II

THE SEX FACTOR IN DETERMINING
THE COURSE OF SYPHILIS

Discussion

Dr. H. M. Hanschell expressed his high appreciation of Colonel Burke's paper, and confessed his inability, through ignorance, to discuss the biochemical points raised by Colonel Burke. It was agreed that syphilis in women showed clinical differences from the infection in men; and morbid histology had revealed differences too in the relative frequency of infection of various viscera in the two sexes. Colonel Burke's thesis was that these differences were due to the greater lipid-content—or was it burden?—of the woman; and that the whole matter was bound up also with the high lipid-content of the spirochæte of syphilis; this high lipid-content being peculiar to, and in the nature of, protozoal parasites. Dr. Hanschell objected that it was not yet known that the spirochæte of syphilis was protozoal and not vegetable. Moreover, there were certain diseases of undoubted protozoal cause, viz., malaria, kala-azar, trypanosomiasis, amoebiasis. These had all been closely and for long studied. No one had yet even suggested any differences in them in man and woman, except that amoebiasis, like syphilis and alcohol, rarely affected the woman's liver. But the best clinical control could be found in yaws, sometimes hailed as the negro's syphilis. The spirochæte of yaws was morphologically indistinguishable from that of syphilis, and the tertiary skin and bone lesions of both diseases identical clinically and histologically. Serologically, too, the diseases could hardly be distinguished. Now, the negro woman carried a lipid burden greater than that of her scraggy testicular male as notably as did her white sister; yet no one had ever suggested any difference in yaws as seen in her from that seen in the negro male, but lipoidally speaking, what was true for syphilis should surely be true for yaws.

Colonel Harrison said: Colonel Burke has raised
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so many novel points that I feel that I should have been in a better position to discuss it if I had had the advantage of reading and reflecting on it beforehand. If I understood Colonel Burke correctly, he suggested that Spirochaeta pallida has a particular affinity for tissue rich in lipoid. I do not see how this squares with the well-known proclivity of the spirochæte for peri-vascular lymph spaces, which seem to be a much more favourable medium for it than is the brain parenchyma. I should have thought that the brain had much more lipoid in it than has the peri-vascular lymph space. I should like to suggest some other explanations of the difference between the behaviour of syphilis in females and that in males. The first is that possibly ovarian secretion is antagonistic to the spirochæte. We know that syphilis in females is milder chiefly during the period between puberty and the climacteric when, in fact, the ovaries are most active. In the same connection it is curious that, while one can almost count on the fingers of one hand the recorded instances of syphilitic lesions in the ovaries, they are almost invariably found in the testis. Another possible explanation of, at any rate, the comparative infrequency of the secondary rash in females is that it occurs in the uterus. We know that syphilis tends to recur in the damaged areas of the body, and every month there is a profound change in the uterus. I suggest that possibly the intensity of the hypothetical rash in the uterus may prevent its development in other parts of the body, as we know that, when a rash is particularly intense in one part, it may be completely absent from other parts. As an example, I would instance the case of a patient, a railway fireman, whose secondary rash was almost confluent on his thighs and legs, but there was no sign elsewhere. In this case the situation of the rash had doubtless been determined by the fact that the man’s legs got very hot at his work. Still another explanation may be that the average female’s cardio-vascular system and brain are not subject to so much stress and strain or risk of injury as are those of the male. On the other hand, Warthin’s researches indicate that the female liver is more apt to show syphilitic lesions than is that of the male. I suggest here that possibly the reason is that, in the past at any rate, women’s livers were much more damaged by corsets than were males’. 
If I understood Colonel Burke rightly, he said that injection of *Spirochaeta pallida* does not produce antibody to the organism. But it has been shown recently that injection of cultivated *Sp. pallida* does produce antibody to the same organisms. I understood Colonel Burke also to suggest that Wassermann substance was a lipo-proteolytic ferment which destroyed the lipoid of the spirochaete. If this were true, one would expect that the addition of serum giving a strongly positive Wassermann reaction would dissolve *Spirochata pallida in vitro*, but it does not occur. The statement that the serum of syphilitic pregnant women very frequently gives negative reactions is debatable. I think that it depends on the method of the test. With us it does not seem to hold, and, on the other hand, there are workers who assert that the serum of pregnant women may give false positives. Colonel Burke drew an inference in favour of his hypothesis from the fact that the liposoluble bismuth compound Bivatol is more active therapeutically than others, but I always understood that the most active preparation of bismuth is a water-soluble one, administered dissolved in water. I suggest that the impression that syphilis is more difficult to cure in women than in men may be due to the fact that a much higher proportion of women than of men begin treatment in later stages, owing, of course, to the fact that it remains so long unrecognised. Lastly, I should like to join issue with Dr. Hanschell on his preference for the term *Spironema pallidum*. In *Parasitology*, 1926, Vol. 18, p. 368, C. Dobell announced that he had verified the finding of Stiles that the name *Spironema* is preoccupied in the vegetable kingdom. We know that the term was abandoned by Schaudinn because it was found that it was preoccupied in the animal kingdom, so that, whether we think the organism of syphilis is animal or vegetable, the term *Spironema* is not applicable to it. Personally, I would prefer the term *Spirochaeta*, solely for the reason that it is more convenient, in writing articles on the subject, to speak of *Spirochata pallida* and other spirochaetes.

Dr. David Nabarro said he had immensely enjoyed the unfolding of the hypothesis put forward by Colonel Burke; he had keenly followed it step by step. He fully agreed with Colonel Harrison that it would have been a
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great advantage to have had the privilege of reading it beforehand.

There were one or two points on which he did not agree with the opener, and that might be because his work was largely concerned with children and with the mothers of those children. He had not seen much primary syphilis in women, any more than in men. It was mainly congenital syphilis which he saw. Colonel Burke had said that women were oftener Wassermann negative than men, but with that the speaker did not agree, as a result of his own experience. He did the Wassermann test on all the mothers of syphilitic children brought to his hospital, the Hospital for Sick Children, Great Ormond Street, and he had found that 90 per cent. to 95 per cent. of the mothers gave a positive Wassermann in the blood. He was not able to get half the fathers to come for examination, but of those who did come he found a negative Wassermann in nearly 70 per cent. of them. Cook and Jeans, in America, had also noted a large percentage of fathers were Wassermann negative when children and their mothers were Wassermann positive. Often one could not glean any history of venereal disease; sometimes gonorrhoea was admitted, but not syphilis. They might have had syphilis, and some treatment or no treatment. The fact remains that 67 per cent. of the fathers of syphilitic children he had tested gave a Wassermann-negative result, a fact he had found it difficult to explain. It might be that in some of them the disease was localised to the testes, and that there was an absence of general manifestations; but they were able to infect their wives, and so the latter bore syphilitic children.

Colonel Burke had said that women were more difficult than men to treat and to cure of their syphilis. All the women the speaker had treated for syphilis had been mothers of the children who were brought to hospital, and in cases in which the mothers were not very old, treatment for two years would usually enable them to give a negative Wassermann. Occasionally, however, he met with a woman who would not have her positive converted into a negative Wassermann when she had been treated for two years. When he got such a case as that he asked himself, "What about the question of congenital syphilis in this mother?" Only a fortnight ago a case in point occurred. A child who had been treated, as well as the
mother, for four years, but without serological cure, came again to hospital, and he inquired into the family history. He found that the mother’s father had had general paralysis of the insane, of which he is said to have died in an asylum, and this fact the speaker confirmed on inquiry. So this mother was a congenital syphilitic though she had never shown manifestations of the disease. Her Wassermann was stubbornly positive, and she had produced a congenitally syphilitic child. This child also had got central nervous system syphilis, like her grandfather. Incidentally she was the only case, in his experience, in which the cerebro-spinal fluid Wassermann reaction had alternated between positive and negative. When meeting with a case in which it was difficult to secure a negative blood Wassermann, it was important to enquire into the possibility of there being congenital syphilis in the parent. In such cases he could not say whether the disease had been passed for three generations, or whether the mother had derived the disease from her husband.

With regard to the question of the incidence in males and in females, he had records of 984 children in syphilitic families—478 boys, 506 girls—and the Wassermann was positive in 62.5 per cent. males, 64.8 per cent. in females, showing that the incidence in children under twelve years of age was practically the same in the two sexes.

He would read the paper at leisure with very great interest, and perhaps he might then be able to find more material for criticism than he could on first hearing it.

Dr. V. E. Lloyd said he would like, briefly, to draw attention to some of the experimental work which had been done in the transmission of syphilis to rabbits. Dr. Louise Pearce, who was present at a meeting of the Society two years ago, had done considerable research on experimental syphilis in rabbits. Two groups of female rabbits were inoculated with human syphilis. The first group of controls were inoculated in the usual way. The second group were inoculated immediately after probable conception; the majority of this group became pregnant. The subsequent course of the syphilis showed some radical differences in progress. In the second group the course of the infection was greatly modified. In a considerable proportion inoculation with syphilis failed completely; in a small proportion very
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slight local lesions developed, which in some cases were followed by no further signs of syphilis. The difference in progress between the two groups was very marked and it had struck him that these differences as well as those which Colonel Burke referred to as occurring in the human species were not due to a difference in sex, but could be attributed to the effect of conception and pregnancy. He, the speaker, had not seen much syphilis in women who had not borne children, but in these women the course of syphilis was not dissimilar to that in man.

Dr. Buckley Sharp remarked that he could not rise to the heights of Colonel Burke; or, possibly, he might have misunderstood the opener. As to the lipoid theory, Colonel Burke seemed to contend that the female was a more suitable environment than the male, because of the greater lipoid content in the female, which was chiefly subcutaneous. In those circumstances, therefore, the spirochæte should thrive and multiply. Assuming that there were more spirochætes for that reason, and that there was more lipoid present, more of the lipo-proteins would be present in the circulation, and, too, more lipo-protein antigen. Colonel Burke got over that difficulty by saying that the increased amount of lipoid already present fixed this antibody, and therefore females had less free antigen in their circulation than in the case of the male. Those two factors seemed to cancel out. A woman would produce more antibody, and she must neutralise a proportionately increased amount, so that it would not affect the end-result.

Colonel Burke agreed that the amount of lipoid in the nervous and cardiovascular system in women was the same as in man, the principal difference between them being in the subcutaneous tissues; and that gentleman assumed that the reason of the comparative immunity of these tissues to damage in women was that they were more saturated with antibodies. He, Dr. Sharp, thought the greater part of the antibody would be fixed in the subcutaneous tissue; there was in women more subcutaneous tissue in proportion than there was brain or cardiovascular tissue. Hence one would expect the latter to be more rather than less vulnerable in women on this hypothesis.

He had intended bringing forward the point that
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Colonel Harrison made, that the increased strain on these organs might determine the greater incidence in men.

As to internal secretion of the ovary being anti-syphilitic, there were points against that idea also. In the first place, he had always thought it was true, but it might be a matter of doubt, that there tended to be a negative Wassermann in pregnancy in a woman who, in other circumstances, had a positive Wassermann. One would think that ovarian secretion would be below par in pregnancy. In the ovum there were two elements: the ovarian part, and the corpus luteum part. The first of these would have a rest during pregnancy rather than be over-active, as no ovulation was going on. He had always regarded this occurrence in women as due to the effect of the placenta, as the disease in women died out if they experienced a succession of pregnancies, even though in the latter they might bear syphilitic children. This difference in child-bearing women might be due to the products of conception, rather than to ovarian activity.

Colonel Burke, in reply, said that at all events his paper had created a discussion, and that was the main idea. Dr. Hanschell had mentioned yaws and other protozoal diseases and wondered whether one might assume that the parasite of yaws was as lipoid-rich as that of syphilis. Colonel Burke did not think that this was so; and, furthermore, he would submit that the resemblances between syphilis and yaws were very superficial and were in fact more apparent than real. So far as the respective parasites were concerned there was undoubtedly a morphological resemblance, but in spite of this, clinical and experimental investigation showed that syphilis and yaws are distinct diseases. In other words, the parasites behave differently. That the two diseases are distinct is borne out by the facts that in yaws the primary lesion is extragenital, that a congenital form of the disease has not been demonstrated, that the cutaneous lesions are so divergent from those of syphilis that there is no alopecia in yaws, that itching is a prominent symptom, and that eye lesions are absent. The two diseases may exist together; but syphilis does not give rise to yaws, nor vice versa. The only resemblance would appear to be, then, in the shape of the parasites,
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and that during the secondary stage of yaws the blood yields a positive Wassermann result.

There is no doubt whatever but that the sex differentiation in animals is a metabolic one—the female being markedly more anabolic and lipoid-rich than the male. This applies alike to the negro woman and to her white sister. That the parasite of yaws has not so great a lipoid content as that of syphilis is apparently supported by the fact that it has not so marked a predilection for highly organised lipoid-rich tissue such as that of the central nervous system. He suggested that the more highly evolved the protozoan parasite was, the more prone was it to attack highly evolved tissues and the more liable was it to cause a positive Wassermann test. That test was essentially an indication of the amount of such tissue attacked. This explained the practical specificity of the Wassermann as a syphilis indicator; less evolved parasites such as the plasmodium malariae and entamoeba histolytica giving less frequently a positive result. With regard to some of the other protozoa to which Dr. Henschell had referred, Colonel Burke thought the point should not be lost sight of that in these—for example, the malarial parasite and the trypanosome—there was an intermediate host other than the human. As he had already suggested, the intermediate or natural host of the Treponema pallidum was the human female; and that this conception went far to explain why no human sex differences existed in malaria and in trypanosomiasis such as were so striking in syphilis.

Colonel Harrison had rightly remarked that the lipoid explanation was only one of a number that might be adduced to account for the sex differences in syphilis. He (Colonel Burke) submitted that not only was it the best explanation, but that it was one upon which any other explanation depended. It was the only one that covered the whole ground. It simply said that lipoid-content was the essential basis of sex differentiation. The points which Colonel Harrison made with respect to ovarian secretion and a uterine exanthem, were very valid. He would point out, however, that they were intimately related to this lipoid metabolic habit which was the characteristic of femaleness. This was, so to speak, the common denominator. It might be put like this—that a
woman did not derive her sex from the possession of uterus and ovaries, but that she derived these organs from her sex metabolism.

It would be generally agreed that trauma had a distinct influence in determining the sites of syphilitic processes. In women one frequently found that the secondary eruption in those who wore old-fashioned tightly-fitting corsets, was most marked where these pressed around the waist.

Colonel Harrison had pointed out that the perivascular lymph spaces which were the favourite sites for the parasites were not more lipoid-rich than the brain. That was true, but the point which he (Colonel Burke) wished to emphasise was that while syphilis was a disease of the perivascular lymphatics generally, it was particularly attracted to the lymph spaces associated with vessels supplying lipoid-rich tissue. He regarded neurosyphilis as being meningo-vascular in the beginning, and at a very early date, as was shown by cerebrospinal fluid abnormalities, neurorecurrence, and so on. The cerebral perivascular spaces, while they communicate externally with the subarachnoid space, also communicate internally with the perineuronal spaces around the nerve cells. If the meningeal condition progressed sufficiently far, then there took place an inward extension from the perivascular to the perineuronal spaces in the parenchyma of the brain. He did not think that this point of Colonel Harrison's was capable of being sustained against the hypothesis.

Assuming that the ovary is richer in lipoid than the testis, the fact that it was practically immune to the Treponema pallidum could be accounted for by the treponemicidal effect of its secretion and also to the combined factors of high anabolism and low organisation. At any rate, it was remarkable that this high anabolism and immunity was in direct contrast with the high katabolism and susceptibility of the testis. This showed that a high degree of anabolism—lipoid-richness—had a protective power. It might be thought that this contradicted the hypothesis in its main lines—that of the parasite having a proclivity for lipoid-rich tissue. Such was not really the case, for the factor of the high organisation of the tissue was a potent—perhaps it might be the most potent—element in attracting the Treponema
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*Pallidum* to it. Where the balance between lipoid-richness and high organisation is such that the scale is tipped in the direction of the former, immunity predominates—as in the female sex and in fatty tissues. Where the scale is tipped the other way then we have susceptibility to attack as in the male and in highly organised tissues such as those of the central nervous system.

He did not intend to convey that in syphilis there was no antibody formation, but only that such formation was not specific. In other words, that the antibody or amboceptor acted against any organism which was lipoid-rich—the higher the lipoid content being, the greater the degree of complement-fixation. He held that although the explanation of the positive Wassermann was the existence of a lipo-proteolytic ferment in the serum, it did not necessarily imply that where the serum was strongly positive, that serum would cause lysis of the treponemata. It is doubtful if the serum of any syphilitic has any parasite-destroying properties. There is evidently a strong element of non-specificity in the human defence mechanism. The action of what has been termed the lipo-proteolytic ferment may be more combinative with lipo-proteins than lytic.

His experience most decidedly was that a negative serology was common in the pregnant woman and in the uncured mother of a syphilitic child. It is probably true, however, that the proportion of negative results increases with the age of the mother and of the suspect child. The younger the mother and child, the more likely was the serology to be positive on account of the activity and short duration of the disease. Stokes found that out of 139 mothers of syphilitic children, 11 per cent. of whom were under two years of age, some 40 per cent. were serologically negative.

He could not agree that the hydro-soluble bismuth salts were more active than those which were lipo-soluble. In his experience, the reverse was the case. This also was the opinion of Iliesco, of Weissenbach, and of Schwartz as expressed at the Strasbourg Conference last year.

He was not prepared to say that after malarial therapy the parasites in the brain were literally or geographically more accessible; but it did seem to him to be fairly clear that after such treatment, the treponemata were more susceptible to the action of chemical agents. It might
also be, of course, that where chemotherapy had been instituted prior to the inoculation of malaria, the effect of the latter was such as to liberate sufficient lipoproteolytic ferment to combine with and render inert those parasites which had survived the ordinary chemical bombardment.

With regard to nomenclature, all that he was anxious about was not what the parasite was called, but how it behaved. Its behaviour was that of a protozoon, and in his view that was of tremendous therapeutic importance.

He was sorry that the President had had to leave in order to return to Scotland. His (Colonel Burke’s) imagination had been referred to in an “accusative” sense. Personally he regarded it as being in the “ablative” case; for surely it was “by, with, or from” a reasonable use of the imagination that one was enabled to interpret any series of facts or observations. Except by bringing into play the faculty of reasoning and expressing one’s interpretation of facts in the form of an hypothesis, one could make no headway. Imagination is a necessary preliminary to any experimental work. The imagination of Columbus led to the discovery of America—and incidentally of syphilis. That of Ehrlich led him along the path towards salvarsan. He respectfully submitted that what was needed in modern syphilo-logy was a little more of this “imagination” and a little less bowing before tradition and the consecrated teaching of the arid text-book. He had this evening merely re-marshalled a series of very old facts and observations and had interpreted them and explained them in a certain way. He had pointed out the biological fact of the anabolic and lipoid-rich nature of the female; he had recalled that syphilis was milder in that lipoid-rich sex; that at periods of enhanced anabolism such as pregnancy and lactation there was an increase of immunity; and from such observations he had propounded the lipoid explanation for the sex differences of syphilis. He could find no other explanation; and so far he had heard nothing which militated against his hypothesis in any way.

He was extremely interested in Dr. Nabarro’s observations, and he could only account for his own low percentage of serologically positive mothers of syphilitic children by assuming that he was seeing the disease at a
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later stage than was Dr. Nabarro. He could recall many cases in women—but not one in a man—where florid cutaneous signs of syphilis were present but the Wassermann was persistently negative.

Dr. Lloyd had mentioned Dr. Louise Pearce's work on rabbit syphilis. As far as he could recollect this work was done on female rabbits and showed distinctly that pregnancy had a modifying influence. He agreed that in the nulliparous woman the syphilis was more of the male type than in the woman who had borne children. But he thought that the difference between male syphilis and female nulliparous syphilis was very much greater than between female nulliparous syphilis and female multiparous syphilis. So then the sex difference—as he held, the lipoid-content—was all-important; and this seemed to be clearly shown even in the female sex where one found during enhanced anabolic periods—pregnancy and lactation—a reduction in the severity of the disease.

He was afraid that Dr. Sharp had not quite understood him, which was, no doubt, due to the faulty way in which he had propounded his thesis. That thesis was that the female, because of her greater lipoid richnes, is a more suitable host for the parasite than is the male. That is to say, there is a better state of symbiosis between the treponema and the female than between it and the male. If the parasite was to thrive and to multiply to excess—say, to the same extent as in the male—the degree of symbiosis would clearly be less. The two would not be living so amicably together. One would not say that there are more parasites in the female than in the male. If there are, then their virulence must be less than those of the male. They live with the female host as "benevolent neutrals." His conception was that the antibody produced by the female host was of such quantity and quality that it was efficiently utilised in reducing the virulence of the organisms and in being bound to lipoid-rich and highly organised tissues. If, as seems probable, the female produces amboceptor more quickly and in greater quantity than does the male, then the hypothesis is that the greater proportion of this becomes bound to the lipoid-rich tissues of the cardiovascular and central nervous systems and also to the subcutaneous structures. Hence the reason why cutaneous signs are milder in women and why neurosyphilis and cardiovascular involve-
ment is relatively rare and trivial. The amount of antibody remaining over from what is anchored to the tissues serves to "narcotise" the parasites, and any remaining after that exhibits itself as a positive Wassermann test. It seemed that the antibody had a greater predilection for combining with highly evolved lipid tissue than with low grade tissue such as fat, although the latter had a higher lipid content.

In reply to Dr. Logan he was unable to say anything so far as altered calcium metabolism was concerned.

In conclusion, he wished to thank the Society for the very kind and courteous manner in which his paper had been received. It was his object to stimulate thought and research. He felt strongly that the line he had sketched out should be thoroughly explored and that was more than a "one man job." He did hope that when he had arrived at a satisfactory lipo-protein mixture, members of the Society would experiment with it. It would indeed be a great thing if by the means he had indicated male syphilis could have its virulence reduced to that of the female disease; and if the cardiovascular and central nervous systems of male syphilitics could be adequately protected. It would be very advantageous if by such means there could be obtained all the benefits of inoculation malaria with the patient remaining ambulant.