PRONTOSIL AND SIMILAR COMPOUNDS IN THE TREATMENT OF PUERPERAL HAEMOLYTIC STREPTOCOCCUS INFECTIONS*

BY

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Since 1936 prontosil and similar compounds have been used extensively in the treatment of puerperal infections due to the haemolytic streptococcus. Fuller (1937) has studied the chemical changes which prontosil undergoes in the body, and he has suggested that the active part of its molecule is sulphanilamide, so that the latter (simpler) compound probably acts in the same way as the more complex. At the isolation block of Queen Charlotte's Hospital prontosil was used in the first part of 1936, and streptocide (a preparation of sulphanilamide) has been employed since. As it is my purpose to study the clinical value of this group of drugs as a whole, I have drawn no distinction between the earlier cases treated with prontosil and the later cases treated with streptocide. I have referred to these drugs collectively as the "new aniline derivatives," and to their use as the "new chemotherapy." Prontosil has been given by intramuscular injection and by mouth in daily doses of 20 to 60 c.cm. (0.5 to 1.5 grammes) intramuscularly, and 6 to 12 tablets (2 to 4 grammes) by mouth. Streptocide has been administered by mouth in daily doses of 8 to 20 tablets (2 to 5 grammes). The maximum doses have been given to patients who appeared to be severely ill, and these doses have been continued until clinical improvement has occurred. After this the dose has been decreased, but smaller amounts have usually been used for as long as a week after the temperature has fallen to normal.

The New Chemotherapy

Some patients have developed marked cyanosis due to met- or sulph-haemoglobinaemia, but in no case has this complication given rise to anxiety, and it has always disappeared on withdrawal of the drug. In a few cases of severe infection the use of the drug has been continued in spite of the cyanosis without any untoward effect. There does not seem to be any constant relation between the dose administered and the tendency to develop cyanosis. Apart from cyanosis no serious ill effects have followed the giving of these drugs.

These aniline derivatives have been used at the isolation block of Queen Charlotte's Hospital since January, 1936, and I have to thank my colleagues on the clinical and laboratory staff for allowing me to report upon all the patients with haemolytic streptococcal infections of the birth canal who were admitted from January, 1936, until March, 1937. It is now a routine practice to employ one or other of these drugs in every case of haemolytic streptococcal infection, but in the early part of 1936 there were some twenty patients to whom they were not given because of the mildness of the infection. These cases are included together with those treated by drugs during 1936–7 because I wish to show broadly what changes there have been in the results at Queen Charlotte's isolation block since the introduction of the new drugs rather than to give details of cases treated. As I have said, it is not my intention to make any comparison between the earlier cases treated with prontosil and prontosil soluble and the later cases treated with sulphanilamide. The first group has already been reported upon by Colebrook, Kenny, and the staff of Queen Charlotte's Hospital (1936). The second group will be the subject of a report to the Therapeutic Trials Committee of the Medical Research Council, and this report will subsequently be published. I have also given the results of cases of haemolytic streptococcal infection admitted to the isolation block in the two years immediately preceding the introduction of the new drugs (1934–5).

There are thus two groups of patients to compare. The outstanding difference in the treatments in these two groups is that the new aniline derivatives were used almost as a routine in the one group and not at all in the other.

TABLE I.—*Results of Puerperal Infections due to the Haemolytic Streptococcus*

	1934–5 Group			1936–7 Group		
	Number of Cases	Deaths	Mortality per cent.	Number of Cases	Deaths	Mortality per cent.
(*a*) Total number of puerperal infections due to the haemolytic streptococcus	210	42	20	157	7	4.5
(*b*) Total number of infections clinically limited to the birth canal	98	0	Nil	104	0	Nil
(*c*) Total number of infections showing definite clinical evidence of localized spread beyond the limits of the birth canal (excluding septicaemia and generalized peritonitis)	50	0	Nil	30	1	3.3
(*d*) Total number of infections in which the haemolytic streptococcus was demonstrated on blood culture (excluding cases in which generalized peritonitis was also proved)	28	11	40	21	5	20
(*e*) Total number of infections in which generalized peritonitis was proved to be present (excluding cases with septicaemia)	18	15	83	1	0	Nil
(*f*) Total number of infections in which both septicaemia and generalized peritonitis were proved to be present	16	16	100	1	1	100

Table I (*a*) shows that the gross mortality in the 1934–5 group was 20 per cent., compared with a mortality of 4.5 per cent. in the 1936–7 group. The reduction in the mortality rate during the period when the new drugs were used is very striking. In their original reports Colebrook and Kenny considered the significance of these improved results, and were cautious in attributing them entirely to the treatment with the new drug. They drew attention to the fact that there had been a progressive fall in the mortality rate from haemolytic streptococcal infections admitted to the North-Western Fever Hospital, London, in spite of the fact that the new treatment was not used in that hospital, and they quoted Mr. James Wyatt's figures in this connexion. They pointed out, however, that the fall in mortality rate at the North-Western Fever Hospital had been progressive over a number of years, whereas there had been no such progressive fall at Queen Charlotte's. The fall from about 20 per cent. to 4.7 per cent. which they quoted from Queen Charlotte's was abrupt, and coincided with the introduction of prontosil into the scheme of treatment.

* Read in opening a discussion in the Section of Obstetrics and Gynæcology at the Annual Meeting of the British Medical Association, Belfast, 1937.

Streptococcal Infection of Birth Canal and Adjacent Tissues

Table I (*b*) shows that so long as the haemolytic streptococcus is confined to the birth canal there is practically no mortality in either group; and Table I (*c*) illustrates that even when the infection has spread to surrounding pelvic and lower abdominal tissues the patient almost invariably recovers, provided that widespread dissemination by the blood stream or by spread all over the peritoneal cavity does not occur. (The one death in the 1936–7 group which occurred in the absence of general peritonitis or septicaemia was due to a pulmonary embolus.) For proof that the infection has spread beyond the limits of the birth canal (apart from proved septicaemia or generalized peritonitis) reliance has been placed on the finding of a definite inflammatory mass in the pelvis or abdomen, and only cases in which such a mass has been demonstrated either clinically or at post-mortem examination have been classified under this heading.

These figures—Table I (*c*)—show that the haemolytic streptococcus is "virulent" only in so far as it is invasive, and that a very large amount of tissue can be infected without causing death from absorption of toxins. In comparing the two groups of patients it will be noted that in the 1934–5 group the infection was clinically limited to the birth canal in only 47 per cent. of the cases. In the 1936–7 group the infection was clinically limited to the birth canal in 66 per cent. This may be interpreted in one of two ways. Either the prevalent haemolytic streptococcus of 1936–7 was less invasive—that is, less "virulent"—than that of 1934–5 or else the chemotherapy of 1936–7 helped to prevent the invasion of tissues around the birth canal.

In many cases of localized spread of infection beyond the limits of the birth canal it is difficult to say precisely when a definite inflammatory mass was demonstrated. Clinically a "sense of resistance" may give place to a "thickening," and it may not be until several days later that an obvious "lump" is found. In spite of this difficulty an attempt has been made to give a figure indicating the proportion of cases in which an inflammatory mass developed after admission to hospital—that is, after the institution of treatment. In the 1934–5 series forty-one of the patients (20 per cent.) had a demonstrable inflammatory mass on admission to hospital, and an additional twenty-nine patients (14 per cent.) developed a mass some time after admission. In the 1936–7 series an inflammatory mass was found in twenty-seven patients (17 per cent.) on admission to hospital, and in nine* patients (6 per cent.) a similar mass developed after admission. There was therefore a notable reduction in the proportion of cases in which an obvious spread of infection occurred after admission to hospital in the period when the new drugs were employed. This may be evidence of the efficacy of the new chemotherapy, or, alternatively, it may be explained on the grounds that the virulence of the haemolytic streptococcus was diminished in the 1936–7 period.

Mortality Rates in Septicaemia

Table I (*d*) shows the mortality rates in proven septicaemia (excluding cases in which general peritonitis was also proved). It was 40 per cent. in the group of patients who did not receive the new drugs. Even 40 per cent. may seem to be a surprisingly low mortality for blood-positive septicaemias due to the haemolytic streptococcus,† but in explanation of this I think that the care with which the bacteriological technique is carried out must be a factor in giving an (apparently) low mortality rate for cases in this class. If a less careful technique had been employed it is probable that some of the less severe septicaemias would not have been detected, so that although the total number would have been less the mortality rate would have been higher. This factor is of no importance in comparing the results in the two groups under review, because the technique of blood culture was identical in both. In the 1936–7 group the mortality for cases of proven septicaemia (excluding cases in which general peritonitis was also present) was 20 per cent.; but before trying to assess the significance of this improvement it is useful to try to measure the severity of the cases in the two groups. Dr. Colebrook and his co-workers have, as a routine, estimated the number of organisms per cubic centimetre in the blood in cases of septicaemia, and as a general rule the clinically milder cases are associated with a lower count than the more severe. The records of these counts are not strictly comparable between various patients, because the number of organisms in the blood may vary greatly in different stages of the disease, and because blood cultures may be repeated more often in some patients than in others. Very roughly speaking, however, if the records show that a count of less than 10 organisms per c.cm. has not been exceeded at any time during the stage of pyrexia the septicaemia is probably "mild." The records of the cases at Queen Charlotte's Hospital show that the lower mortality from septicaemia in the 1936–7 period was associated with a relative increase in the proportion of "mild" cases, in comparison with the 1934–5 period. This diminished invasion of the blood stream in the 1936–7 period is what we might expect to find if the new drugs were effective in checking the invasiveness of the haemolytic streptococcus, but, alternatively, a falling off in the virulence of the prevalent haemolytic streptococcus of 1936–7 would also manifest itself in the same way.

In the 1934–5 group a positive blood culture was obtained within twenty-four hours of admission in thirty-one cases (15 per cent.) of all cases infected with the haemolytic streptococcus. In the 1936–7 group the corresponding figure was twenty-two (14 per cent.). In the 1934–5 group ten cases (5 per cent.) developed a septicaemia some time after admission. In the 1936–7 group only one patient developed a septicaemia (and in this case the first blood culture was not taken until several days after admission). The incidence of septicaemia before admission does not greatly differ in the two groups, and this is some evidence that there was not any considerable difference in the invasiveness (virulence) of the prevalent streptococcus in the two periods. If this is so the diminished incidence of septicaemia developing after treatment with the new drugs is some evidence that the good results are due to the drugs rather than to a hypothetical decrease in the virulence of the infecting organism.

Generalized and Generalizing Peritonitis

Table I (*e*) and (*f*) gives the results when "generalized" and "generalizing" peritonitis occurred, but there are good reasons for exercising very great caution in interpreting these figures. The outcome of any peritoneal infection depends upon whether the tendency of the tissues to localize the infection overcomes the tendency

* Among these nine patients in the 1936–7 group there were four who did not receive any treatment by the new drugs, so that, by excluding the four cases, there were only five (3.2 per cent.) who developed a demonstrable mass after treatment with the new drugs.

† If the results for four years (1932–5) are analysed the mortality at Queen Charlotte's was 47 per cent.

of the organisms to generalize the infection, and the issue is often in the balance for some days. Unless laparotomy is performed, post-mortem examination is the only way in which a certain diagnosis of "generalized" or "generalizing" (as opposed to "localized" or "localizing") peritonitis can be made. The frequency and the readiness with which laparotomy has been employed at Queen Charlotte's Hospital has varied from time to time, so that the opportunities for proving a diagnosis of "generalizing" or "generalized" peritonitis have also varied. It is not necessarily of significance, therefore, that there were thirty-four such cases in 1934–5, against two cases in 1936–7. Changes in proved post-mortem findings are, however, significant. In the 1934–5 group (210 patients) generalized peritonitis was found post mortem in twenty-nine cases. In the 1936–7 group (157 patients) it was found post mortem in only one case. The relative rarity of this proved necropsy finding in the latter group must mean either that the invasiveness (virulence) of the prevalent streptococcus was very much less in the 1936–7 group or else that the new chemotherapy was very effective in preventing the widespread dissemination of the infection.

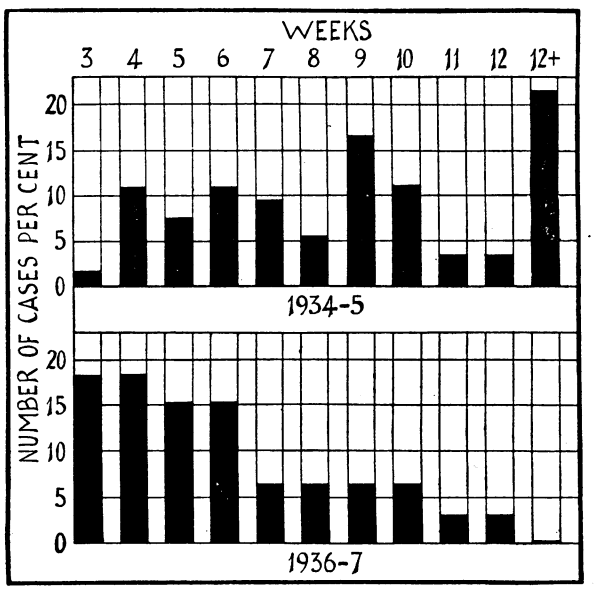
Results from the New Chemotherapy

It is clear from the above analysis that since the introduction of the new chemotherapy there has been a very great improvement in the results obtained at the isolation block of Queen Charlotte's Hospital. The improved results are demonstrated: (1) by a considerable fall in the total mortality rate; (2) by a reduction in the proportion of cases in which the infection spread beyond the limits of the birth canal, and by the relative infrequency with which an inflammatory mass developed after treatment had been instituted; (3) by a significant fall in the mortality rate in cases of proved septicaemia associated with a relative decrease in the proportion of severe cases of septicaemia, and by a fall in the incidence of septicaemia developing after the treatment had been instituted; and (4) by the relative infrequency with which generalized peritonitis has been found post mortem. There is no doubt about these facts. There is some doubt about their meaning.

Although they can be explained by assuming that the new aniline derivatives have supplied a highly effective remedy for haemolytic streptococcal infections, most of them can also be explained by assuming that the virulence of the haemolytic streptococcus has diminished spontaneously in the period during which the new drugs have been employed. There are few features revealed by the results so far discussed that cannot be accounted for on either hypothesis. These good results are mainly an expression of diminished invasion of tissues (including the blood stream) by the organisms. This may be the result of increased resistance on the part of the tissues—that is, it may be due to the chemotherapy—or it may be due to diminished virulence of the organism itself. It is a matter of personal fancy which of these alternative explanations will appeal to any of us as individuals, but the accumulated experience of the past shows that a fortuitous change in the virulence of a prevalent organism is no more improbable than the discovery of an effective chemotherapeutic substance.

Is there any method, apart from the test of time—and in this case the time must necessarily be many years—by which we can get evidence in this urgent question? Can it be shown that in non-fatal cases where invasion of tissues has actually occurred the new chemotherapy is effective in hastening the resolution of the disease? The accompanying diagrams show the time taken for patients to recover sufficiently to be discharged from hospital in cases having a localized spread of infection outside the birth canal (as proved by the demonstration of an inflammatory mass in the pelvis or abdomen). Some such patients died from an associated septicaemia or general peritonitis. All deaths have been excluded, and the cases have been grouped according to the number of weeks that elapsed between the confinement and the time the patient returned home. The number of patients in each group has been expressed as a percentage of the whole.

When the cases are arranged in this way it appears that there was a considerable shortening in the time of the average illness in the 1936–7 period as compared with the 1934–5 period. If we take these diagrams at their face value the improvement during the period of chemotherapy cannot be accepted as evidence of diminution in the virulence of the prevalent haemolytic streptococcus



Diagrams showing the duration of the illness (interval between confinement and discharge from hospital) in non-fatal cases in which an inflammatory mass was demonstrated beyond the limits of the birth canal. The percentage distribution of patients is indicated by the height of the columns. The results for 1934–5 are compared with those for 1936–7.

during this period, because we are dealing only with cases with demonstrable invasion of tissues outside the birth canal, and invasion of tissues is in fact the clinical manifestation of virulence. To suggest that, although the streptococcus of 1936–7 invaded the tissues in these selected cases, it was less virulent than the streptococcus of 1934–5, which did precisely the same thing, is to ignore what we know of the morbid anatomy of haemolytic streptococcal infections. We know, for example, that the virulence of the diphtheria bacillus depends upon its ability to produce a very potent toxin, and not at all upon its power of invading tissues. Clinical and pathological experience has taught us that the haemolytic streptococcus behaves in an entirely different way. It kills the patient only in so far as it invades her tissues widely, and the conception of a relatively avirulent haemolytic streptococcus that invades tissues widely is a contradiction in terms that finds no support in practical experience.

Taken at their face value, therefore, the diagrams indicate that the shortened convalescence in the patients treated with the new aniline derivatives is to be attributed to the treatment rather than to another variable factor. This is the most significant piece of direct evidence that I have

been able to find that disallows the alternative explanation that the improvement in results was due not to the treatment but to a fortuitous change in the virulence of the prevalent streptococcus. There are, however, two reasons for questioning the value of these diagrams. In the first place they refer to only small numbers of patients (fifty-six in 1934–5 and thirty-two in 1936–7), so that statistically they are open to criticism. In the second place, although I consider that invasion of tissues is the best possible clinical measure of virulence in haemolytic streptococcal infections, it is not possible to assert that the tissues were equally widely invaded in the two groups concerned. Great care has been taken to include only those patients in whom a definite inflammatory mass was demonstrated, but it is just possible that the average size of the mass was considerably greater in the 1934–5 series than in the 1936–7 series. If this were so it might be evidence of a minor variation in virulence of the streptococcus in the two series. No further analysis on these lines has been attempted, because it would incur the possibility of statistical and observational errors so great as to negative any results.

Conclusions

The new aniline derivatives have been employed at Queen Charlotte's Hospital since 1936; in the doses in which they have been given their use appears to be free from serious danger and has been followed by a very great reduction in the mortality rate for haemolytic streptococcal infections. Analysis of the causes of this improvement in mortality rate shows that it is associated mainly with a decrease in the widespread invasion of tissues by the haemolytic streptococcus rather than with a greater tendency to resolution of the disease once widespread invasion of tissues has occurred. This feature makes it necessary to consider whether the improvement since January, 1936, is due to the efficacy of the treatment or whether it is due to a change in the virulence of the prevalent organism. It is possible that both factors may be concerned. In non-fatal cases in which tissues beyond the limits of the birth canal have been invaded by the haemolytic streptococcus there is some clinical evidence that the new drugs do actually hasten the resolution of the inflammatory process, and this is a good reason for believing that the treatment, rather than a change in the virulence of the organism, is responsible for the improvement in this direction.

While I am unwilling to guess how far the new drugs have been responsible for the undoubted improvement which has followed their clinical use, there is every reason to continue to employ them until their value or otherwise is firmly established.

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The first number of the seventh volume, dated March, 1935, of the *Index to the Literature of Food Investigation*, which has only just been issued, covers the literature published in 1934. It is hoped, states a prefatory note, to complete during the next twelve months abstracts of the literature published during 1935 and 1936, which will form vol. vii, No. 2, and vol. viii. Meanwhile the first part of vol. ix, covering papers published this year, is in preparation. Copies of the *Index* may be obtained from H.M. Stationery Office, London, price 5s.

OTITIS EXTERNA*

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By this term otologists refer to certain types of inflammatory lesion of the external auditory canal. These are all infections of the skin lining the canal. Since, however, this skin is directly continuous with that covering the auricle and surrounding parts, obviousiy the infections need not always originate in or be confined solely to the anatomical boundaries of the canal. Therefore, in discussing their aetiology and treatment we should not limit ourselves too strictly to this part of the external ear.

Aetiology

As a cause of the lesion the most important factor is naturally the invading organism or virus. Those of external origin give rise to the commoner types of eruption and include the pityrosporon, acne bacillus, *Staphylococcus albus, Staphylococcus aureus,* and *Streptococcus longus.* The rarer forms may be due to various fungi, especially those of the aspergillus variety, to the *Bacillus pyocyaneus,* the bacillus of diphtheria, Plaut-Vincent's organism, and very occasionally the tubercle bacillus. On the other hand, the infective organism or virus may reach the skin of the ear by way of the blood stream, producing eruptions that can be recognized as exanthematous, syphilitic, or influenzal.

Their location, and in the case of organisms their site of growth in the various structures of the skin, bring about defence reactions which in turn determine different characteristics in the form of the lesions. The defence reactions include the usual phenomena of inflammation—for example, hyperaemia, oedema, exudation of leucocytes, etc.—but to these must be added another very important one—namely, the so-called eczematous reaction, which it is agreed always indicates cell sensitization. As to the relation of this reaction to that of true eczema opinion is still divided, but we may assume that for clinical purposes the results of both are much the same. With regard to the site of growth we find that certain organisms appear to have a special predilection for definite structures of the skin. For example, the pityrosporon and the aspergillus confine themselves chiefly to the stratum corneum, the *Streptococcus longus* to the deeper layers of the epidermis, even extending to the dermis, whilst the acne bacillus, *Staphylococcus albus* and *Staphylococcus aureus* favour the pilo-sebaceous follicle. In turn the defence reactions of the epidermis to the first group of above-mentioned micro-organisms may result in such clinical manifestations as a simple scaliness or dandruff, a more intensive desquamation, or as a definite cuticular inflammation, primarily perifollicular, so that the affected part takes on the appearance of a seborrhoeic dermatitis. When the deeper layers of the epidermis are invaded by the *Streptococcus longus* the resulting lesion may then be the subcorneal vesicle of impetigo, the streptococcal fissure, or the ecthymatous ulcer. Finally one must mention the defence reactions of the pilo-sebaceous follicle to invasion by the acne bacillus, and *Staphylococcus albus* and *aureus,* a group of organisms referred to by some dermatologists as the seborrhoeic triad. Of this group the *Staphylococcus aureus*

* Read in the Section of Oto-rhino-laryngology at the Annual Meeting of the British Medical Association, Belfast, 1937.