TABLE 1

URINARY EXCRETION OF PENICILLIN FOLLOWING THE ORAL INGESTION OF PENICILLIN

| Subject | Total excretion following ingestion of 100,000 Oxford units | Total excretion following ingestion of 100,000 Oxford units and 10 gm Na HCO3 |
|---|---|---|
| A ..... | 22,200 | 12,700 |
| A ..... | 33,600 | |
| B ..... | 8,800 | 1,950 |
| C ..... | 16,300 | 4,300 |

excretion for the three subjects is indicated by Fig. 1. The maximum excretion occurred during the first hour and all penicillin had essentially disappeared from the urine by the end of 6 hours. No untoward reactions were noted in any of the three subjects.

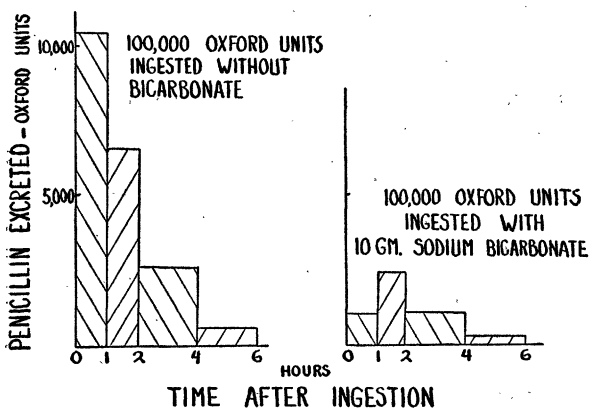


FIG. 1. The rate of urinary excretion of penicillin following its oral ingestion by human subjects.

It has been suggested[3] that the simultaneous administration of sodium bicarbonate might decrease the amount of destruction of penicillin in the gastrointestinal tract. Results of studies in which 100,000 Oxford units of penicillin were ingested along with 10 grams of sodium bicarbonate are also shown in Table 1. It will be seen that in each of the three subjects the amount of penicillin excreted was quite definitely decreased. In subject A the amount of penicillin excreted was approximately half of that noted when the penicillin was ingested alone, whereas the excretion of penicillin by subjects B and C was only 20 to 25 per cent. as great when the bicarbonate was taken along with the penicillin. The reason for the decrease in penicillin excretion is not readily apparent. In the first place the bicarbonate may sufficiently decrease gastric emptying so that there is more destruction of the substance in the stomach. This is consistent with the results indicated in Fig. 1 which show that the maximum penicillin excretion occurred in the first hour when the penicillin was ingested alone, but when sodium bicarbonate was also ingested the maximum penicillin excretion was delayed and occurred between 1 and 2 hours. A second possibility is that the alkaline urine which is excreted following bicarbonate ingestion causes a destruction of the compound while the urine is in the bladder.

Comparison of the quantity of penicillin excreted after oral ingestion with that after intravenous administration suggests that some of the compound is destroyed in the intestinal tract. However, it would appear from the above data that if the doses of penicillin administered orally are larger than those that are effective by intravenous administration, then one might reasonably expect that an adequate amount of the drug will be absorbed and will provide a therapeutic effect in the treatment of infections by susceptible organisms. For instance, the amount of penicillin excreted by each of the subjects after oral ingestion was of the same order of magnitude or larger than the quantity used in many single clinical intravenous or intramuscular injections. A possible added advantage of oral administration is that the absorption continues over some period of time so that the effects of an elevated blood level of penicillin will be prolonged.[6]

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## PROLONGING EFFECTIVE PENICILLIN ACTION[1]

"PROLONG penicillin" has now become a slogan for clinical research workers seeking to extend the effective action of this wonder-working but evanescent drug. When administered in saline solution by intramuscular injection, over half of the penicillin is soon excreted in the urine, requiring renewed dosages every two or three hours. Effective levels have recently been prolonged by using a penicillin beeswax-peanut oil mixture.[2] The authors of this report have tried a new approach to the problem involving the well-known principle of chilling, in order to slow down the circulation in and around the site of the intramuscular injection..

### MATERIALS AND METHODS

This simple method was first tried, beginning Sep-

[6] Since completion of the above study 10 additional studies have been made of the excretion of penicillin following the oral ingestion of 100,000 Oxford units. The excretion pattern and total excretion of penicillin corresponded with the results described above.

[1] The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

[2] "A Method of Prolonging the Action of Penicillin," by M. J. Romansky and G. E. Rittman. SCIENCE, vol. 100, No. 2592, p. 196, Sept. 1, 1944.

tember 13, 1944, on a series of ten patients, nine with a diagnosis of gonorrhea and one with an acute urethritis and extra-cellular diplococci. The penicillin was administered intramuscularly in saline solution, with one therapeutic injection on each subject.

An ice bag was applied on the arm of Subject No. 1, at the deltoid muscle for one hour prior to and for five hours after the injection of 50,000 units of penicillin. The result was that an effective blood level was maintained for 5 hours as compared to 2½ hours usually maintained by a similar dose of penicillin in saline without the advantage of cold applications. The patient's smears became negative for G.C., within six hours and he remained bacteriologically negative and free from symptoms for the remaining two weeks in the hospital.

Subject No. 2 was iced for two hours prior to the injection of 50,000 units and the chilling technique was continued for a period of 6 hours.

Subjects Nos. 3 and 4 each received a single dose of 100,000 units and the area around the intramuscular injection was iced 2 hours before and 6 hours afterwards. The blood penicillin levels at the end of 6 hours were bacteriostatic. In these first four cases blood specimens were obtained for only six hours following the intramuscular injection.

In the remaining six subjects the upper arm was iced 2 hours before and 12 hours after a single intramuscular injection of 50,000 units except that subject No. 10 received an injection of only 30,000 units. In order to obtain the maximum chilling from the ice bag, the bags of melted ice were replaced every few hours with bags of ice. In addition the ice bag was supported or encased in a harness (see Fig. 1) and attached by elastic bands to the upper arm and an elastic anchor around the neck. Effective bacteriostatic levels were maintained for a period of 12 hours in five out of six cases.

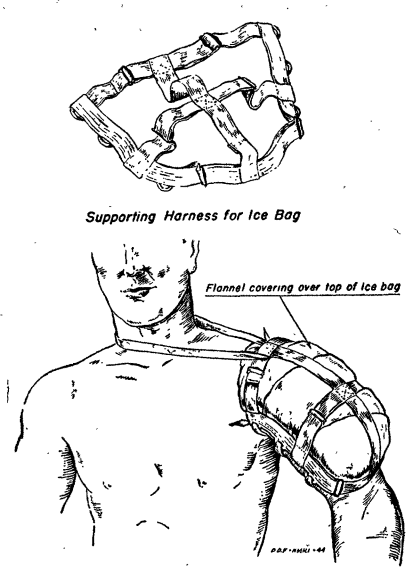


FIG. 1

## RESULTS

All patients, except Subject 10, conform to a general pattern of effective and prolonged blood penicillin levels, following a single intramuscular injection. All patients except No. 10 became bacteriologically and clinically negative and remained so during their stay of from one week to two weeks at the hospital. In the case of No. 10, the urethral discharge stopped the evening of the day he received 30,000 units of penicillin, but at noon the next day the discharge recurred and laboratory reports were again positive. This was the only exception in obtaining protracted bacteriostatic levels.

## COMMENT

Before the chilling technique was introduced, a Naval Hospital which had administered intramuscularly a total of 100,000 units of penicillin in two doses, 6 hours apart, to each of 20 gonorrhea patients, failed in 45 per cent. to effect a cure. Ten additional patients with gonorrhea had been given a single intramuscular injection of 50,000 units. Of these cases 80 per cent. were not cured. Therefore it is significant that with the use of the chilling technique, there were no failures in all the cases* which received a single intramuscular injection of 50,000 units.

Additional patients are being given this dosage with the chilling technique. When further studies confirm these findings it may be concluded that continuous chilling applied at and around the site of the intramuscular injection will have the following advantages.

(1) Bacteriostatic levels of penicillin can be maintained by 2 or 3, instead of from 8 to 12 intramuscular injections in 24 hours.

(2) The application of an ice bag two hours in advance of the injection also renders the injection painless.

(3) There is a 50 per cent. saving in the total amount of penicillin required for each patient.

## SUMMARY

(1) Single injections of penicillin in saline administered intramuscularly with ice applications at the site of the injection produced and maintained bacteriostatic levels for six to twelve hours in nine out of ten patients, nine of whom were diagnosed as

* The chilling technique has since been applied consecutively to eight additional gonorrhea patients. All were cured bacteriologically and clinically by a single intramuscular injection of 50,000 units of penicillin in saline solution.

having gonorrhea and one urethritis with extracellular diplococci.

(2) There was one failure, Subject No. 10, who received only 30,000 units.

(3) Eight of the patients with gonorrhea and the one patient with urethritis were cured (bacteriologically and clinically) by this single intramuscular injection of penicillin.[3]

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## STUDIES ON THE RELATION OF PNEUMOTROPIC STREPTOCOCCI TO INFLUENZA VIRUS[1]

SEROLOGICALLY distinct pneumotropic streptococci, which were used in these experiments, were isolated in studies of influenza and other respiratory infections in our brain-containing mediums, dextrose-brain broth and soft dextrose-brain agar (0.2 per cent. dextrose and 0.2 per cent. agar). These mediums are highly favorable for the isolation of specific types of streptococci and for obtaining pure cultures without loss of specificity.

White mice were inoculated intranasally with these streptococci, which had been subjected to one or more serial dilution cultures alternately in dextrose-brain broth and dextrose-brain agar.[2] The streptococci that grew at the end point of growth were used. All streptococci inoculated were so far removed from the original source that the possibility of passive transfer of "natural" influenza virus was eliminated. By serial intranasal passage, through mice and embryonated chicken eggs, of emulsions and filtrates of emulsions of pneumonic lungs thus obtained, and of allantoic fluid of infected embryonated eggs, a pneumotropic, filtrable infectious agent, transmissible in series, was obtained. The filtrable infectious agent was obtained from each of twenty-nine cultures of pneumotropic streptococci: fourteen cultures from the nasopharynges or blood of thirteen persons having acute epidemic influenza, eight cultures of streptococci from a milk supply and two from a strain isolated from freshly fallen snow during epidemics of influenza and five strains isolated by me from "natural" influenza virus which had been sent to me for study.

Under conditions employed successfully by others, influenza virus was obtained, by intranasal inoculation of mice, from filtrates of nasopharyngeal washings of six out of thirty patients during the acute stage of influenza.

Each of the strains of the filtrable infectious agent obtained from twenty-nine cultures of pneumotropic streptococci has been passed successively through from six to eighteen serial passages. Lesions of lungs occurred in altogether 1,130 (57 per cent.) of 1,900 mice inoculated with test material.

After a number of serial intranasal passages of the filtrable infectious agent obtained from pneumotropic streptococci, the incidence, type and degree of gross and microscopic lesions that developed in the lungs of mice were essentially the same as the incidence, type and degree of those that developed after intranasal inoculation of "natural" influenza virus. The incidence of isolation of streptococci from pneumonic lungs of mice that had received the experimental infectious agent and those that had received "natural" influenza virus also was similar. Isolations of streptococci and incidence of lesions, especially in the first number of serial passages, often ran parallel but, in general, isolations of streptococci diminished progressively with serial passages.

Strains of streptococci isolated from pneumonic lungs in the two groups of mice, those receiving the experimental infectious agent and those receiving "natural" influenza virus, had moderate pneumotropic virulence. Five strains of streptococci from the latter group, far removed from virus, yielded the infectious agent on successive passage of lung material, beginning with the streptococcus. The streptococci from both groups were agglutinated specifically by the influenza antistreptococcic serum and by convalescent influenza serum.

The infectious agent produced from streptococci was as filtrable as "natural" influenza virus and remained viable on preservation in 50 per cent. glycerin for as long as three months.

The invasive power of both the experimental infectious agent and virus and of the influenzal type of streptococcus was neutralized by the influenza antistreptococcic serum and by convalescent influenza serum but not by normal horse serum or normal human serum.

Mice that were immunized intranasally or intraperitoneally with vaccines prepared from freshly isolated streptococci that had been isolated from nasopharynges or blood of persons having symptoms of

[3] The cooperation of Commander G. J. Thompson (M.C.), U.S.N.R., chief of the Urological Service, and Lieutenant P. V. Wooley, Jr., officer in charge of the Bacteriological Laboratory, is appreciated. The blood assays were made by Barbara C. Unsworth, PhM1c, and W. E. Lenert, PhM3c, using a serial dilution method. The sketch of the ice-bag harness was made by J. DiFerdinando, PhM3c, S-V, U.S.N.R.

[1] Preliminary report.

[2] E. C. Rosenow, *Arch. Path.*, 26: 70, 1938.