SOME OBSERVATIONS ON PENICILLIN

ITS DOSAGE AND ADMINISTRATION IN INFANCY*

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These observations are based on a series of seventy-eight cases, under the age of one year, treated at the Hospital for Sick Children, Great Ormond Street. Thirty-seven of these infants were neonates (under the age of one month).

Prior to penicillin treatment, blood cultures, post-nasal swabs, rectal swabs, and swabs from any obvious site of infection were taken. Analysing the bacteriological results the predominance of *Staphylococcus aureus* as the causative micro-organism was striking. Infections with gram-negative bacilli were, of course, not included in this group, since they are not susceptible to penicillin treatment.

TABLE 1

MICRO-ORGANISMS ISOLATED FROM 78 INFANTS UNDER ONE YEAR PRIOR TO PENICILLIN TREATMENT

<i>Staphylococcus Aureus</i>	..	59 cases: 75 per cent. (14 per cent. with other organisms.)
<i>Haemolytic Streptococcus</i>	..	18 cases: 23 per cent. (10 per cent. with other organisms.)
<i>Pneumococcus</i>	..	11 cases: 14 per cent. (6 per cent. with other organisms.)
<i>Staphylococcus Albus</i>	..	2 cases.
<i>Klebs Loeffler Bacillus</i>	..	1 case.

TABLE 2

(SUB-GROUP OF TABLE 1)

MICRO-ORGANISMS ISOLATED FROM 37 NEONATES UNDER ONE MONTH PRIOR TO PENICILLIN TREATMENT

<i>Staphylococcus Aureus</i>	..	30 cases: 81 per cent. (13 per cent. with other organisms.)
<i>Haemolytic Streptococcus</i>	..	11 cases: 30 per cent. (16 per cent. with other organisms.)

It is also worthy of note that in a series of twenty-five cases of bacteraemia, *Staphylococcus Aureus* was isolated from the bloodstream in nineteen instances (76 per cent.).

This very high incidence of *Staphylococcal* infections constitutes a marked change of the predominant bacteriological flora compared with such

statistics as are available of former years. Has a decade of sulphonamides pushed the highly sensitive organisms, such as haemolytic streptococci and pneumococci into the background, whereas it has but slightly touched the *Staphylococcus aureus*?

Since penicillin is much more powerful in its action on *Staphylococcus aureus* than even the most active sulphonamide (*Sulphathiazole*) its place in infantile infections appears to be established *eo ipso*.

Dosage and administration. The problem of dosage is not yet finally solved. As a practical suggestion, however, a dosage scheme of 1000 units per pound expected body weight per 24 hours is recommended, the expected body weight being calculated from the birth weight and age. A convenient figure near the calculated 24-hour requirement is made up in normal saline to contain one dose in 1 c.c. Injections are given every four hours intramuscularly, coinciding where possible with feeding times. Intermittent dosage has been found superior to a continuous intramuscular drip, since the risk of secondary infections by excreta is thus at a minimum.

Because of its rapid excretion by the kidneys, penicillin is usually given three-hourly. Impaired renal function leads to prolonged retention of penicillin in the body. Since renal function is not fully established in infancy, four-hourly spacing of injections is suggested. Similarly six-hourly injections in premature infants were tried and found to be quite satisfactory.

In trying to justify this proposed dosage scheme, penicillin levels were assessed in blood serum taken at varying intervals of the four-hour period between two injections.

Thirty-six serum samples of four infants were assessed for their penicillin content, first on the basis of 1000 units per pound body weight, and then of 3000 units per pound body weight. Estimations were made at half an hour, one hour, two, three and four hours after injections. The average results are set out in the following figure (Fig. 1).

In the adult, 1000 units per pound body weight correspond to a total of 160,000 units per 24 hours, or 20,000 units three-hourly, and 3000 units per pound body weight to 60,000 units three-hourly.

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FIG. 1.

FIG. 2.

TABLE 3

AVERAGE PENICILLIN LEVELS IN SERUM

	Adults, 3-hourly	Infants, 4-hourly
1000 units per lb. body weight.	0.09 units/c.c.	0.12 units/c.c.
3000 units per lb. body weight.	0.21 units/c.c.	0.23 units/c.c.

Hudson et al. (1945) have compiled graphs on the 20,000 and 60,000 units basis. They also worked out a so-called 'average level.' The total surface area of the vertically shaded curve equals a rectangle (shaded horizontally) whose ordinate indicates the 'average level' (Fig. 2).

There is a close similarity in the 'average levels' in adults on three-hourly and in infants on four-hourly dosage (see Table 3). This would appear to support the wider spacing of injections in infants.

More penicillin levels were estimated at the latter period of the four-hour interval, i.e. three and four hours after an injection, in order further to justify the proposed four-hourly administration. These investigations were carried out on sixty-one infants, on 1000 units per pound body weight per 24 hours (Table 4).

0.02 units per c.c. appears to be the minimal effective level since it just inhibits the Oxford standard strain of *Staphylococcus aureus* as well as the standard haemolytic streptococcus which has been used in some of these estimations. It is worthy of note that 33 per cent. at four hours and 18 per cent. at three hours fell below 0.02 units per c.c. This, however, has not affected their rate of clinical and bacteriological recovery, compared with the infants in whom the levels were adequate throughout.

TABLE 4

PENICILLIN LEVELS IN SERUM ON THE DOSAGE OF 1000 UNITS PER POUND BODY WEIGHT

	Units per c.c.	No. of cases	Per cent.
At 3 hours after injection.	0.16	5	8
	0.08	9	15
	0.04	15	25
	0.02	21	34
	less than 0.02	11	18
	0.02	11	18
At 4 hours after injection.	0.16	2	3
	0.08	2	3
	0.04	7	11
	0.02	30	50
	less than 0.02	20	33
	0.02	20	33

This gives an average of 0.04 units at three hours.

This gives an average of 0.02 units at four hours.

Finally, further evidence in support of the proposed dosage scheme was adduced by an analysis of the sensitivity to penicillin of 123 strains of micro-organisms, isolated from cases in this series (Table 5).

It would appear that 86 per cent. of the strains analysed below are sensitive to the 'average penicillin level' of 0.12 units per c.c. obtained on the 1000 units per pound body weight basis. Only one case died in each of the 'less sensitive' and 'relatively insensitive' groups although treated on the same dosage; 3000 units per pound body weight

would but slightly affect the issue so far as penicillin-sensitivity is concerned. It would not cover the 'relatively insensitive group' if the 'average penicillin level' of 0.23 units per c.c. be taken as an indication.

TABLE 5
PENICILLIN SENSITIVITY TESTS ON
123 BACTERIAL STRAINS

Staphylococcus Aureus	..	..	..	86 strains
Haemolytic Streptococcus	..	..	..	20 strains
Pneumococcus	..	..	..	8 strains
Staphylococcus Albus	..	..	..	7 strains
Meningococcus	..	..	..	1 strain
Klebs Loeffler Bacillus	..	..	..	1 strain

GROUP I Sensitive	GROUP II Less sensitive	GROUP III Relatively insensitive
(Inhibited by less than 0.1 units per c.c.).	(Inhibited by 0.2 not by 0.1 units per c.c.).	(Not inhibited by 1.0 unit per c.c.).
106 strains or 86 per cent.	7 strains or 5.7 per cent.	10 strains or 8.3 per cent.

Factors other than the penicillin-sensitivity of micro-organisms, however, might have an important bearing on the question of higher dosage in certain cases. These problems are still under investigation.

Discussion and summary

A bacteriological survey of a group of seventy-eight infants selected for penicillin treatment yielded *Staphylococcus aureus* in 75 per cent., in 81 per cent. of thirty-seven neonates, and in 76 per cent. of twenty-five cases of septicaemia.

A dosage scheme of 1000 units per pound expected body weight per 24 hours is suggested. This is divided into six doses and each dose made up in 1 c.c. normal saline, given every four hours intramuscularly.

Average penicillin levels on this four-hourly dosage scheme were compared with those in adults on a comparable dosage given at three-hourly intervals, and similar results obtained.

Levels were assessed three and four hours after an injection; they were still bacteriostatic in the majority of cases.

Eighty-six per cent. of all bacteria other than gram-negative bacilli tested for penicillin-sensitivity were susceptible to the average penicillin level obtained with this dosage. Three-fold increase of dosage did not affect the issue materially.

REFERENCE

- Bodian, M. (1945). *Proc. Roy. Soc. Med.*, **38**, 572.
Hudson, R. V., Meanock, I. R., and Selbie, S. R. (1945).
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