conciliatory; you will reject useful advice and friendly assistance; you will lose your sense of objectivity. In the group which I am called upon to direct, atmosphere is everything. We are all harnessed to one common cause, and everyone furthers it to the best of his strength and ability. Frequently we cannot distinguish what is mine and what is thine, but through this our common cause only gains.

"Thirdly, passion. Remember, science requires your whole life. Even if you had two lives to give it would still not be enough. Science demands of man effort and supreme passion. Be passionate in your work and in your quests. . . ."

PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS*

BY

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In February, 1945, 14 centres were appointed by the Medical Research Council to investigate the value of penicillin in subacute bacterial endocarditis. By March, 1946, 269 patients had been treated, and the results were reported in this *Journal* (Christie, 1948). These patients have been followed for a further two years, and, in addition, 139 new cases have been treated. From the more recent results it is clear that some recommendations made in the previous report must be revised.

Results of Investigation

By March, 1946, 58 previously untreated patients had received 500,000 units of penicillin daily for one month; four (7%) relapsed or died infected. Since then another series of 71 previously untreated patients have been treated by the same system of dosage, and 14 (20%) have relapsed or died infected (Table I). No reason has been found for

TABLE I.—Patients Treated for 28 Days with Daily Dose of 500,000 Units. (No Patient had Previously Received Penicillin)

	No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Months)	Relapsed or Died Infected
Before March, 1946	58	25	3	1	29	43	7%
After March, 1946	71	22	2	12*	35	20	20%
Total	129	47	5	13	64	30	14%

* One patient relapsed with the same organism after 1½ years.

the higher rate of relapse and uncontrolled infection in the second series—in fact, it may have been due to chance—but the therapeutic implication seems to be that the standard daily dosage should be greater than 500,000 units.

A closer relation between the sensitivity of the infecting organism and the results of treatment can now be shown (Table II). When the resistance of the organism does not exceed that of the standard Oxford staphylococcus the relapse rate after 500,000 units a day is low; with slightly more resistant organisms the relapse rate increases.

More recently 18 previously untreated patients have received 2,000,000 units daily for at least one month; none of these relapsed or died infected (Table III). In

*Report to the Medical Research Council on 408 patients treated in 14 centres appointed by the Penicillin Clinical Trials Committee.

TABLE II.—Comparison of Results of Treatment with Sensitivity of Organism to Penicillin. (Resistance Expressed as a Multiple of the Resistance of the Standard Oxford Staphylococcus.) All Patients Received 500,000 Units a Day for 28 Days. No Patient had Previously Received Penicillin

Result of treatment	Coefficient of Resistance						Total
	1 or Less	2	3-6	8-16	32 or More	Not Known	
Died controlled	23	6	4	2	—	12	47
Died uncontrolled	—	1	1	—	1	1	5
Relapsed	5*	3	2	—	3	—	13
"Cured"	33	12	4	2	—	13	64
Total	61	23	11	4	4	26	129
Relapsed or died infected	8%	22%	27%	0%	100%	4%	

* One patient relapsed with the same organism after 1½ years.

none was the resistance of the infecting organism more than twice that of the Oxford staphylococcus. Another 13 patients who had relapsed after previous treatment were given 2,000,000 units a day for at least one month (Table III). The infection was uncontrolled in four, but in all of these the coefficient of resistance of the infecting

TABLE III.—Patients Treated for 4 to 6 Weeks with a Daily Dose of 2,000,000 Units

	No. Treated	Died with Infection Apparently Controlled	Died with Infection Uncontrolled	Relapsed	"Cured"	Average Follow-up (Months)	Relapsed or Died Infected
No previous treatment with penicillin	18	9	—	—	9	11	0%
Previously treated with penicillin	13	1	—	4	8	16½	31%

organism was at least 64. The infection in another patient was eliminated although the coefficient of resistance was 32.

Revised System of Dosage.—These results indicate that a dose of 2,000,000 units of penicillin a day for four or six weeks is adequate in most cases. This dosage may be expected to cure the infection in nearly every patient when the coefficient of resistance of the infecting organism is not more than 4 or 8. The coefficient of resistance of the infecting organism is rarely over 8, but when it is there is a greater risk of relapse. The blood should be cultured several times both during and after treatment; if infection continues or recurs at least 10,000,000 units a day should be given. Very resistant organisms (i.e., those with a C.R. of over 32) are unlikely to be controlled by fewer than 10,000,000 units a day, and may not respond to 40,000,000. Treatment with other antibiotics, alone or combined with penicillin, or the use of substances such as "caronamide," which delay the excretion of penicillin, have then to be considered.

Delayed Relapses and Reinfections.—In patients who relapse after treatment the blood culture becomes positive usually within 60 days. But in 14 patients infection recurred after periods ranging from 4 to 50 months, and in five of these the second infecting organism clearly differed from the first. Many patients have now been followed up for four years, and the incidence of delayed relapse or reinfection among them has been found to be about 2% per annum.

Bacteriologically Negative Cases.—Only the 408 patients with a positive blood culture have so far been considered, but reports of 35 patients with negative blood cultures have

been collected by six of the centres (Table IV). Three facts have been established: (a) with the comparatively small doses of penicillin used only 6 of 26 previously untreated patients were cured; (b) the fever returned or was not controlled in 11 of the 26 previously untreated cases; (c) in the 13 who died with uncontrolled fever, organisms were seen post mortem in the vegetations of 6. It is not known whether larger doses will produce better results, but it is

TABLE IV.—*Bacteriologically Negative Cases*

	Dosage	No. Treated	Died with Fever	Controlled	Died with Fever Uncontrolled	Fever Returned	"Cured"
No previous treatment with penicillin	2,000,000 units for 1 month or more	2	2	—	—	—	—
	500,000 units for 1 month (approx.)	15	5	6	3	1	1
	250,000 units for 1 month (approx.)	7	2	1	—	—	4
	Unclassifiable	2	—	1	—	—	1
	Total	26	9	8	3	6	6
Previously treated with penicillin	2,000,000 units for 1 month or more	1	—	1	—	—	—
	500,000 units for 1 month (approx.)	4	3	1	—	—	—
	250,000 units for 1 month (approx.)	2	—	2	—	—	—
	Unclassifiable	2	1	1	—	—	—
	Total	9	4	5	—	—	—

suggested that these patients should be given 2,000,000 units a day and that the dose should be increased if the clinical response is unsatisfactory. In view of the importance of establishing the coefficient of resistance of the infecting organism it is unwise to abandon blood cultures until at least three have proved negative. An anaerobic culture should always be included.

Factors Affecting Prognosis.—In general the recent results confirm the conclusions regarding prognosis and causes of death discussed in the previous report. A detailed analysis of these patients will be incorporated in a review of the subject which is now being prepared.

Conclusions

Patients with subacute bacterial endocarditis should be given at least 2,000,000 units of penicillin a day for a month or six weeks.

When the infecting organism is highly resistant to penicillin, or when it cannot be isolated, it is difficult to estimate the appropriate dose. Some factors involved in making this assessment are discussed.

The incidence of delayed relapse or reinfection is approximately 2% per annum.

REFERENCE

Christie, R. V. (1948). *British Medical Journal*, 1, 1.

SUDDEN OBESITY AND PSYCHOLOGICAL TRAUMA

BY

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It has long been recognized that loss of weight can accompany psychotic and psychoneurotic illnesses such as depression and anorexia nervosa. Clinicians also meet atypical cases of depression in which there is an increase of weight, and this has been vaguely linked with endocrine disturbances, such as may occur at the female and male climacteric. This paper is concerned with a group of cases showing a sudden onset and rapid development of obesity, with or without amenorrhoea and menstrual disturbances, which gives rise to a syndrome of obesity, anxiety, tension, and depression.

The investigation first arose when it was observed that some obese patients who failed to respond satisfactorily to the usual methods of treatment dated their obesity and also some psychoneurotic symptoms to a specific incident that might well have inflicted psychological trauma. We found that too little attention had been paid to the emotional factors in the first instance, and the patients had been treated on an organic basis for long periods. We do not claim that the treatment pursued with this group is primarily aimed at reducing weight, but we have used it to alleviate the associated mental distress and have found that patients often show a parallel reduction of weight and become more amenable to accepted methods of treatment of obesity.

The problem of obesity has been extensively investigated by physiologists for many years, and no essential underlying disorder of metabolism has been convincingly demonstrated. Newburgh (1942) reviewed the subject and came to the conclusion that excessive intake of calories with reduced activity could account for almost every case. He explained the irregularity of loss of weight when on a strictly limited calorie intake as being due to fluid retention, and quoted an example that demonstrated this point clearly.

Effect of Lesions of the Hypothalamus

Lesions of the hypothalamus in animals in which the anterior lobe of the pituitary has either been removed or left intact result in obesity (Hetherington, 1943). This obesity does not, however, follow extensive damage to the hypophysis provided the hypothalamus is intact. These clear-cut experiments of Hetherington's have solved the controversy that has lasted for over 30 years between Fröhlich, who maintained that damage to the hypophysis was the necessary factor, and Erdheim, who believed the essential lesion must be in the hypothalamus. Animals that have had suitably placed lesions in the hypothalamus not only show an increase in appetite that accounts for their obesity in almost all instances, but the manner in which they eat their food changes from the normal habit of the species.

The appetite of the animals operated on is described as voracious, savage, or wolfish by various authors, and rats

According to a report (B.U.P.) Dr. Robert Coghill, who played an important part in the development of penicillin mass-production, told a meeting of the American Chemical Society that, although 200 antibiotics had been investigated, only six have appeared on the market, and of these two are of limited use only. While the term "miracle drug" could legitimately be applied to penicillin, Dr. Coghill stated that the chief miracle in connexion with one or two currently used antibiotics would be if they were still in use in five years' time. He added, "The truth of the matter is, unfortunately, that the vast majority of antibiotics are for a variety of reasons utterly worthless for human therapy."