

TREATMENT WITH PRONTOSIL OF PUERPERAL INFECTIONS DUE TO HÆMOLYTIC STREPTOCOCCI *

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In a previous paper we reported the treatment of streptococcal peritonitis in mice by the injection of Prontosil soluble, and gave an account of 38 cases of human puerperal fever treated by injections of the dye together with oral administration of the less soluble compound, Prontosil.† The present paper deals with our experience in treating a further series of 26 consecutive cases, and summarises the impressions gained to date.

During the next few months it is proposed to treat a new series of patients with the nearly related compound, *p*-aminobenzenesulphonamide, which has given results even better than prontosil in experimental infections of animals, and confers a much greater bactericidal power upon the blood. A comparison of the clinical results obtained with the two substances will be published later.

The Twenty-six New Cases

With the exception of one case, whose temperature did not exceed 100° F. at any time while in hospital, all were notifiable as "puerperal fever," and with the same single exception all were infected by hæmolytic streptococci belonging to Group A (Lancefield). The pathological conditions are summarised in Table II.

Dosage.—The two compounds, prontosil and prontosil soluble, have been employed as before in all cases, the former by the mouth, the latter by intramuscular injection. Our present practice is shown in Table I.

The injections are diminished *pari passu* with the fall of the temperature and discontinued one or two days after this has reached the normal level. The doses by the mouth are also diminished from 12

6 tablets with clinical improvement, but the 6 tablets are continued for several days after the normal temperature has been reached. In the gravest cases

TABLE I

—	By mouth.	By intramuscular injection.
Gravely ill patients.	12 tablets per diem. Total 4 g.	20 c.cm. every 8 hours. Total 1.5 g.
Cases of moderate severity.	6 tablets per diem.	20 c.cm. every 8 hours.
Mild cases.	" "	10 or 20 c.cm. twice daily.

large doses have been continued for a week or more. The Figure shows a typical scheme of dosage.

No other treatment has been given beyond a daily vaginal douche, the application of Antiphlogistine to the abdomen when there is tenderness, and sedative drugs as required. The general care of the cases has remained the same for the past two years.

TABLE II

	Cases.
1. Infection limited to uterus, vagina, and perineum	17
2. Infection involving pelvic cellular tissues, Fallopian tubes, pelvic peritoneum, or veins	3
3. Infection of birth canal associated with generalised peritonitis (in one other case peritonitis was suspected)	1*
4. Infection of birth canal associated with septicæmia (hæmolytic streptococci in blood culture)	6

* With positive blood culture.

ANALYSIS OF RESULTS OF TREATMENT

None of the patients has died. In one patient, admitted on the 25th day with an abdomino-pelvic mass, the treatment appeared to have no beneficial effect, but the inflammatory mass slowly resolved. Eleven others (42 per cent.) were mild cases which would almost certainly have recovered without any special treatment. The rapid and complete recovery of the remaining 14, more severe, cases makes it seem probable that the treatment assisted recovery. In at least three cases it was more than probable. Six of these 14 cases (23 per cent. of the whole series) gave a positive blood culture (hæmolytic streptococci) on admission; in one case the signs and symptoms pointed definitely to a generalised peritonitis, while in one other there was reason to suspect the beginning of that condition.

The clinical details of the two most severe cases were as follows:—

Mrs. F. 1-para; admitted on fifth day of puerperium, with temperature of 103° F. and pulse of 140 rising to 150, signs and symptoms of generalised peritonitis, and a positive blood culture. (This combination has almost invariably in our experience proved fatal.) After three days' treatment her temperature and pulse-rate became persistently normal, and all signs of peritonitis disappeared.

Mrs. S. 1-para; developed fever to 105° F. on third day, and on admission was very gravely ill. Blood culture gave a growth of more than 5000 colonies per c.cm. on the first two days, and over 3000 on the third day, most, if not all, of the colonies being hæmolytic streptococci although there were also some anaerobic streptococci present in fluid cultures made at the same time. On the fourth day of treatment a blood culture was sterile and the temperature fell to normal, remaining so except for one slight rise (to 100° F.) on the following day. She was discharged in good health 21 days after admission to hospital and has suffered no relapse (see Figure for temperature and details of treatment).

In view of the fact that blood cultures yielding such a large number of hæmolytic streptococci (equivalent

* A further report to the Therapeutic Trials Committee of the Medical Research Council. A preliminary report by the same workers on the treatment with prontosil of human puerperal infections, and of experimental infections in mice, appeared in THE LANCET of June 6th, 1936 (p. 1279).

† Prontosil soluble and Prontosil were submitted to the Therapeutic Trials Committee by Messrs. Bayer Products Ltd., who now call the latter product "red Prontosil," in contradistinction to the colourless compound, *p*-aminobenzenesulphonamide.

(Continued from previous page)

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to something like 30 millions in the whole blood stream) have never previously been observed by us except in the terminal stages of a fatal infection, this patient's prompt recovery was astonishing.

TOXIC EFFECTS

These have been much the same as in the previous series—i.e., a very mild degree of urinary tract

us that at least half of the "probable" cases ordinarily develop into undoubted cases of generalised peritoneal infection. On this assumption, we have to conclude that not less than 8 cases (12 per cent. of those treated by prontosil)—and possibly 11 cases (17 per cent. of those treated)—were likely to have had a generalising spread of infection to the abdominal peritoneum, and that, in all except one case, this process was checked by the natural defensive mechanisms powerfully assisted by vigorous treatment with prontosil. If that conclusion is erroneous, we are driven to the alternative judgment that the occurrence of generalising peritonitis, which had continued steadily throughout the previous five years, stopped abruptly at the end of 1935, an alternative which seems to us extremely improbable.

(c) The well-known tendency of puerperal infections by the hæmolytic streptococcus to spread to the cellular tissues of the parametrium and the pelvic walls, has been conspicuously absent in these 64 prontosil-treated cases. No case has developed a palpable pelvic or abdomino-pelvic inflammatory mass after treatment began. By contrast with this, it is instructive to note that among the 20 cases which were considered too mild on admission

to need treatment with prontosil, four subsequently developed a spread of infection to the pelvic cellular tissues, with irregular fluctuations of temperature, and the formation of a palpable inflammatory mass. These

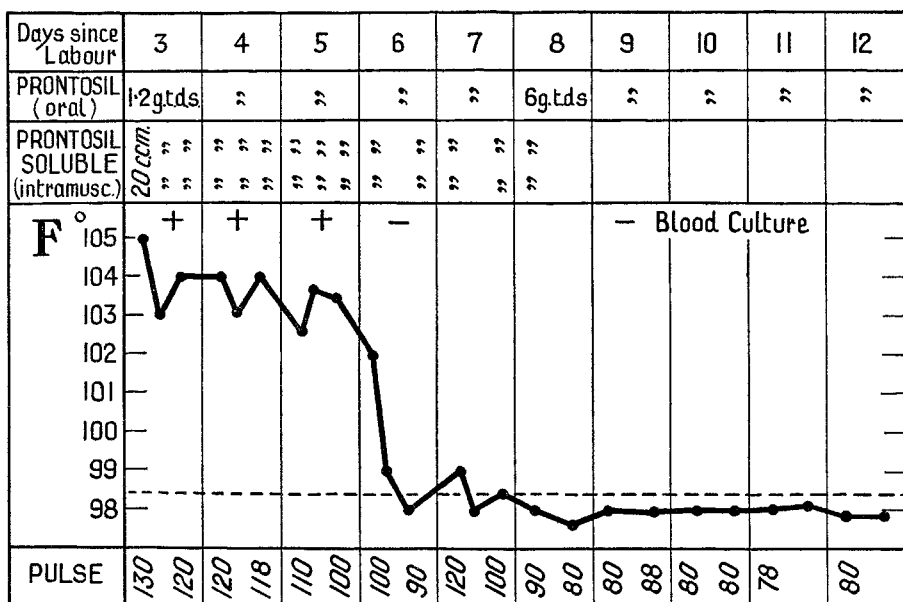


Chart showing a typical scheme of dosage in a case of puerperal septicaemia.

irritation, as shown by the presence in the urine of epithelial cells and occasionally a few red blood-cells; the cells have disappeared from the urine on cessation of treatment. There have been no further cases of sulphæmoglobinæmia, possibly owing to the fact that magnesium sulphate is not now given to any patient under treatment by prontosil.

Commentary upon the Whole Series of Sixty-four Cases

Table III. shows our experience of this series of cases, in contrast with all the similarly infected cases which had been admitted to the Isolation Block during the previous five years. The following points are worthy of notice:

(a) There has been a sudden and remarkable fall in the death-rate for all cases admitted with an infection by the hæmolytic streptococcus. The significance of this is discussed below.

(b) While there has been also a manifest falling-off in the deaths from peritonitis, it should not be assumed that the incidence of that condition has shown a similar decline. The figures given for 1931-35 refer to proven peritonitis—i.e., proven by the finding of streptococcal exudates in the peritoneal cavity, either at laparotomy or at autopsy. The one death during 1936 was also in a case proven by post-mortem examination. Since neither laparotomy nor post-mortem examination was performed on any of the other cases presenting the clinical features of generalised or generalising peritonitis, it is impossible to say precisely in how many of the 64 cases that condition was present when the treatment by prontosil was begun. Members of the honorary staff of the hospital who have been observing puerperal infections for a number of years were of opinion that general peritonitis was almost certainly present in 4 patients in addition to the one who died, while in 6 more there was reason to think that spread of infection to the abdominal peritoneum was probably beginning. (In several other cases the clinical signs were only suspicious.) Previous experience has taught

TABLE III

Death-rate for all cases infected by *Hæmolytic Streptococci* (Queen Charlotte's Hospital)

Year	Number of cases (all grades).	Deaths.	Deaths from peritonitis.*	Blood-positive cases (hæm. strept.) without general peritonitis, and death-rates.
1931	98	31 = 31.6 %	23	—
1932	90	19 = 21 %	16	1 (died = 100 %)
1933	97	20 = 20.6 %	14	9 (6 deaths = 66 %)
1934	120	20 = 16.6 %	16	15 (4 deaths = 27 %)
1935	90	22 = 24.4 %	15	13 (7 deaths = 53.8 %)
1936 Jan.-Aug.	64 (treated by prontosil)†	3 = 4.7 %	1	8 (2 deaths = 25 %)

* Hæmolytic streptococcus cases only.

† In addition to these 64 cases there were 20 cases also infected by hæmolytic streptococci in the early part of the year, which were considered too mild to need special treatment—and also one recent case which was treated by *p*-aminobenzenesulphonamide. None of these 21 cases had general peritonitis or septicaemia, and none of them died. The death-rate for the 85 cases infected by hæmolytic streptococci during 1936 (Jan.-Aug.) was 3.5 per cent.

four cases had to be kept in hospital for 30, 40, 60, and 65 days respectively. The limitation of the streptococcal invasion in the prontosil-treated cases has also been reflected in the temperature charts, and by the duration of stay in hospital. The great majority of cases treated with prontosil have shown a prompt fall of temperature within 24-72 hours from the beginning of treatment, and their temperatures thereafter have remained normal, with none of

the secondary rises and irregular fluctuations which so often in the past have heralded the extension of infection to the pelvic tissues. In no case has it been necessary to keep a patient in hospital for many weeks, waiting for the slow resolution of one of these inflammatory masses. Data based on the duration of stay in hospital are notoriously open to criticism, but it is perhaps worthy of record that the average stay in hospital for the 61 prontosil-treated patients who recovered was 18 days, while that of the 61 consecutive non-fatal cases immediately before the introduction of prontosil was 31.3 days.

(d) There has been no occasion to readmit any of these patients to the wards, and all of them, on their follow-up visits to the hospital weeks or months after discharge, have appeared to be in very good health.

(e) Analysis of the cases giving a positive blood culture (hæmolytic streptococci) is also instructive. No less than 12 of the 64 cases (19 per cent.) were of this kind. Of these 12, 9 recovered (75 per cent.). Of the three who died, one had a generalised peritonitis on admission and almost certainly for several days before. Of the remaining two cases, one was found at autopsy to have extensive thrombophlebitis; in the other, an autopsy was not obtained, but there is very little doubt that a similar condition was responsible for death. Among the remaining nine cases who recovered, there were three in whom it appeared very probable that infection of the abdominal peritoneum had already commenced on admission.

DISCUSSION OF CLINICAL RESULTS

The death-rates shown in Table III., with the considerations put forward above, make it difficult to resist the conclusion that the remarkable improvement in the clinical results has been chiefly due to the introduction of treatment with prontosil. That conclusion is strongly supported by the analogous and unmistakable curative effects obtained in experimental animals. There are, however, other possible, albeit improbable, explanations of our clinical results which ought to be kept in mind. We might have been deceived by the purely fortuitous admission of an unusually mild group of cases; or, on the other hand, by a spontaneous and rather sudden diminution of "virulence" (killing power) of the hæmolytic streptococcus for the human subject. In view of the importance of arriving at a correct evaluation of the effect of prontosil, we have been at some pains to examine both these possibilities.

First, is there any evidence that, by the mysterious operations of chance, the 64 cases treated with prontosil have included an unusually large proportion of mild cases and a correspondingly small proportion of severe ones? This question is to some extent capable of investigation, for it is well known that the great majority of deaths in puerperal fever due to infection by the hæmolytic streptococcus occur in two groups of cases—viz., the group of "generalised peritonitis" and that of "septicæmia" (cases with hæmolytic streptococci actually detected in the blood stream).

An analysis of the 64 cases treated with prontosil and of all the similar infections in recent years is shown in Table IV. There has clearly been no great reduction in the incidence of septicæmia (and it should be borne in mind that in the prontosil-treated series there were 3 cases admitted with an unusually heavy blood-stream infection). The true incidence of "general peritonitis" is more difficult to assess for the reasons explained above, but even if we make some allowance for mistaken diagnosis in a few of

the cases, it seems unlikely that there has been such a change as to account for the very large reduction in the death-rate.

A careful review of our prontosil-treated cases seems, therefore, to justify the view that their infections as a whole were of approximately the usual severity. There remains the second question: has the "virulence" of the streptococcus for man diminished during the present year? This, of course, is very difficult to answer with assurance, but there are undoubtedly certain data which suggest that a change of this kind may be taking place—just as it has already taken place in scarlet fever.

Let us first consider our own experience at Queen Charlotte's Hospital. It was explained in our first

TABLE IV

Incidence of Peritonitis and of Septicæmia among cases infected by Hæmolytic Streptococci. (Queen Charlotte's Hospital)

	Death-rate of all the cases included.	Cases.	Peritonitis (generalised or generalising).	Septicæmia (hæmolytic streptococci in blood culture).		
				Total.	(a) Associated (b) not associated with peritonitis.	
					(a)	(b)
1934	16.6%	120	18 = 15%	26 = 21.6%	11 = 9.2%	15 = 12.5%
1935	24.4%	90	16 = 17.7%	18 = 20%	5 = 5.5%	13 = 14.4%
1936 Jan.- Aug.*	4.7%	64	† 8 = 12.5% ? 11 = 17.2%	12 = 18.7%	1 cer- tainly 3 almost cer- tainly } = 6.25%	8 = 12.5%

* Only cases treated by prontosil.

† See subsection (b) under Commentary upon the 64 cases.

paper on this subject † that at the beginning of the year we did not treat every case of infection by hæmolytic streptococci with prontosil, but only the more severe cases. Actually, 20 cases were excluded on this account or for some other reason—e.g., suspicion of nephritis, &c. And to these 20 cases we may add one mild case recently treated by *p*-aminobenzenesulphonamide instead of prontosil. If these 21 cases (all non-fatal infections, localised in the pelvis) are added to the 64 analysed in Table IV., the incidence of septicæmia changes from 18.7 to 14.1 per cent., and that of general peritonitis from 12.5 to 9.4, or from 17.2 to 13 per cent., according to whether we consider that there were 8 or 11 cases in this category.

A more striking reduction in the number of severe cases is shown by a study of the records of puerperal fever cases admitted to the North Western Fever Hospital, London. We are greatly indebted to the medical officer of health, London County Council, and to Mr. James Wyatt for permission to quote the figures for 1935 and the first half of 1936 before their official publication. These records show:

(a) That the fatality-rate for all cases admitted with hæmolytic streptococcal infections, which in 1933 was actually a little higher (22 per cent.) than ours at Queen Charlotte's Hospital, has progressively declined—to 11 per cent. in 1934, to 7.8 per cent. in 1935, and to 5.26 per cent. during the first half of 1936. (No prontosil was used during these periods.)

(b) That the incidence of cases of "general peritonitis" during these years 1934-35 and 1936 has also been

‡ Colebrook, L., Kenny, M., and the members of the Honorary Staff of Queen Charlotte's Hospital, THE LANCET, 1936, i., 1279.

declining—e.g., it was 7·4 per cent. in 1934, 4·7 per cent. in 1935, and 2·6 per cent. in 1936.

(c) That the incidence of "septicæmia without peritonitis," although it has not actually declined, has been always lower than that at Queen Charlotte's Hospital during these three years—e.g., in 1934 it was only 5 per cent., in 1935 it was 6·4 per cent., and in the first half of 1936 it was 8 per cent.

It seems evident, therefore, that, whatever the reason may be, the average severity of the cases admitted to the London County Council hospital is decreasing, and the figures seem also to indicate that it is considerably less than that of the cases admitted to Queen Charlotte's Hospital.

Apart from this question of the difference in severity of the two groups of cases, the falling death-rate in the London County Council experience might appear to throw doubt on our conclusion that prontosil has been largely responsible for the striking improvement in the clinical results at Queen Charlotte's Hospital. It should be pointed out, however, that, whereas at the London County Council hospital the fall in death-rate has been progressive over a number of years without prontosil treatment, at Queen Charlotte's Hospital it was as high as 24 per cent. even in 1935, and has fallen to 4·7 per cent. only since the beginning of 1936 when prontosil was first used. While, therefore, we are prepared to admit that a natural decline in the severity of the disease may well have played a part in this change in fatality, § we feel that our present high opinion of the value of prontosil and related compounds is probably justified, particularly in view of the impressive results of animal experiments and the clinical data summarised in Table IV. We find it difficult to resist the conclusion that the treatment has profoundly modified the course of the infection in 20–30 of the more severe cases in our series of 64 patients, and consider, therefore, that its further trial in hæmolytic streptococcal infections is highly desirable.

Problems for the Future

It should be clearly realised that we are only at the beginning of the scientific and clinical investigation of these new chemotherapeutic agents. Many important questions are at present quite unsettled. We do not know with any certainty whether it is necessary to use such large doses as have been employed in our cases, although clinical experience, unguided by blood tests, has seemed to point that way. We do not know what is the relative value of oral and parenteral administration, nor whether oral administration alone might have been adequate. If parenteral administration appears to be necessary, could we eliminate the unpleasantness of the frequent large intramuscular injections, by one or at most two injections of a stronger suspension of prontosil—thus constituting a depôt from which absorption might proceed slowly for days or weeks? In the mouse this plan has worked very successfully, but we have not yet tried it in human beings. The suspension appears to be remarkably non-irritant in mice.

Experiment.—Ten mice were injected with about 23,000 virulent streptococci (100 or more M.L.D. of the

§ Further evidence of a reduced average severity of puerperal fever infections by the hæmolytic streptococcus has recently come to us from Sheffield by the kindness of Dr. C. G. Paine, bacteriologist to the Jessop Hospital. Dr. Paine has analysed the cases in the same way as we have done for the Queen Charlotte's Hospital and the L.C.C. cases. His records show that the death-rate for cases infected by hæmolytic streptococci—which in 1935 was approximately the same as ours at Queen Charlotte's Hospital—has been considerably lower in the first half of 1936: and that this reduction has been associated with the admission of a smaller proportion of cases of general peritonitis and of septicæmia without peritonitis.

Richards strain) into the peritoneum. Half of them received no subsequent treatment and all were dead within 30 hours. The other 5 were given 7·5 mg. of prontosil soluble subcutaneously three hours after the infecting dose of streptococci, and five hours later 50 mg. of prontosil suspended in gum arabic also subcutaneously. Four of these five animals have remained quite well for four weeks and their urine has had an orange colour during all that time. The fifth died of a hæmolytic streptococcus infection on the 24th day.

How far the chemotherapeutic effect of these drugs is limited to infections by the hæmolytic group of streptococci is also not known with any certainty. We have used them in only a few cases of infection by other streptococcal species and always, so far, without success. Pending further investigation in the laboratory, there would seem to be no scientific basis for their employment in non-hæmolytic streptococcal infections.

Another problem of fundamental importance, which we are now investigating, is that of the relative efficacies of prontosil and *p*-aminobenzenesulphonamide. Finally, we have yet to determine how far these new remedies will lend themselves to the prophylactic control of infections by hæmolytic streptococci. We have always kept before us a glimmer of hope that some day we might have an effective chemotherapeutic or immunising agent which would render any woman temporarily immune from danger of infection if her confinement had been conducted in circumstances which made such infection likely. The work of the last few years has taught us that very many women are delivered in such circumstances. There are those delivered in private houses where there is, or has recently been, somebody with an "open" lesion infected by hæmolytic streptococci—e.g., tonsillitis, scarlet fever, otitis media (or associated long-standing ear discharges), whitlow, an infected injury, impetigo, erysipelas. There are those confined at home or in institutions by a healthy "carrier" or by somebody who has recently suffered from a respiratory tract infection, perhaps only a "cold." And there are those exposed to the manifold risks of infection in institutions where there is, or has been, puerperal sepsis. Experiments with mice, which will be reported later, and also observations of the increased killing power of the blood following the administration of *p*-aminobenzenesulphonamide, seem to offer good promise of success in the preventive control of these infections, but we think it would be a mistake to urge the widespread clinical application of the prophylactic use of the drugs until they have been more fully explored in the laboratory. While there are already indications that the sulphonamide is likely to be more useful than the original prontosil for the purpose, we have had warnings that its toxicity for man is by no means negligible. The question of this toxicity is being further examined.

QUEEN MARY'S HOSPITAL FOR THE EAST END.—The Duke of Gloucester presided at a Mansion House dinner given for the funds of this hospital on Nov. 17th. A new operating section which will cost £15,000 is needed, and there is a considerable overdraft at the bank which is causing anxiety. During the evening £9000 was raised.

ST. MARY'S, PADDINGTON.—On Nov. 18th the Duchess of York opened the first section of the new nurses' home at this hospital, and unveiled a tablet to the anonymous donor whose personal gifts have amounted to £107,000, and made possible the erection of the home and of a paying patients' wing. The new building makes provision for 21 sisters, 145 nurses, and 40 maids.