. But this does not explain why in one case the foetus should be spirochæte-negative with a negative W.R. and in another spirochætes should be present and the W.R. positive. In other words why should the ferments act in one case and be impotent in another? Further, I have noted this peculiarity, that these spirochæte-negative foetuses recur in successive pregnancies, that is to say if one is observing a mother in whom latent syphilis is suspected but in whom the W.R. is negative, and one examines the products of conception, the

secondary evidences of syphilis such as enlarged liver, spleen and placenta may be found but no spirochætes, and this condition of matters will probably recur in successive pregnancies. The case of Mrs. L., cited above (page 533), is an example of this. Why should the chorionic ferments be habitually powerful in these cases and always impotent in others?

Again, admitting that some or all of these cases *are* syphilitic, it does not follow that the negative condition of the W.R. is due to pregnancy. In what proportion of old-standing cases of syphilis in men does the W.R. become negative without treatment in course of time? According to my own figures, even if we admit that all the above five cases with negative Wassermann reaction are syphilitic, the reaction has only become negative in 10 per cent. of women who have undergone repeated pregnancy.

It is not an infrequent experience to find a mother suffering from old syphilis and giving a repeatedly strongly positive W.R. while her husband's W.R. is negative. (Nos. 234 and 283 are examples of such cases.) Has the husband in this case escaped infection by his syphilitic wife or has his Wassermann reaction become in course of time negative? If the latter, it goes to show that the reaction tends in course of time, and even in the absence of treatment and of pregnancy, to become negative.

WASSERMANN REACTION IN CASES OF FRESH SYPHILIS.

Out of 46 cases of fresh infection the expectant mother gave a strongly positive reaction in 38 (82 per cent.).

One was at the	3rd	month	of	pregnancy.
Two were at the	4th	"	"	"
Three were	"	5th	"	"
Five were	"	6th	"	"
Ten were	"	7th	"	"
Seven were	"	8th	"	"
Two were	"	9th	"	"
Eight were in labour.				

In our the reaction was weakly positive.

Details of these four are as follows:—

No. 45. Mrs. A., 2-para. Condylomata present. Wassermann reaction doubtfully positive at eight months; received six intravenous injections N.A.B. (2.25 gr.) from then till delivery: on day after delivery W.R. negative; also negative 18 days after delivery; child full-time and apparently healthy. The ulcers may not have been true syphilitic condylomata. The patient had a profuse yellow discharge and there was no rash or sore throat. The presence of syphilis is not proven in this case.

No. 80. Mrs. B., primigravida, æt. 21, no history of infection; husband, æt. 32, has recently been under treatment for syphilis. He had contracted syphilis 11 years before in America and on his return had to attend the Edinburgh Royal Infirmary on account of heart disease. This led to diagnosis of syphilis for which he was under treatment during his wife's pregnancy, and led to his wife coming under observation. Her W.R. was negative (fourth month) on two occasions, but doubtfully positive after a provocative N.A.B. She was then given five intravenous injections of N.A.B. together with mercury and tonics. One week before delivery she developed marked jaundice with epigastric pain and vomiting. The urine was bile-stained but contained no albumen. Three days after development of jaundice premature labour set in; a 7½ months child was born which was "blue" from birth and died two days after. At post-mortem examination there were extensive hæmorrhages found in the lungs and cerebral ventricles. The child weighed 1,500 grms., length 42 cm., liver 70 grms., spleen 5 grms. Epiphyses healthy and no spirochætes were found in the foetal organs. Placenta bile-stained but not enlarged. Cord blood negative. The mother's W.R. was negative one day, ten days and nine weeks after delivery. There is therefore in this case no conclusive evidence of syphilis ever having been present in the mother. The premature labour was probably due to the toxic condition of the mother caused by the combined arsenical and mercurial treatment. This view is supported by the fact that the mother's W.R. was negative nine weeks after delivery, that the child was spirochæte-negative and the cord blood negative.

No. 399. Mrs. D., 4-para. Two children alive and well, third died of pneumonia; all full-time; admitted in labour after normal pregnancy, but husband under treatment for secondary syphilis. Mrs. D. had no treatment during her pregnancy. Her W.R. was negative nine days after delivery; cord blood weakly positive (four doses of complement deviated); child full-time, apparently healthy; W.R. negative at eight days old. Weighed 3725 grms. In this case there was no evidence of infection of the mother. It may have been a case of paternal infection of the ovum alone, the mother escaping, but if it had been one would expect a severe infection of the child and that the child's Wassermann reaction would have become strongly positive shortly after birth, or is it an example of conceptional syphilis? Or, again, it is possible that the father had not acquired the disease at the time of conception, and that after acquiring it he had no further intercourse with his wife during the pregnancy. The healthy child rather points to this solution, although the weakly positive cord blood is difficult to explain.

No. 175. N.C., aged 23, 2-para, had multiple condylomata on

vulva and around anus, admitted in labour: no treatment, child apparently healthy, weighed 8 lbs. and was born at full-time. Cord blood negative. Mother's blood weakly positive seven days after delivery.

In the first and last of these four cases, therefore, whatever may have been the effect upon the Wassermann reaction, the signs of syphilis were not modified for well-marked condylomata were present. In the second case (No. 80, page 524) the presence of syphilis in the mother or foetus is not proved, and as pointed out above the prematurity may have been the result of the arsenical poisoning of the mother, for birth took place while the symptoms were acute. Neither is the presence of syphilis proved in the third case (No. 399).

None of these four apparent exceptions can therefore be adduced as conclusive evidence in support of the statement that the Wassermann reaction is modified by pregnancy.

In only one case was the reaction negative during pregnancy in a recent syphilitic, namely No. 157, and that was after treatment. It has therefore no bearing upon the question at issue.

There is thus among the fresh syphilitics no conclusive evidence that the Wassermann reaction is modified to any marked extent during pregnancy. None of the cases in which there appears to be such a modification are convincing. In none is the evidence incontrovertible.

What would be a convincing case?

The statements in literature upon the two questions under discussion are generally vague, and it would be useful if in future investigators would keep in mind the following points:—

- (a) The parents should be under observation during the pregnancy. Repeated Wassermann reactions in the mother during pregnancy should be negative. There should be no evidence of primary or secondary syphilis in the mother during her pregnancy.
- (b) The presence of syphilis in the husband should be beyond doubt. Preferably it should be in the secondary stage, as it is possible that in the tertiary stage he may not infect his wife.
- (c) The mother should be known not to be suffering from old-standing syphilis which would prevent a reinfection during the pregnancy.
- (d) The foetus should be syphilitic, it being kept in mind that the only absolute evidence of the presence of syphilis is the finding of the spirochæta pallida in the foetal tissues.

- (e) The patient should be observed for the appearance of a strongly positive Wassermann reaction in the months following delivery; or after the menopause when the special protective substances that are supposed to be present in the serum of women, and especially of pregnant women, are said to disappear.

Comparison of the mother's Wassermann reaction with the reaction of the cord blood.

Out of a total of 53 cases of syphilis in which the mother's and cord blood W.R. were obtained the results were as follows:—

Both strongly positive	in 20 or 38 per cent.
Both negative after treatment of the mother	„ 7 „ 13 „
Mother's blood more strongly positive than the cord blood	„ 17 „ 32 „
Mother's blood less strongly positive than cord	„ 2 „ 4 „
Reactions not comparable	„ 7 „ 13 „

(In the seven cases in which the reactions are not comparable, although the mother's blood had been strongly positive early in pregnancy, in all cases a fairly long course of treatment had been given and continued up till time of onset of labour and no W.R. had again been taken during the pregnancy. It may or may not have been altered by the treatment. As the mother's W.R. immediately before delivery therefore was not known, one cannot usefully compare the reaction of the cord blood with it.)

The above tables show that there is a tendency for the reaction of the cord blood to be somewhat weaker than that of the mother. I would suggest that this may be due to the fact that the cord blood obtained for the W.R. is venous, and therefore pure blood. It would correspond to arterial blood in the adult.

SUMMARY.

1. In cases of old-standing syphilis in multiparæ a history of infection or of primary or secondary manifestations is rarely given (2 per cent.), while in primigravidæ signs of syphilis are usually present at time of examination (70 per cent.). When such evidences are not present in a primigravida, she is usually elderly with an old-standing infection. As every multipara has been a primigravida at some period, this seems to prove that the reason why a history is not found in multiparæ is not that it has never been present but that it has been forgotten or is knowingly denied. There seems to be no escape from this conclusion.

(2) A study of the Wassermann reactions in 100 cases of syphilis during pregnancy suggests that pregnancy has little or no influence in modifying the Wassermann reaction.

(3) The Wassermann reaction on the blood from the umbilical cord is a reliable means of diagnosis of syphilis in the child. The reaction differs but little from that of the mother's blood, but on the whole tends to be slightly less strongly positive than the latter. It is suggested that this may be due to the fact that it is purified (arterial) blood obtained from the umbilical vein.

REFERENCES.

1. Colles' Works edited by McDonnell. New Sydenham Society, p. 256.
2. McDonagh. "Biology and Treatment of Venereal Diseases," 1915.
3. Quoted by McDonnell, Colles' Works, p. 290.
4. Hendry, R. A. *Proc. Roy. Soc. Med.* (Sect. Obstet. and Gynæcol.), 1921, xiv, 209.
5. Routh, Amand. *Proc. Roy. Soc. Med.* (Sect. Obstet and Gynæcol.), 1921, xiv.
6. Neisser, A. *Beitr. zur Pathol. und Therapie der Syphilis.* Berlin, 1911. (Springer).
7. Manouélian. *Gynécol. et Obstétrique*, 1921, 3.
8. Nattan-LARRIER et Brindeau. *Comp. Rend. Soc. Biol.*, t. 60.
9. McIntosh, J. "Syphilis," p. 64.
10. Von Reuss, A. R. "Diseases of the New-Born," p. 507.