Potassium output showed only inconspicuous fluctuations. In one patient the daily excretion of phosphorus was liberally increased during treatment.

Attempts were made to maintain 3 of the group by the daily administration of ACTH, 25 mg, or by weekly administration of 100 mg in divided doses. With both systems, fairly satisfactory control was secured for intervals of 6-8 weeks. Three to 4 weeks after discontinuation of medication, indications of relapse began to appear. In one instance, later repeated courses of ACTH failed to bring about diuresis, a decrease in serum cholesterol or an increase in serum proteins. The second patient has had no further treatment since Oct. 6; he shows no evidence of salt and water retention; the blood urea is at the control level. The serum cholesterol is 294 mg% and the total protein is 6.6 g% with an albumin value of 3.4 g%. Prior to treatment the total protein was 4.0 g %; the albumin 1.1 g %. The third patient discontinued treatment on the same date. He showed no tendency to redevelop edema until 3 months later, at which time the serum proteins diminished sharply.

Conclusions. It is concluded that an appropriate stimulus to the adrenal cortex by the administration of adrenocorticotropin is capable of producing marked modifications in the nephrotic syndrome. These modifications include reduction in serum cholesterol and urine protein, increase in serum proteins and profound diuresis. With one exception the diuresis occurred after discontinuance of ACTH, and the improvement in nitrogen balance and serum values continued for several weeks.

Adrenocorticotropin was furnished through the courtesy of Dr. John R. Mote of Armour Laboratories.

Received March 16, 1950. P.S.E.B.M., 1950, v74.

Effect of Penicillin Dosage Schedule on Treatment of Experimental Typhoid Infections in Mice. (17810)

A. KATHRINE MILLER, DOROTHY L. WILMER, AND W. F. VERWEY.
(Introduced by L. Earle Arnow.)
From the Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pa.

It has been reported by Zubrod(1) and by White and his co-workers(2) that, for the treatment of experimental streptococcal infections in mice, the total amount of penicillin required does not vary over a fairly wide range of dosage schedules. Since it is our opinion that the major problems of penicillin therapy are now centering around the management of infections caused by organisms of high penicillin resistance, we have studied the relationship between dosage schedules and the amount of this antibiotic agent required to protect mice infected with the Panama No. 58 strain of *Salmonella typhosa*. This organism has been selected because it is quite resistant to the action of penicillin in comparison with the highly susceptible streptococci used by the above mentioned workers. When *Salmonella typhosa* was used as the infecting agent, it was found that there were marked differences in the amount of penicillin required for therapy depending upon the number and frequency of the doses employed.

These data, which can be obtained with adequate precision only from animal experimentation, are being presented because it is believed that the findings have important application to the use of penicillin in the treatment of infections in human patients, where it is desired to use the antibiotic agent with maximum efficiency and economy.

1. Zubrod, Charles G., *Bull. of the Johns Hopkins Hospital*, 1947, v81, 400.

2. White, H. J., Baker, M. J., and Jackson, E. R., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 199.

Methods and materials. Female mice of the C.F. 1 strain weighing 16-18 g, were infected intraperitoneally with 0.5 cc of 5% mucin containing 10,000 minimum lethal doses of Panama No. 58 strain of *Salmonella typhosa*, and were treated on different dosage schedules by the intramuscular injection of 0.05 cc of an aqueous solution of crystalline penicillin G. Therapy was confined to a 24-hour period, and, in all cases, the first injection was given at the time of infection (*i.e.*, at zero hour). The animals were observed for a period of 7 days, after which time the amount of penicillin required to protect 50% of the animals (PD_{50}) was calculated by the method of Reed and Muench(3).

Results. Average results from 3 experiments are shown in Fig. 1. It can be seen that in these experiments the PD_{50} was found to vary with the treatment schedule. The total amount of penicillin required to protect 50% of the infected animals when treatment was confined to a single injection at zero hour was 3300 units. When 2 doses were given, one at zero time and the second 12 hours later, individual doses of 2450 units or a total of 4900 units were required. In this phase of the work, as the number of equally spaced injections increased, the total amount of penicillin used also increased, although the size of the individual doses decreased.

Included with the above experiments, using the same preparations of challenge organism and comparable groups of mice, was a study

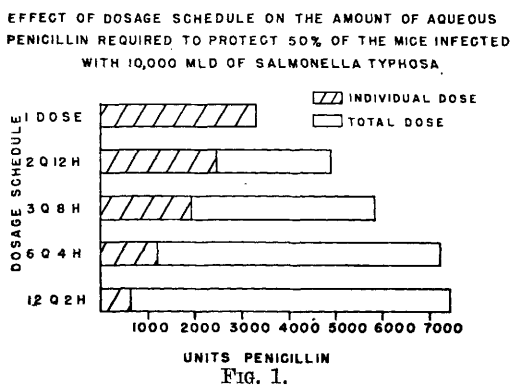

FIG. 1.

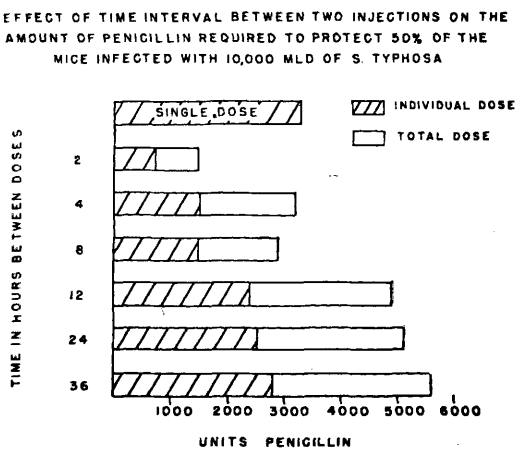

FIG. 2.

to determine the effect of the time interval between 2 injections on the PD_{50} penicillin value. Here all the infected mice were treated with 2 equal doses of the antibiotic agent: the first injection was given at zero hour; the time of the second treatment varying from 2 to 36 hours after the first. Fig. 2 shows the average results from this phase of the three experiments.

The total amount of penicillin needed to protect 50% of the mice when the 2 injections were spaced two hours apart was 1500 units, an amount approximately one-half that required for the single injection treatment. When the injections were spaced at 4- or at 8-hour intervals, the amount of penicillin required approximated the single dose schedule. Increasing the interval between injections to 12, 24, or 36 hours greatly increased the PD_{50} value.

Discussion. These data show that in the treatment of an acute typhoid infection in mice the amount of penicillin necessary to protect 50% of the animals does vary with the dosage schedule used. In a previously published paper(4), it was suggested that the intensity of penicillin therapy may be represented as a function of the relationship between the concentration of penicillin and the time during which this antibiotic agent remains at or above a minimal antibacterial

3. Reed, L. J., and Muench, H., *Am. J. Hyg.*, 1938, v27, 493.

4. Verwey, W. F., and Miller, A. Kathrine, PROC. SOC. EXP. BIOL. AND MED., 1947, v65, 222.

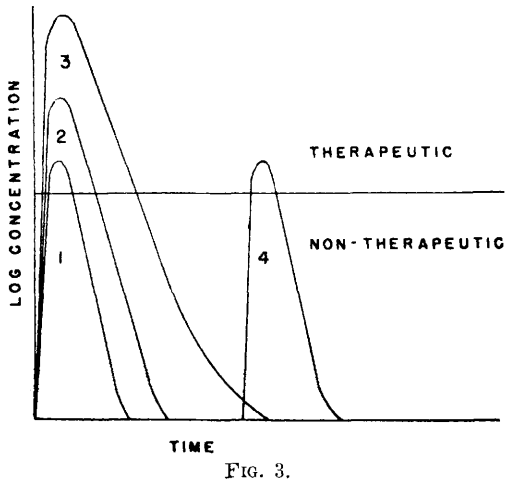

FIG. 3.

concentration in the body. If this concept is visualized in terms of a curve in which penicillin concentration is plotted against time, then intensive therapy is represented by that area of the curve that is above a minimal baseline. The position of this baseline on the ordinate is dependent on the sensitivity of the infecting organism. When the baseline is high, as for a resistant organism, and the size of each injected dose is small, then a proportionally large amount of each dose contributes only to the area below the baseline which does not represent intensive therapy. This is illustrated by curve 1 of Fig. 3. As the unitage of the individual dose is increased, the proportional amount of the injected penicillin that contributes to the effective area progressively increases as in curves 2 and 3. This would result in more efficient therapy, and would explain the corresponding decrease in the total amount of penicillin that was required in our experiments as the number of equally spaced injected doses decreased from 12 to 1 and the size of the individual doses increased from 620 units to 3300 units.

For therapy to be confined to a single injection, however, (*e.g.*, curve 3) it is necessary that this one dose of penicillin be sufficient to destroy most or all of the invading organisms. If the size of this dose is too small (*e.g.*, curve 1) the concentration of penicillin that diffuses into the area of infection may be so low that some of the infecting organisms may be injured but not destroyed. Some cells, indeed, may escape completely any deleterious effect of the antibiotic agent. In the absence of further therapy, these survivors later may multiply and re-establish the infection, leading to the death of the animal. When a second small injection closely follows the initial dose (curve 4, following curve 1), the residual organisms may be eliminated by the resulting augmentation of the killing effect of the antibiotic agent. As the interval between the two treatments is lengthened beyond the period of recovery for the injured and surviving organisms, the size of the individual effective dose gradually increases until each dose approaches the concentration required to protect with a single dose.

Summary and conclusions. When mice were infected with a relatively penicillin-resistant *Salmonella typhosa,* it was found that the penicillin PD_{50} varied with the treatment schedule. A smaller total amount of penicillin was required for protection when the treatment was given as a single injection than when 2, 3, 6, or 12 doses were divided equally within a 24-hour period. When the time interval between 2 doses was varied from 2 to 36 hours, it was found that the PD_{50} for the 2 dose 2-hour schedule represented an even smaller total amount, and, therefore, a more economical use of penicillin than did the single injection schedule.

These data would suggest that in the treatment of infections caused by organisms of high penicillin resistance, the common practice of dividing the total daily amount of penicillin into frequently injected doses may be an inefficient means of therapy. It would appear that the total amount of penicillin to be used in one day would be more effective if given as a few large doses. This procedure would result in the higher plasma penicillin concentrations and the correspondingly increased tissue concentrations required for a bacteriocidal action against relatively resistant organisms.

Received March 16, 1950. P.S.E.B.M.,1950, v74.