

hazards of the operation. The margin of safety is less in those aged over 50, but the two deaths in those aged over 60 were due to errors of technique (effluent-loop obstruction and gangrene of colon) and had no relation to the age of these patients.

INTERCURRENT DEATHS

The causes of the 12 intercurrent deaths were verified by necropsy, laparotomy, or examination of the death certificate, as follows:

Pneumonia	Verified by necropsy.
Car accident	letter.
Pulmonary tuberculosis (3 cases)	necropsy.
Heart-failure (2 cases)	" "
Pneumonia	death certificate.
Carcinoma of gall-bladder (2 cases)	laparotomy (A. H. V.).
Subarachnoid hæmorrhage	" "
Carcinoma of gastric remnant	" "

LATE DEATHS

Two late deaths were due to the original ulcer or operation. One patient was discharged apparently fit and well but was readmitted with suppurative pancreatitis, from which he died eight weeks after his first operation. The second died of uræmia. Post-operative catheterisation had caused cystitis, and though discharged in reasonable comfort the patient ultimately developed prostatic symptoms and died at home.

(To be concluded)

PENICILLIN AND SULPHONAMIDES IN TYPHOID FEVER

EXPERIENCE OF PHYSICIANS IN MILITARY HOSPITALS IN THE MIDDLE EAST

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IN 1946 Bigger observed that, though the growth of *Salmonella typhi* was influenced little by either penicillin or sulphathiazole acting independently, a combination of these two agents prevented the growth of artificially cultured typhoid organisms. He believed that this action was synergistic, the sulphathiazole being bacteriostatic and the penicillin bactericidal, and that, to be effective, the dose should be proportional to the number of organisms present. He suggested that it might be possible to administer these substances in vivo in concentrations sufficient to sterilise the blood-stream during the septicæmic stage of typhoid fever, so allowing the antibodies of the host to deal with organisms in the tissues.

A little later in the same year McSweeney (1946) described the results which he had obtained in a clinical trial of this combined therapy. The 6 cases of typhoid which he treated showed dramatic improvement, and he recommended that during a four-day period a patient should be given 10 mega units of penicillin and 34 grammes of sulphathiazole and that the course should be repeated after two days' rest. In no instance did he initiate treatment before the tenth day, and more usually it was delayed until the third week of the illness. The response was rapid. Except in his first case, where small doses had been used, the blood was sterilised, the temperature settled, and the toxæmia strikingly abated; moreover these effects were apparent during the first course of treatment.

Cases of typhoid fever are constantly under observation in the Middle East, and in the autumn of 1946 and early months of 1947 a number of patients were treated with penicillin and sulphathiazole in British military hospitals.

Unfortunately, however, though the doses given were comparable with those advocated by McSweeney, his methods of administration were closely followed only on rare occasions. When the first patients came under treatment the supplies of penicillin were limited. It was therefore decided to restrict the combined therapy to patients who were seriously ill and in whom the diagnosis of typhoid fever had been confirmed bacteriologically.

There cannot be any doubt when a new remedy is truly specific for the disease or diseases which it is designed to treat. Thus it was clear from the outset that sulphonamides reacted specifically against such bacteria as meningococci, streptococci, and pneumococci, and that penicillin did against diseases due to these and certain other organisms. On the other hand, the response to penicillin and sulphonamides of subacute bacterial endocarditis due to *Strep. viridans* was less dramatic, and a considerable volume of research was required to prove beyond doubt that the treatment was effective.

It was clear by the New Year of 1947 that typhoid fever did not respond to the treatment we were giving in the dramatic and specific way that pneumonia did, but it seemed possible that it might be reacting in the leisurely way of subacute bacterial endocarditis. To obtain a more accurate opinion, and with a view to standardising the dosage and methods of administration of the therapeutic agents, a questionnaire was circulated to the physicians at the various hospitals concerned. This paper is based on the answers to those questions. My task has been to correlate the reports of various doctors and nursing sisters, and I have tried to present the results in a manner as impersonal and unbiased as possible.

GENERAL CONSIDERATIONS

Doubts about the efficacy of a therapeutic agent are most readily resolved by comparing the course of a disease among patients living under identical conditions save that half their number, selected at random, are given the treatment which is the subject of the trial. To ensure that the present investigation was adequately controlled, the treated and the untreated patients should have had similar preventive inoculation records, should have been admitted to hospital at a comparable stage of the disease, and should have received similar symptomatic and dietetic treatment; furthermore, the disease should have been acquired from the same source in comparable circumstances and should have been of comparable severity in the two groups.

Inoculation records were as follows:

	Penicillin and sulphonamides	
	Not given	Given
<i>Up to date</i>		
Inoculated less than 6 months before onset of illness	4	4
Inoculated more than 6 and less than 12 months before onset	9	4
Inoculated more than 12 and less than 18 months before onset	1	2
Inoculated more than 18 and less than 24 months before onset	5	3
Total	19	13
<i>Not up to date</i>		
Inoculated more than 24 months before onset	0	1
Never inoculated	13	5
Total	13	6

Army requirements for T.A.B. inoculation involve annual maintenance doses.

Except that the control group is larger than the treated group, there is little difference between the two. The only soldier whose inoculation record was out of date was a man who had refused further injections after his initial dose of T.A.B. three years previously. The uninoculated patients were all civilians. Most of the patients had been in the Middle East less than a year and were men in their early twenties.

It is often difficult to be certain exactly when an attack of typhoid fever starts and therefore to decide the duration of illness before admission to hospital. But in this respect there appears to be no essential difference between those who had penicillin and sulphonamides and those who did not. On the other hand, though an attempt was made to ensure, even in the acute stages, a fluid diet yielding at least 1250 calories a day, there were undoubtedly minor differences in the diets of various patients. Similarly, symptomatic treatment varied slightly according to the whim of the doctors concerned.

Since there was no single epidemic of sufficient size to allow of statistical analysis, cases occurring in small outbreaks have had to be combined. These have originated from different sources, have been due to different strains of organism, and have varied much in severity. Experience has shown that the severity of an epidemic

TABLE I—RESULTS OBTAINED AT CENTRE A (EGYPT)

Case no.	Day admitted	Day on which penicillin and sulphonamides started	Days of pyrexia	Days in hospital	Remarks
1	3	6	19	63	—
3	3	6	26	26	Died of heart-failure; albuminuria
5	4	6	33	61	—
7	2	6	24	47	Albuminuria; persistent tachycardia
9	1	6	28	48	Intestinal hæmorrhage; typhoid not proved bacteriologically
2	3	—	45	63	Persistent tachycardia
4	3	—	22 + 10	66	Relapse in 8th week
6	2	—	9	9	Died; parotitis; albuminuria
8	1	—	28	49	—
10	3	—	50 + 19	112	Relapse

Case 6 had small doses of penicillin for parotitis.

bears no relationship to the phage type of the organism, and, though in each epidemic cases seem to conform to a pattern, there is no way of forecasting how serious the outbreak will be. Such differences are important in analysis; for example, the patients in two epidemics which developed almost at the same time were treated by similar methods by the doctors and nurses of the same hospital. Toxæmic cases were seen in both epidemics, yet in the first outbreak all of 20 patients recovered, whereas in the second 6 of 9 died. If large doses of penicillin and sulphonamides had been given to one set of patients and not to the other, false conclusions might easily have been drawn. Even if the necessary conditions for a controlled investigation had been satisfied, it is doubtful whether the total number of cases was adequate, or the criteria for measuring improvement sufficiently well defined, to enable conclusions to be drawn by statistical methods. Indeed the only factual observation which is worth citing is the effect of treatment on blood-culture. Of 11 cultures taken during treatment with combined penicillin and sulphonamides 8 were positive, and of 9 specimens taken immediately after the course of treatment 6 were still positive.

An undoubted reduction in mortality would be significant; but, as pointed out above, the death-rate varies so widely in different epidemics that hundreds of cases would have to be observed before a reliable index of mortality could be obtained. There is no great difference in the time spent in hospital between the patients given penicillin and sulphonamides in addition to the routine treatment of typhoid and those given the

TABLE II—RESULTS OBTAINED AT CENTRE C (IRAQ)

Case no.	Day admitted	Day treatment started	Days of pyrexia	Days in hospital	Remarks
1	2	8 & 19	26	72	Sporadic; 2 courses Hæmaturia
2	4	7	27	66	
3	5	—	39	80	Bronchopneumonia Not proved bacteriologically
4	5	—	35	79	

Case 3 had penicillin in small doses for bronchopneumonia.

routine treatment only; but even these figures are likely to be vitiated by complications, such as femoral thrombosis, which may delay the discharge of a patient for long after the active disease has abated. The duration of fever may be hard to define if a continuing slight swing makes it impossible to decide when the temperature has subsided, or if, after days or even weeks of normal temperature, there is a sudden burst of pyrexia. Finally, there is no satisfactory way of recording the degree of toxæmia; and a patient who is considered to be "dangerously ill" because he has passed blood per rectum may be in far less danger than his neighbour who only looks "a bit toxic." Similarly, what may prove to be a fatal perforation of the intestine may be the first symptom which brings the patient under observation.

For these reasons I do not think it feasible to analyse statistically the reports on which this paper is based. The facts are set down for those who like manipulating figures, but for the rest it will be sufficient to quote the impressions of those who observed the effects of treatment in each epidemic.

RESULTS

Centre A (Egypt) (table I)

In this moderately severe outbreak (phage type A) 10 cases were divided, by the method of alternate admissions, into two groups. Besides the routine treatment of typhoid fever, patients in the first group received 600,000 units of penicillin and 1.5 g. of sulphathiazole every three hours, and a total dose of about 20 mega units and 50 g. in four days, sulphadiazine being substituted when vomiting was troublesome. Blood-culture, temperature, and complications were little affected. The patients in the second group received routine treatment only.

Lieut.-Colonel H. J. Anderson reported that in his opinion treatment with penicillin and sulphonamides had proved useless; and that the frequent injections which were necessary interrupted the patients' rest—a view supported by the nurses. A similar opinion was expressed by Major H. M. Wotzilka and Major T. D. Kellock, medical specialists at the hospital.

Centre B (Egypt)

There were two small outbreaks, one consisting of 3 (phage type D), and the other of 2 (phage type E), cases in British personnel. In each outbreak one patient was given "specific" treatment, while the other, rather milder, cases were given the standard treatment. Clinical particulars of the latter cases are not available for analysis. The specific treatment of the 2 patients was started on the tenth and fourteenth day respectively, and both were admitted during the first week of illness. Of the first patient Major E. L. Frankel writes:

"In my opinion the administration of penicillin and sulphathiazole did not affect the course of the disease, which ran a similar course to the other 2 (control) cases. The doses employed were 250,000 units of penicillin three-hourly and 6 g. of sulphathiazole daily, and the drugs were given for eight days."

The second patient developed bronchopneumonia, and "the treatment appeared to have a beneficial effect on the lung condition . . . but the primary disease was unaffected

with regard to pyrexia, blood-count, and toxæmia. The drugs were given in the same doses as to the previous patients, and treatment was continued for six days." (The reference to the blood-count is a reply to a question asking whether large doses of sulphathiazole had any effect on the white cells.)

Centre C (Iraq) (table II)

One patient in a small outbreak of 3 cases (Craigie Old Be) and 1 sporadic case of typhoid (Craigie Old B2) were treated with 10 mega units of penicillin given by intermittent intramuscular injection over four days, together with 30-32 g. of sulphathiazole. Concentrations

TABLE III—RESULTS OBTAINED AT CENTRE D (CYPRUS)

Case no.	Day admitted	Day treatment started	Days of pyrexia	Days in hospital	Remarks
1	3	17	56	75	—
2	4	32	?	95	Relapse on 29th day
3	3	15	63	124	Toxic myocarditis; abscess of buttock
4	3	16	40	49	—
5	7	9	25	72	—

of penicillin in the blood were insufficient to inhibit the growth of organisms in vitro (0.6 unit per ml.).

Lieut.-Colonel T. A. Kemp writes of case 1:

"This is the only case that has been given McSweeney's course in every detail—two-hourly injections of penicillin, sulphathiazole rather than the more recent and less toxic sulphonamide preparations, and two courses of treatment. He was a sporadic case, so that no controls are available for comparison. However, he continued to 'crop' profusely throughout the first course, his toxæmia was unaffected, and my own impression was that the natural history of the disease was quite uninfluenced by the treatment with penicillin and the sulphonamide."

And of case 2 he says:

"The massive course of penicillin and sulphonamide may have had a slight effect on the course of the disease, as the onset was very severe. Personally I doubt it, as he continued to 'crop' throughout the course of treatment and the character of the chart is not dissimilar from . . . (that of a patient receiving normal treatment) in the same epidemic. The second course was not given."

Some cases of paratyphoid were also treated; and, commenting on the treatment as a whole, Lieut.-Colonel Kemp says:

"The treated and control cases differed only in that the more severe cases were generally selected for treatment. Bronchitis, abdominal distension, and diarrhoea were more frequent and severe in the treated cases, which I take to be merely a reflection of the severity of the initial infection. One case of intestinal hæmorrhage and one of hæmaturia occurred after therapy, and one case of intestinal hæmorrhage occurred before therapy. There was no bleeding among the controls. None of the records shows the dramatic improvement that is to be expected when specific therapy is applied to a disease process."

Major I. M. Sinha, medical specialist to the hospital, agreed with these views.

Centre D (Cyprus) (table III)

There were two outbreaks of typhoid among uninoculated civilians. Illness in the first epidemic of 9 cases ranged from moderate to severe. The 4 cases judged to be most severe were given, in four days, 10 mega units of penicillin by intermittent intramuscular injection and 37 g. of sulphathiazole. (The first case treated received only 7.5 mega units and 28 g.) The second outbreak was mild. It consisted of 10 cases, in only 1 of which was the combined treatment given. Particulars of control cases are lacking, except that the average period spent in hospital was 49 days.

Sulphathiazole and penicillin were not given concurrently in case 2; the abscess developing at the site of a penicillin injection in case 3 was opened, and the pus contained living typhoid bacilli.

Capt. A. H. Banton comments: "In no case was any beneficial result of this line of treatment apparent, either in fall of temperature or diminution of toxæmia."

Centre E (Palestine) (table IV)

This was an outbreak of 13 moderately severe cases (phage type B3). Five of these, the worst cases (A in table IV), were given penicillin in doses ranging from 10 to 12 mega units, by intermittent intramuscular injection, and 48-52 g. of sulphathiazole by mouth in four days; 4 mild cases (B in table IV) were not given specific treatment; and 4 moderately ill cases (C in table IV) were given penicillin in "ordinary" doses. Particulars are also given of 4 sporadic cases (D in table IV) which received the large doses of penicillin and sulphathiazole.

On behalf of Lieut.-Colonel R. R. Henderson, Captain A. I. MacLeod, physician in charge of the typhoid ward, wrote:

"In September and October, 1946, massive doses of penicillin and sulphathiazole were given in 4 sporadic cases of typhoid fever and 1 case of paratyphoid-B fever. There were no adequate controls for these patients (nos. 14-17), but in none were dramatic results obtained

"There was no effect on the temperature or pulse-rate, which continued to rise and fall according to the previous tendency, and the effect on the general condition was difficult to assess."

Nevertheless, in the case-notes of one of these patients he had recorded "no effect on fever—in fact temperature level went up—but definite relief of toxæmia." Despite this improvement, two days after the course had finished the patient deteriorated and died.

The opportunity for a better-organised clinical trial came in November, 1946, when the larger outbreak occurred. Apart from the patients on full treatment, 4 were given penicillin alone, in doses of 50,000 units three-hourly, and 4 were not given specific treatment—they were "on the whole the mildest of the series, though one had a typhoid bacilluria and persistent tachycardia which delayed his convalescence."

TABLE IV—RESULTS OBTAINED AT CENTRE E (PALESTINE)

Group	Case no.	Day admitted	Day treatment started	Days of pyrexia	Days in hospital	Remarks
A	1	5	8	42	72	Sulphonamide rash; relapse 32nd day
	2	9	13	44	73	Intestinal hæmorrhage
	3	4	9	28	70+	Sulphonamide rash; femoral thrombosis; pulmonary infarct
	4	3	6	19	61	Severe vomiting
	5	3	10	33	73	—
B	6	7	—	19	44+	—
	7	2	—	10	45	—
	8	8	—	32	70	Typhoid bacilluria; persistent tachycardia
	9	3	—	13	44	—
C	10	6	9	12	12	Perforation; died
	11	7	14	42	76	—
	12	9	13	24	58	—
D	13	3	6	17	51	—
	14	4	14	23	23	Sporadic
	15	3	9	22	50+	Sporadic
	16	1	17	31	72	Sporadic; in hospital at onset
	17	2	9	28	62	Sporadic

"Those who received the massive penicillin doses did not realise that they were being dealt with differently. They fully realised that they were receiving tablets which made them feel sick. All patients were given phenobarbitone gr. 1 b.d., which was found of value both in reducing nausea and in helping all to sleep. In only 2 cases was there any hint of an effect on the fever. Steady improvement seemed to be the rule, no matter what the treatment. There was no bacteriostatic effect in the blood, let alone a bactericidal effect. Penicillin levels were estimated in 2 cases and were found to be $\frac{1}{2}$ -2 units per ml. within the limits of accuracy (50-100% either way!). Since very adequate sulphathiazole levels seem to have been obtained here, the only method of improving treatment is by boosting the blood-penicillin level."

It may be added that Lieut.-Colonel Anderson and Major Wotzilka gave penicillin to 2 patients in massive doses without influencing the course of the disease or the blood-culture. In 1 case 24 mega units was given in twenty-four hours by continuous intravenous drip, and in the other 3 mega units was given by intramuscular injection every three hours for twenty-four hours.

Centres F and G (Egypt)

Unfortunately circumstances made it impossible to get full details of either of these outbreaks. The first consisted of about 20 cases of typhoid (phage type C), and penicillin in doses of 60,000 units three-hourly and sulphathiazole were used for seven days. This treatment was regarded as of value in minimising the chest infection, and Captain Bannister and the nurses with whom she was associated "received a distinct impression that treatment with penicillin and sulphathiazole was helpful in lessening toxæmia in the severe cases."

The second outbreak also involved some 20 cases. Penicillin was given in conventional doses to prevent chest complications, but only in 2 cases was McSweeney's (1946) dosage adhered to. Lieut.-Colonel A. Leese, who saw these cases, was "convinced that massive penicillin had no effect."

DISCUSSION

The conclusions drawn both by doctors and nursing sisters in M.E.L.F. was that treatment with penicillin and sulphonamides would have to produce much more dramatic results in the way of a rapid cure of the illness if the disturbance to the patient of repeated injections was to be counterbalanced.

There are reasons which may explain why we did not obtain the results obtained by McSweeney. The most obvious is that his methods were not strictly followed. Then it is possible that we were dealing with insensitive organisms. This is unlikely, since many different epidemics were under treatment, but it has to be remembered that Evans (1946), in experiments with 66 different strains of *S. typhi*, demonstrated well-marked variations in sensitivity to penicillin which were not related to the phage type of the organism. Again, commercial preparations are said to contain three or four different penicillins, some of which may be biologically inert (*Lancet* 1946), and we may have been unlucky in our choice of preparation. Finally, treatment was rarely instituted early in the first week, when presumably it would be most effective in dealing with the infection; but it must be pointed out that in McSweeney's cases treatment was also started late in the illness.

I wish to thank my colleagues for the excellent records which they have generously allowed me to study and from which I can only draw one conclusion—i.e., that the ideal treatment for typhoid fever as it occurs in the Middle East has yet to be discovered.

I am indebted to Major-General F. Morris, C.B.E., K.H.S., director of medical services, M.E.L.F., for permission to publish this paper.

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PHYSIOLOGICAL JAUNDICE OF THE NEWBORN

SOME NEW MEASUREMENTS OF THE FACTORS CONCERNED

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THE plasma of the human infant at birth contains a concentration of bilirubin which on the average considerably exceeds the figure for normal adults; the concentration increases rapidly after birth to reach a peak at 2-5 days and thereafter slowly decreases (Hirsch 1913, Yllpø 1913). There are wide variations between different infants.

At present two main theories of the causation of this icterus hold the field. The first view, which appears in almost all British textbooks, both of hæmatology and of pædiatrics, is that the jaundice is due to hæmolysis; it is said that in utero the foetus acquires an abundance of red cells and hæmoglobin as a response to the anoxic conditions of foetal life; after birth the infant no longer requires this high oxygen-carrying power, and the excess red cells are destroyed, causing jaundice (Goldbloom and Gottlieb 1929). The second theory ascribes a major rôle to the liver. It is held that, though the bilirubin comes from excessive hæmolysis in the postnatal period, the main factor determining the appearance of jaundice is a functional immaturity of the liver which renders it unable for the first few days of life to excrete the extra load of bilirubin (Yllpø 1913, Rich 1930). This second theory is almost universally accepted by workers in this field.

The evidence in favour of the second theory and against the first theory may be briefly summarised as follows:

(1) In utero the percentage of hæmoglobin in the foetus is only slightly higher than that in the adult. The very high hæmoglobin values sometimes encountered in the newborn are mainly due to the "transfusion" that the infant receives from the placenta at birth (DeMarsh et al. 1942). From the high levels attained after birth there is only a slow rate of fall, and this rate is not correlated with the intensity of the jaundice (Mitchell 1929).

(2) Those infants who show the greatest degree of bilirubinæmia excrete less and not more bile pigment in the stools and urine (Yllpø 1913, Snelling 1933, Ross et al. 1937).

(3) The concentration of serum-bilirubin in the cord blood is correlated with the subsequent course of the bilirubin changes in the same infant; this strongly suggests that the development of jaundice is not determined mainly by post-natal hæmolysis (Hirsch 1913, Yllpø 1913, Davidson et al. 1941).

Though it is now widely accepted that the liver of the newborn infant is functionally immature, there is less agreement about the extent of postnatal hæmolysis. Thus, for instance, Weech (1947), in a comprehensive review of the subject, considered that an accelerated destruction of hæmoglobin began within a few hours of birth, whereas Findlay (1946) concluded that there was no evidence of increased hæmolysis during the neonatal period—"in fact, rather the reverse."

The question can be most satisfactorily settled by a direct measurement of the survival of the newborn infant's erythrocytes, and a brief preliminary account of some such measurements is given here.

METHOD

It may be assumed that blood taken from the placenta at birth is representative of the infant's blood, and it is highly probable that the erythrocytes of this blood, if transfused to a second newborn infant, will survive in