

ADDRESSES AND ORIGINAL ARTICLES

**TREATMENT OF
106 CASES OF PUERPERAL FEVER BY
SULPHANILAMIDE**

(STREPTOCIDE)

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(Concluded from p. 1242)

Discussion

A NUMBER of interesting questions arise in connexion with the clinical results reported last week. We shall discuss only a few of them.

IS THE HIGH RECOVERY-RATE DUE TO
CHEMOTHERAPEUSIS ?

How far are we justified in attributing the high recovery-rate in this series of cases (and in the series previously treated by sulphamido-chrysoidine and P.S.) to the chemotherapeutic agents employed? Although this question was discussed at some length in our report dealing with the red dyes (1936b) its importance justifies some further comment.

Our experience of puerperal infections by the hæmolytic streptococcus at Queen Charlotte's during the past seven years—comprising some 700 cases, investigated more fully, we believe, than any previous series of cases—leaves no room for doubt that the clinical results observed since the beginning of 1936 have been very much better than those obtained before that time. The improvement has shown itself in the greatly diminished death-rate, in the more rapid decline of pyrexia, and in the much lower incidence of parametritis and pelvic cellulitis. The beginning of this period of improved results coincided with the introduction of the new remedies. But there is also some evidence—not conclusive, we think—that the puerperal infections by hæmolytic streptococci have been on the average a little less severe during the same period. As Gibberd (1937) expressed it there has been somewhat less tendency for the infections to assume an "invasive character"—i.e., to extend beyond the genital tract tissues by the blood stream or the general peritoneal cavity. In Gibberd's opinion it was almost impossible, in view of this diminished invasiveness of the streptococcus, to arrive at any decision as to the parts played respectively by that fortuitous change in the disease process and by the new chemotherapeutic remedies. That conclusion seemed to us so important that we re-examined our data from a new angle—determining the mortality-rates among all the cases in which there was unmistakable evidence of "invasiveness." Such evidence was considered to be present in cases having hæmolytic streptococci in the blood stream (positive blood culture)—with or without signs of generalised peritonitis in addition. We do not contend that the segregation of "invasive cases" by this

criterion gives us data entirely satisfactory for statistical analysis, but they seem to us good enough for the detection of big effects—and probably the best that we can obtain from human puerperal fever. The figures and mortality-rates (for which we are indebted to our colleague R. M. Fry) are shown in Table III. It will be seen that among the 22 septicæmic cases treated by the red dyes and sulphamido-chrysoidine, although they were "invasive cases," the death-rate has been very much lower than among the cases in the same category observed during the years 1932–35. This suggests, we think, that the reduction in case-mortality (among these cases at any rate) has been effected more by the treatment employed than by lack of invasiveness of the streptococci.

We would submit, further, that if it cannot be stated *with certainty* at present that the drugs in question have played an important part in the control of the infection in our puerperal cases, we are nevertheless justified in regarding that conclusion as *highly probable* if we take into account not only the clinical data here presented but also certain collateral evidence. The collateral evidence we have in mind is of three kinds:—

(1) The fact—now demonstrated in many laboratories all over the world—that these drugs, sulphamido-chrysoidine, P.S., and sulphamido-chrysoidine, P.S., and sulphamido-chrysoidine, P.S., are certainly able to control experimental infections by hæmolytic streptococci in laboratory animals—viz., mice, rats, and rabbits—not only when given at the same time and by the same route as the infecting streptococci but when given by a

TABLE III

DEATH-RATE FOR ALL BLOOD-POSITIVE CASES (HÆMOLYTIC
STREPTOCOCCI) WITH OR WITHOUT GENERALISED
PERITONITIS

Year.	Cases.	Deaths.	Death-rate (per cent.).
1932	14	13	93
1933	24	18	75
1934	26	15	58
1935	18	12	67
Totals	82	58	Aver. 71
1936 and first* quarter of 1937 (Prontosil and sulphamido-chrysoidine treatment) ..	22	6	27.3

* The cases for 1936 and first quarter of 1937 only were chosen because Gibberd's analysis (1937) had dealt with that period.

different route (including the oral) and after an interval of some hours.

(2) The fact that a curative effect in human beings has been demonstrated beyond all reasonable doubt in two distinct classes of infection by hæmolytic streptococci: (a) in acute meningitis (proven by culture from the cerebrospinal fluid); and (b) in certain extremely chronic infections of subcutaneous tissue and of bone which had previously proved resistant to all therapeutic measures. The evidence with regard to meningitis is that whereas before the introduction of sulphamido-chrysoidine recovery was a rare event—Gray (1935) has computed it at 3 per cent.; he was able to find only 66 recoveries in all the literature since 1901—there have been no less than 26 recoveries reported during the past few months. 27 30 1 18 21 13 23 7 26 19 20 2 3 24 Another case in the care of L. N. Silverthorne of Toronto was seen by one of us (L. C.) but has not yet been reported. The evidence with regard to chronic infections consists only of a few isolated cases, but in these the immediate response to treatment by sulphamido-chrysoidine after years of suppuration was so dramatic that it was almost

impossible to resist the conclusion that the drug was directly responsible for their recovery.

These cases comprise the one already reported by us (Purdie and Fry 1937) of chronic infection of the skin and subcutaneous tissues which had refused to heal for three years following puerperal sepsis but healed completely within six weeks under treatment by sulphanilamide; and another case of very extensive suppuration (not puerperal in origin) involving cellular and bony tissues of the pelvis, with many sinuses which had persisted for several years. One of us (L. C.) was privileged to see this case in New York by the courtesy of Dr. Hugh Auchincloss, but it has not yet been reported. The patient's rapid recovery under treatment by sulphanilamide was very remarkable; and it is perhaps worthy of note that the chronicity of the lesions did not interfere with the curative influence of the drug.

(3) The fact that the blood of patients under treatment by sulphanilamide (and to a smaller extent by the red dyes) acquires a very greatly enhanced power of killing hæmolytic streptococci, even when these are of high mouse virulence. This observation, first reported by one of us (L. C.) with Buttle and O'Meara (1936), has since been confirmed many times by our colleague E. D. Hoare. Although we do not know that this greatly increased capacity to kill the streptococci is a *sine qua non* for the checking of the infective process there can be little doubt that, when present, it must assist the checking.

To sum up, while we admit that a diminished severity of the infective process may have been in part responsible for the satisfactory results observed in these 100 cases, there seems to us very little doubt that the treatment by sulphanilamide has also played an important part. To make an even approximate estimate of the proportionate influence of these two factors would be worthless. There is, in our view, abundant support for the continued use of sulphanilamide or sulphamido-chrysoidine and P.S. in puerperal infections by hæmolytic streptococci, but not for their use in similar infections due to other organisms (apart from the *B. coli* infections of the urinary tract). In order to avoid the prolonged administration of these drugs to unsuitable cases, with risk of toxic effects, we would again urge the importance of a bacteriological examination of a vaginal swab taken as early as possible from every case of puerperal pyrexia.

THE RELATIVE EFFICACY OF SULPHANILAMIDE AND SULPHAMIDO-CHRYSOIDINE AND P.S.

Is sulphanilamide more or less effective than sulphamido-chrysoidine and P.S. in the treatment of human puerperal infections—and, if so, why? The clinical evidence here presented seems to suggest that sulphanilamide (as we have used it) has given slightly less satisfactory results than the treatment by the red dyes (combined oral and intramuscular). Although the proportion of very severe cases has been somewhat smaller in the present series the death-rate has been a little higher, the fall of temperature has often not been quite so dramatic, and a secondary rise has occurred rather more frequently. Parametritis of a mild type also occurred in a few cases, whereas it was not noticed in the prontosil series. It seems to us more probable that these differences indicate a slightly greater curative effect of the red dyes (in combination) than that they were due to fortuitous circumstances. Until we know more about the mode of action of these substances it is scarcely profitable to speculate why this should be so. We do not yet know whether the curative effect is closely related to the concentration of sulphanilamide in the patient's blood and tissues. Nor do we know whether

the portion of the sulphamido-chrysoidine molecule which is not converted into sulphanilamide in the body plays any part in the curative process. The investigation of these problems is proceeding. Meanwhile, from the strictly practical point of view, it would seem desirable, when confronted with a very severe infection, to employ the intensive combined treatment by the red dyes (for dosage see Colebrook, Kenny, et al. 1936b); while for the less severe (and more usual) cases treatment by sulphanilamide by mouth alone would seem to be adequate and less expensive.

OPTIMUM DOSAGE OF SULPHANILAMIDE

We are unable to speak of dosage with great assurance. The prompt remission of pyrexia in most of our cases of average severity leads us to think that the doses we have used have been approximately optimal. Possibly the febrile disturbances after the cessation of treatment would have occurred less frequently if we had employed slightly larger doses. In this connexion it should be borne in mind that absorption of the drug from the alimentary canal—and also its elimination—may vary considerably in different persons. Dr. Fuller has indeed found some evidence of such variation but further data must be obtained before any general statement can be made with regard to it.

For the present, in view of the fact that a large number of patients are liable to develop met- or sulphæmoglobinæmia—and a smaller number other toxic disturbances—we do not feel that the large doses employed by Foulis and Barr (1937) are either necessary or desirable for the treatment of infections of average severity. The problem is more difficult when we are confronted with a very severe infection, involving an obvious threat to the patient's life. Is any advantage gained in such circumstances by the use of large doses? or is there any risk of doing harm by them? The facts at our disposal are as follows:—

(a) In experimental animals with a severe infection, provided that we avoid doses which give rise to toxic symptoms, large doses of sulphanilamide are usually more effective than small doses—e.g., while repeated doses of 2.5 to 5 mg. will save the majority of mice infected with 10–100 M.L.D., larger doses, 10 to 20 mg. repeated, will be necessary to save the majority of mice infected with 1000–10,000 M.L.D.

(b) Large doses—12 to 15 grammes per diem for a few days—have been well tolerated by our most severe cases. They have not shown more tendency to produce met- or sulphæmoglobinæmia than do smaller doses—nor have they provoked more serious toxic effects.

(c) Broadly speaking, the concentration of sulphanilamide in the blood (and urine) has varied with the dose given, suggesting that there has not been difficulty in absorbing the larger doses (12 to 15 grammes per diem).

The blood concentration in 20 patients receiving 3 to 6 g. per diem was usually between 1 in 60,000 and 1 in 20,000: in patients receiving 8 to 12 g. daily concentrations of 1 in 15,000 to 1 in 7000 have been reached. (We have not sufficient data at present to say whether the bactericidal power of the blood for streptococcus increases *pari passu* with the concentration of sulphanilamide—or what concentration gives the optimal bactericidal power.)

To sum up, pending a decision as to whether the curative effect is dependent chiefly upon the concentration of sulphanilamide in the patient's blood and tissues (which may, for the time being, be taken as probable), it would seem advisable to use large doses, 8 to 15 g. daily for a few days in the very

severe infections, and to reduce the quantity if there appears to be any adverse effect; in any case to reduce it as soon as there is definite clinical improvement.

AGAINST WHAT MICRO-ORGANISMS IS SULPHANILAMIDE THERAPY EFFECTIVE?

Is sulphanilamide therapy effective (a) only against some of the serological types of group A hæmolytic streptococci; (b) against hæmolytic streptococci belonging to groups other than A; (c) against the micro-organisms, other than hæmolytic streptococci, which cause puerperal sepsis?

(a) It has sometimes been suggested that failure to control a hæmolytic streptococcus infection might be due to the insusceptibility of the infecting strain to the action of the drug.

Buttle, Gray, and Stephenson (1936) reported the protection of mice infected with five different "Griffith" types and one other strain whose type had not been determined. We understand that they did not encounter any mouse-virulent strain which was uninfluenced by the drug.

Supplementing this evidence we have determined the serological type of strains from a number of our cases—some of them clinically successful and others in which treatment was not successful. Fifteen strains from the conspicuously successful cases fell into 7 different serological types, and fifteen from the unsuccessful cases into 8 different types. Type 11 was represented six times in the successful groups, and five times in the unsuccessful. Type 27 was represented three times in the successful and twice in the unsuccessful group. Type 4 occurred once in each group.

So far as our own results go, therefore, and the evidence from experimental animals, there is at present no support for the idea that only some serological types or strains of group A are susceptible to sulphanilamide.

(b) The evidence with regard to hæmolytic streptococci of groups other than A is very scanty.

A satisfactory curative effect in experimental infections of mice has been obtained both at Queen Charlotte's and in other laboratories, with at least one strain of hæmolytic streptococci belonging to group B (the "Aronson-Neufeld" strain, usually referred to in America as O.90); but it cannot be assumed that a similar degree of curative effect will be obtained with other group B strains.

With one group C strain (S.34) we have obtained only a slight protective effect in mice.

With group G strains, we have been unable, so far, to increase the virulence for mice sufficiently to allow of satisfactory therapeutic trials of the drug. We are proceeding with this, and with the further investigation of the other groups.

Clinical trials of sulphanilamide in puerperal infections by streptococci of groups B, C, and G have been too few to allow of any conclusion, or even a definite impression. The results obtained in mice, although admittedly very incomplete at present, seem to warrant further trial in human infections by the streptococci of these three groups; and, since cases of this kind are not common, it is to be hoped that the outcome of such trials, whether favourable or unfavourable, will be reported.

With regard to infections by hæmolytic streptococci of groups D, E, F, &c., we know of no evidence bearing upon their susceptibility to the action of sulphanilamide. In group D ("hæmolytic enterococcus"), however, it has been our experience, like that of other observers (Bliss and Long 1937, Kenny et al. 1937, Helmholz 1937) that infections of the urinary tract are uninfluenced by the drug.

(c) So far as we are aware, no systematic investigation has yet been made (nor perhaps can be made) into the curative value of sulphanilamide (or

sulphamido-chrysoidine and P.S.) in experimental infections of laboratory animals by the strictly anaerobic streptococci, *Bacillus coli*, *Streptococcus viridans*, or the non-hæmolytic, aerobic streptococci. Our clinical experience of genital tract infections by these organisms has not been sufficient to indicate whether or no sulphanilamide or the red dyes have any value in these conditions. Up to the present we have seen no striking curative effect. (The special question of *B. coli* infections in puerperal cystitis and pyelitis is reserved for consideration in a further report.)

Our experience of staphylococcal infections (see above) has been sufficiently favourable to warrant further trial in such cases until a compound is available which shows a better curative value in experimental infections.

Summary

1. 106 cases of puerperal sepsis have been treated by sulphanilamide—usually by mouth alone: 100 of them were infected by hæmolytic streptococci (92 belonging to group A Lancefield); 3 were infected by anaerobic streptococci; 3 by staphylococci.

2. The clinical course of the 100 cases infected by hæmolytic streptococci has been on the whole similar to that of the 64 cases previously treated by sulphamido-chrysoidine and P.S. (1936b), although resolution of the infective process has seemed a little less spectacular. The average stay in hospital has been 19.7 days as compared with 31.3 days in 1935.

3. There were eight deaths among the 100 cases* but only three of them can be regarded as deaths from straightforward sepsis in patients who lived long enough for chemotherapy to have a fair trial. The mortality-rate for all cases (199) infected by hæmolytic streptococci since the beginning of 1936 (when treatment by sulphamido-chrysoidine and P.S. was begun) has been 5.5 per cent. as compared with the average of 22.8 per cent. for the preceding five years. The significance of this change is discussed.

4. "Drug fever" was suspected in several instances.

5. Some degree of cyanosis developed in 58 cases and was usually associated with met- and sulph-hæmoglobinæmia.

6. Other toxic manifestations of the drug observed much less frequently have included prostration, paræsthesia, headache, visual disturbances, and joint pains. No generalised rashes have developed.

We wish to acknowledge the very valuable coöperation of Dr. Alice Woodhead who was in charge of some of the patients while resident medical officer at the Isolation Block; and of Sisters P. M. Burn and A. Parry throughout the investigation.

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* Fifteen more cases have been treated during the preparation of this paper—with no deaths. The death-rate for all cases of infection by hæmolytic streptococci, therefore, since August, 1936, has been 7 per cent.

LOCALISED DISEASE OF THE POPLITEAL ARTERY

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(WITH ILLUSTRATIONS ON PLATE)

DIRECT visualisation of the blood-vessels by the injection of opaque contrast media can now be regarded as an established diagnostic measure. As a means of studying the pathological anatomy of peripheral vascular disease arteriography is of great importance, revealing the early stages of disease previously unrecognised. In a previous paper (Boyd 1937) the value of these investigations in the recognition of thrombosis of the popliteal and femoral arteries was stressed and the possibilities of surgical relief were outlined.

Routine arteriography in early arterial disease during the last few years has clarified the indications for this investigation, and correlation of the symptoms with the radiological picture has enabled us to recognise clinically certain syndromes, the pathological bases of which in the past have been merely speculative.

The classic symptom of intermittent claudication is known to be due to insufficient blood-supply to the muscles during exercise. While this fact is well known it is not generally recognised that in the absence of other symptoms and of calcification of the vessels as revealed by X ray examination, the underlying arterial condition is often thrombosis of the popliteal and femoral vessels. It has been shown, moreover, that thrombosis occurs as a complication of an inflammatory or degenerative process in the arterial wall, and that the earliest site of disease is in the segment of the popliteal artery that lies at the level of the condyles of the femur.

The consequences of this lesion of the popliteal artery give rise to two distinct clinical pictures with different pathological bases. Most commonly the disease process gradually narrows the vessel until stasis and clotting occurs, the consecutive clot extending upwards as far as the origin of the anastomotic magna artery. Occasionally, however, thrombosis does not occur, the diseased segment remaining patent and leading to a very different train of events.

This paper is based upon four cases of the latter variety of localised disease of the popliteal artery

investigated in the wards of the surgical professorial unit, St. Bartholomew's Hospital.

CLINICAL RECORDS

Our attention was drawn to the importance of localised disease of the popliteal artery by the following case.

CASE 1.—A man, aged 41, was admitted to hospital in June, 1935, with a history of attacks of phlebitis in both legs extending over some years and a painful ulcer on the dorsum of the right foot in the cleft between the 4th and 5th toes, which had remained unhealed for one year. Exercise increased the pain, which spread into the calf muscles after walking for 4 minutes.

On examination the limb was normal in appearance except for the distal part of the foot and toes, which were slightly cyanosed, and the presence of an ulcer $\frac{1}{2}$ in. in diameter on the dorsum of the foot between the 4th and 5th toes. There were well-marked postural colour changes. Femoral, popliteal, and dorsalis pedis pulses were present, but the posterior tibial pulse could not be felt. The Wassermann reaction was negative; blood pressure 168/118 mm. Hg. Temperature tests under spinal anaesthesia showed normal response on the left side but no rise in the affected foot.

Arteriography of the popliteal region showed localised narrowing and irregularity of the lumen over $1\frac{1}{2}$ in. of the popliteal artery at the level of the condyles of the femur (Fig. I on Plate).

Operation.—Thrombo-angiitis obliterans was diagnosed and was treated by lumbar ganglionectomy. The post-operative course was uneventful and the limb became warmer and the toes a better colour than before operation.

Progress.—A few days after leaving hospital the patient experienced great pain in his 5th toe which became pale and cold, and a day or two later black. He was readmitted with gangrene of the 5th toe and the limb was amputated through the thigh.

Pathology.—The external appearance of the popliteal artery was normal, the narrowing seen in the arteriogram being probably partly due to spasm. The lumen was filled with soft recent clot of a few days' duration. The diseased segment was narrowed by internal thickening, and by adherent mural clots of longer duration which were partly organised. Histologically the vessel wall showed the fatty changes characteristic of atheroma.

Reviewing the case afterwards it occurred to us that the sudden vascular accident that precipitated gangrene in the toe might have been embolism by a detached fragment of mural clot or atheromatous material from the diseased segment of the artery. The vessels of the foot showed the typical changes of thrombo-angiitis obliterans and were much narrowed, so that the impaction of a small clot might easily have finally cut off the blood-supply of a toe that was already in a precarious condition. It was also possible that spasm of the diseased segment might impair the blood-supply of the toe to such an extent that gangrene would occur.

Physical signs depend upon the extent of the disease in the other vessels. Pulsation was present in femoral and popliteal arteries in all cases, but either the dorsalis pedis or posterior tibial, and in one case both, were impalpable. Arteriography is the only means of accurate diagnosis. The findings are constant. There is localised narrowing and irregularity of the lumen in the segment of the popliteal artery that lies at the level of the condyles of the femur. This segment is the least supported part of the vessel and is subject to constant strain with movements of the knee, which no doubt accounts for the localisation of disease to this segment.

CASE 2.—A man, aged 55, was admitted in August, 1933.

History.—August, 1930: began to have pain in left foot, 2nd toe became painful, ulcerated, healed slowly. June, 1931: severe pain in 4th toe, ulcerated, healed

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