The Robert Campbell Memorial Oration

Delivered by

LEONARD COLEBROOK, Esq., M.B., B.S. LOND.

Member of the Scientific Staff, Medical Research Council;
Honorary Director, The Bernhard Baron Memorial Research
Laboratories, Queen Charlotte's Maternity Hospital, London

in the

WHITLA MEDICAL INSTITUTE
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DURING the last two years of the Great War your president and I had to make our way to work every day through wards crowded with wounded men, the great majority of them suffering from a streptococcus infection of their wounds. And in 1918 in those same wards we saw dozens of men die from the deadly streptococcus pneumonia that so frequently followed influenza during the epidemic.

The end of the war came, and we had not got very far with the problem of controlling these infections. Sir Almroth Wright had shown that they were so common and so deadly because the streptococcus was able to propagate more freely in human blood and wound-exudates than any other microbe, but we had learned very little more than that. Nor for some years was there any very important advance. Recently things have happened, and I count it a great honour to have been asked by the trustees of the Robert Campbell Memorial Fund to tell you something about these recent happenings.

It is a story that would have given great pleasure to Mr. Campbell. He was a progressive surgeon who started his professional career just at the time when surgeons were beginning to realize the importance of aseptic technique. That was a great triumph, but Robert Campbell must often have felt that it was a very incomplete triumph. Too often he must have been unable to do the operation he wished to do because the wound was infected. Very often he must have stood by a patient's bedside and watched the streptococcus take charge, he himself being unable to do anything to check it.

Let us first consider the astonishing variety and the importance of these infections by hæmolytic streptococci. I can touch upon only a few points—and very briefly. Puerperal infections by this microbe account for something like 1,200 deaths every year in England and Wales alone; and for every death there are four or five non-fatal illnesses. Apart from their importance to the race, these deaths are peculiarly tragic, occurring as they do so often just at the crowning moment of a young woman's life, when her first child is born.

The part played by this streptococcus in connection with war wounds has never, I think, been fully realized. Every large hospital became a hotbed of streptococcus infection, with the result that something like ninety per cent. of wounds which were not sewn up immediately became infected, and the number of deaths attributable to this complication must have been enormous. Even in the surgery of civil life, in spite of modern aseptic technique, the threat of sepsis is by no means eliminated. A few years ago one of our most distinguished surgeons went through the records of all the 'clean' operations performed in his own hospital. He found that no less than two per cent. of such operations were followed by sepsis—a figure very near that for the incidence of infection by hæmolytic streptococci in maternity work. In many ear, nose, and throat hospitals especially, the frequent occurrence of streptococcal sepsis and of scarlet fever is, I understand, causing much concern. And in this connection I need hardly remind you that a very large proportion of

the deafness of children (and the retarded development so often resulting from it) can be traced back to otitis media and mastoid infections by the hæmolytic streptococcus, and these in turn usually to a throat infection by that microbe.

Similar throat infections seem to play some part (the nature of which is not yet clear) in the etiology of rheumatic fever. If that is confirmed, and if the throat infections can be controlled, we may be able to eliminate much of the crippling heart disease of children and young adults.

I have said nothing about septicæmia, erysipelas, whitlow, cellulitis, but you will agree, I think, that this inventory of evils attributable to infection by the hæmolytic streptococcus places that microbe quite in the front rank of the enemies of the human race.

Recognition of the part played by this microbe in all these different pathological conditions has come very slowly; indeed, it is by no means common knowledge yet. Perhaps we bacteriologists are chiefly to blame for that, because we have been very slow to learn about the microbe itself. The association of a streptococcus with suppurative processes was described—and the microbe named—so long ago as 1884, by Rosenbach—and the relationship vigorously championed by Pasteur—but very little prograss was made towards a satisfactory differentiation of this from other streptococci for twenty years. In 1903 Schottmuller,[1] a German physician, made an important contribution when he reported that by incorporating blood in his nutrient medium he was able to distinguish the streptococci associated with acute septic processes, such as cellulitis and erysipelas, from others, by the zone of hæmolysis which developed round their colonies. Unfortunately, very little attention was paid to this discovery until Howard Brown published his monograph confirming and amplifying it in 1919.[2] Even to-day the "blood-agar plate" which is so essential for the recognition of the hæmolytic streptococci is not used for routine examinations in the laboratories of some of our largest hospitals.

The recognition of distinct serological types among the strains of hæmolytic streptococci isolated from human infections (Dochez, Avery, and Lancefield, 1919;[3] Griffith, 1935;[4] and others), and the demonstration by the Dicks[5] of the production of an exotoxin which appears to be responsible for the rash of scarlet fever, were further advances in our knowledge during the post-war years; but perhaps the most far-reaching step was that taken in 1933 by Mrs. Lancefield,[6] who studied streptococci from many sources (not only from human infections), and found that those which form a hæmolytic zone round the colony comprise several "groups" which can be differentiated fairly sharply by serological and biochemical tests. She further showed—and this has been abundantly confirmed—that the great majority of the strains derived from human septic infections (puerperal fever, "surgical sepsis," scarlet fever, erysipelas, etc.) belong to one group (A).

The Prevention of Infections by Group A Hæmolytic Streptococci.

What is the source of the streptococci which cause all these infections, and how are they transmitted to the patient? On these questions also we have learned much

during the past few years. As a student I was taught that septic infection usually resulted from the transfer of the streptococcus from case to case, by hands, instruments, clothes, etc. I fancy this is still commonly believed; and it may be true as regards surgical sepsis, because septic cases are, unfortunately, often cared for in surgical wards along with clean cases. But with modern aseptic and antiseptic technique, such transfer from case to case ought not to occur. In maternity work, I believe, it is quite unusual for infection to be conveyed in that way. Much more commonly it is due to transfer of the streptococcus from the respiratory tract, and sometimes probably from infected dust.

The investigation carried out at Queen Charlotte's by my sister Dora Colebrooke,[7] has brought us as near to proof of this as we are likely to get. She set out to trace the source of infection in sixty-three cases admitted to Queen Charlotte's with puerperal fever (hæmolytic streptococcus infection), by taking throat and nose swabs from all the contacts of these cases, and from the mother herself, and sometimes also from members of her family. But my sister was not content with merely isolating hæmolytic streptococci from one or other of these contacts. By a very laborious piece of work she determined whether the suspect strains were really identical or not with that isolated from the mother's uterus or blood. In this way she was able to find a "possible or probable" extragenital source of infections in connection with forty-eight of the sixty-three mothers investigated. In her very cautious summary she concludes that transfer of the streptococcus had probably occurred from an "attendant-contact," i.e., doctor or nurse or midwife, in just half the cases, and, with one exception, always from the throat or nose; while in nearly twenty per cent. of them the infection had probably come from a member of the mother's family. In thirteen per cent. it appeared probable that the infection had travelled from the mother's own throat or nose, most likely by the agency of her hands.

I referred to the possibility of dust-borne infections. In our single rooms at Queen Charlotte's it has been quite clearly shown (White[8]) by exposing blood-agar plates that the dust in the environment of the patient discharging hæmolytic streptococci becomes contaminated by that microbe. A large number of colonies were sometimes grown on such plates when the air was stirred as by making the bed or sweeping the floor, whereas none was grown on plates exposed in the wards housing patients not infected by hæmolytic streptococci.

It seems clear, then, that in framing our preventive measures for the future—for maternity work, but also medical and surgical work—we have to keep in mind many possible sources of infection: the respiratory tract (*particularly when inflamed*) of doctors and nurses, but also the patient's, and members of his or her family; dust; transfer from a septic case, etc. Quite possibly there are others that we do not yet reckon with, for this microbe is very widely distributed.

The ideal preventive measure to meet this difficult situation would be artificial immunization of the whole community against hæmolytic streptococcus (of group A at any rate), analogous to that which is being attempted in some communities against diphtheria, but at present this is not in sight. Group A strains comprise

many distinct types, just as the different races of mankind comprise distinct families with their special characteristics, and immunity to one particular streptococcal type does not seem to imply immunity to others. So far we have not found any means of overcoming that difficulty.

What can be done to prevent dissemination of the dangerous strains? In the conditions of our modern life—herding together at close quarters in buses, trains, cinemas, etc.—this is evidently very difficult, but much more could be done than is being done to prevent the transfer of such strains *in special circumstances*. In maternity and surgical work, for example, where the patients are exposed to special risks because they have open wounds, much can be done to "trap" the streptococcus at its exit from the respiratory tract of the dangerous carriers by the intelligent use of efficient masks, and by the strict exclusion from contact with such patients of all persons who have an infection of the respiratory tract—a "cold," tonsillitis, a sinus infection, etc. And we can do much also to "trap" the streptococcus at its point of entry to the vulnerable tissues of the patient, by more efficient antisepsis, the use of rubber gloves, the exclusion of infected dust, etc.

To the same end we must, of course, be more vigilant than heretofore in the detection of the early cases of hæmolytic streptococcus infection, whether in maternity or surgical work, with a view to their immediate segregation from other "clean" cases; and in connection with every such case it should become part of the normal routine to institute an inquiry as to the possible source of the infection, lest this source may continue to be a danger to other patients. All this means making much more use of our bacteriological laboratories in the fight against hæmolytic streptococcus infection, just as we are doing in the case of diphtheria and syphilis. It means also, especially in regard to maternity work, that our administrative services must be much more wideawake to the dangers arising from the mixing up of clean midwifery cases with infected surgical and medical cases in small general hospitals and mixed nursing-homes, where there is no possibility of adequate segregation. May I put it to you individually, gentlemen, that you would not feel very happy if you knew that your wife was being confined in the same institution where there were also mastoid, erysipelas, or tonsillitis cases. The doctors, nurses, and wardmaids in contact with the latter cases may become throat-carriers, and transmit the streptococcus to those in charge of the maternity cases; the dust will cerainly be infected, and be disseminated by air-currents, boots, etc.; and, owing to ignorance or insufficient supervision, a nurse may sometimes attend both patients, especially when the staff is reduced at night. These are not just imaginary happenings. There is good reason to believe that they actually do occur—and not very infrequently—under our present too-casual arrangements. New Zealand showed us the way of dealing with this situation several years ago, when it took legislative steps to prevent the mixing up of maternity and infected cases in institutions which could not provide complete segregation. That policy has been followed by a remarkable decline in puerperal sepsis. Why do we lag behind in safeguarding the mothers?

Much more can be done, too, by propaganda and more teaching in regard to the sources of infection, antisepsis, etc.; there is an enormous amount of ignorance to

be overcome. An obstetric friend of mine was called in not long ago to put on forceps in a difficult case. In the middle of the proceedings the nurse in attendance dropped her handkerchief on the perineum. Not wishing to make a scene at the moment, my friend remonstrated rather mildly. The nurse replied: "Oh, it doesn't matter, doctor; it was only an old one."

The Treatment of Hæmolytic Streptococcus Infections by Prontosil and Para amino-benzene-sulphonamide.

May I begin by calling your attention to the muddle we are getting into by the multiplication of trade names for these new therapeutic remedies. The term 'prontosil' is now commonly used without any qualifying adjective for three quite distinct chemical substances, and there are already some sixteen different trade names for the simple substance para amino-benzene-sulphonamide. This being so, I feel it is essential for the future to fall into line with ordinary scientific practice as far as may be, and avoid all such trade-registered names, using instead a suitable abbreviation of the descriptive chemical term. A special difficulty arises in the case of prontosil, in that two of the substances to which that name is given are red dyestuffs—the one "prontosil red," sparingly soluble, used for oral administration, and the other "prontosil soluble," much more soluble, for injection. In this communication, however, it will not be necessary to distinguish between the two, and I shall therefore refer to the two substances comprehensively as "the red dyes" or (not quite properly in the case of the soluble compound) as sulphamido-chrysoidine. For para amino-benzene-sulphonamide I shall use the proper abbreviation "sulphanilamide."

The discovery of sulphamido-chrysoidine seems to have come about in this way. Many years ago German chemists found that in order to make aniline dyes fast for fabrics, they required to have a double nitrogen bond uniting two benzene rings, and an $SO_2\ NH_2$ group (sulphonamide) in the para position on one of the rings. Somebody later on made the intelligent guess that this same constitution might confer on these dyes a high destructive affinity for certain microbic protoplasms. Domagk and his co-workers[9] therefore "tried out" a number of such dyestuffs in animals which had been experimentally infected with various pathogenic bacteria. He found that the red dyestuff sulphamido-chrysoidine, if given to mice by stomach-tube within an hour or two after their infection with hæmolytic streptococci (intraperitoneal), would save most of the animals. Later it was found by Tréfouel, Nitti, and Bovet[10] at the Pasteur Institute that the simpler substance sulphanilamide, which had only one benzene ring, but still the $SO_2\ NH_2$ group, would save mice equally well.

We confirmed these curative effects in animals at Queen Charlotte's, and also showed that although the red dyes had practically no power to kill hæmolytic streptococci in blood or in water outside the body (as Domagk had stated), it was quite otherwise with sulphanilamide. Unlike the ordinary antiseptic, this substance conferred a high bactericidal power upon human blood *in vitro*, but had only a

feeble effect in watery solution. The blood of patients under treatment by sulphanilamide had a greatly increased bactericidal effect upon hæmolytic streptococci after the first few hours, and, what was more surprising, the blood of patients treated by the red dyes had a similar power—although it developed much more slowly, i.e., ten to twenty-four hours after the first dose. The explanation of this latter finding was provided by my colleague Fuller,[11] who showed that a large part of the red dyes is converted in the body into sulphanilamide, and excreted as such. His work, and that of Marshall Emerson and Cutting,[12] further showed that these substances are extremely diffusible in the body—even appearing in the cerebro-spinal fluid in considerable quantities. It is probable that they owe much of their remarkable therapeutic effect to this attribute.

We now come to the important questions : Do these compounds really exert a curative effect in the naturally occurring infections of man? and if so, how do they act? It is important to remember that in the human diseases we have to treat, the bacteria are well entrenched in the tissues—a very different state of affairs from that in the experimentally infected animal. We were in a particularly fortunate position at Queen Charlotte's for judging the clinical effects of treatment, because for five years before the introduction of the red dyes we had not been giving our puerperal fever patients any specific treatment. The death-rate for all such patients infected by hæmolytic streptococci had continued high, the average being 22.8 per cent. During 1935 it had actually been twenty-four per cent. Since the beginning of 1936, when we began to use the red dyes, the death-rate for all the two hundred cases thus infected (with no exceptions at all) has dropped to 5.5 per cent. Along with this remarkable fall there has been a complete change in the clinical picture. The temperature charts show it best. Almost with regularity the fever comes down to normal within one to four days from the commencement of treatment, and it usually remains down. The stay in hospital has been reduced from an average of thirty-one days to one of nineteen days. And the troublesome cases of parametritis that we used to see have practically disappeared. Is all this due to the treatment, or is it due to a coincident and sudden change in the disease process? Scarlet fever formerly had a high mortality in Belfast and elsewhere, and is now a very mild disease. But that change has happened gradually. There is some evidence that puerperal infections have become milder of late, but it is very difficult to be sure of it. Certainly fewer cases are developing the more grave complications such as peritonitis and septicæmia during the last two years, but that is precisely what would happen if we had an effective remedy.

My colleague Dr. Fry recently sorted out all the cases which had had a positive blood-culture (hæmolytic streptococcus) during the past six years, regarding these as cases in which there was definite evidence that the streptococcal strain had an "invasive" character. He found that whereas during the four years before sulphamido-chrysoidine was introduced (eighty-eight in number), these cases had a mortality-rate of seventy-one per cent., those for the last two years (twenty-two cases) had a mortality-rate of only twenty-seven per cent. That seems to me to indicate that even in "invasive" cases the drugs have had a very definite effect.

I feel that in trying to arrive at a decision on this important question, we ought to take into account *all* the available evidence bearing upon it — not only the evidence from our puerperal fever cases. We ought to take into account that animals are certainly cured; that the blood of human patients acquires a remarkable increase in its power to kill hæmolytic streptococci; and also the fact that recoveries are now being reported quite frequently under circumstances which make it almost impossible to doubt a favourable action of the drug. Particularly valuable from this last point of view are the results obtained within the last eighteen months in streptococcal meningitis. As you know, this infection has always carried a death-rate of well over ninety per cent. A recent survey put it at ninety-seven per cent. (Gray[15]). In the past few months no less than twenty-five recoveries have been reported after treatment by sulphamido-chrysoidine or sulphanilamide.

Let us by all means keep an open mind and a critical attitude in adjudicating upon clinical events. With regard to our puerperal fever results, I conclude that while a diminished severity of the disease may have played some part in the improvement in results, I feel it is highly probable that the largest part of that improvement has been due to the drug treatment.

I will pass now to speak very briefly of two or three practical points that emerge from our experience with these compounds.

First, as to the relative value of sulphanilamide and of the red dyes. We have treated the last 115 cases with Streptocide, a preparation of sulphanilamide supplied by Messrs. Evans, Sons, Lescher & Webb to the Therapeutic Trials Committee of the Medical Research Council for clinical trial, and have tried to compare the results obtained with those we got from the first sixty-four cases treated by the red dyes during 1936. The comparison has been reported fully in the "Lancet" of 27th November and 4th December, 1937. Broadly speaking, the results were similar, but we felt that those obtained with the red dyes, notwithstanding a rather lower scale of dosage, were slightly more impressive than those obtained with Streptocide. I do not wish to stress this conclusion, as it is manifestly impossible to assess clinical results with accuracy. Fortuitous circumstances may have contributed to the results; the dosage of sulphanilamide may not have been optimal, and it is quite possible that further experience will show that there is no real difference.

Secondly, as regards dosage of sulphanilamide. It is too early to dogmatize on this question, and we have little to guide us at present except accumulated clinical experience. The dosage of the red dyes was described in the "Lancet" a year ago (December 6, 1936), and of sulphanilamide in the more recent papers just referred to. Four to six grammes daily during the febrile period, falling to three grammes as the temperature drops, has appeared to give us satisfactory results in most cases. It is advisable to continue the drug for a few days after the temperature is normal, but not longer than ten to fourteen days as a rule.

Thirdly, I would emphasize that we have seen no good results so far in puerperal infections caused by microbes other than the hæmolytic streptococcus (I am excluding the urinary infections by B. coli in the puerperium—in these we have obtained very satisfactory results). It not unfrequently happens now that a patient

is admitted on account of continuing fever, who has been having treatment by sulphanilamide or the red dyes for a week or more. We find she has no infection by hæmolytic streptococci, and stop the drug, with the result that the temperature immediately settles down to normal. I shall refer to this again in a moment.

Finally, I will tell you what toxic effects we have experienced with these drugs. By far the most conspicuous has been cyanosis. More than fifty per cent. of the cases treated by sulphanilamide have shown some degree, usually slight, of leaden blueness of the lips and finger-nails. It is uncertain how often this occurs with the red dyes—we noticed it only on three occasions, but I suspect that we may have missed it fairly often. Cyanosis has usually been associated with the presence of met- or sulph-hæmoglobin in the blood, but in the great majority of patients this change seems to have done no harm. In three cases it was accompanied by profound exhaustion, but we could not be sure how far the two conditions were related, nor how far the patient's infection was responsible for the exhaustion. Headache has occurred in some cases, and also depression, while a few have complained of "spots before the eyes," a slight dimness of vision, tingling or numbness of the extremities, but in no cases have these effects been severe.

Perhaps the most interesting observation, apart from cyanosis, has been what American writers have called "drug fever." In some six or seven patients, a little while after the fall of the temperature to normal, it began to rise again while the drug was still being given. There were no signs of a recrudescence of the infection —convalescence was proceeding normally—and on discontinuing the drug the temperature quickly fell. Rather more often there has been a recurrence of fever a few days after stopping the drug. In these cases there may have been a slight "sub-perceptible" recrudescence of the infection; at any rate, the fever quickly subsided on restarting the drug.

It seems clear, then, that patients taking these drugs ought to be under careful supervision, and that indiscriminate prescription of them for all sorts of conditions is not warranted, either by clinical experience or by scientific observation.

That brings me to speak for a moment about their employment for the *prevention* of infection by hæmolytic streptococci. Experiments with mice certainly suggest that by giving a dose a few hours before an infection occurs, and once or twice a day for three or four days after, we can altogether prevent the development of the fatal infection, and, as I told you, we can demonstrate a greatly increased killing power in the blood of patients taking these compounds.

It does seem possible, therefore—indeed, I think probable, that they will prove to have some usefulness as prophylactic agents, but here again they should be used with discretion, particularly in maternity work. There are frequent occasions when a woman is known or suspected to be exposed to special risk of a hæmolytic streptococcus infection—for example, when there is an outbreak of sepsis in a maternity institution, or when she herself has a tonsillitis or an infected wound or erysipelas, or again, when a member of her family has a similar possible source of infection; in such special circumstances it seems to me quite legitimate and wise to

give the mother fifteen grains of sulphanilamide two or three times daily for four days (not longer) *from the beginning of labour*. It should not be given as a routine before labour.

Possibly also such prophylactic treatment may find useful application in connection with tonsil operations, but in this case it would be well to bear in mind the transient cyanosis induced by the anæsthetic.

A more lasting immunity will probably never be achieved by the drugs, but it may be obtained some day by means of vaccine therapy. At present it is not in sight, because the strains of streptococci included in group A are themselves divided into many different types, and immunity to one does not imply immunity to all.

In conclusion, I would say that we seem to have got a new weapon in our hands which is going to prove very valuable. It will, however, sometimes fail. Let us make haste slowly. Let us find out when it should be used, what harm it may do—above all, how it works. When that is known, it may prove to be the biggest advance in medical knowledge for many years.

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