

An abstract of the findings in 36 cases in which fairly complete observations were made is given in the accompanying Table. The sulphanilamide content of the C.S.F. towards the end of the first 24 hours, by which time an effective concentration has usually

TABLE SHOWING CONCENTRATION OF SULPHANILAMIDE IN CEREBRO-SPINAL FLUID REACHED IN FIRST 24 HOURS, AND MAXIMUM VALUE DURING THE FIRST FEW DAYS OF TREATMENT

| Case No. | Age. | C.S.F. sulphanilamide. | | | | | Sulphanilamide dosage (g. per day) and remarks.* |
|----------|-----------|------------------------|-------------------------|---------------------|-------------------|------------------------|--|
| | | Mg. per 100 c.cm. | Hours after first dose. | Total to date (g.). | Mg. per 100 c.cm. | Days after first dose. | |
| 1 | 5 m. | 5.2 | 18 | 2.5 | 9.3 | 1 1/2 | 3.0. Died. |
| 2 | 9 " | 5.2 | 14 | 2.0 | 7.4 | 7 | 3.0, later 2.0 |
| 3 | 10 " | 3.5 | 17 | 2.5 | 10.7 | 1 1/2 | 3.0 |
| 4 | 1 1/2 yr. | 5.0 | 17 | 2.5 | 13.2 | 1 1/2 | 3.0 |
| 5 | 1 3/4 " | 4.0 | 15 | 2.0 | 6.6 | 1 1/2 | 3.0 |
| 6 | 2 3/4 " | 2.0 | 19 | 2.5 | 4.0 | 1 1/2 | 3.0 |
| 7 | 4 " | 4.9 | 20 | 2.5 | 6.1 | 3 | 3.0 |
| 8 | 4 " | 8.0 | 22 | 3.25 | 10.7 | 2 | 4.5 |
| 9 | 5 " | 1.8 | 17 | 3.75 | 3.8 | 1 1/2 | 4.5. No serum. |
| 10 | 5 " | 10.5 | 17 | 5.0 | 19.5 | 2 1/2 | 6.0 |
| 11 | 5 " | 8.5 | 24 | 3.75 | 9.7 | 3 | 4.5 |
| 12 | 7 " | 3.8 | 24 | 6.0 | 5.0 | 3 1/2 | 6.0 |
| 13 | 8 " | 4.8 | 11 | 3.0 | 7.5 | 1 1/2 | 6.0 |
| 14 | 8 " | 2.2 | 10 | 2.25 | 4.9 | 1 1/2 | 4.5 |
| | | (Blood 5.9) | | | | | |
| 15 | 8 " | 2.6 | 17 | 5.0 | 4.1 | 2 1/2 | 6.0 |
| | | (Blood) | | | | | |
| 16 | 15 " | 0.8 | 17 | 7.0 | 4.9 | 7 | 9.0, later 6.0 and 3.0 |
| 17 | 15 " | 1.2 | 19 | 5.0 | 2.0 | 1 1/2 | 6.0 |
| | | (Blood 4.1) | | | | | |
| 18 | 15 " | 0.6 | 10 | 3.0 | 1.9 | 1 1/2 | 6.0 |
| 19 | 17 " | 2.5 | 18 | 8.0 | 6.5 | 2 1/2 | 9.0 |
| | | (Blood 4.6) | | | | | |
| 20 | 18 " | 0.8 | 19 | 5.0 | 5.1 | 2 1/2 | 6.0 |
| 21 | 21 " | 1.6 | 16 | 7.5 | 5.4 | 1 1/2 | 9.0 |
| 22 | 22 " | 4.1 | 18 | 8.5 | 9.5 | 4 | 9.0, later 6.0 |
| 23 | 23 " | 2.3 | 15 | 6.0 | 11.8 | 2 1/2 | 9.0. No serum. |
| 24 | 26 " | 2.8 | 15 | 6.0 | 3.4 | 1 1/2 | 9.0. Died. |
| 25 | 26 " | 2.0 | 24 | 9.0 | 4.2 | 1 1/2 | 9.0, later 6.0 |
| 26 | 28 " | 3.5 | 18 | 7.5 | 3.0 | 1 1/2 | 9.0, later 6.0 |
| 27 | 28 " | 3.2 | 19 | 8.5 | 5.0 | 1 1/2 | 9.0 |
| 28 | 28 " | 9.2 | 26 | 12.5 | — | — | 10.5. No serum. |
| 29 | 28 " | 2.9 | 18 | 10.0 | 5.1 | 2 3/4 | 12.0, later 6.0. No serum. |
| 30 | 29 " | 2.9 | 23 | 6.0 | — | — | 6.0 |
| 31 | 38 " | 7.2 | 22 | 7.5 | — | — | 9.0 |
| 32 | 39 " | 3.3 | 20 | 4.0 | — | — | 6.0 |
| 33 | 45 " | 2.8 | 13 | 7.0 | 4.3 | 1 1/2 | 9.0. Died. |
| 34 | 47 " | 2.5 | 21 | 6.0 | 4.7 | 1 1/2 | 6.0 |
| 35 | 55 " | 4.9 | 17 | 5.0 | 6.4 | 1 1/2 | 6.0 |
| 36 | 61 " | 2.0 | 17 | 5.0 | 4.0 | 2 1/4 | 6.0 |
| | | (Blood 4.3) | | | | | |

m. = months; yr. = years.

* Serum was also given in all cases, except where noted.

Notes

Case 1. Sulphanilamide was stopped 3 1/2 days after treatment commenced. In spite of high concentration during this early period, meningitis then recurred, masked by enteritis.

Case 16. Patient eventually recovered, but sterility of the C.S.F. was obtained much more slowly than in patients with a higher sulphanilamide level.

Case 18. In spite of the persistently low sulphanilamide level, a normal and rapid recovery took place.

Case 24. Sulphanilamide dosage reduced to 3.0 g. per day after 24 hours. C.S.F. sulphanilamide fell to 1.3 mg. per 100 c.cm. on third day; meningococci reappeared and persisted.

Case 33. Post-mortem examination showed acute purulent bronchitis with oedema of lungs, cirrhosis of liver, and acute glomerulonephritis. Exudate, with meningococci, was still present.

been reached, is recorded in each case, and a further value at a later period is shown in most cases. In many cases the concentration takes several days to

reach a maximum, the sulphanilamide dosage being kept constant. For example, one patient aged 7, who received 1.0 g. every four hours, showed values of 4.1, 4.6, 10.0, and 26.8 mg. per 100 c.cm. on successive days. After the first few hours the sulphanilamide concentrations in the blood and C.S.F. are usually very similar, but during the early hours, while the concentration is rising, the sulphanilamide content of the blood is always very much higher than that of the C.S.F.; one or two examples are shown in the Table.

There is very considerable variation in the speed with which an effective value is reached, and in the eventual level maintained in different patients on equivalent dosage; two particularly striking examples are quoted in Dr. Banks's paper. This variation is presumably due more to differences in the rates of excretion in different subjects than to a variation in the permeability of the meningeal barrier, as the blood-sulphanilamide level shows similar variations. The values obtained are of the same order as those recorded by Crawford and Fleming (1938); they are on the whole lower than those found by Marshall, Emerson, and Cutting (1937) for similar dosage in normals; it is possible that the administration of large amounts of fluid to the patients may have led to increased loss through the kidneys.

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TREATMENT OF PNEUMONIA WITH 2-(p-AMINOBENZENESULPHONAMIDO) PYRIDINE

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PHYSICIANS TO DUDLEY ROAD HOSPITAL, BIRMINGHAM

THE natural corollary to the valuable experimental work by Whitby (1938) on the treatment of pneumococcal infection in mice with M. & B. 693 was its trial in clinical medicine. As soon as it had been ascertained that the drug could be given with safety to healthy human beings and that moderate doses were well tolerated and free from untoward effects, opportunity was afforded us of trying its effect in a series of patients suffering from pneumonia.

From March to the middle of June of this year more than 200 cases of lobar pneumonia were admitted to Dudley Road Hospital, Birmingham. About half of these were treated with M. and B. 693, the others, admitted to the wards of our colleagues, serving as controls and receiving the usual routine non-specific treatment. Admissions to each group occurred for the most part on alternate days. This paper records our findings in 100 of these cases, unselected except that 3 patients dying within twenty-four hours of admission have been excluded, since in these the drug did not have a fair trial. A corresponding selection was made in the control group. The diagnosis in every case was based on a characteristic history and unequivocal signs of lobar consolidation. X ray confirmation was obtained in many, and rusty sputum and the presence of herpes lent additional evidence in several more.

It is difficult to assess impartially the results of treatment in pneumonia other than by consideration of the case-mortality rate. The dramatic improvement which may occur at the crisis tends to focus undue attention on the treatment being employed at that time. Many new methods of treatment when first employed appear to meet with success, but this is not always substantiated by experience. The striking fall in mortality following the use of M. & B. 693 has, however, led us to publish this paper now in the hope that our findings may be confirmed.

METHOD OF ADMINISTRATION AND DOSAGE

M. & B. 693 is made up in 0.5 g. tablets and is given by mouth. The tablets have a faintly bitter taste which is, however, insufficient to cause nausea. They are insoluble but may be crushed and given in suspension or may be swallowed whole.

At the beginning of this investigation, when the clinical effects were unknown, small doses were given. For the first five weeks, when approximately 60 per cent. of the cases were admitted, the average dose was 1 tablet four-hourly for 3 to 4 days, followed by 1 tablet twice daily for a further 2 or 3 days, giving an average total of 12 g. Later on, larger initial doses were given and careful watch was kept on the blood picture, frequent white cell counts being made. When it became apparent that there was no tendency to the development of granulopenia many of these counts were discontinued and it was decided to administer large doses during the 72 hours immediately following admission, the routine being to give 2 g. (i.e., 4 tablets) statim, and 1 g. four hourly thereafter, making an average total intake in the later cases of about 25 g. In a few cases this dosage was exceeded and a maximum of 9 g. has been given in the first 24 hours, with beneficial result. It was found that with this method the temperature and toxic symptoms, especially delirium, subsided more rapidly.

Cyanosis appeared in about a quarter of the intensively treated patients, but disappeared promptly when the drug was withdrawn. Spectroscopic examination of the blood revealed the presence of methæmoglobin in 6 of these cases. There was no sulphæmoglobinæmia.

Except in two cases (41 and 70), no special treatment was given in addition to the M. & B. 693, beyond such sedatives as were necessary to ensure adequate rest. Case 41 was venesected, 450 c.cm. blood being withdrawn with prompt relief. Case 70, who persistently refused all fluids, was given an intravenous dextrose-saline without effect.

INCIDENCE AND MORTALITY

The *age* of patients ranged in both treated and control cases from 8 to 68 years. The *sex*-incidence was 61 per cent. males and 39 per cent. females in the treated series, and 67 per cent. males and 33 per cent. females in the control series. *Typing* of the pneumococcus from the sputum was attempted in all cases in which sputum was available and gave the following results: Type I, 28; Type II, 8; Type III, 3; Group IV, 5. In the remainder it was impossible to identify the type. Such small numbers are insufficient for correlating the mortality figures with the type, but further work on this is being done. *White blood-cell counts* were made in 54 cases. At the beginning the counts were made irregularly throughout the period of treatment, but when the giving of larger doses became a routine practice, counts were made im-

mediately on admission to the ward, again 4 hours later, and thereafter at 12 or 24 hour intervals.

Although the virulence of the pneumococcus may vary from year to year, and from one season to another, yet the case-mortality rate appears to remain fairly constant. Thus Joules (1933), in a survey of 497 cases from Selly Oak Hospital, Birmingham, found a gross rate of 25.6 per cent. (20.6 per cent. excluding cases that died within 36 hours of admission). Davies, Graham-Hodgson, and Whitby (1935) found a rate of 19 per cent. in their series of 859 cases from the Middlesex and Royal Free Hospitals, London.

The case-mortality rates at Dudley Road Hospital have been investigated for the past two years and give the following figures. From January to April, 1937, 195 cases of lobar pneumonia were admitted giving a rate of 25.6 per cent. From January to March this year 136 cases were admitted with a case-mortality rate of 30 per cent., giving an average combined rate of 27.8 per cent., very similar to the figure obtained in the present control series (Table I). Davies, Graham-Hodgson, and Whitby point out that all observers have noted the great increase in mortality with age and that if the selection of cases be limited to those between 10 and 40 years of age, the rate is considerably reduced (to 8.6 per cent. in their series and 12.5 in Joules's). In our series it is reduced from 8 per cent. to 3 per cent., and in the controls from 27 per cent. to 16 per cent. Of the 8 fatal cases 6 died during the first few weeks of this investigation when we were giving small doses (an average of 3 g. daily) and we now consider such small dosage inadequate in severe cases. Furthermore, 4 of these were suffering from pre-existing complications. In the control series a third of the deaths occurred in the first five weeks and two-thirds in the following six weeks, which suggests that there was no diminution in the spontaneous virulence of the epidemic (see below).

The severity of the disease has been depicted in the protocols by the traditional one, two and three plus signs. It is interesting that there were 26 per cent. "three plus" cases, which approximates closely to the generally accepted case-mortality figure. Of these 26 cases 19 survived. The age-incidence is given in Table I:—

TABLE I.—CASE-MORTALITY RATE
TREATED CASES

| Age in years— | 8-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60 and over. | Total. |
|---------------|------|-------|-------|-------|-------|--------------|--------|
| Cases .. | 31 | 20 | 18 | 13 | 13 | 5 | 100 |
| Deaths .. | 1 | 0 | 1 | 2 | 3 | 1 | 8 |

CONTROL CASES

| | | | | | | | |
|-----------|----|----|----|----|---|---|-----|
| Cases .. | 25 | 19 | 24 | 22 | 6 | 4 | 100 |
| Deaths .. | 1 | 5 | 5 | 9 | 4 | 3 | 27 |

DETAILS OF THE EIGHT FATAL CASES

In the first five weeks when small doses of M. & B. 693 (average 3 g. daily) were in use 6 deaths occurred. Of these cases 2 were given the larger doses at present considered to be adequate.

CASE 6 was a man of 45 admitted on the fourth day of illness with consolidation at the left base. Group IV pneumococci were present in the sputum. The initial white blood count (W.B.C.) was 19,400

SAMPLE OF PROTOCOLS (EVERY FIFTH CASE)

| No. | Sex. | Age. | Lesion. | Day of illness. | Degree of illness. | Temp. fell: day of illness. | Pre-existing complications. | Dosage. | | Effects. | Complications of pneumonia. | Result. |
|-----|------|------|-----------|-----------------|--------------------|------------------------------------|-----------------------------|---|-------------|---|---|---------|
| | | | | | | | | Method. | Total (g.). | | | |
| 1 | M. | 28 | RUL | 4th | + | 7th | .. | 0.5 g. q.q.h., 3 days. | 7.5 | Normal course. | .. | Cured. |
| 6 | M. | 45 | LLL | 4th | +++ | Low intermittent T. until death. | .. | 1 g. on admission; 2.5 g. daily, 3 days. | 8.5 | .. | .. | Died. |
| 11 | F. | 51 | RLL | 5th | +++ | 6th | Chronic nephritis. | 0.5 g. q.q.h., 4 days. | 10.5 | .. | .. | Died. |
| 16 | M. | 51 | RLL | 8th | + | 9th | Chronic bronchitis. | 0.5 g. q.q.h., 3 days; 0.5 g. t.d.s., 1 day. | 7.5 | Prompt response in 12 hours. | .. | Cured. |
| 21 | F. | 12 | LLL | 4th | ++ | .. | .. | 1 g. q.q.h., 5 days; 0.5 g. q.q.h., 1 day. | 36 | Cyanosis (methæmoglobinæmia). | Staph. empyema L. base; drained 18th day. | Cured. |
| 26 | M. | 42 | R→LUL | 4th | +++ | 7th | .. | 0.5 g. q.q.h., 4 days; 0.5 g. b.d., 1 day; 1st course. 0.5 g. t.d.s., 3 days; 0.5 g. q.q.h., 5 days; 0.5 g. b.d., 1 day; 2nd course. | 9.5 18 | W.B.C. fell to 4200 during 1st course; rose steadily during 2nd course. | Appeared to be dying with 2nd area of pneumonia until dosage increased on 10th day after admission. | Cured. |
| 31 | F. | 17 | LLL | 7th | +++ | .. | Syn-pneumonic empyema. | 0.5 g. q.q.h. | 36 | .. | .. | Died. |
| 36 | F. | 21 | RLL | 6th | + | 7th | .. | 0.5 g. q.q.h. | 9 | Prompt response in 24 hours. | .. | Cured. |
| 41 | M. | 57 | RUL | 4th | +++ | T. raised irregularly for 16 days. | In extremis on admission. | 0.5 g. q.q.h. | 36 | .. | Spread to LLL. Temporary glycosuria controlled by insulin, 10 units b.d. | Cured. |
| 46 | M. | 33 | LLL | 2nd | + | 3rd | .. | 0.5 g. q.q.h. | 6 | Prompt response in 24 hours | .. | Cured. |
| 51 | F. | 32 | LLL | 4th | + | 8th | .. | 0.5 g. q.q.h. | 15 | Normal course. | .. | Cured. |
| 56 | M. | 44 | LLL | 3rd | ++ | 5th | .. | 0.5 g. q.q.h. | 12 | Normal course. | .. | Cured. |
| 61 | M. | 57 | LLL | 4th | ++ | .. | .. | 0.5 g. q.q.h. | 8 | .. | Advanced myocarditis. | Died. |
| 66 | F. | 14 | LLL→LUL | 2nd | +++ | 4th | .. | 1 g. q.q.h., 3 days; 0.5 g. q.q.h., 1 day; 0.5 g. q.q.h., 3 days. | 20 9 | Dramatic response. | .. | Cured. |
| 71 | M. | 43 | LLL | 2nd | + | 4th | .. | 1 g. q.q.h., 7 days; 0.5 g. q.q.h., 4 days. | 45 | 693 contd. for 10 days as spike of T. on 3rd day. | .. | Cured. |
| 76 | F. | 18 | LLL→apex. | 3rd | ++ | 9th | .. | 1 g. q.q.h., 7 days; 0.5 g. q.q.h., 2 days. | 47.5 | .. | Lung collapse. | Cured. |
| 81 | M. | 24 | L. apex. | 4th | ++ | 5th | .. | 1 g. q.q.h., 3 days; 0.5 g. q.q.h., 2 days. | 26.5 | Response in 24 hours; cyanosis. | .. | Cured. |
| 86 | M. | 25 | RLL | 2nd | ++ | 4th | .. | 2 g. stat., then 0.5 g. q.q.h. | 42 | Prompt response in 36 hours. | Resolution delayed for 2 weeks. | Cured. |
| 91 | F. | 67 | RLL | 3rd | +++ | 4th | .. | 2 g. stat., then 1 g. q.q.h. | 6 | Prompt response in 24 hours. | .. | Cured. |
| 96 | M. | 21 | LLL | 1st | + | 3rd | .. | 2 g. stat., then 1 g. q.q.h. | 20 | Prompt response in 36 hours. | .. | Cured. |

OTHER CASES REFERRED TO IN TEXT

| | | | | | | | | | | | | |
|----|----|----|-----|-----|-----|---------------|--|---|----|---------------------------------|---|--------|
| 19 | M. | 18 | RLL | 2nd | + | 4th | .. | 0.5 g. q.q.h., 4 days; 0.5 g. b.d., 2 days. | 12 | Response in 48 hours. | .. | Cured. |
| 32 | F. | 65 | LLL | 8th | +++ | 9th | .. | 0.5 g. q.q.h. | 12 | .. | Empyema; chest aspirated on 18th day and staph. pus withdrawn. Spont. absorption. | Cured. |
| 35 | M. | 40 | RLL | 4th | +++ | 9th | Bronchitis. | 0.5 g. q.q.h. | 12 | .. | Signs of fluid R. base with rise of T. after 3 weeks. Spont. absorption. | Cured. |
| 37 | M. | 28 | LLL | 1st | ++ | 4th | .. | 0.5 g. q.q.h., 4 days; then b.d. 12 days. | 24 | .. | Empyema (sterile pus). Spont. absorption on 14th day. | Cured. |
| 70 | M. | 55 | LLL | 4th | +++ | T. persisted. | Heavy smoker; alcoholic; chronic bronchitis. | 1 g. q.q.h., 5 days. | 27 | 693 appeared to have no effect. | Delirium. Tympanites. | Died. |

q.q.h. = four hourly.

and three days later was 24,200. Low intermittent temperature continued till the patient died six days after admission. The total dosage of M. & B. 693 was 8.5 g. in four days. Permission for post-mortem examination was not granted.

CASE 11 was a debilitated woman of 51 admitted on the fifth day of illness with pneumonia at the right base. The W.B.C. was 28,200; no sputum was obtained. The urine contained a cloud of albumin and granular casts. The patient's temperature fell from 102° F. to normal in 36 hours without any reduction of toxæmia. The total dosage of M. & B. 693 was 10.5 g. in four days. The patient died five days after admission. Post mortem the R.L.L. showed red hepatisation and fibrinous exudate over the pleura. The L.L.L. showed patchy broncho-pneumonia, greyish in colour. The coronary arteries were atheromatous and the kidneys showed chronic nephritis.

CASE 12 was a man of 44 who was admitted on the eighth day of his illness with consolidation at both bases. He gave a history of chronic bronchitis since being gassed in the war. Group IV pneumococci were found in the sputum. The initial W.B.C. was 8400 and five days later it was 22,000. The patient's temperature fell from 99.8° F. to 97° F. in 36 hours, without any improvement in the general condition; slight jaundice developed on the day after admission. The patient received 9.5 g. of M. & B. 693 in five days. He died six days after admission. No P.-M.

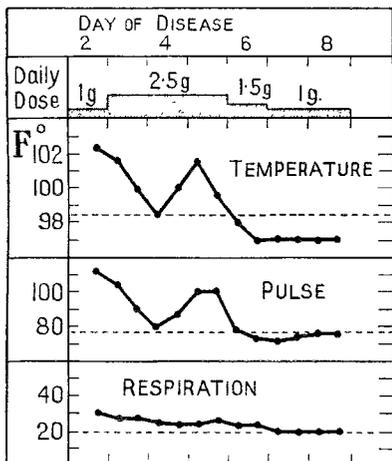


FIG. 1 (Case 19).—Secondary pyrexia. Admitted April 23rd.

temperature remained unsettled and he died on the fourth day in hospital. No P.-M.

CASE 31 was a girl of 17 who was admitted on the eighth day of a L.L.L. pneumonia and who had a syn-pneumonic empyema. Hæmolytic staphylococci and pneumococci were cultured from the pus. The patient received 36 g. of M. & B. 693 which had no apparent effect and death occurred thirteen days after admission. Post mortem a pyopneumothorax and underlying consolidation at the left base were shown.

CASE 61 was an obese man of 57 who was admitted on the fifth day of a L.L.L. pneumonia complicated by myocarditis and chronic bronchitis. He died on the seventh day after 8 g. of M. & B. 693 which had had no effect. No P.-M.

CASE 68 was a woman of 39 admitted on the fourth day of illness with consolidation at both bases. Type II pneumococci were found in the sputum. The initial W.B.C. was 10,500 and there was no increase in the first week after which it rose to 31,000 and 27,000 in the second week. The toxæmia and remittent temperature continued till the patient died on the nineteenth day after admission. She had received a total of 51 g. of M. & B. 693 in nine days. Post mortem, resolving pneumonia at both bases and small scattered staphylococcal abscesses were shown.

CASE 70 was a man of 55 admitted on the fourth day of illness with Type I pneumonia at the L.L.L. and who had had chronic bronchitis for eight years.

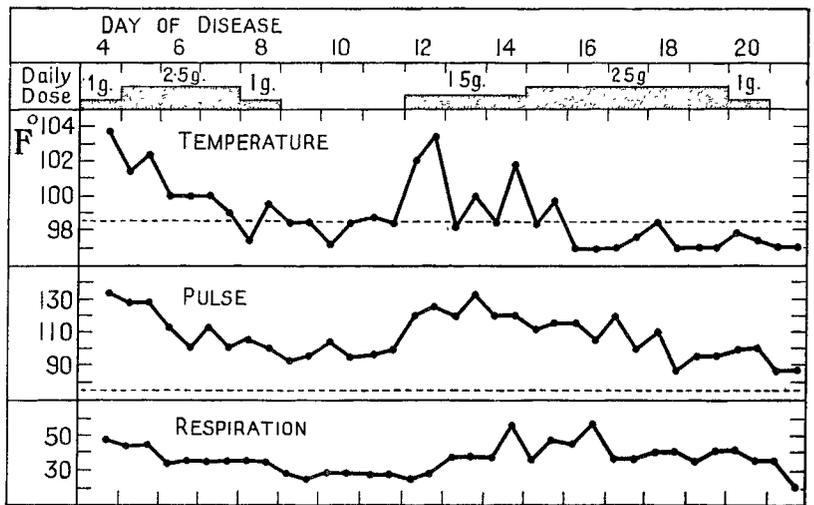


FIG. 2 (Case 26).—Spread from right upper lobe to left upper lobe on twelfth day. Admitted March 29th.

The daily W.B.C. were 8100, 13,800, and 21,000. Blood culture was sterile on the day before the patient died. He continued febrile and delirious until death five days after admission. He received 27 g. of M. & B. 693 in five days, but did not respond to treatment. Post mortem the L.L.L. showed red hepatisation with a central grey area. Early pneumonia was present in the upper half of the R.L.L.

EFFECTS OF THE DRUG

The concentration which M. & B. 693 attains in the blood and its subsequent fate in the body are problems outside our scope, but they are under investigation elsewhere. The effects of the drug on the temperature, the white blood-cells, and the incidence of complications were studied. There was no evidence of renal damage as determined by routine examination of the urine and post-mortem findings.

Temperature.—Table II shows the day of illness on admission to the hospital both of the treated cases and of the controls. It will be seen that they

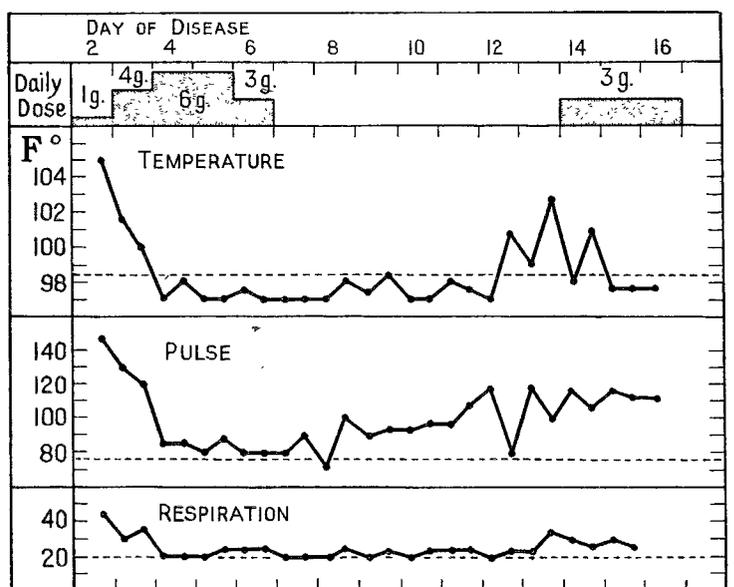


FIG. 3 (Case 66).—Secondary pyrexia associated with spread of disease from left base to left apex. Admitted April 26th.

are fairly comparable. Table III shows the day of disease on which the temperature fell.

Table II and Table III (the latter referring only to those patients who survived) should be read in conjunction with the following figures showing the

number of cases in which the temperature fell within 24 and 48 hours of admission to hospital.

Among the treated cases the temperature in 37 fell within the first 24 hours and in a further 23 in the next 24 hours, making a total of 60 in which the temperature fell within 48 hours. Among the controls, the temperature in 16 fell in the first 24 hours and in 18 in the second, making a total of 34 in which the temperature fell within 48 hours.

Thus, taking into consideration the similarity of the two series in Table II, and making allowance for the crisis to be expected in any lobar pneumonia, the treated cases showed a distinct advantage over the controls. The fall of temperature was in most cases accompanied by diminution of toxæmia and in those patients with delirium the sensorium cleared rapidly. It did not, however, take the place of a normal crisis, being less dramatic and followed by a more gradual clinical improvement. When small doses of M. & B. 693 were being employed, it was found in some cases that the temperature, having become normal for one to three days, rose again. Fig. 1, from Case 19, is an illustration. In a few other cases this secondary pyrexia was accompanied by a spread of the pneumonic process. Thus Case 26, a patient with a right upper lobe pneumonia, developed a left upper lobe involvement on the twelfth day (nine days after admission) (Fig. 2). In Fig. 3 the secondary pyrexia is shown occurring eleven days after admission in Case 32 and associated with a spread from the left base to the left apex.

TABLE II

| Day of illness on admission | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | — |
|-----------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|
| Cases treated | 2 | 17 | 21 | 28 | 10 | 11 | 4 | 7 | 0 | — |
| Controls .. | 6 | 8 | 31 | 25 | 13 | 7 | 5 | 3 | 2 | — |

TABLE III

| Day of illness on which temp. fell.. | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | Later |
|--------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|
| Cases treated | 0 | 1 | 11 | 18 | 14 | 11 | 14 | 4 | 8 | 11 |
| Controls .. | 0 | 1 | 2 | 6 | 11 | 9 | 13 | 6 | 7 | 17 |

Whatever the explanation of these anomalies may be, since resorting to larger doses of M. & B. 693 no further such cases have been encountered.

White blood count.—No case of granulopenia was observed. In 3 cases the counts fell to below 5000, a point of no evil prognostic significance as all three recovered. The highest count obtained was 58,000 and there were two of over 40,000: these also made a normal recovery. There was no evidence that M. & B. 693 had any constant effect on the white cells; high counts before the crisis fell rapidly after it and those which were slightly raised remained nearly stationary. One case in the control series showed a fall from 13,000 on the third to 1100 on the eleventh day with almost complete agranulocytosis and was fatal. In the treated series 4 fatal cases showed low initial figures, rising slowly with successive counts. One patient (Case 26) showed a fall from 12,000 to 4200 in two days and then developed further consolidation during the second week. In this second attack, similarly treated with M. & B. 693, the white blood count remained apparently unaffected, giving counts of 17,900 and 15,900. He ultimately recovered (see also Fig. 2).

Table IV shows some of the serial counts obtained in the later cases when the large doses were being employed; the figures are not significantly different from those observed in the control cases.

TABLE IV

| Case .. | 64 | 88 | 92 | 95 | 97 | 99 |
|---|--------|--------|--------|--------|--------|--------|
| W.B.C. before treatment .. | 33,000 | 11,400 | 18,500 | 13,900 | 12,400 | 28,100 |
| After 4 hours—i.e., 2 g. of M. & B. 693 | 35,800 | 14,900 | 17,500 | 10,300 | 12,400 | 44,300 |
| After 24 hours .. | 18,200 | 11,100 | 15,000 | 26,400 | 6,900 | 30,800 |
| " 48 " .. | 16,350 | 17,300 | 11,550 | 16,000 | 5,800 | 39,100 |
| " 72 " .. | 24,100 | 22,400 | — | — | 4,800 | — |

Complications encountered were the cases of secondary spread previously mentioned, 2 cases in which resolution was delayed for two weeks, 2 cases of pulmonary collapse, and 6 of empyema. Of the empyemas 2 were pneumococcal (both Type I), 3 grew *Staphylococcus aureus*, and 1 was sterile. The incidence of empyema was higher than in the control series in which there was only 1. It was also higher than the average figure of 2–3 per cent. given by Osler. We have no explanation to offer either for the number of empyemas or the high incidence of staphylococcal infection.

Of the empyema cases 2 (Nos. 37 and 32) absorbed spontaneously after a single diagnostic aspiration; one of these was staphylococcal and the other sterile. Of the others 3 were drained and recovery ensued. The sixth (Case 31) had a syn-pneumonic empyema and died. Culture of the pus showed *Staphylococcus aureus* and pneumococcus. A further case (No. 35) showed X ray evidence of fluid at the right base which was absorbed gradually without aspiration.

The protocols of the 100 cases treated are available for inspection.*

SUMMARY

The results of treatment of 100 cases of lobar pneumonia with M. & B. 693 are given. The case-mortality rate was 8 per cent. as compared with 27 per cent. in a control series observed at the same time.

Addendum

RESPIRATORY INFECTIONS IN CHILDREN

M. & B. 693 has also been used in the children's wards in cases of pneumonia, broncho-pneumonia, otitis, and upper respiratory infection.

The cases of broncho-pneumonia treated numbered 40, with 2 deaths. Both of these, girls of 4 and 5 years old respectively, also had pneumococcal peritonitis. One infant, aged 1 year, with broncho-pneumonia, who developed whooping-cough and was too ill to be transferred to the fever hospital, responded in twenty-four hours to 0.25 g. four-hourly. The youngest patient treated was 6 weeks old. The others were all comparatively mild cases; consequently it is too early yet to form an opinion as to the place M. & B. 693 may take in the treatment of pneumococcal infections in infancy. There was no difficulty in getting any of the babies to take the tablets, which were crushed and suspended in milk or glucose-saline, nor was there any vomiting or diarrhoea afterwards. No toxic manifestations were observed.

* The protocols will be issued with the reprints of this article.—ED. L.

The ease of administration and the abolition of the necessity for any injections make the drug particularly adapted to the requirements of pædiatrics.

Table V gives the dosage which may be employed according to age.

TABLE V

| Age .. | 1-3 mth. | 6 mth. to 1 yr. | 2 yr. | 3 yr. | 5 yr. |
|----------------------|--------------|-----------------|--------------|--------------|--------------|
| Dose in tablets (t.) | ½ t. 4-hrly. | ½ t. 4-hrly. | ¾ t. 6-hrly. | 1 t. 6-hrly. | 1 t. 4-hrly. |

In severe cases an initial double dose may be given if necessary—e.g., to a child of 3, the first dose might be 2 tablets, followed by 1 tablet six-hourly.

We are indebted to Dr. F. W. Ellis, medical superintendent of the hospital, for permission to publish these cases; to our colleagues for access to their wards and case records; to Dr. William Whitelaw and his staff for the pathological findings; and to Dr. W. R. Thrower for his help during the course of the investigation and for suggestions as to dosage of the drug. Messrs. May and Baker kindly provided a constant supply of the tablets and gave us every facility for the preparation of this paper

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RUPTURE OF A CÆSAREAN SCAR

TREATED BY SIMPLE DRAINAGE
AND FOLLOWED BY PREGNANCY

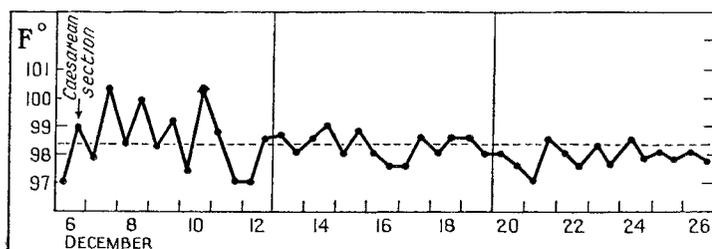
By HUMPHREY ARTHURE, M.B. Lond., F.R.C.S. Eng.,
M.C.O.G.

OBSTETRIC REGISTRAR AT CHARING CROSS HOSPITAL

MANY cases of ruptured Cæsarean scars have been reported, but it is an accident that still merits attention if its incidence is to be materially reduced. The following case is of interest in that it gave an opportunity for studying the condition of the uterus two years after the rupture, which was treated by simple drainage.

CASE-HISTORY

The patient was a woman of 31. Her *first pregnancy* in 1934 was terminated by a Cæsarean section because of disproportion; the pelvis was of



Temperature chart after Cæsarean section in 1934.

the "high assimilation" type, with a contracted outlet. The classical operation was performed using a longitudinal incision in the body of the uterus. The placenta was lying anteriorly, and a live male child weighing 8 lb. 2 oz. was delivered. The uterine incision was sewn up with catgut in three layers: a continuous suture in the decidua to close the uterine cavity, a series of deep mattress sutures in

the myometrium, and a continuous suture for the peritoneal coat. After closing the abdomen the cervix was dilated digitally to allow free drainage of the lochia. The abdominal wound healed satisfactorily, but there was a moderate degree of pyrexia, with a maximum of 100.4° F., for four days after the operation.

In the *second pregnancy* in 1936 it was intended to perform a repeat Cæsarean at term, but at the 36th week the patient was admitted to hospital because of slight antepartum hæmorrhage. Whilst she was in the ambulance there were very vigorous fetal movements (? expulsion of foetus into the peritoneal cavity), but on admission no foetal movements could be felt and the foetal heart could not be heard. The foetus was lying obliquely with the head in the left iliac fossa; this was confirmed by radiography, but Spalding's sign was absent. At no time did the patient show signs of shock or complain of pain. As there was no recurrence of the hæmorrhage she was discharged eight days later at her own request.

Two months later, about the 44th week of pregnancy, she was readmitted and stated that no further foetal movements had been felt. Radiography now confirmed that the foetus had died and medical induction was therefore attempted; this failed and surgical induction was carried out with bougies. A week later the cervix was dilated under an anæsthetic and the bougies removed; the membranes were then ruptured and some purulent discharge came away. On culture this showed a mixed growth of staphylococci, *Streptococcus viridans*, and diphtheroid bacilli. Although the woman had previously been afebrile, her pulse-rate and temperature rose after this operation and her general condition steadily deteriorated. A fortnight later it was decided to perform a laparotomy. Lying in front of the ruptured uterus a gestation sac was found which chiefly consisted of omentum and contained a decomposing foetus in purulent fluid. The foetus was removed and two large drainage-tubes were inserted into the peritoneal cavity. The placenta was left in situ and the uterus was not disturbed. Convalescence was remarkably uneventful and the patient left hospital after five weeks with the abdominal wound almost healed.

The *third pregnancy*, which was in the present year, occasioned the patient such mental anxiety that immediate termination was considered, and this was in fact carried out on March 11th, the abdominal route being used because it was thought that the pregnancy might be partly or wholly extra-uterine. On opening the abdomen fairly extensive adhesions to the parietes were found. The uterus contained a three months' gestation, and there was but a single adhesion of omentum attached to the right side of the fundus and upper part of the body. When this was separated the peritoneal surface of the uterus was seen to be intact. Hysterotomy and sterilisation were performed. The anterior wall of the uterus was carefully examined, but there had been such complete union that it was difficult even to recognise the actual site of rupture. Sections of the scar are unfortunately not available because the uterus was not removed.

DISCUSSION

The ætiology of rupture of a Cæsarean scar has been exhaustively studied by Eardley Holland (1920) and others, who have shown that sepsis is the most important factor. In the present case there was little evidence of sepsis after the original Cæsarean section (see Figure), but Holland has shown that sepsis may be present with only slight fever. The use of catgut instead of inabsorbable suture material has also been blamed, because of the rapid absorption which takes place in the involuting uterus. The low incidence of rupture (4 per cent.) compared with the frequency with which this suture material is used makes it