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PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS

REPORT TO THE MEDICAL RESEARCH COUNCIL ON 269 PATIENTS TREATED IN 14 CENTRES
APPOINTED BY THE PENICILLIN CLINICAL TRIALS COMMITTEE

BY

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Secretary of the Committee

Between February, 1945, and March, 1946, 269 patients suffering from subacute bacterial endocarditis were treated in the 14 centres appointed by the Medical Research Council in Belfast, Birmingham, Bristol, Cardiff, Edinburgh, Glasgow, Leeds, Liverpool, London (St. Mary's, Middlesex, and St. Bartholomew's Hospitals), Manchester, Newcastle-upon-Tyne, and Sheffield. The patients were unselected, and were investigated and treated according to a co-ordinated plan.

Results in Previously Untreated Cases

When this investigation was first planned not only was penicillin scarce but very few cases of recovery had been described, and for these reasons amounts of penicillin were used which are now known to be inadequate.

The first group of 52 patients received a total of 5 million units, but the daily dose was varied (Table I). This experi-

TABLE I.—*Patients Receiving a Total of 5 Million Units of Penicillin, Given in Courses of 5, 10, and 20 Days. (No case had previously received penicillin)*

Dose	Total No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Days)	Relapsed or Died Infected
1 mega unit for 5 days	18	3	2	13	0	—	83%
0.5 mega unit for 10 days	16	4	0	8	25%	665	50%
0.25 mega unit for 20 days	18	6	0	4	44%	579	22%

ment clearly showed that, within these limits of dosage, the duration of treatment was of greater importance than the amount of penicillin given daily—a conclusion which may now be a commonplace but which at that time was of some importance.

In the next group of 158 patients the duration of treatment was established at 28 days, but the daily dose was varied (Table II). Of 17 patients who received 100,000 units a day for 28 days, 7 (41%) relapsed or died infected. Of

TABLE II.—*Patients Treated for 28 Days with a Daily Dose of 0.1, 0.25, and 0.5 Mega Unit. (No case had previously received penicillin)*

Dose	Total No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Days)	Relapsed or Died Infected
0.1 mega unit a day	17	4	0	7	35%	579	41%
0.25 mega unit a day	83	30	2	11	48%	447	16%
0.5 mega unit a day	58	22	3	1	55%	423	6.9%

83 patients receiving 250,000 units a day for 28 days, 13 (16%) relapsed or died infected. Of 58 patients who received 500,000 units a day for 28 days, 4 (6.9%) relapsed or died infected. Only occasionally can failure be explained on the basis of a highly resistant organism; in the four failures referred to above the coefficient of resistance expressed as a multiple of that of the Oxford staphylococcus was 2, 2, 6, and 32.

Twenty-two previously untreated patients received other systems of dosage, and the results in this group, although not instructive from a therapeutic point of view, are shown in Table III.

TABLE III.—*Patients Receiving Courses not Included in Tables I or II. (No case had previously received penicillin)*

Dose	Total	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Re-lapsed	"Cured"	Average Follow-up (Days)
0.25 mega unit a day for from 5 to 6 weeks	3			1	2	426
0.5 mega unit for 21 days	11	1		2	8	650
0.5 mega unit for 5 weeks	4	2			2	341
0.5 mega unit for 2 weeks, increased to 1 mega unit for 2 weeks	4		1		3	395

Except in a few cases penicillin was given either by three-hourly injection or by continuous intramuscular infusion. No difference in the therapeutic results can be demonstrated, and opinion on the merits of these two methods is divided. In some cases the dosage given was only approximately as stated; these exceptions were indicated in a previous report in the *British Medical Journal* of March 16, 1946 (p. 381).

Relapses

Patients who have relapsed are in a separate category with regard to both treatment and prognosis. Of 42 patients who had relapsed after a long course of treatment 59% again relapsed or died infected (Table IV): it can be calculated from Tables I, II, and III that had these patients not previously been treated unsuccessfully only 14% would have been expected to relapse or die infected. Patients who relapse after a short course of penicillin also appear to be slightly more resistant to subsequent treatment (Table V).

The conclusion is justified that if a patient does not respond to a course of penicillin he is less likely to respond to a second course. This may mean that resistance of the

TABLE IV.—Patients Previously Treated with a Course of Penicillin, of 20 Days or More

Dose	Total No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Days)	Relapsed or Died Infected
0.5 mega unit for 10 days ..	2			2			100%
0.25 mega unit for 20 days ..	5		4		1	540	80%
0.25 mega unit for 28 days ..	10	1	3	5	1	551	80%
0.5 mega unit for 20 days ..	4		3		1	394	75%
0.5 mega unit for 28 days ..	17	4	4	3	6	411	41%
0.5 mega unit for 6-8 weeks	4	2	1		1	270	25%
Total	42	7	15	10	10		59%
Expected numbers from Tables I, II, and III		14.1	1.3	4.5	22		14%

TABLE V.—Patients Previously Treated with only a Short Course of Penicillin, of 5 to 10 Days' Duration

Dose	Total No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Days)	Relapsed or Died Infected
1 mega unit for 5 days ..	2			1			
0.5 mega unit for 10 days ..	4			2	2	631	
0.1 mega unit for 28 days ..	4		1	1	1	607	75%
0.25 mega unit for 20 days ..	8	3	1	1	3	634	25%
0.25 mega unit for 28 days ..	10		1	3	6	544	40%
0.5 mega unit for 28 days ..	10	3	2		5	465	20%
Total	35	6	5	7	17		34%
Expected numbers from Tables I, II, and III		11.7	0.9	6.6	15.8		21%

organism to penicillin has been acquired; but that is probably seldom an important factor, since in 50 patients that relapsed and were treated again an increase in resistance was observed only in 12—in five the increase was less than threefold, and in seven it was more than threefold—and in three the resistance decreased. Another possibility is that these patients belong to a selected group of those who are naturally resistant to treatment. The nature of this resistance is not known, but it is conceivable that in some individuals the infecting organisms are so buried in avascular tissue that the drug does not reach them in lethal concentration. Whatever may be the cause, it is clear that patients who have relapsed should be given a more generous system of dosage. A course of 2 million units a day for eight weeks is suggested, but it is possible that even larger doses should be given.

Relapses seldom occur more than a month after treatment (Table VI), but a long period of follow-up shows that

TABLE VI.—Relapses after Treatment

Interval between Treatment and Relapse	Relapse after Treatment Lasting 20 Days or More	Relapse after Treatment Lasting 10 Days or Less
0-10 days	20	19
11-20 "	14	3
21-30 "	7	4
31-40 "	—	1
41-50 "	3	—
51-60 "	2	1
Over 60 "	3*	1†

* Relapsed after 130, 250, and 390 days.

† Reinfected with different organisms after 161 days.

a small risk remains even after a year or more of good health. Whether these delayed relapses are due to re-infection or are an indication of dormant infection in the heart valves is uncertain.

The Infecting Organism

In 245 patients the infecting organism was a *Streptococcus viridans*, in 17 a non-haemolytic streptococcus, in 3 a staphylococcus, in 2 a micro-aerophilic streptococcus, in

one *Haemophilus influenzae*, and in one the organism was not identified. Patients from whom a positive blood culture was not obtained were excluded from this series. The relationship of the sensitivity of the infecting organisms to the results of treatment is most interesting (Table VII).

TABLE VII.—Comparison of the Results of Treatment with the Sensitivity of the Organism to Penicillin. (Resistance expressed as a multiple of the resistance of the standard Oxford staphylococcus.) None of the Patients had Previously been Given a Long Course of Treatment

Dose		Coefficient of Resistance						Total
		1 or Less	2	3-6	8-16	32 or More	Not Known	
0.1 mega unit a day for 28 days	Died controlled	3	1					
	Died uncontrolled					1		
	Relapsed "Cured"	7	1				1	
0.25 mega unit a day for 20 days	Died controlled	6	1	2			1	
	Died uncontrolled	5			1			
	Relapsed "Cured"	6	2	1			2	
0.25 mega unit a day for 28 days	Died controlled	17	7	3			3	
	Died uncontrolled	1		2				
	Relapsed "Cured"	11	1	1			1	
0.5 mega unit a day for 20 days	Died controlled	28	10	4	1		3	
	Died uncontrolled	1						
	Relapsed "Cured"	4	1	1		1		
0.5 mega unit a day for 28 days	Died controlled	11	6	2	1	1	5	
	Died uncontrolled		2	1				
	Relapsed "Cured"	23	1	3	2	1	1	
All doses	Died controlled	36	16	7	2	2	9	70
	Died uncontrolled	1	2	3	2	—	—	10
	Relapsed "Cured"	23	4	2	—	—	2	31
Total		67	22	9	3	2	6	109
Relapsed or died infected ..		19%	13.6%	24%	28%	50%	12.1%	18.7%

The percentage of patients who relapsed or died uncontrolled did not appear to be affected by the resistance of the organism over a considerable range. However, our experience during the past year and that of others suggests that when the coefficient of resistance is more than about 8, daily doses larger than 500,000 units should be given, probably over a period longer than 28 days. The system of dosage adopted must depend on the resistance of the organism, and recently we have used as much as 40 million units a day. Fortunately the incidence of organisms more than eight times as resistant as the Oxford staphylococcus is low. The majority were as sensitive to penicillin as the Oxford staphylococcus, sometimes more sensitive; and Table VII clearly shows that even this degree of sensitivity is no indication for a reduction in dosage.

Foci of Infection.—It is generally accepted that every effort should be made to remove foci of infection, particularly in the teeth, and this should be done while the patients are receiving penicillin. There is no proof in this series of the efficacy of this procedure, but so long as any uncertainty exists as to the likelihood of reinfection it seems reasonable to assume that foci of infection should be eradicated.

Causes of Death

In this series 131 patients, or 49%, have died, but many of these received what would now be considered inadequate treatment. Of those whose infection was apparently controlled about 35% have subsequently died of various complications. The majority of deaths occurred either during treatment or soon after treatment was completed (Table VIII). Heart failure caused 40% of the deaths, and was a major cause in another 16% (Table IX). Comparatively few died of uraemia, emboli, or haemorrhage, and in 19% the cause of death was mixed or uncertain. The

TABLE VIII.—Interval between Treatment and Death

	Died with Infection Apparently Controlled	Died with Infection Not Controlled	Total
Died during treatment ..	29	8	37
" 0-49 days after ..	32	19	51
" 50-99 " ..	15	4	19
" 100-149 " ..	8	3	11
" 150-199 " ..	1	2	3
" 200-249 " ..	3	1	4
" 250-500 " ..	6	0	6

TABLE IX.—Cause of Death

	Died During Treatment	Died After Treatment	Percentage of Total Deaths
Heart failure ..	7	45	40
Heart failure and other causes	7	14	16
Uræmia ..	3	5	6
Emboli ..	6	9	11
Haemorrhage ..	4	6	8
Mixed or uncertain ..	10	15	19
Total ..	37	94	100

remarkably high death rate from heart failure is of considerable interest and will be referred to later.

The heart valves were examined at necropsy in 47 cases. In 39 of these infection had apparently been controlled by penicillin, and yet what appeared to be living organisms were seen in the heart valves of 13; organisms of uncertain viability were seen in 4; and organisms which appeared to be dead in 9. In the remaining 8 patients infection was not clinically controlled; in 6 of these, apparently living organisms were seen in the heart valves, and in 2 no organisms could be demonstrated. It would be unwise to draw definite conclusions from these results until further evidence of the viability of the organisms is forthcoming. Nevertheless it is disconcerting, to say the least, to find apparently living organisms in the heart valves of one-third of patients in whom, according to the usual clinical criteria, infection had been controlled.

Factors in Prognosis

Death from heart failure and other complications is now a much greater hazard to the patient than the risk of failure to respond to penicillin, and it is therefore of clinical importance as well as of academic interest to estimate this hazard when treatment is started. Tables X-XIII show the significance of certain clinical observations made before treatment began.

The nature of the primary cardiac lesion (Table X) appeared to be of slight significance; the highest death

TABLE X.—Relation of Primary Cardiac Lesion to Prognosis

Primary Cardiac Lesion	Total No.	"Cured"	Died	
			No.	%
Rheumatic { Mitral ..	120	69	51	43.0
{ Aortic ..	29*	15	14	48.5
{ Mitral and aortic ..	90	37	53	59.0
{ Unspecified ..	1	1	—	—
Total ..	240	122	118	49.0
Congenital { Septal defect ..	12	8	4	33.0
{ Others ..	17	8	9†	53.0
Total ..	29	16	13	45.0

* Including 10 patients in whom a rheumatic history was not given: 5 of these died.

† Including 5 patients with bicuspid aortic valves.

rate was found in combined mitral and aortic lesions (59%), and the lowest in septal defects (33%). Four patients had a patent ductus arteriosus; three of these recovered and one died with the infection uncontrolled. There were 5 patients with mitral stenosis and auricular fibrillation, and one of these died.

Evidence of heart failure (Table XI) is of considerable importance. Of those with no evidence of heart failure

TABLE XI.—Relation of Heart Failure to Prognosis

Degree of Heart Failure Before Treatment	Total No.	"Cured"	Died				Deaths (%)
			During Treat- ment	Within 50 days	Within 100 days	After 100 days	
None ..	201	128	20	23	9	21	36
Moderate ..	40	10	8	16	6	—	75
Severe ..	28	0	9	12	4	3	100
Total ..	269	138	37	51	19	24	49

36.4% died, and of those with moderate heart failure 75% died. The 28 patients who had severe heart failure when treatment was started all died.

The duration of infection (Table XII) is also significant: of those recently infected 34% died, while of those infected for six months or more over 60% died.

TABLE XII.—Relation of Duration of Infection to Prognosis

Duration of Infection	Total	"Cured"	Died	
			No.	%
0-9 weeks ..	94	62	32	34
10-19 " ..	91	45	46	51
20-29 " ..	59	22	37	63
30-39 " ..	13	4	9	69
Over 40 " ..	12	5	7	58
Total ..	269	138	131	49

The state of nutrition of the patient (Table XIII) was of surprising importance. The questionnaire filled in before treatment was started gave a choice of four categories.

TABLE XIII.—Relation of the State of Nutrition to Prognosis

State of Nutrition	Total No.	"Cured"	Died During Treatment	Died After Treatment	Total Died	
					No.	%
Good ..	102	71	11	20	31	30
Poor ..	125	56	14	55	69	55
Bad ..	26	9	8	9	17	65
Emaciated ..	16	2	4	10	14	87.5
Totals ..	269	138	37	94	131	49

Of those in a "good" state of nutrition 30% died; when nutrition was "poor" 55% died; when it was "bad" 65% died; and only 2 out of 16 "emaciated" patients recovered—a mortality rate of 87.5%. The significance of nutrition when analysed appears to be independent of the duration of infection or of the incidence of heart failure. For instance, there were 201 patients without evidence of heart failure: in 90 of them nutrition was good and 26% died, in 101 nutrition was poor or bad and 41% died, and of 10 who were emaciated 80% died. These results emphasize the need for an adequate calorie intake as with other prolonged fevers.

The ages of these patients ranged from 7 to 67, with a mean of 31 years (S.D. $\pm$ 11.9). Age was of doubtful prognostic significance except in the group over 50. In those under 50 the death rate was 46%, and in 26 patients over 50 it was 69%.

Discussion

It is not within the scope of this report to review the literature on the treatment of subacute bacterial endocarditis, and the emphasis on our own results is not due to any lack of appreciation of the pioneer work in America on the use of penicillin in this disease. Our own series is the largest yet published, and our conclusions regarding treatment are in accord with those of most who have worked in this field.

Although penicillin can now be expected to control the infection in about 90% of patients, a closer inspection of our results shows several features which are far from satisfactory and which reveal our ignorance of several important aspects of this disease: (a) In the majority of patients who relapse no good reason can be given for the failure of penicillin; in only a few could it be explained on the basis of a highly resistant organism. (b) The remarkably high incidence of heart failure, both during and soon after apparently effective treatment, is not explained. (c) The presence in the heart valves of what appeared to be living organisms in about one-third of patients who died after apparently effective treatment suggests that dormant infection may be an important sequel of treatment with penicillin.

For these and other reasons we believe that further intensive research on this disease is indicated, with particular emphasis on higher dosage and on careful analysis of post-mortem material. The following centres are continuing this work, and it is hoped that an adequate number of patients will be referred to them: Belfast (Queen's University, Institute of Pathology). Birmingham (Professor Wilkinson, Queen Elizabeth Hospital). Bristol (Professor Bruce Perry, Bristol Royal Infirmary). Edinburgh (Dr. A. R. Gilchrist, Royal Infirmary). London (Sir Alexander Fleming, St. Mary's Hospital; Professor Christie, St. Bartholomew's Hospital; Dr. G. E. S. Ward, Middlesex Hospital). Manchester (Professor Crichton Bramwell, Royal Infirmary). Leeds (General Infirmary).

Conclusions

The administration of 500,000 units of penicillin a day for 28 days can be expected to control the infection in about 90% of patients suffering from subacute bacterial endocarditis, but about 35% of these die of heart failure and other complications.

Larger doses should be given for a longer period of time to patients who relapse and to patients in whom the infecting organism is more than eight times as resistant as the Oxford staphylococcus.

Of the relapses 90% occurred within a month of treatment, but a danger of relapse persists after a year or more of good health.

Evidence of heart failure or of poor nutrition is of great importance in prognosis. The duration of infection and the nature of the primary cardiac lesion are also of some significance.

What appear to be viable organisms are not infrequently found in the heart valves of those who have died after the infection has apparently been controlled.

This report is made on behalf of a large number of clinicians and bacteriologists who have taken part in this investigation. Dr. J. E. Cates and Dr. P. J. N. Cox have also assisted in the analysis of results. Mr. J. A. Heady and Professor Bradford Hill have given valuable help and advice on statistical analysis.

One of the special duties of the local health department is to disinfect verminous properties and persons. *Insect Pests*, by W. C. Harvey and H. Hill (2nd ed., pp. 347, 14s.; H. K. Lewis and Co., London, 1947), is a useful handbook for the medical officer or sanitary inspector, particularly for its account of practical procedure and legislative control. The biological data about the various pests form the weakest section of the book; there are also some errors and misspelt specific names. The quality of the illustrations varies: about half are photographs which, for such difficult subjects, are fairly good; the rest are drawings and are rather poor. The authors have enlarged this edition to include information about mosquitoes and moths (clothes moths), which for some mysterious reason they discuss in the same chapter. There is an informative chapter on the new insecticides, such as D.D.T., and the authors have taken pains to describe the practical applications of these materials.

INTRAVENOUS ALIMENTATION*

BY

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The proper functioning of the body in all or any of its parts demands a sufficiency of all essential nutrients. I mention this obvious fact merely for emphasis. When injury or disease of an incapacitating degree occurs nutrition is nearly always interfered with and malnutrition may be said to have begun. The two main causes are: (a) the direct effect of the disease or injury leading to destruction of tissues and loss of nitrogen, and (b) inability (or disinclination) to take and retain food. If destruction of tissue continues unchecked malnutrition becomes progressive and a vicious circle begins; the disease causes digestive upsets or anorexia, or both, which in turn aggravate the disease. The clinician then has on his hands the original, diseased state complicated by starvation or semi-starvation. He will attempt to break the vicious circle by removing the cause of the tissue destruction or by checking it, and he will probably try to supply nutrients to the tissues so as to combat the malnutrition and assist the body to overcome the primary condition. In chronic conditions, too, these considerations are relevant, and superadded infections, bed sores, or hypostatic pneumonia may develop and make further contribution to the vicious circle.

By malnutrition I mean derangement of the physiological processes concerned in the supply of essential nutrients in sufficient amounts to any and every part of the body and with their metabolism. Although it includes in the broad sense the effects of excess of some or all nutrients, such considerations are not germane to this paper, and I therefore restrict the meaning of the term to the effects of failure of all nutrients or of some to reach the tissues in sufficient quantities. Malnutrition in this sense might be caused by inability to swallow food—e.g., in stenosis of the oesophagus and comatose states; by inability to retain and digest food—e.g., in cyclic vomiting; by failure of absorption—e.g., in persistent diarrhoea. In infective states of long duration, happily less common now than before the introduction of the sulphonamide drugs and penicillin, malnutrition is a prominent feature, partly because of anorexia and partly because of impaired digestion and assimilation; and if stupor and the "typhoid state" supervene inanition becomes absolute and a fatal issue is a matter of time. If the clinician were able to supply nutrients to the body, not merely to stave off starvation but also to supply the elements to reconstruct the damaged tissues and to form antibodies, the outlook would at once be transformed.

Thanks to researches in recent years, we are now able by means of intravenous alimentation to meet such situations with much greater confidence than formerly. Hydrolysates of protein suitable for intravenous use were first prepared about seven or eight years ago. Before that time intravenous alimentation was confined to the use of saline and glucose solutions, the value of which is strictly limited because of the absence of protein.

Protein Requirements

In the conditions we have been considering it is protein that is specially required.

Metabolizable Proteins.—The intestinal villi cannot absorb proteins until they have been hydrolysed by digestion

* Substance of a lecture given to the North of England Branch of the British Medical Association on May 8, 1947.