

## CHEMOTHERAPY OF STREPTOCOCCAL INFECTIONS WITH *p*-BENZYLAMINO-BENZENE-SULPHONAMIDE

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DURING the past winter 150 cases of scarlet fever, 47 cases of erysipelas, and 18 cases with other types of streptococcal infection were treated with Proseptasine (*p*-benzylamino-benzene-sulphonamide), an ample supply of which was placed at our disposal by the makers, Messrs. May and Baker.

### SCARLET FEVER

In the scarlet fever test group no antitoxic serum was given. As controls, 150 alternate cases were treated with serum when considered necessary (56 cases) and the remainder expectantly. The dose given was 0.75 to 6 g. per day according to age by mouth in tablet form, divided into four-hourly doses. The full dose was given for two days, and half the quantity for another two to four days according to the course of the illness. The maximum quantity given in all to any one patient was 22.5 g. The results are shown in the Table.

It will be observed that in the test series, 53 (35 per cent.) developed one or more of the complications tabulated, whilst 84 (56 per cent.) of the control cases showed some complications. This difference is statistically significant. The sum of the individual complications is almost identical, but the complications in the test series occurred in fewer patients. The mean duration of the primary fever from onset to termination was twelve hours longer in the test series. Since antitoxin was administered to a third of the control series, this might be expected, for antitoxic serum undoubtedly reduces pyrexia. Our

results would suggest, therefore, that the drug has some effect on the invasive side of this streptococcal infection and the results might be better if the drug could be given earlier. If spaces such as nasal sinuses, the middle ear, or bone are infected, the organism is probably less accessible to the drug. Possibly a combination of drug and serum would be more effective, and this is now being investigated.

### ERYSIPELAS

The results here were very striking. A series of 47 cases of erysipelas of varying severity, from mild to very severe, was treated with similar doses of the drug. The youngest patient was four months; three were 70, 81, and 87 respectively. In 31 cases the temperature was normal within twenty-four hours, in 12 within forty-eight hours, in 3 within seventy-two hours, and in 1 only did pyrexia continue until the fifth day. The spread of the disease was arrested within twenty-four hours in every case. Two developed relapses ten days after the primary attack, which responded at once to further doses of the drug. All the cases made satisfactory recoveries, even the aged ones.

### OTHER STREPTOCOCCAL INFECTIONS

In 15 severe cases of *tonsillitis*, notified as diphtheria, there was recovery within forty-eight hours of treatment with the drug.

In one case of *puerperal sepsis*, showing signs of early involvement of the broad ligament, which gave a pure growth of hæmolytic streptococcus from the cervix, the temperature settled within eighteen hours and the patient made an uninterrupted convalescence with rapid resolution of the infiltrated broad ligament.

One very ill patient with *cellulitis* involving the fauces arising from an impacted wisdom tooth lost his fever within seventy-two hours and recovered.

In one case of influenzal pneumonia with a turbid *pleural effusion*, from which a pure growth of hæmolytic streptococci was cultured, the effusion dried up after two aspirations following the administration of the drug and the patient recovered. In our former experience, such effusions invariably became purulent and necessitated operation for cure.

TEST SERIES OF SCARLET FEVER CASES TREATED WITH PROSEPTASINE

Cases showing complications

CONTROL SERIES (56 CASES RECEIVED ANTITOXIC SERUM)

Cases showing complications

| AGES .. .. .                                     | TEST SERIES OF SCARLET FEVER CASES TREATED WITH PROSEPTASINE |      |       |       |         |           | CONTROL SERIES (56 CASES RECEIVED ANTITOXIC SERUM) |      |       |       |         |           |
|--|--|------|-------|-------|---------|-----------|--|------|-------|-------|---------|-----------|
|  | 0-5  | 5-10 | 10-15 | 15-20 | Over 20 | All ages. | 0-5  | 5-10 | 10-15 | 15-20 | Over 20 | All ages. |
| Cases .. .. .                                    | 27   | 72   | 24    | 9     | 18      | 150       | 28   | 67   | 33    | 9     | 13      | 150       |
| Cases with complications .. .. .                 | 12   | 25   | 8     | 2     | 6       | 53        | 14   | 44   | 16    | 4     | 6       | 84        |
| Mean day of disease on admission                 | 2.1  | 2.4  | 2.2   | 1.6   | 2.3     | 2.3       | 1.7  | 2.9  | 3.3   | 1.4   | 2.5     | 2.6       |
| Mean duration of pyrexia after admission .. .. . | 3.2  | 3.6  | 2.8   | 3.1   | 3.2     | 3.3       | 3.0  | 2.2  | 2.2   | 3.4   | 3.3     | 2.5       |
| Adenitis .. .. .                                 | 9  | 17   | 2     | 1     | —       | 29        | 10   | 8    | 6     | 2     | 1       | 27        |
| Otitis .. .. .                                   | 5  | 5    | —     | —     | 1       | 11        | 2  | 4    | 4     | —     | —       | 10        |
| Secondary tonsillitis .. .. .                    | 2  | 2    | 1     | 1     | 3       | 9         | 1  | —    | 2     | 2     | 3       | 8         |
| Endocarditis .. .. .                             | 1  | 2    | —     | —     | —       | 3         | 3  | 4    | —     | 1     | 1       | 9         |
| Rheumatism .. .. .                               | —  | —    | 1     | —     | 2       | 3         | —  | 2    | 4     | 2     | 2       | 10        |
| Albuminuria .. .. .                              | 1  | 8    | 3     | —     | —       | 12        | 5  | 4    | 5     | 2     | 3       | 19        |
| Nephritis * .. .. .                              | —  | 3    | 2     | 1     | —       | 6         | —  | 4    | 1     | —     | —       | 5         |
| Mastoiditis .. .. .                              | —  | 1    | —     | —     | —       | 1         | —  | 1    | —     | —     | —       | 1         |
| Died .. .. .                                     | —  | —    | —     | —     | —       | —         | 1†   | 1‡   | —     | —     | —       | 2         |

\* 1 case of nephritis developed uræmia.

† Abdominal case died after exploration.

‡ Died following nephritis.

## TOXIC EFFECTS

One child with erysipelas developed a macular rash; two very fat women complained of nausea and vomited once; no case showed any cyanosis or clinical signs suggesting sulphæmoglobinæmia. It seems, therefore, that the drug produces few toxic symptoms in the doses we gave and is well borne at all ages.

## SUMMARY

The administration of proseptasine to scarlet fever patients reduced the number of patients having complications from 56 per cent. in the control series to 35 per cent. The drug seems to affect chiefly the invasive stage and results might be better if it could be given earlier.

In erysipelas the spread of the disease was arrested in 24 hours in all of 47 cases. In 31 cases the temperature was normal within 24 hours and in a further 12 within 48 hours. A similar result was seen in other types of streptococcal infection.

## SOME OBSERVATIONS ON A CASE OF PULMONARY OEDEMA

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WE have made two observations on a patient with pulmonary œdema which seem so important that we are recording them now, as it may be long before we have the opportunity of making detailed investigations on another patient with this condition.

The patient, a woman aged 64, has been seen at intervals by one of us (G. G.) since 1925. In that year she developed the symptoms of a mild toxic goitre, and was treated by Sir Thomas Dunhill with rest and iodine. Glycosuria and hyperglycæmia were also present at that time, and were treated with dietetic restrictions and insulin. The symptoms abated, and after two to three years did not cause any further trouble. The diabetic condition improved greatly with insulin, and she was able to take 180 g. of carbohydrate without insulin in 1928. Since then the diabetic condition has become worse and in January, 1936, she needed 18+16 units for a diet containing 130 g. of carbohydrate. At that time she was complaining of lassitude and had a slight degree of pyrexia. No cause for this fever was discovered and the temperature gradually decreased and the symptoms abated. In March she was again feeling unwell with slight pyrexia, and then had an acute attack of *B. coli* pyelitis, which lasted for five weeks. An intravenous pyelogram showed that she had a large cyst of the kidney, which was thought to be congenital. The *B. coli* infection was at first treated with alkalis and later with mandelic acid; the symptoms were quickly relieved with mandelic acid but it was not until August that the urine was rendered sterile.

Her general health had greatly improved, but she was still easily tired, and was only up for about five hours in the day. She had occasionally noticed a little wheezing and tightness of the chest when falling asleep.

On Dec. 1st, 1936, she had a slight coryza, and on Dec. 4th at midnight a feeling of tightness of the chest. This was followed at once by an acute attack of pulmonary œdema. She became ashy grey in colour. P. 140, R. 36, B.P. 180/100. Many râles were heard over both lungs, but there was little expectoration. She was given at intervals injections of Asthmolysin 1 c.cm., atropine sulphate gr. 1/100, Coramine 2 c.cm., and atropine gr. 1/150. The acute attack lasted about two hours and she gradually recovered. She was seen two days later by Sir Maurice Cassidy, who agreed that the attack was one of acute pulmonary œdema. The electrocardiogram was quite

normal. She was kept in bed for 4 weeks but was then allowed to resume her ordinary convalescent life. She still had a slight pyrexia (99–99.5° F.). Blood pressure was 160 to 180/80; hæmoglobin, 82 per cent.; colour-index, 0.7; red cells, 5,600,000; and white cells, 23,000.

On Feb. 6th, 1937, she had another acute attack which started suddenly at midnight. The respiration was 40, pulse 144. Many râles were heard all over the lungs and there was again little expectoration, but she vomited several times. She was given at intervals coramine 2 c.cm., morphine gr. 1/6, atropine gr. 1/100, coramine 2 c.cm., atropine gr. 1/150. The attack passed off in about 2 hours. She was very unwell the next day, vomiting several times and passing a great deal of sugar in the urine, and was seen by G. G. on this account. The following were the results of examinations made of the blood: sugar, 230 mg. per 100 c.cm.; urea, 52 mg. per 100 c.cm.; alkali reserve, 63.5 vols. (Dr. H. E. Archer).

The blood-urea had been estimated several times during the previous illness and was usually between 32 and 36 mg. per 100 c.cm. The rise to 52 mg. suggested that the kidney might have failed because of the acidæmia which was probably present during the acute attack of dyspnoea. As both the attacks started so suddenly the possibility of her being sensitive to some substance was considered. Her rooms were always full of flowers, but no unusual flower had been brought into the rooms in the last few days.

A week later the general condition was better. The blood-urea was 32 mg. per 100 c.cm. and the diabetic condition was under much better control with 22+23 units of insulin. The blood pressure was 170/80. The patient was allowed to get up after tea on this day, and while walking in her room complained of a tight sensation in her chest. She was put to bed at once and given, at 5.50 P.M., morphine gr. 1/4, atropine gr. 1/50, adrenaline 0.5 c.cm. In spite of this treatment the symptoms developed rapidly, and when she was seen by R. B. at 6.5 P.M. was in great distress. She was given, at 6.5, coramine 1.7 c.cm.; at 6.20, morphine gr. 1/6, atropine gr. 1/100; at 7.10, atropine gr. 1/100. The blood pressure was 200/80, a rise of 30 mm. from the morning. The pulse-rate was 140 and feeble, and the respiration 46. Moist râles were heard all over both lungs. During the next one and a half hours she vomited two or three times, bringing up a good deal of fluid. Two hours after the onset she was seen by G. G. The attack was then passing off, although she was still very ill. The respiration was 40 and the pulse 140; moist râles were heard all over the lungs. Ten c.cm. of blood was collected at this stage for analysis. An injection of adrenaline 0.5 c.cm. was then given subcutaneously, after ascertaining that the point of the needle was not in a vein by first withdrawing the plunger of the syringe. Ten minutes later the breathing was quieter and she said she felt better. The blood pressure at this stage was 170/100, pulse-rate 144. Half an hour later another 0.5 c.cm. of adrenaline was injected, using the same precautions, and the condition continued to improve. An hour later she was well enough to be left although the pulse was still 120 and the blood pressure 170/80.

When the estimation of the blood-sugar was made that night it was noticed that the blood flowed up the pipette with difficulty. This condition had been observed before in a case of diabetic coma (Graham, Spooner, and Smith 1926) and a week previously in a case of severe vomiting after influenza (G. G.). The hæmoglobin was estimated at over 130 per cent. on a Sahli apparatus, and the next day by Dr. H. F. Brewer, using a standard Haldane apparatus, at 135 per cent. When the blood had stood for a while the amount of plasma was very small compared with the number of red cells, but a hæmatocrit estimation was not made. The alkali reserve was 49 vols.; blood-urea was 36 mg. per 100 c.cm., and blood-sugar 260 mg. per 100 c.cm. The hæmoglobin had been 82 per cent. in January and two days after the attack was 80 per cent.

## DISCUSSION

The two observations to which we wish to draw attention are the rise in the blood pressure and the increase in the hæmoglobin percentage, as we believe they may throw light on the cause of the condition.