PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS

REPORT TO THE MEDICAL RESEARCH COUNCIL ON 147 PATIENTS TREATED IN 14 CENTRES APPOINTED BY THE PENICILLIN CLINICAL TRIALS COMMITTEE *

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ONLY eighteen months ago few patients suffering from bacterial endocarditis had been treated with penicillin in this country, and the results both here and in the U.S.A. were far from encouraging. Early in 1945 reports were received from America which suggested that better results might be obtained with larger doses given for longer periods. An attempt to determine the best system of dosage was clearly indicated, both to save life and to prevent wastage of a valuable drug still in short supply. Since subacute bacterial endocarditis is an uncommon disease, it was decided that this could be best achieved by a coördinated effort, and in February, 1945, an announcement was made in this journal [1] of the formation of research centres in Belfast, Bristol, Edinburgh, Leeds, Liverpool, London (St. Mary's, Middlesex, and St. Bartholomew's Hospitals), Manchester, and Sheffield. In April four further centres were formed, in Birmingham, Cardiff, Glasgow, and Newcastle. The response to this announcement can be gauged from the fact that by the end of September, 1945, the treatment of 147 patients had been completed. Since that date many more have been treated, but these will be included in a later report, since an adequate follow-up is essential in assessing the results of any treatment of this disease.

THERAPEUTIC RESULTS

Penicillin was given either by three-hourly injection or by continuous intramuscular infusion. No difference in the therapeutic results could be demonstrated, and opinion on the merits of these two methods is divided. Most are agreed, however, that both methods should be available if the treatment of subacute bacterial endocarditis is to be undertaken.

In the first group to be treated the dose was planned to show the relative importance of duration of treatment and the total amount of penicillin given. An answer to this question is given in table I, which summarises the results in 46 patients, all of whom received 5 mega (million) units of penicillin but over different periods of time—20 patients were given 1·0 mega unit a day for five days and all relapsed or died; 12 were given 0·5 mega unit a day for ten days and of these 3 were apparently cured; 14 were given 0·25 mega unit a day for twenty days and of these 7 have remained well. These patients have been under observation for over six months, and, since relapses if they occur almost invariably take place within six weeks of treatment (table V), the conclusion appears to be justified that, within these limits of dosage, the duration of treatment is of much greater importance than the total amount of penicillin given. Increased dosage is no substitute for long treatment.

The results of treatment in a further series of 66 patients are shown in table II; all received penicillin for twenty-eight days but the dose was varied, one group receiving 0·1 mega unit a day, another 0·25 mega unit a day, and another 0·5 mega unit a day. In the first group 43% recovered, in the second group 50%, and in the third group 61% have remained cured after an average follow-up of four months. It should not be forgotten that no matter how effective penicillin may prove to be in the treatment of this disease, a significant death-rate will remain from causes such as heart failure, uræmia, and major emboli. These deaths, many of which occurred during treatment, have little or no bearing on the efficacy of penicillin, and when this is borne in mind the therapeutic results shown in table II are all the more remarkable—11 out of 18 patients receiving 0·5 mega unit a day for twenty-eight days have remained cured. In only one of the 7 patients who died was there any evidence that the penicillin had failed to control the septicæmia, and the infecting organism in this case was more than 32 times as resistant to penicillin as the standard Oxford staphylococcus. For previously untreated patients 0·5 mega unit a day for twenty-eight days seems to be a most satisfactory system of dosage.

Another small group of 12 patients received 0·5 mega unit a day for twenty-one days: of these, 1 died, 2 relapsed, and 9 have remained well after an average follow-up of 244 days.

Lastly, there were 11 patients who received a system of dosage which did not fall into any of the categories described above: 5 of these died, 1 relapsed, and 5 have remained well for an average period of 172 days.

EFFECT OF INADEQUATE TREATMENT

It is of considerable practical importance to know whether inadequate treatment, besides wasting time and penicillin, is prejudicial to later success. The results of treatment in patients who had already received a short course of penicillin are given in table III. A comparison

TABLES I TO IV—RESULTS OF TREATMENT WITH VARIOUS DOSAGE SCHEDULES

I—*Five mega units given in 5, 10, or 20 days (46 cases)*

Daily dose (mega units)	Duration of penicillin treatment (days)	Died	Relapsed	"Cured"	Av. follow-up (days)
1·0	5	6 (1)* (30%)	14 (70%)	0	..
0·5	10	2 (1) (17%)	7 (58%)	3 (25%)	217
0·25	20	4 (3) (29%)	3 (21%)	7 (50%)	249

II—*Daily dose of 0·1, 0·25, and 0·5 mega units for 28 days (66 cases)*

0·1	28	3 (3) (21%)	5 (1) (36%)	6 (43%)	198
0·25	28	13 (5) (38%)	4 (3) (12%)	17 (5) (50%)	117
0·5	28	7 (39%)	0	11 (61%)	114

III—*Previously treated with a 5–10 days' course of penicillin (26 cases)*

1·0	5	0	1	0	..
0·5	10	0	0	2	220
0·1	28	0	2	1	232
0·25	20	4 (3)	1 (1)	3 (3)	260
0·25	28	0	3 (2)	6 (4)	162
0·5	28	0	0	3	175
Total	..	4 (15%)	7 (27%)	15 (58%)	..

IV—*Previously treated with a 20–28 days' course of penicillin (26 cases)*

1·0	5	0	1	0	..
0·5	10	0	1	0	..
0·1	28	0	0	1 (1)	214
0·25	20	1 (1)	1 (1)	1 (1)	200
0·25	28	2	3	2	107
0·5	20	0	1 (1)	0	..
0·5	28	2	6	4	134
Total	..	5 (19%)	13 (50%)	8 (31%)	..

* Figures in parentheses (other than percentages) represent number of patients in whom dosage was only approximately as stated.

* This report is submitted on behalf of the large number of workers who took part in the investigation.

1. *Lancet*, 1945, i, 225.

of this table with tables I and II does not suggest that previous treatment with a short course is prejudicial to later success, in the patients who survive.

The results of treatment in patients who had already received a long course of penicillin are given in table IV. A comparison of this table with tables I and II shows that if a patient does not respond to a long course of treatment he is less likely to respond to a second course. There are two possible explanations. Lack of response to the first course may indicate natural resistance to penicillin therapy, so that this forms a selected group of resistant cases. Alternatively, the explanation may be that an ineffectual course of treatment may increase the resistance to penicillin.

Repeated estimations of the resistance of the infecting organism to penicillin were made in this series but no convincing evidence of changes in sensitivity was found. Sixteen patients received more than one long course (twenty days or more) of treatment, and in only 2 of these was there any evidence of a change in sensitivity; in both there was a threefold increase in resistance to penicillin as measured by the ordinary dilution methods. Clinical evidence bearing on the question of acquired resistance to penicillin is also meagre, and is confined to two small groups. The first group was of 7 patients in whom septicæmia was uncontrolled during treatment; in 2 it was uncontrolled from the start, but in the other 5 the infection had been previously controlled by a similar or smaller daily dose of penicillin, suggesting that resistance to penicillin had increased; in all of these 5 patients the first course, which seemed at the time to be effective, involved a daily dose of only 0·1–0·25 mega unit. In the second group there were 5 patients who relapsed after a second long course of penicillin; in all the dosage of penicillin was greater in the second than in the first course, and yet the interval before relapse was reduced rather than increased.

This evidence is, to say the least, not incompatible with acquired resistance to penicillin. Delay in controlling the infection also exposes the patient to the many dangerous complications of this disease, and it is therefore safer, from the patient's point of view, to assume that inadequate treatment is prejudicial to later success.

RELAPSES

Short courses of treatment, of ten days or less, are usually followed by relapse within a few days. Even after long courses most relapses occur within thirty days of cessation of treatment, and relapse after fifty days is extremely rare (table V). The conclusions drawn from

TABLE V—CASES RELAPSING AFTER LONG COURSE OF TREATMENT (20 DAYS OR MORE) AND AFTER SHORT COURSE OF TREATMENT (10 DAYS OR LESS)

Days between treatment and relapse	Relapses— after long course	Relapses— after short course	Days between treatment and relapse	Relapses— after long course	Relapses— after short course
0–10 ..	14	17	41–50 ..	2	0
11–20 ..	7	3	51–60 ..	0	1
21–30 ..	6	2	Over 60 ..	1 (130 days)	..
31–40 ..	0	1			

tables I, II, III, and IV, in which the period of follow-up varied from 107 to 260 days, are therefore not unreasonable. There is still, of course, the chance of reinfection, but this was only proved in one patient of this series; this patient relapsed, and *Streptococcus fœcalis* was recovered from the blood 161 days after apparent cure from an infection with *Strep. viridans*.

The treatment of relapses presents a special and often difficult problem. Of 16 patients who relapsed after a course of penicillin which lasted longer than twenty days, all but 4 relapsed or died after a second course which was either longer or of higher dosage than the first. Four patients have received more than two long courses of penicillin, but only one of these has finally responded: she relapsed after 0·5 mega unit for ten days, again after 0·1 mega unit for twenty-eight days, and again after 0·5 mega unit for twenty-eight days, but has now remained well for sixty days after a fourth course of 0·5 mega unit a day for forty-two days. It is this system of dosage—0·5 mega unit a day for six or eight weeks—that we propose usually to adopt in patients who have relapsed.

TABLE VI—COMPARISON OF RESULTS OF TREATMENT WITH SENSITIVITY OF THE ORGANISM TO PENICILLIN. NONE OF THESE PATIENTS HAD PREVIOUSLY BEEN GIVEN A LONG COURSE OF TREATMENT

Daily dose (mega units)	Duration (days)	Result	Resistance to penicillin* 1 or less	2	3–5	8–10	32–64
0·1	28	Died ..	1	2	..	..	..
		Relapsed	*6*	*1*	..	..	..
		Cured ..	6	..	..	1	..
0·25	20	Died ..	1	..	2	..	..
		Relapsed	*4*	..	..	..	..
		Cured ..	7	1	1	..	..
0·25	28	Died ..	6	2	2	..	..
		Relapsed	*3*	*1*	*1*	..	..
		Cured ..	14	3	2	1	..
0·5	20	Died ..	..	..	..	1	..
		Relapsed	..	*1*	*1*	..	..
		Cured ..	4	2	1	..	1
0·5	28	Died ..	3	1	..	..	2
		Relapsed	..	..	..	..	..
		Cured ..	8	3	2	1	..
Total ..		Died ..	11	5	4	1	2
		Relapsed	*13*	*3*	*2*	..	..
		Cured ..	39	9	6	3	1

* Resistance is expressed as a multiple of the resistance of the standard Oxford staphylococcus.

THE INFECTING ORGANISM

Of the 147 patients included in this series, 146 were infected with streptococci and one with a strain of *Hæmophilus influenzæ* which was almost completely resistant to penicillin. Of the streptococci, 136 are described as *Strep. viridans*, 8 as a non-hæmolytic streptococcus, 1 as an anaerobic streptococcus, and 1 as a microaerophilic streptococcus.

The sensitivity to penicillin was measured by the ordinary dilution methods and compared with the standard Oxford staphylococcus. To facilitate tabulation this has been expressed as a coefficient of resistance, and it is clear from table VI that there is a surprising lack of correlation between this coefficient and the results of treatment. There were 16 patients infected with comparatively insensitive streptococci having a coefficient of resistance between 3 and 10; 5 of these have died, 9 have been apparently cured, and only 2 have relapsed. These results compare favourably with those in patients infected with more sensitive organisms. There were 3 patients infected with streptococci more than thirty-two times as resistant as the Oxford staphylococcus, and this degree of insensitivity may be of therapeutic significance. One of these 3 was cured after receiving 0·5 mega unit a day for twenty-one days, but in the other 2 septicæmia remained uncontrolled while they were receiving 0·5 mega unit a day, and both ultimately died. A fourth patient was infected with an extremely resistant strain of *H. influenzæ* and he relapsed six days after receiving 0·5 mega unit a day for twenty-three days.

These results suggest that the resistance of the organism to penicillin as measured by ordinary titration methods is of no clinical significance within a wide range. Only when the organism was more than ten times as resistant as the Oxford staphylococcus did this measure-

ment appear to be of therapeutic and prognostic importance. This unexpected result may only reflect some inherent inaccuracy in the methods employed in measuring sensitivity, but this does not affect its clinical importance since these methods are in general use.

COMMENTS

Of the 147 patients treated in this series, 50 have died and 81 have been apparently cured, but it should not be forgotten that the systems of dosage at first used were inadequate. Of the remaining 16 patients, some are still under treatment and in a few treatment has been discontinued for one reason or another.

This report is concerned only with evidence which has a bearing on the treatment of subacute bacterial endocarditis. It is expected that a more complete analysis of these and other patients treated within the scope of this investigation will be made at a later date.

SUMMARY

The results here reported provide further evidence of the therapeutic value of penicillin in subacute bacterial endocarditis.

If the administration of penicillin is continued for ten days or more, almost any system of dosage will occasionally produce excellent results. Relapse is, however, more likely to occur if treatment is not both protracted and intensive.

From the evidence available it is safer to assume that inadequate treatment is prejudicial to later success.

In previously untreated patients 0·5 mega unit a day for twenty-eight days has given better results than any other system of dosage employed.

The resistance of the infecting organisms as measured by ordinary titration methods appeared to be of no clinical importance within a wide range. Only when the organism was more than ten times as resistant as the standard test staphylococcus did this measurement appear to be of therapeutic and prognostic significance.

BLOOD-LOSS IN BATTLE CASUALTIES

USE OF TRANSFUSION FLUIDS *

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TRANSFUSION of blood or plasma is now an indispensable procedure in the resuscitation of the severely wounded and has become almost a routine method of treatment. The relative values of blood and plasma have, however, never been conclusively established. The preference throughout the B.L.A. was for blood rather than plasma, a tendency which increased the difficulty of supply. This preference for blood is a general one, based on the clinical experience of many surgeons. The present report deals with an attempt to assess by laboratory means the accuracy of this view and to define more clearly the general course of the hæmatological changes which may follow wounding and the reliance which may be placed on simple laboratory procedures as aids to effective treatment. For this purpose patients were studied at C.C.S., where resuscitation and primary surgery are generally undertaken.

Our first approach was an attempt to estimate the amount of blood lost by different groups of battle casualties. It was hoped that from this knowledge rational recommendations for treatment might be formulated. It soon became clear that some aspects could only be solved by a much more elaborate investigation, but it is believed that the problem has been narrowed down. Most of our patients were studied for 48 hours, but a smaller group was followed for a week or more.

* Based on a report submitted to the Deputy Director of Pathology, 21 Army Group, in April, 1945.

LABORATORY METHODS

The blood samples have been obtained by venepuncture, usually from the median cephalic vein. Relatively large needles ("giving" transfusion needles) with 3 in. of rubber tubing attached have been used for this purpose. Congestion of the veins has been reduced to the minimum possible, and usually the blood would flow gently without the use of a tourniquet. No suction has been used, and our samples have been remarkably free from hæmolysis. The needles have been sterilised by autoclaving and then dried in an oven at a temperature not exceeding 80° C. The anticoagulant used has been the ammonium-potassium oxalate mixture of Heller and Paul, 2 mg. per c.cm. of blood, dried in 10 mg. amounts in ½ oz. bottles at a temperature not exceeding 80° C.

Total red blood-cells, total leucocytes, and *reticulocytes* have been counted by standard hæmatological methods.

The *transfused (donor) red-cell count* has been estimated with a technique of differential agglutination based on that of Ashby (Dacie and Mollison 1943). Special sera containing the α and β iso-agglutinins in high titre were kindly supplied for this purpose by the late Dr. G. L. Taylor. The response per bottle of blood transfused in millions of donor red-cells per c.mm. of recipient's blood has been termed the "survival" of that blood.

The *patient's red-cell count* has been calculated by subtracting the transfused red-cell count from the total red-cell count.

The *cell volume* (hæmatocrit value) has been estimated with Wintrobe's tubes centrifuged at 3000 revs. per min. for 45 min.

Plasma volume has been estimated with Evans-blue dye; the method of extraction and estimation has been that of Harington et al. (1940). Our early observations were made with a Klett visual colorimeter; later with a photo-electric colorimeter we made serial observations on the same patient.

Plasma bilirubin has been estimated with a Lovibond comparator.

CELL-VOLUME (HÆMATOCRIT) CHANGES WITHIN 48 HOURS OF WOUNDING

We thought it useful as a start to follow the cell-volume (hæmatocrit) changes of as many men as possible for a limited time to obtain a general idea of the severity of blood-loss and the response to transfusion of a representative group of battle casualties. We have studied only those men whom the transfusion officer thought to be in need of transfusion. Patients with burns, head injuries, or complicated injuries to limbs and abdomen or chest, and those who had already received transfusions at field ambulances have been excluded; otherwise there has been no deliberate selection.

The decision to transfuse has in all cases been made by the transfusion officer on clinical grounds, and we have usually been in agreement with him. The type and severity of the injuries have been held to be most important in making the decision. The pulse-rate, blood-pressure, and general appearance of the patient have seemed to be less reliable. The latter often accurately reflect the gravity or otherwise of the patient's condition but exceptions are common; in particular we have noticed systolic blood-pressures within the normal range, or even slightly raised, in severely wounded men who have lost considerable quantities of blood. Simple laboratory tests, such as the estimation of hæmoglobin or cell volume, if carried out on a casualty when first admitted, are similarly of little value in deciding the extent of the blood-loss and whether a transfusion should be started. Too much depends on the time which may have elapsed since the man was wounded. In fact, in only 23 out of 75 patients seen within six hours of wounding and who later received transfusions on general clinical grounds was there any certain evidence (a cell volume reduced to 40% or below by spontaneous hæmodilution) that there had been any loss of blood at all.

It is appreciated that the cell volume of any particular sample of blood withdrawn from a shocked patient may not be representative of the cell-to-plasma ratio of the blood taken as a whole. No doubt it would have been possible and better to have collected samples, say, from the femoral vein rather than from the most easily punctured vein, but this was felt to be hardly practicable.