6. The death-rate in bacteræmic cases was at least double that in non-bacteræmic cases due to the same type.

We wish to thank Dr. W. M. Elliott for permission to carry out the investigation; Messrs. C. F. Thackray for supplies of rabbit serum; Mr. T. B. Gallie for technical assistance; and Sisters Grant and McFiggins for their coöperation.

REFERENCES

Anderson, T., Cooper, E. D., Cairns, J. G. and Brown, D. R. (1939) *Lancet*, **2**, 776.
Brown, J. W. and Finland, M. (1939) *Amer. J. med. Sci.* **197**, 369.
Bullowa, J. G. M. and Wilcox, C. (1935) *Arch. intern. Med.* **55**, 558.
Cruickshank, R. (1933) *Lancet*, **1**, 563, 621 and 680.
Fleming, A. (1938) *Ibid*, **2**, 74.
Gaisford, W. F. (1939) *Proc. R. Soc. Med.* **32**, 1070.
Horsfall, F. L., Jr., Goodner, K., MacLeod, C. M. and Harris, A. H., Jr. (1937) *J. Amer. med. Ass.* **108**, 1483.

SULPHATHIAZOLE IN TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA

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MOST of the more important information now available concerning 2 (para-aminobenzenesulphonamido) thiazole, generally known as sulphathiazole and also in this country as M. & B. 760 and Thiazamide, has been summarised in leading articles in the *Lancet* (May 11, 1940) and the *British Medical Journal* (June 22, 1940). The majority of the clinical reports have described studies of the usefulness of the drug in the treatment of staphylococcal infections and the only published clinical trials in pneumococcal infections are those of Gsell (1940), and of Flippin et al. (1940) who treated 100 cases of pneumococcal pneumonia of different types with a 12% mortality.

It was decided to employ sulphathiazole in a series of pneumococcal lobar pneumonias at Dudley Road Hospital and to use alternate patients treated with sulphapyridine as controls. Children were not included since they tolerate sulphapyridine so well that it seemed unnecessary.

The first case to receive the drug was admitted on April 3, but the admissions of cases of lobar pneumonia to hospital this spring and summer have been the fewest on record, and this has been the experience we understand at other large hospitals in Great Britain. Any hope of our being able to produce an adequate number to be of statistical value was soon found to be out of the question, and this report refers to only nineteen cases.

We adopted a similar method of investigation to that employed in our original study of sulphapyridine (Evans and Gaisford 1938)—namely, strict clinical criteria of diagnosis, X-ray examination, sputum typing and daily blood-counts. In addition, the assistance of a whole-time technician allowed us to make full biochemical investigations, frequent blood-level determinations (on an average 10 in each patient during the 48 hours of treatment and the subsequent 24 hours), daily red-cell counts, hæmoglobin estimations, as well as differential blood-counts being made. Every possible specimen of urine was examined for sulphathiazole content, albumin, casts and cells, and on an average 12 specimens of urine were examined chemically and microscopically for each patient. Fractional test-meals were also carried out in a number of the control cases receiving sulphapyridine to see if the vomiting was in any way related to the amount of hydrochloric acid present in the stomach, or whether this level was affected by the drug, but the results obtained were inconclusive.

The dosage employed was similar to that with sulphapyridine—namely, 2 g. (4 tablets) on admission and repeated 4-hourly for three doses and then 1 g. (2 tablets) 4-hourly for 24 to 36 hours, as necessary, ending the course with 1 tablet three times or twice during the final 24 hours after the temperature had fallen to normal. One patient was given an initial intravenous dose of a solution of the sodium salt containing 1 g. of sulphathiazole in 20 c.cm. of normal saline, followed by a similar one after 4 hours, treatment being then continued by mouth. The average total dosage was 14·5 g. Intramuscular injection was not used in any case.

RESULTS

It was only because we found no evidence that sulphathiazole was superior or equal to sulphapyridine in the treatment of pneumococcal lobar pneumonia that it was thought worth while placing on record this preliminary note, for there were but ten cases of true lobar pneumonia treated with sulphathiazole during the investigation. Two other cases were also investigated, but radiography revealed no evidence of consolidation. There were no deaths and only one patient had any complication—a man of 55 with a type II pneumonia who developed an empyema which was subsequently drained and a good recovery resulted. During the same period there were no deaths among the nine sulphapyridine cases and only one with a complication—a sterile serous effusion. Pneumococci were isolated from five of the cases receiving sulphathiazole, three being type II, one type III and one type IV.

TYPICAL RESULTS OF BLOOD EXAMINATIONS ON A SINGLE CASE TREATED WITH SULPHATHIAZOLE

Day of disease ..	2nd	3rd	4th	5th
Red cells per c.mm. in millions	5,080	5,380	5,460	4,780
Hæmoglobin % (Sahli) ..	102	103	106	100
Colour-index	1·0	0·97	1·0	1·0
White cells per c.mm. ..	35,200	31,800	17,100	11,100
Polymorphonuclears % ..	84	88	85	68
Lymphocytes (small) % ..	8	5	10	19
,, (large) % ..	0	3	—	1
Hyalines %	0	4	2	8
Eosinophils %	0	0	0	3
Basophils	0	0	0	0
Myelocytes %	1	0	1	0
Metamyelocytes % ..	7	0	2	1

Fall in temperature.—The rapid fall in temperature seen with sulphapyridine was not so striking in the cases treated with sulphathiazole, and in nearly all of these there was a 12-hour lag, so that the average time between the beginning of treatment and the fall in temperature was 36–48 hours. Characteristic temperature charts of cases treated with the two drugs are shown in figs. 1 and 2.

Nausea and vomiting.—Only one patient who received sulphathiazole vomited and none complained of nausea. It was by no means certain in the patient who did vomit that this was due to the drug since he had done so repeatedly before admission. One nurse, not included in this series, who had severe nausea and vomiting when treated with sulphapyridine last year showed no signs of intolerance to a course of sulphathiazole in May, 1940.

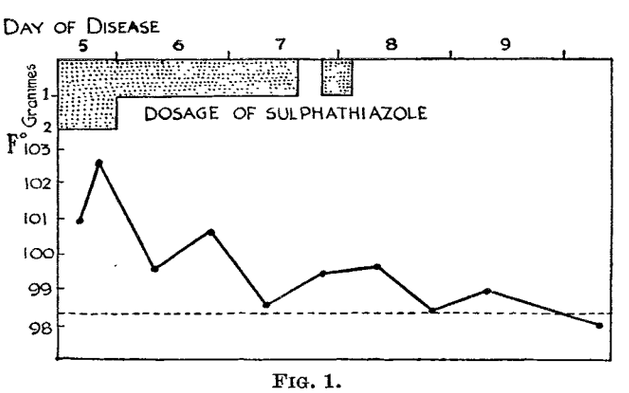

FIG. 1.

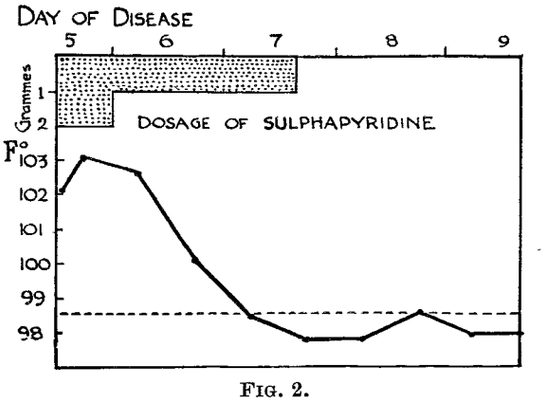

FIG. 2.

Blood-counts.—In none of the cases treated with sulphathiazole was there any significant alteration in the blood-count as the result of the treatment. The number of red cells and the hæmoglobin percentage remained almost constant in each case and no differential count showed any tendency to granulopenia, as may be seen in the table, which is representative of our findings.

Blood levels.—Fig. 3 shows graphically the maximum and minimum blood concentrations of free and total sulphathiazole obtained in two cases (A and B) with details of the oral administration of the drug. The curves for the remaining patients lay between these two with one exception where there was a delay in the rise of the blood level for 18 hours, but this patient eventually attained a concentration of 14·2 mg. per 100 c.cm. of total and 13·5 mg. per 100 c.cm. of free sulphathiazole and maintained high concentrations for some time after the dosage had been reduced. This retention of the drug was probably due to renal dysfunction, albumin and casts being present in all specimens of urine examined both before and after treatment. There is insufficient evidence to enable us to suggest an optimal blood concentration, since excellent clinical results have been obtained when the blood contained as little as 3 mg. per 100 c.cm. of the unchanged drug and poor results have been noted with much higher levels.

Action on urinary system.—Experimental work in animals has suggested that renal damage might occur after sulphathiazole, and cases of hæmaturia, anuria and concretions in the tubules have been reported clinically in America and this country. These findings are not

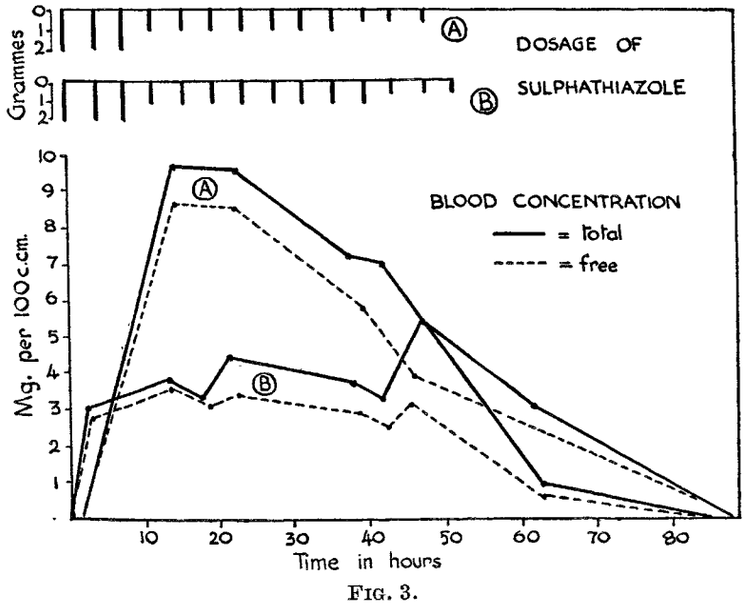

FIG. 3.

surprising in view of the fact that the acetyl derivative of sulphathiazole is even less soluble than that of sulphapyridine; but in our cases, apart from transient albuminuria seen before treatment was begun and representing a not unusual febrile phenomenon, there was no evidence of any renal damage and no red cells or casts were seen.

CONCLUSIONS

This preliminary trial of sulphathiazole in ten cases of pneumococcal lobar pneumonia has shown that the drug is of value and acts similarly to sulphapyridine, though producing a less prompt fall in temperature. With this temperature lag there is a correspondingly longer period of acute illness. This renders sulphapyridine the drug of choice in severe cases.

The chief point in favour of sulphathiazole is that it does not cause vomiting.

It is possible that a combination of sulphapyridine and sulphathiazole may come to be a valuable routine in the treatment of pneumonia, the first large doses given being sulphapyridine (e.g., the first 8 tablets) and the following ones sulphathiazole. In this way vomiting can be obviated entirely. An alternative is the use of a mixture of the two drugs from the outset—e.g., 2 tablets of sulphapyridine given with 2 tablets of sulphathiazole four-hourly for the first three doses, and then 1 tablet of each. The first method has already been used since these investigations were undertaken with very satisfactory results.

We are indebted to Dr. T. M. Anderson, medical superintendent of the hospital, for permission to publish these cases; to Messrs. May and Baker for supplies of sulphathiazole; and to Mr. W. A. Freeman who carried out the biochemical investigations.

REFERENCES

Evans, G. M. and Gaisford, W. F. (1938) *Lancet*, **2**, 14.
Flippin, H. F., Schwartz, L. and Rose, S. B. (1940) *J. Amer. med. Ass.* July 20th, p. 248.
Gsell, O. (1940) *Schweiz. med. Wschr.* **70**, 342.

TOXIC MANIFESTATIONS OF CALCIUM THERAPY IN HEART FAILURE

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WITHIN recent years intravenous administration of calcium gluconate has been employed in the treatment of cardiac failure. Although at times beneficial this procedure is not entirely without risk.

In animals large intravenous injections of calcium salts lead to a very rapid reduction of blood-pressure, inhibition of the cardiac and respiratory movements and arrest of urinary secretion. Smaller injections produce changes in the tonus of skeletal muscles. In man an intravenous injection of 4 c.cm. of a 10% solution of calcium chloride has produced dizziness, collapse, respiratory embarrassment and generalised muscle spasm; recovery ensued in five minutes (Lloyd 1928). The rate of injection was not reported but in view of later findings it is almost certain that the solution was given too rapidly. Liebermann (1933) states that while very large amounts of calcium can be given if the rate of administration is sufficiently slow even small doses may prove fatal when given quickly. McGuigan and Higgins (1938) stress the importance of this and suggest that the administration of 10 c.cm. of a 10% solution of calcium gluconate should take at least two minutes. When this rate is not exceeded there is little discomfort. The first sensation to be experienced by the patient is a feeling of heat in the mouth, sometimes associated with a metallic taste. A sense of heat is complained of at the site of injection; this rapidly spreads over the surface of the body. In some cases there has been slight flushing of the cheeks and in others a slight and transient increase in the respiratory rate. In all over 100 patients have been given injections of 10% calcium gluconate. There were no febrile reactions and only 2 developed any serious symptoms and in both this was due to digitalisation.

CALCIUM AND DIGITALIS

It is obvious that if calcium is to be used clinically careful consideration must be given to the possibility of toxic effects arising from its combination with digitalis. The work done on the pharmacology of calcium has demonstrated a close similarity between its action and that of digitalis.

Loewi (1918) stressed the close relationship between the actions of the two drugs on the heart and even suggested that the main effect of the digitalis glucosides was obtained by sensitising the heart muscle to calcium. Cheinisse (1922) was of the opinion that calcium enhanced the action of digitalis in patients with cardiac œdema. Our own results with œdematous patients appear to support this hypothesis. According to Billigheimer (1924) the actions of calcium and digitalis are similar except that those of the former are more transient. He found that no ill effects resulted from using the two in combination, and indeed he recommended this in order to obtain the combined action. Gold and Edwards (1927) were able to reduce the minimum lethal dose of ouabain in dogs by producing hypercalcæmia. Mandelstamm (1926) found that the effect of strophanthin in rabbits was enhanced by increasing the calcium content of the cardiac muscle but that the glucoside did not sensitise the heart to