after a single therapeutic dose of x rays in the interpretation of the consequences of exposure to irradiation of greater and possibly lethal proportions.

Summary

The pattern of symptoms following a single therapeutic dose of x rays has been described, based on the findings in a group of 50 patients. The pattern was found to consist of three well-defined phases: a latent period extending from the administration of the x rays to the onset of symptoms; a period of acute disturbance which persisted for approximately between one and a half and four hours after the onset of symptoms, depending on the degree of upset; and a recovery period which in the most acutely disturbed patients extended over four to five days. In those patients in whom the period of acute disturbance was not associated with vomiting the latent period was found to be significantly longer than in those who vomited.

A brief description has been given of the general radiation syndrome produced in man and in many types of mammals following a single mid-lethal dose of x rays, in which four general periods of reaction can be discerned: the periods of initial reaction, acute reaction, subacute reaction, and chronic reaction.

The similarity between the pattern of symptoms following therapeutic doses of x rays and the symptoms of the period of initial reaction of the general radiation syndrome has been stressed, and attention has been drawn to the possible value of using clinical studies based on single therapeutic doses of x rays to interpret what may occur when, either accidentally or under conditions of war, much higher doses are received.

No account has been given of the physiological disturbances produced by therapeutic doses of x rays, which will form the subject of a later communication.

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APPENDIX

The mean length of the latent period in the less severely upset group of patients (Group A) has been compared with that in the more severely upset group (Group B). The distribution of the different lengths of the latent periods within each group, the value of the mean and t and P values of the difference of the means are shown below.

	Length of Latent Period (Hours)							
	1-1.49	1.50-1.99	2.0-2.49	2.5-2.99	3.0-3.49	3.5-3.99	4.0-4.49	4.5-4.99
Group A (19 patients)	0	1	2	7	0	7	2	0
Group B (23 patients)	5	4	4	4	1	2	1	2

Mean length of Group A = 3.06 hours } Difference of mean
Mean length of Group B = 2.44 hours } lengths = 0.62 hr.
The t value of the difference is 2.10, indicating that $P < 0.05$ and that the difference is significant.

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ORAL N,N'-DIBENZYLETHYLENE-DIAMINE PENICILLIN IN CHILDREN

BY

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The greatest drawback to the use of oral penicillin has been, in our experience, the variability with which it is absorbed into the blood stream. Several penicillin derivatives have been tried in different dosages, with and without antacids, before and after meals, and scaling the dosage according to body weight. While in a good proportion of cases therapeutic blood levels have been obtained by the oral route, with no preparation have consistent levels been observed; this has meant that, when any case has been treated with oral penicillin, blood-level estimations have been essential to confirm that the antibiotic was being absorbed.

Recently a new salt N,N'-dibenzylethylenediamine penicillin has been available (Szabo, Edwards, and Bruce, 1951); this is referred to here as "penidural." It has been the subject of a recent report by Fletcher and Knappett (1953) as a long-acting repository penicillin following intramuscular injection; we have investigated it from the point of view of reliability of absorption following oral administration.

Side-effects.—Several adults have complained of borborrygmi and urgency at stool during the first 24 hours of treatment but not subsequently. No children of any age have been disturbed, and the palatability of the product has made its administration easy.

Material and Methods

Penicillin blood levels were estimated, using a dilution technique with a strain of *Staphylococcus aureus* of sensitivity to 0.03 µg. of penicillin per ml. A total of 101 children of all ages were given 300,000 units of penidural and their blood levels were estimated three to four hours after administration for reliability of absorption. In addition a small series of 17 adult volunteers were investigated with the same preparation.

The penidural was given irrespective of the times of meals and whether the stomach might be full or not.

Results

Fig. 1 shows that the antibiotic was reliably absorbed in all of the 118 cases in which it was administered, and Table I shows the levels obtained in the 101 children. In several

TABLE I.—Serum Penicillin Levels in 101 Children Three Hours After 300,000 Units of Penidural

Weight in lb.	0.06 unit per ml.	0.125 unit per ml.	0.25 unit per ml.	0.5 unit per ml.	Total Cases
0-10	—	1	4	—	5
11-20	—	5	2	1	8
21-30	7	4	6	1	18
31-40	10	13	—	2	25
41-50	8	8	1	—	17
51-60	5	7	—	—	12
61-70	5	5	1	—	11
71 and over	1	4	—	—	5
TOTALS	36	47	14	4	101

TABLE II.—Serum Penicillin Levels in Units per ml. at 3 p.m. on Consecutive Days. 300,000 Units of Penidural Given Six-hourly Throughout

Case No.	3 hours	27 hours	51 hours	75 hours
1	0.06	0.25	0.25	0.25
2	0.125	0.25	0.25	0.25
3	0.25	0.5	1.0	1.0
4	0.125	0.5	0.5	0.5

FIG. 1

FIG. 2

cases hourly penicillin levels were estimated and a cumulative effect was seen following a second oral dose. Fig. 2 shows one such typical example, in which there were satisfactory blood levels for six hours, but no residual level at 12 hours after a single dose. When a second dose was given at six hours, not only were the levels for the succeeding six hours higher than in the first period but there was also a residual level at 12 hours.

In Table II are shown the blood levels at 24-hour intervals in four consecutive patients of differing weights and ages to whom six-hourly penidural was being given. Blood samples were taken at the same time each afternoon, three hours after the last dose of the drug. Each shows the same increase in blood levels as is depicted in Fig. 2. There was some indication in the figures shown in Table I that better blood levels were obtained when penidural was given before meals.

Discussion

Penidural is the first oral preparation of penicillin which has in our experience been reliably absorbed in 100% of patients, irrespective of size and weight and using a standard dosage of 300,000 units. No attempt has been made to work out a graded system of dosage according to body weight, but it is possible that in the smaller children thera-

peutic blood levels might be obtained with lesser amounts of penidural. The emergence of a reliable oral penicillin seems to bring this drug into line with the newer antibiotics where penicillin-sensitive organisms are being dealt with.

In the treatment of acute infections blood levels during the first six hours with this oral penicillin alone cannot be regarded as adequate, and in five cases of acute illness in which penidural has been used therapeutically a single intramuscular injection of a large amount of crystalline penicillin has been used to augment the blood level during this period. In these cases—two of osteomyelitis and three of pneumonia—the results obtained have been as good as those which would have been anticipated had intramuscular penicillin been chosen for treatment.

A rational scheme of treatment of acute infection appears to be an initial intramuscular injection of 600,000 units of penidural (Fletcher and Knappett, 1953) and 100,000 units of crystalline penicillin, with 300,000 units of penidural orally, the treatment continuing thereafter only with oral penidural. Such a scheme will produce reliable therapeutic penicillin levels and should be adequate to treat infection by penicillin-susceptible organisms. Abuse of this new penicillin preparation is likely to enhance the growing number of strains of penicillin-resistant bacteria, and it is hoped that the growing menace of penicillin-resistant staphylococci will not be unnecessarily increased by improper dosage or dose-spacing.

We are indebted to Messrs. John Wyeth, Ltd., London, for a plentiful supply of penidural.

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COMBINED ORAL PENICILLIN AND SULPHADIMIDINE IN ACUTE MIDDLE-EAR INFECTIONS

BY

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Modern antibacterial drugs have revolutionized the treatment of acute otitis media, and the role of surgery in this condition is of rapidly diminishing importance. Before the discovery of antibiotics, sulphonamide administration was an established part of the therapy of this condition (Hall, 1948). Owing to the limitations imposed by toxicity upon the attainable blood sulphonamide level, and the diversity of the invading organisms, it is not surprising that sulphonamides alone are often unable to quell the infection.

The Literature

The commonest causal agents are *Staph. aureus* and *Str. haemolyticus*; consequently much better results follow the use of penicillin as the antibacterial agent (György *et al.*, 1946; Lierle and Paul, 1946; Robinson *et al.*, 1948; Jersild and Kiørboe, 1950). However, this still leaves the dangerous residue of insensitive Gram-negative bacilli, notably *Bact. coli* and *Proteus* strains, which are often present in varying numbers in a mixed infection. Elimination of the main infecting bacteria allows, and even stimulates, these fellow-travellers to multiply rapidly and restore the severity of the original disease condition.

Of the newer antibiotics, streptomycin carries with it a danger of vestibular damage and is unlikely to commend itself for the treatment of infections in the aural cavities. Chloramphenicol and aureomycin, with a wider antibacterial range, approach more closely to being ideal drugs for the