

## PENICILLIN AND SULPHATHIAZOLE IN TYPHOID FEVER\*

CLINICAL TRIAL

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CONSIDERABLE interest was aroused when Bigger (1946) found that typhoid bacilli are killed, or effectively inhibited, in the test-tube by the combined action of penicillin and sulphathiazole. Bigger suggested that typhoid fever might be treated with a combination of the two drugs, and McSweeney (1946) followed this suggestion and claimed good results in a few cases treated in this way.

The typhoid outbreak that occurred in Aberystwyth in July-August, 1946, offered an opportunity, now fortunately rare in this country, for a trial of the combined penicillin-sulphathiazole treatment. On the suggestion of the Public Health Laboratory Service (directed by the Medical Research Council for the Ministry of Health) and with the coöperation of the Welsh Board of Health arrangements were made for a clinical trial.

A general account of the outbreak has been published by Evans (1947). The vehicle of infection was ice-cream infected by a urinary carrier, and the total number of cases was estimated at 202. Of these, 97 were reported from the borough of Aberystwyth and 30 from the adjoining rural districts, and 75 were scattered throughout the country as single cases or as small groups of cases in patients who had returned home from holiday at Aberystwyth. The infecting organism was a strain of Vi-phage type C, and most of the cases outside the Aberystwyth area were verified at the Central Enteric Reference Laboratory as belonging to the outbreak by typing the strains of typhoid bacilli by the Vi-phage technique (Craigie and Yen 1938, Craigie and Felix 1947).

Because of insufficient accommodation at the local hospital only 57 patients were treated in Aberystwyth and 82 cases were admitted to nine hospitals in South Wales. This unavoidable decentralisation made it rather difficult to devise a plan that could be uniformly followed regarding selection of cases for drug treatment and for controls, details of treatment, laboratory examinations, &c.

Another complicating factor was the great number of children among the patients, owing to the fact that the Aberystwyth ice-vendor used to sell his ice-cream regularly outside the elementary school (Evans 1947). Since typhoid usually takes a milder course in children, it was considered advisable to limit the clinical trials, so far as possible, to cases in adults.

The general impression was that the cases in this outbreak were, on the whole, not of a very severe type. According to information collected by the Welsh Board of Health and the Central Enteric Reference Laboratory

there were only 5 deaths among the 139 Aberystwyth cases treated in ten hospitals in Wales. The exact number of deaths among the 63 cases infected in Aberystwyth and notified in various parts of the United Kingdom could not be ascertained. Thus the case-fatality rate in this outbreak was 3.6% as compared with 9.7% in the milk-borne outbreak of 1936 in Bournemouth, and 14% in the water-borne outbreak of 1937 in Croydon.

Of the fatal cases 2 occurred among 61 patients who had no drug treatment, 2 among 57 patients receiving penicillin and sulphathiazole, and 1 among 6 patients treated with penicillin alone. These figures do not suggest that the low case-fatality rate in the Aberystwyth outbreak can be attributed to the effect of treatment. The case-fatality rate among the untreated cases was only 3.3%; and, even if it is admitted that, on the whole, the cases receiving treatment were slightly more severe than those in the untreated series, it seems very improbable that in the complete absence of specific treatment the case-fatality rate in this outbreak would have approached that at Bournemouth or Croydon.

Since the object of the trial was to find out whether the favourable results claimed by McSweeney (1946) could be confirmed on a greater number of cases, it was decided to follow as closely as possible the procedure McSweeney had adopted. This was to give two courses, each comprising about 10,000,000 units of penicillin and 34 g. of sulphathiazole, each course lasting four days. When the arrangements for the trial were made, three of the hospitals had enough suitable cases to permit of selecting a group of patients for the drug treatment and a comparable group for controls. It was, however, impossible to adhere in all details to a uniform procedure, and this makes it necessary to describe separately the clinical and laboratory observations made in each of the three hospitals.

AT TANYBWLCH FEVER HOSPITAL, ABERYSTWYTH

Gwen Bevan and Marjorie V. N. Suds

A total of 57 patients from the Aberystwyth outbreak were treated at the local hospital. Nearly all were admitted in a week, filling the hospital to capacity, and for some time facilities for carrying out controlled treatment were inadequate. A few of the patients were very ill. Many had relapses after their temperatures had subsided a few days. The relapses often were more severe than the original fever. One patient died of intestinal hæmorrhage and another of myocardial failure before treatment with the two drugs was begun.

By the time adequate supplies of penicillin became available most of the more severely ill patients were in the third or fourth week of the disease. Table 1 shows that 4 patients received their first course of penicillin-sulphathiazole in the second week, 9 in the third week, and 7 in the fourth week; 1 patient (case 7) was given the treatment during a severe relapse. Admittedly conditions were not ideal for a scientifically planned trial, but Bigger (1946) and McSweeney (1946) had aroused hopes that the patients might benefit from the drug treatment, and we aimed at selecting the most severe cases that were considered to be in need of a special therapy.

The assessment of the severity of the cases was made easier by the fact that the treatment was begun during the later stages of the illness with the symptoms of the disease fully developed. The cases were classified according to their severity immediately before the start of treatment, the sole criterion being the clinical condition. Blood-culture and estimation of the O-antibody titre, recommended by Felix (1924) as additional criteria of the severity of the disease, could not be carried out in many of the cases at the height of the outbreak.

\* A report to the Medical Research Council.

Table I summarises the results of the combined penicillin-sulphathiazole treatment. Before the beginning of the treatment each case was classed separately under the headings "severity of toxæmia" and "severity of pyrexia," and from these two criteria the "total severity" was derived. For the sake of simplicity this "total severity" alone is indicated in table I. After the treatment the "effect on toxæmia" and "effect on pyrexia" were assessed separately and are recorded in table I separately. Of the 25 cases listed in the table only 6 were in children under the age of 14.

#### *Cases Treated with a Single Course of Penicillin-sulphathiazole*

Cases 1-10 received only one course of the combined drugs. This group included 2 mild cases, 1 relapse, 4 moderately severe, 2 severe cases, and 1 case classed as very severe. There was no appreciable effect on the pyrexia in any of these patients. Cases 5, 6, and 9 showed some clinical improvement during or after their course of treatment, which was completed on the 17th, 31st, and 22nd day respectively. It is, however, difficult to assert that the improvement was due to the drugs.

Case 10, a girl aged  $4\frac{1}{2}$  years, illustrates the difficulties in assessing the effects of the treatment in the individual case. This little girl was the youngest patient in the series and the one to receive the drug treatment at the earliest stage in the disease (6th day). Her clinical state seemed to be "very severe," and the considerable improvement in toxic symptoms following the 4-day course was labelled as "dramatic," in spite of the fact that the temperature curve remained unaffected. The laboratory findings did not tally with the clinical assessment of the severity of this case. Blood-culture had not been done before the administration of the drugs was begun, but a specimen of serum taken on the 6th day of illness showed an O-agglutinin titre of 1 in 500, indicating that the prognosis was good (Felix 1924). Typhoid bacilli were never isolated from the girl's blood or faeces.

#### *Cases Treated with Two Courses of Penicillin-sulphathiazole*

This group consisted of 11 cases (cases 11-21). None of the patients showed any definite improvement as a result of the first 4-day course. Cases 11 and 20, both women aged 24, were treated in the third week of the disease and seemed to show some transient improvement with their first course. However, the second course, which followed after an interval of only three days, did not produce any response whatsoever in either of the 2 patients.

Cases 17, 18, and 19 merit special comment because they were treated with double the usual dosage of penicillin—i.e., 400,000 units every two hours.

Case 17, a boy aged 16, showed no improvement at all after the first course of 10,000,000 units (19th-23rd days). He developed a relapse, and a course of 20,000,000 units proved ineffective (40th-44th days). A further course of 20,000,000 units was given on the 48th-52nd days of illness, and the boy eventually recovered after having received 50,000,000 units of penicillin and 99 g. of sulphathiazole.

Case 18, a woman aged 30, classed as having moderately severe typhoid, did not respond to the first course of 10,000,000 units, and her blood-culture was positive after the completion of the course (26th-30th days). A course of 20,000,000 units was given on the 43rd-47th days, and this was followed by recovery.

Case 19, a woman aged 44, appeared to have improved after her first course (9th-11th days). However, she had an attack of cholecystitis, and a course of 20,000,000 units of penicillin (51st-55th days) had no effect. The patient excreted typhoid bacilli in her faeces for nearly six months.

#### *Cases Treated with Anti-typhoid Serum*

When the failure of the combined penicillin-sulphathiazole treatment became evident, recourse was had to specific serum therapy. To 5 patients whose condition caused grave anxiety was given Felix's anti-typhoid (Vi + O) serum, prepared at the Lister Institute (Hodgson

1944). Cases 20 and 21 were first treated with penicillin and sulphathiazole, but the condition of both patients deteriorated during treatment. Case 22 received first a course of sulphathiazole and subsequently serum, whereas cases 24 and 25 were given anti-typhoid serum alone. Of the 5 serum-treated patients 4 promptly showed definite improvement, whereas case 22 showed no appreciable effect of the serum treatment; but this patient, too, recovered. Thus there was no fatal case in the 25 cases treated with penicillin, sulphathiazole, and anti-typhoid serum.

#### *Controlled Group of Treated Cases*

As already mentioned, it was impossible at the height of the outbreak to carry out a controlled trial of the drug treatment. As soon as conditions at the hospital returned to normal, an attempt was made to observe the effects of the combined penicillin-sulphathiazole treatment more accurately by selecting a small group of cases for the drug treatment and a comparable group for controls. Since there were no fresh admissions, only cases in the third and fourth week of the disease were available, and from these 16 suitable cases were chosen for the trial and divided into two groups. The corresponding cases in each of the two groups of 8 patients tallied fairly closely with regard to age, day of illness, and severity of disease. No patient under 15 or above 40 years of age was included in the two groups.

Each patient in the treated group received a course of 10,000,000 units of penicillin and 33 g. of sulphathiazole given in 4 days, as recommended by McSweeney (1946). No significant difference could be detected between the 8 cases that received the drug treatment and the corresponding 8 control cases. The 8 treated cases that were controlled in this way are included in table I and are marked with an asterisk. The table shows that 3 of these patients (cases 12, 17, and 18) were given further courses of penicillin-sulphathiazole treatment. The 8 control patients that had no drug treatment are not tabulated.

#### *Blood-culture*

Table I shows that it has not been possible in this series of cases to examine specimens of blood in a systematic manner before and after the drug treatment. Nevertheless 4 patients (cases 15, 16, 18, and 21) yielded a positive blood-culture after the completion of a full course of penicillin-sulphathiazole.

#### *Faecal Excretion*

The dates of the last positive specimen of faeces recorded in the 16 cases in the controlled series were as follows:

Treated group (8 cases): 21st, 26th, 41st, 48th, 59th, 60th day, and in 2 cases the specimens were negative throughout convalescence.

Untreated group (8 cases): 24th, 27th, 37th, 47th, 49th day, and in 3 cases the specimens were negative throughout convalescence.

The average dates of the last positive stool for the group of patients treated with penicillin and sulphathiazole and for the group of cases that were not given any special treatment were as follows:

Treated group (20 cases): 28 days since onset (6 days since last day of fever).

Untreated group (31 cases): 25 days since onset (7 days since last day of fever).

Of the patients treated with penicillin and sulphathiazole, 2 remained persistent excretors (cases 19 and 24) and so did 2 cases in the untreated group. These cases were not included in the calculation of the average dates.

Thus, faecal excretion of the typhoid bacillus was not shorter in the treated cases than in the controls. But, had it been possible to examine in each case more specimens early in convalescence, the average periods of

faecal excretion in the two groups would almost certainly have been found to be considerably longer, because in calculating the average some cases were included that had already become negative when examinations were first started. At Carmarthen, for example, where it was possible, in view of the small number of cases, to institute bacteriological examinations early in convalescence, the average duration of excretion appeared to be longer (see below).

AT TUMBLE ISOLATION HOSPITAL, CARMARTHEN  
Rees Evans and M. T. Parker

Of the first 20 patients admitted the occupants of alternate beds were selected for treatment. This group was compared with the remaining patients who were intended to be used as controls, and found to be roughly equal in age and sex distribution. At first sight there appeared to be about equal numbers of severely ill patients in the two groups. Patients admitted later were allotted alternately to the two groups. Two patients

in the control group had subsequently to be removed, one because the diagnosis of typhoid fever had not been established finally, and the other because it was due to a strain of *Salm. typhi* not belonging to Vi-phage type C and therefore was unrelated to the Aberystwyth outbreak. Thus there are 12 cases in the treated group and 10 in the control group.

Unfortunately the subsequent history of the cases showed that rather more severely ill persons had been included in the treated group than in the control group. This was unavoidable, since it was considered essential to start treatment at the earliest opportunity, to secure the maximal effect.

*Method of Treatment*

Seventeen courses of treatment were administered to the 12 patients. In every case the first course was begun within 3 days of admission; 3 patients who showed no sign of remission were given a further course 6-10 days after the end of the first. Two additional courses were given during relapses.

TABLE I—RESULTS OF TREATMENT OF 25 TYPHOID CASES AT TANYBWLCH FEVER HOSPITAL

Case no.	Sex and age (years)	Clinical course	Duration of pyrexia (days)	Treatment			Effect on—		Blood-culture	
				Day of illness	Penicillin (mega units)	Sulpha-thiazole (g.)	Toxaemia	Pyrexia	Before treatment	After treatment
* 1	M15	Mild	19	33-37	10.0	33	Nil	..	-	N.S.
* 2	F16	Mild	11	21-25	10.0	33	Nil	..	-	N.S.
3	M12	Mod. severe	31	18-21	7.6	28	Nil	Nil	N.S.	-
4	F13	Mod. severe	35	15-18	7.2	27	Nil	Nil	N.S.	-
5	F50	Mod. severe	50	14-17	7.2	27	Improved	Nil	N.S.	-
* 6	F38	Mod. severe	32	27-31	10.0	33	Improved	Nil	+	-
7	F36	Relapse (severe)	36	30-34	10.0	33	Nil	Nil	+	-
* 8	F15	Severe	31	21-25	10.0	33	Nil	Nil	-	-
* 9	M17	Severe	26	18-22	10.0	33	Improved	Nil	+	-
10	F4 1/2	Very severe	17	6-10	2.4	24	Vastly improved	Nil	N.S.	-
11	F24	Mod. severe	40	15-18 21-25	7.2 10.0	27 33	Improved Nil	Slight Nil	N.S. N.S.	- N.S.
*12	F35	Mod. severe	43	26-30 39-43	10.0 10.0	33 33	Nil Improved	Nil Improved	N.S. N.S.	- -
13	F23	Mod. severe	42	24-28 37-41	10.0 10.0	33 9	Nil Improved	Nil Nil	- N.S.	- -
14	F14	Severe	40	17-20 23-27	7.2 10.0	27 33	Nil Nil	Nil Nil	N.S. -	N.S. -
15	F10	Very severe	29	12-15 18-22	7.2 10.0	27 33	Nil Slight	Slight Slight	N.S. N.S.	+ -
16	M14	Very severe	78	17-20 26-32	7.2 14.4	27 27	Nil Nil	Nil Nil	N.S. +	+ -
*17	M16	Very severe with relapse	27 + 16	19-23 40-44 48-52	10.0 20.0 20.0	33 33 33	Nil Nil Improved	Nil Nil Improved	- - -	- - -
*18	F30	Mod. severe with relapse	30 + 12	26-30 43-47	10.0 20.0	33 33	Nil Improved	Nil Improved	- -	+ -
19	F44	Severe, with attack of cholecystitis	27 + 3	9-11 51-55	7.2 20.0	27 30	Improved Nil	Slight Nil	N.S. -	N.S. -
20	F24	Very severe	60	17-22 25-35 36-38	8.1 24.0	45 27	Improved Nil Definite	Nil Nil Definite	N.S. - N.S.	N.S. - N.S.
21	F21	Very severe	48	9-12 16-20 16-18	7.2 10.0	27 33	Slight Much } improved	Nil Much improved	N.S. N.S.	- +
22	F9	Very severe	66	24-29 35-37	None 46 ml. anti-typh. serum	30	Nil Nil	Nil Nil	N.S. N.S.	N.S. N.S.
23	M11	Very severe	..	21-26	None	30	Nil	Nil	N.S.	-
24	F28	Severe	33	23-25	100 ml. anti-typh. serum		Improved	Improved	-	-
25	F57	Very severe with relapse	72	34-36	100 ml. anti-typh. serum		Improved	Improved	-	-

N.S. = No specimen of blood examined. "Duration of pyrexia" column: 27 + 16 means 27 days in primary attack and 16 in relapse.  
\* These 8 cases were controlled by 8 corresponding cases that had no drug treatment.

The standard course consisted of 9,600,000 units of penicillin in two-hourly doses, and 32 g. of sulphathiazole in three-hourly doses during 96 hours. For children under 8 years of age the dosage of sulphathiazole was halved. Sixteen of the seventeen courses were completed. In one case the patient died after receiving 3½ days' treatment. (In addition, a partial course, which is not included in the above total, was given to a patient after intestinal perforation.)

#### Results

*General.*—The cases treated were too few for the effects to be fully assessed. It was easy to see that the treatment had no dramatic effect, but it was very difficult to be sure that it was useless.

The cases seen by us were very variable in severity. There appeared to be an unduly high proportion of mild cases, and it was not always possible to say at first sight which of the cases were destined to pursue a mild course. Several of the mild cases in the untreated group were of short duration, and this makes it necessary to be very cautious in asserting that the treatment cut short the febrile period in those cases where remission rapidly followed the administration of penicillin and sulphathiazole.

*Severe Cases.*—Two severe cases continued to worsen during treatment. In one of them the patient died, presumably from toxæmia and bronchopneumonia, on the 4th day of treatment (18th day of disease). In the other intestinal perforation took place on the 8th day after the institution of treatment (31st day of disease) and caused death from general peritonitis.

Two severe cases received their first course of treatment in the second week of disease without any clinical improvement being apparent. In one of them, intestinal hæmorrhage occurred during the treatment. In both cases a second course of treatment was given later in the first bout of fever, without any evidence of clinical improvement, though lysis began soon after the end of the course (26th and 27th day of disease respectively). One of them relapsed on the 41st day, and a third course of treatment was without apparent effect.

Two severe cases showed some clinical improvement during the first course of chemotherapy. It is noteworthy that these were the only children among the severe cases.

In one of these two children the apparent clinical improvement was not very pronounced. There was, however, a definite reduction of temperature coincident with the treatment. On admission there was continuous fever around 103°F which fell to 101°F on the second day of treatment (6th day of disease) and thereafter was irregularly remittent between 99° and 101.6°F. However, a second course of chemotherapy had no further effect on the fever, which persisted until the 28th day of disease.

In the other child there was much clinical improvement on the second day of treatment. The patient had been severely ill, drowsy, and pallid, with a rapid irregular pulse on admission. The temperature fell critically on the second day of treatment (12th day of disease) and thereafter was irregularly intermittent for a further 7 days, while the clinical condition improved steadily. However, during a relapse beginning on the 33rd day of disease, a further course of treatment had no apparent effect on the fever or the toxæmia.

*Moderate and Mild Cases.*—In some of the less severe cases it is even more difficult to assess the effects of treatment. In 4 of these, subsequent inspection of the temperature charts suggested that lysis had already begun before the institution of treatment, but the irregularity of the fever makes it difficult to be sure. Short mild cases were common in both the treated and the untreated groups, but clinical mildness was not always associated with a short fever. Thus, though the treatment probably had no effect in shortening the course, in some cases it is impossible to be sure.

TABLE II—RESULTS OF FÆCAL CULTURES IMMEDIATELY BEFORE, DURING, AND AFTER TREATMENT

Case no.	Days of disease when treatment was given	Result of fæces culture			
		0-4 days before course	During course	0-4 days after course	6-10 days after course
1	16-20	-	+	-	+
2	6-10	+	+	+	+
3	6-10	+	+	N.S.	+
4	19-23	+	+	+	+
5	24-28	+	N.S.	+	+
6	8-12	-	+	+	+
7	15-18	+	+	+	N.S.
8	7-11	N.S.	+	N.S.	+
	21-25	+	+	+	-
9	23-27	-	+	+	N.S.
	12-16	+	+	+	+
10	22-26	+	+	-	-
	46-50	-	+	+	+
11	5-9	-	+	-	+
	19-23	+	+	+	-
12	11-15	-	-	+	+
	36-40	+	-	+	+

N.S. = No specimen examined.

In 1 case of moderate severity there was no evidence that improvement followed the course of treatment given at the end of the third week; and a mild ambulant case continued to have irregular intermittent fever for a fortnight after the end of treatment.

#### Complications and Relapses

None of the usual complications developed among the untreated cases. One of the least severe had an attack of delusional insanity during convalescence. Among the treated cases there was one instance each of intestinal hæmorrhage and of perforation. Both developed after the beginning of treatment. There were two relapses in the treated group and none in the control group. There is thus no evidence in this series of cases that the treatment reduced the incidence of complications or relapse.

#### Blood-culture

Blood-cultures were positive in 8 of the 12 cases just before treatment. A repetition of the test 36 hours after the cessation of treatment showed that only 2 out of 12 were still positive. The first conclusion that can be drawn from this is that treatment does not lead to a permanent sterilisation of the blood. It is less easy to decide whether the treatment had any effect on the bacteræmia.

Of the 6 patients in whom the blood-culture became negative after treatment 2 were already afebrile by this time (on the 12th and 14th day of disease) and 2 were in the fourth week of disease. The remaining 2, however, negative on the 11th and 17th day of disease, continued pyrexial for over a fortnight after treatment, and thus might have been expected to have had a positive blood-culture at this stage.

Some attempt at a quantitative blood-culture technique was made, and it was noted that in the 2 severe cases in which the culture was still positive 36 hours after the cessation of the first course of treatment the number of organisms was apparently less than before treatment.

In the 3 cases in which a second course of treatment was given in the later stages of the first bout of fever the blood-culture was negative both before and after. In the 2 relapses the culture was positive before and negative after treatment. It is possible, on these findings, that the treatment may have led to some reduction of the degree of bacteræmia.

#### Fæcal Excretion

With the criterion of six negative specimens as an indication of the cessation of excretion, and with the

exclusion of the 2 fatal cases in the treated group, the average dates of the last positive stool were:

Treated group (10 cases): 52.4 days since onset (23.9 days since last day of fever).

Untreated group (10 cases): 37.5 days since onset (16.8 days since last day of fever).

In 1 case in the treated group, which was retained in hospital after six negative specimens had been obtained, excretion began again after an interval of 31 days, and eleven further positive stools were obtained between the 92nd and 142nd days of disease. This second period of excretion has not been included in the calculation of the average figure for the group.

There is thus no evidence that the treatment reduced the period of faecal excretion of the typhoid bacillus.

Even if the treatment had no lasting effect on the excretion of organisms in the faeces, it might have been expected to cause their temporary disappearance. The result of cultures performed before, during, and after the seventeen courses of treatment are shown in table II. There was no evidence of temporary cessation of excretion. This finding came as something of a surprise in view of the well-known fact that the administration of each of the two drugs to temporary excretors during convalescence, or to chronic carriers, almost invariably leads to transient cessation in the excretion of typhoid bacilli. The inability of the drug treatment to produce a similar effect during the actual attack of typhoid fever is therefore of special interest.

The method of culture used was direct plating of the specimen on to Wilson and Blair's medium (Tabel's modification), together with primary enrichment in Kauffmann's tetrathionate broth followed by plating on Wilson and Blair's medium.

Positive urinary cultures were few and rather sporadic, and no chronic urinary carriers developed among the treated or the untreated cases.

#### AT SKETTY ISOLATION HOSPITAL, SWANSEA

Idwal Pugh and A. F. S. Sladden

Of 19 patients from the Aberystwyth outbreak transferred to the Swansea County Borough Isolation Hospital for treatment 14 of suitable age were selected for the trial: 6 were given the penicillin-sulphathiazole treatment, and 8, so far as possible of comparable age, formed the control group. No patient under the age of 14 was given the drug treatment.

In general the cases in the treated group seemed to be more acutely ill than their controls. In the treated group the severity of illness was assessed as moderate in 3 cases, severe in 2 cases, and very severe in 1 case. In the control group there were 4 mild cases, 3 of moderate severity, and 1 very severe case.

The standard course was penicillin 200,000 units every two hours for 4 days, together with sulphathiazole 1 g. every three hours. In 5 of the treated cases the same course was repeated after an interval of 48 hours, bringing the total dosage to about 20,000,000 units of penicillin and 32 g. of sulphathiazole. In the sixth case the dosage of penicillin was doubled during the second course.

#### Results

In 3 moderately severe cases—a boy aged 16, a woman aged 50, and a woman aged 57—there was no appreciable benefit from the drug treatment; in these cases the treatment was begun on the 9th, 12th, and 16th day of illness respectively.

A boy aged 14, classed on clinical grounds as severe, received the first course on the 15th day of illness. There was immediate reduction of temperature but no apparent effect on the toxæmia. The blood-culture had been negative on the 14th day—i.e., before the treatment began—and O-agglutination to a titre of 1:125 had been obtained on a specimen of serum taken as early as the 4th day of illness. According to Felix (1924)

these two findings indicate that the patient was less severely ill than the clinical assessment suggested.

A woman aged 23, classed as a severe case, was given the first course on the 11th day of illness. There was no evidence of any effect on pyrexia or toxæmia, and typhoid bacilli were isolated from the blood 24 hours after the completion of the first course of treatment (15th day). The second course was followed by fall in temperature and well-marked clinical improvement, but three weeks later the patient had a severe relapse, from which she eventually recovered.

The sixth case, in a woman aged 22, classed as very severe, received the first course on the 13th day of illness and showed no appreciable response. Blood-culture was positive on the 11th day (before treatment) and negative on the 18th day (two days after completion of the first course). A double dose of penicillin was given in the second course during the 19th–22nd days (400,000 units of penicillin every two hours), and this coincided with rapid improvement. This case therefore received about 30,000,000 units of penicillin and 64 g. of sulphathiazole.

All the patients in the two groups recovered in due course. Most of them had troublesome sickness after administration of sulphathiazole. One of the patients with a mild attack in the control group continued to excrete typhoid bacilli for over eight months and had her gall-bladder removed. The dates of the last positive stool for the remaining cases in the two groups were:

Treated group (6 cases): 15th, 52nd, 63rd day, and in 3 cases the specimens were negative throughout convalescence.

Untreated group (7 cases): 36th, 44th, 47th day, and in 4 cases specimens were negative throughout convalescence.

The small number of cases treated does not allow any firm conclusion to be drawn. It is, however, justifiable to state that the dosage of penicillin and sulphathiazole used by McSweeney (1946) was inadequate for the treatment of the more severe type of case. There was no opportunity of adequately investigating the possible effect of doubling the dosage of penicillin or increasing it even further.

#### Sensitivity of Aberystwyth Typhoid Strain to Penicillin and Sulphathiazole

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It was thought that the disappointing results of the clinical trials might be due to an unusually high degree of insensitivity of the Aberystwyth strain to the combined action of penicillin and sulphathiazole. Cultures isolated from the blood of 2 patients and from the faeces of a third during convalescence from the Aberystwyth outbreak were therefore compared in in-vitro tests with four typhoid strains belonging to different Vi-phage types (one strain each of Types A and E1, and two strains of Type N—formerly Type Richmond). The data from the test-tube experiments will be published elsewhere. Briefly, the three Aberystwyth strains showed a slightly greater sensitivity to penicillin alone than did the four strains of different Vi-phage types. The effects of sulphathiazole alone and of penicillin-sulphathiazole mixtures on the Aberystwyth strains were apparently very little different from their effects on the other four strains.

The failure of the combined penicillin-sulphathiazole treatment cannot therefore be attributed to a particularly high degree of insensitivity of the Aberystwyth strain to the action of the two drugs.

#### Summary and Conclusions

Our experiences of the combined penicillin-sulphathiazole treatment during the Aberystwyth outbreak have been disappointing.

Of 39 patients who received courses of treatment similar to those adopted by McSweeney (1946) most

were treated in the second and third weeks, as were also McSweeney's patients. We did not observe the speedy disappearance of toxæmia and subsidence of pyrexia described by McSweeney.

Three small groups of patients treated with penicillin-sulphathiazole were compared with three untreated control groups, and there was no evidence of an appreciable clinical effect of the drug treatment.

There were no fatalities in our largest group of 25 treated cases (table I), but 5 of the patients whose condition caused the greatest anxiety had been given Felix's "Vi + O" anti-typhoid serum.

A considerable proportion of patients yielded positive blood-cultures shortly after completion of their courses of penicillin-sulphathiazole treatment.

Fæcal excretion of typhoid bacilli during convalescence was not shorter in the treated groups than in the controls.

In one of the treated groups that was suitably examined for the purpose (table II) there was no evidence of even a temporary disappearance of typhoid bacilli from the fæces.

The typhoid strain responsible for the Aberystwyth outbreak was not more resistant to the action of penicillin and sulphathiazole than were four other strains with which it was compared in in-vitro tests.

We consider it necessary to warn against the indiscriminate use of penicillin-sulphathiazole in the treatment of typhoid fever.

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WEIGHT CHANGES IN PREGNANCY

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THIS paper records the maternal weight changes during pregnancy observed by assistant medical officers, health visitors, and clerks under the administrative direction of one of us (J. A. S.) and analysed statistically by the other (B. B.).

INVESTIGATION

The primary object of the investigation was to determine, in so far as regular weight observations throw light on the subject, whether the war-time dietary, including the extra rations available to pregnant women, sufficed to maintain good health. No women refused to cooperate, and the tables and charts therefore include all women attending the centres who fulfilled the prescribed conditions—namely, attendance for weighing

TABLE III—MOTHERS WHO DID NOT GAIN WEIGHT

Between weeks of pregnancy	No. of mothers	No. who did not gain weight
16-20	360	10 (2.8%)
20-24	644	10 (1.6%)
24-28	875	35 (4.0%)
28-32	1170	64 (5.5%)
32-36	1221	74 (6.1%)
36-40	1014	150 (14.8%)

as nearly as possible to the weeks of pregnancy at which it was decided to record the weights, with an outside limit of a week from these periods. The charts and tables contain evidence that the war-time dietary was, by this criterion, adequate, and bear out the conclusions based on other forms of investigation to evaluate the same facts.

The number of published systematic observations of weight changes in pregnancy, however, is not extensive, and the findings in this series may therefore be worth reporting for their own sake. For practical purposes they appear to be applicable to peacetime conditions.

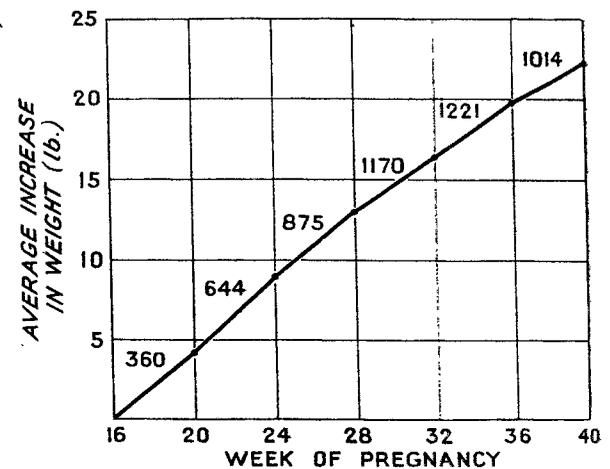


Fig. 2—Average increments of weight of all expectant mothers. Number of mothers weighed in each period is shown on curve.

The routine monthly weighing of all expectant mothers, stripped except for a dressing-gown of known weight, was begun in Fulham antenatal clinics in September, 1941. The records were summarised up to the beginning of 1944, and certain preliminary figures supplied to the Ministry of Health. Other preoccupations of common concern necessitated the deferment of the detailed analysis until now.

At the start of the observation it was felt necessary to exclude those who did not attend the clinic regularly or did not commence attendance until later than the 16th week of pregnancy. Four-weekly measurements (16th, 20th, 24th week, &c.) to term were made, and no greater deviation than a week either way from the standard times was allowed. Where this condition could not be fulfilled, the records have been excluded from this analysis. It should, however, be pointed out

TABLE I—INCREMENTS ACCORDING TO INITIAL WEIGHT—CONTINUOUS RECORDS FROM 16TH WEEK ONLY

Initial weight (st.)	No. of mothers	Mean initial weight (lb.)	Mean increment (lb.) between stated weeks of pregnancy					
			16-20	20-24	24-28	28-32	32-36	36-40
Under 8	54	106.48	3.81 ± 0.40	4.19 ± 0.25	3.25 ± 0.26	2.73 ± 0.25	3.12 ± 0.26	2.09 ± 0.35
8-	142	118.99	4.27 ± 0.16	4.79 ± 0.19	3.82 ± 0.23	3.68 ± 0.20	2.58 ± 0.21	2.69 ± 0.28
9-	91	132.12	4.38 ± 0.28	4.59 ± 0.27	3.90 ± 0.28	3.18 ± 0.22	2.74 ± 0.30	2.40 ± 0.34
10-	53	145.29	4.39 ± 0.39	4.65 ± 0.39	3.96 ± 0.33	3.36 ± 0.38	2.97 ± 0.36	2.15 ± 0.51
11-	14	158.44	4.14 ± 0.58	4.34 ± 0.48	2.34 ± 0.58	3.67 ± 0.76	3.12 ± 0.89	2.23 ± 1.42
Over 12	6	182.04	3.96 ± 1.47	3.46 ± 1.60	4.63 ± 1.22	2.92 ± 0.45	3.54 ± 1.19	2.13 ± 2.17
Total ..	360	126.89	4.24 ± 0.14	4.59 ± 0.14	3.73 ± 0.15	3.35 ± 0.13	3.19 ± 0.15	2.43 ± 0.18