None of the therapeutic procedures prevented the formation of antistreptolysin or antifibrinolysin. The administration of salicylates, sulfadiazine, and/or a short course of penicillin failed to diminish the percentage of individuals exhibiting an antibody response, or the mean increase in antistreptolysin. The latter was greater in certain treated groups than in the controls. This result is probably not significant for the reasons stated below.

When penicillin was administered over a longer interval, the frequency of the antifibrinolysin response was decreased. An antistreptolysin response was also observed less often in those individuals in whom bacteriological relapse did not occur.

These latter observations suggest that the exhibition of penicillin in amounts adequate for the elimination of the hemolytic streptococcus from the throat may interfere with the formation of these antibodies. It is necessary to be very guarded in reaching such a conclusion based upon the study of small groups f individuals infected by a variety of types of Group A streptococci, since it has been demonstrated that the different types vary in their ability to stimulate the production of antistreptolysin (*4*) and antifibrinolysin (*2, 4*), and that great individual differences exist between various human beings in their ability to react to the antigenic stimulus of infection by these organisms (*3*).

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Blood Levels of Penicillin After Oral Administration With Various Antacids

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Many antacids have been employed with apparent success (*2, 3, 5, 6, 7, 12*) in an attempt to protect penicillin from destruction when given orally. Considerable discrepancy appears in the results reported, and it was felt that a comparison of the effectiveness of various antacids in a group of normal adults would be desirable. Though there may be considerable variation in gastric acidity from time to time in the same individual, comparative studies made largely on the same group of individuals, under stated conditions, should be more valid than those made on different groups with a variety of illnesses.

Methods

Subjects were allowed to have a soft diet, low in protein and fat. They were given 100,000 units of calcium penicillin along with the equivalent of 2.5 grams of one of the antacids. Aluminum hydroxide, magnesium trisilicate, and magnesium hydroxide were given as magmas or gels. The penicillin was freshly mixed with these preparations before use according to the method of Welch (*12*). Trisodium citrate and aluminum dihydroxy amino acetate were used in tablet form with penicillin incorporated in them. Seven control tests were made with penicillin administered in tap water, and in one case it was given in tap water to a pernicious anemia patient. Blood samples were obtained at hourly intervals for 4 hours, and urines were collected up to 6–12 hours. Blood levels of penicillin were determined by the Fleming Slide cell method (*4*) and urine concentrations by the Oxford cup method (*1*).

TABLE 1

Blood Levels of Penicillin After the Oral Administration of 100,000 Units of Calcium Penicillin in Tap Water

Subject	½ hr.	1 hr.	1½ hrs.	2 hrs.	3 hrs.	4 hrs.	Per cent excretion
*S	...	0.06	0.03	0	0	...	6.6
*S	...	.12	...	.03	0	...	....
*W	.12	.12	...	.06	0	...	15.9
†S	0	0	0	0	...	...	1.9
†W	...	0	0	0	0	...	1.5
†S	...	.12	0	0	0	...	1.25
†W	.03	0	0	0	0	...	0.48
‡R	...	0.24	...	...	0.24	0.03	24.2

* Empty stomach.
† Full stomach.
‡ Pernicious anemia.

TABLE 2

Blood Levels of Penicillin After Oral Administration With 100,000 Units of Calcium Penicillin in Aluminum Hydroxide Gel

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
K	0	0.06	0.015	0.015
L	0.03	0.015	0.015	0
R	0.12	0.06	....	0
F	0.12	0.03	0.03	0
W	0.24	0.12	0.015	....
G	0.03	0.03	0.03	0.03
ST	0.24	0.24	0.06	0
Average	0.11	0.079	0.03	0.007

Results

Of the tap water controls (Table 1) these tests were made with 100,000 units on an empty stomach, and

four tests were made on the same subject after a full meal. Penicillin levels were present up to one and a half to two hours when given on an empty stomach, but in only one instance was the drug demonstrable in the blood at the end of one hour when given on a full stomach. Penicillin was demonstrable in the urine as early as three minutes after administration. When given on an empty stomach the excretion varied from 6.6 to 15.9 per cent. When given on a full stomach the excretion varied from 0.48 per cent to 1.9 per cent. A pernicious anemia patient given 100,000 units orally in tap water showed a blood level of 0.24 units/cc. up to three hours and a level of 0.03 at four hours. Excretion in the urine was 24.2 per cent.

TABLE 3

BLOOD LEVELS OF PENICILLIN AFTER ORAL ADMINISTRATION OF 100,000 UNITS OF CALCIUM PENICILLIN WITH MAGNESIUM TRISILICATE

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
G	0.03	0.06	0.015	0
W	0.12	0.03	0.015	0
S	0.24	0.06	0.06	0.03
ST	0.24	0.03	0.03	0.03
C	0.24	0.03	0	0
Average	0.175	0.042	0.024	0.012

TABLE 4

BLOOD LEVELS OF PENICILLIN AFTER ORAL ADMINISTRATION OF 100,000 UNITS OF CALCIUM PENICILLIN WITH TRISODIUM CITRATE

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
F	0.12	0.12	0.06	....
R	0.48	0.24	0.06	0
ST	0.12	0.06	0.015	0.015
C	0.12	0.12	0.015	0.015
F	0.12	0.06	0.015	0.03
S	0.06	0.06	0.015	0.015
Average	0.17	0.11	0.03	0.018

Blood levels for the five antacids studied are shown in Tables 2, 3, 4, 5, and 6. It is obvious that all the antacids gave striking increases in blood levels of penicillin as compared to the tap water controls. The highest average levels at the end of the first hour were with trisodium citrate and magnesium trisilicate. The highest average levels at the end of the second and third hours were with aluminum dihydroxy amino acetate. The highest levels at the end of four hours were with trisodium citrate and aluminum dihydroxy amino acetate. This may be correlated with the fact that these two preparations were given in tablet form. The lowest results were obtained with milk of magnesia. The differences with the other antacids employed were not striking.

In two experiments calcium penicillin was adsorbed on aluminum hydroxide according to the method reported by Welch (*12*) and was given on an empty stomach in doses of 25,000 units every two hours for four doses. Blood and urine samples were taken hourly for seven hours. Urine collections continued at intervals up to 24 hours. No penicillin was demonstrated in the blood at any time by our method, and only traces appeared in the urine after nine hours. One subject given an initial dose of 50,000 units of this preparation followed by 25,000 units every hour for four hours showed hourly blood levels of 0.06, 0.12, 0.24, 0.12, 0.12, and 0.03. The excretion was 10.3 per cent.

TABLE 5

BLOOD LEVELS AFTER THE ORAL ADMINISTRATION OF 100,000 UNITS OF CALCIUM PENICILLIN WITH ALUMINUM DIHYDROXY AMINO ACETATE

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
W	0.06	0.03	0.03	0
S	0	0.12	0.06	0.03
H	0.24	0.12	0.06	0.03
J	0.24	0.24	0.03	0
B	0.12	0.24	0.03	0
S	0.06	0.03	0.03	0
A	0.12	0.24	0.06	0.06
Average	0.12	0.14	0.043	0.017

TABLE 6

BLOOD LEVELS OF PENICILLIN FOLLOWING THE ADMINISTRATION OF 100,000 UNITS OF CALCIUM PENICILLIN WITH MILK OF MAGNESIA

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
ST	0.06	0.03	0	0
S	0.24	0.24	0.12	0
ST	0.03	0.015	0	0
K	0.24	0.03	0	0

DISCUSSION AND SUMMARY

The five antacids used orally with penicillin in this study showed marked effects in maintaining the blood levels of the drug. With the exception of milk of magnesia, there were no striking differences with the various antacids. In no instance were the blood levels maintained as well as in the pernicious anemia patient who received the drug in tap water alone. Results with antacids are similar to the results obtained with the administration of penicillin in enteric coated capsules (*10, 11*), but the levels are far inferior to those obtained by the intravenous drip (*8*) or intramuscular administration in oil (*9*). It is apparent that maximum efficiency for the oral administration has not been attained.

Confirmation is lacking in my results of the prolonged blood levels of penicillin, as reported by Welch (*12*) when given in single or in divided doses with aluminum hydroxide gel.

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Studies on the Toxicity of Streptomycin for Man: A Preliminary Report[1]

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The advent of a new therapeutic agent, such as streptomycin (*4*), inevitably arouses curiosity about its efficacy on the one hand and about its potential and actual toxicity on the other. The parenteral administration of streptomycin to susceptible laboratory animals has produced fatty metamorphoses in the parenchymal cells of the liver and to a lesser extent in the tubular epithelium of the kidneys. These histological changes, which have been demonstrated by Mushett (*3*) are reversible and disappear rapidly after the drug is discontinued. Since both crude and crystalline streptomycin preparations produce these changes readily, their appearance must be attributed to a toxic property intrinsic in the antibiotic itself. Because of the lesions demonstrated in the viscera of experimental animals, the authors have attempted to evaluate the effect of parenteral streptomycin on the renal, hepatic, and hematologic functions of man. In the course of these experiments some clinical reactions have been encountered and will be discussed below.

Nine patients, whose ages ranged from 15 to 61 years, served as subjects. The total dosages of streptomycin varied from 1,850,000 units administered over a period of 48 hours to 72,250,000 units given over a period of 56 days. Six of the nine patients received the antibiotic by intermittent intramuscular injections at 3- or 4-hour intervals. Two patients were given the drug by continuous intravenous infusion and one patient by continuous hypodermoclysis. One patient also received 40,000,000 units of streptomycin orally over a period of 11 days in addition to that administered parenterally. The following tests were performed just prior to beginning streptomycin and were repeated within 96 hours following termination of the administration: urea clearance, bromsulfalein, retention, cephalin cholesterol flocculation, and complete blood counts, including differential leucocyte counts. In addition, urinalyses were done at frequent intervals before, during, and following the experimental trial.

The results of these laboratory tests have been compiled in Table 1 together with the doses of streptomycin and the duration of administration. No impairment of hepatic or renal function was detected by the serial bromsulfalein, cephalin cholesterol flocculation, and urea clearance studies. The urines of two subjects (J.P. and I.S.) exhibited abnormalities of the formed elements during the experimental period. On the eighth day of streptomycin administration J.P. developed a microscopic hematuria which subsided a few days after the drug was discontinued. I.S. became intolerant of the antibiotic on the eleventh day of administration, as manifested by fever and arthralgia. At this time a slight albuminuria was noted, and the urinary sediment contained numerous hyaline and finely granular casts. These abnormalities persisted for 72 hours after the drug was discontinued and were no longer apparent when the formal post-streptomycin evaluation was conducted 96 hours after the conclusion of the experimental trial.

Since no significant decrease of the hemoglobin or erythrocyte levels was encountered in any case, it would appear that in these experiments streptomycin exerted no suppressive effect on erythropoiesis and produced no hemolytic reaction. The total and differential leucocyte counts of eight subjects exhibited no unexpected abnormalities. In the case of C.F., however, a leucopenia of 3,550 cells per cubic millimeter and a neutropenia of 48 per cent were detected at the termination of a 45-day trial. This depression of leucocytes persisted for only a few days, after which the white cell values returned to normal range.

Two additional patients, both desperately ill of tuberculous meningitis, received parenteral streptomycin. Since their precarious condition did not permit formal toxicity studies, the clinical data of these patients are not included in Table 1. One of these patients died after 7,000,000 units of the drug had been administered by continuous hypodermoclysis over a period of 3 days and the second patient expired after receiving 15,000,000 units by similar route over a period of approximately 4 days. Post-mortem histological examination of the liver and kidneys revealed no lesions which could be attributed to the action of streptomycin.

Although no evidence of serious organ toxicity has been demonstrated, undesirable reactions have occurred with the relatively crude preparations of strep-

[1] These studies were aided by grants from the executive board and board of governors of the Horace H. Rackham School for Graduate Study of the University of Michigan. The streptomycin used in these studies was furnished by Merck and Company, Inc., Rahway, New Jersey. The material was supplied as a dry powder of varying degrees of purity, the active principle being present as the hydrochloride.