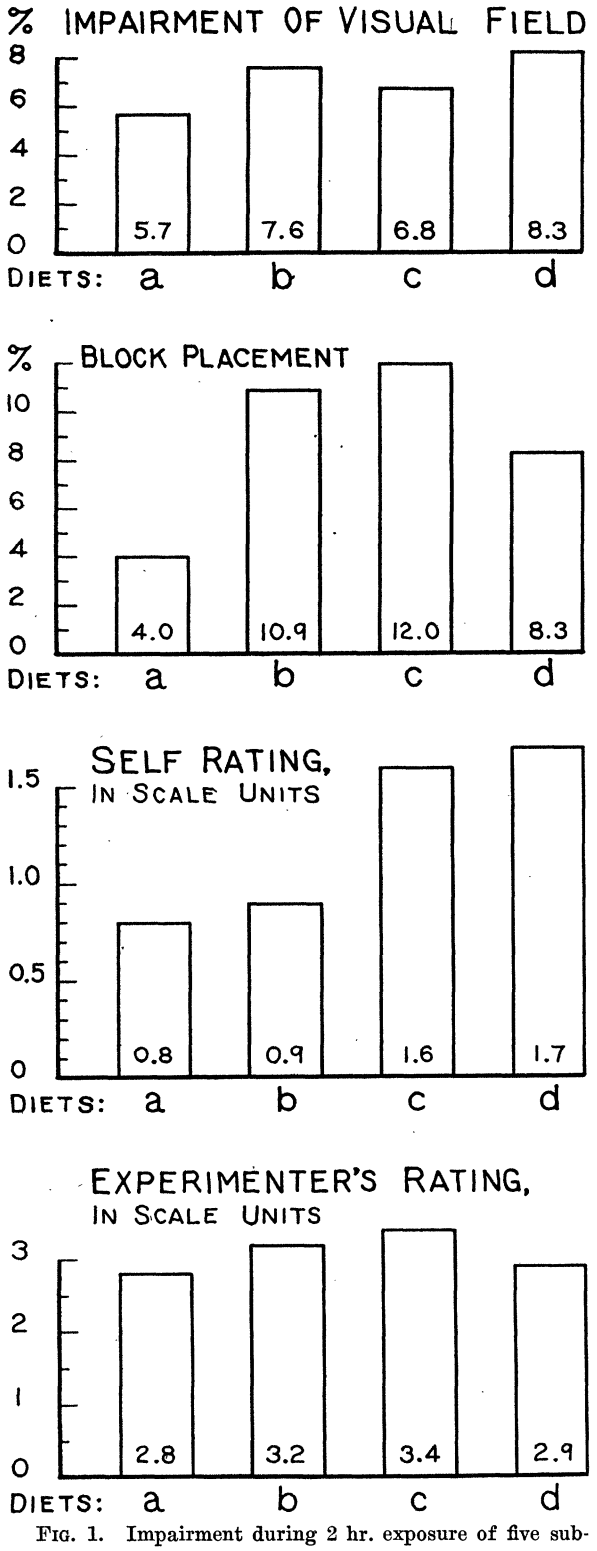

FIG. 1. Impairment during 2 hr. exposure of five subjects at 15,000 ft. Height of column in each case represents degree of impairment. Composition of test meals, in per cent. of total (1000) calories: *a*, carbohydrate 70, protein 10, fat 20; *b*, carbohydrate 55, protein 20, fat 25; *c*, carbohydrate 25, protein 40, fat 35; *d*, carbohydrate 20, protein 10, fat 70.

intervals, the last set beginning at 6 hours after lunch and ending within the ensuing hour.

Eight subjects were divided into two equal groups and exposed on four different days. On each of the experimental days one group consumed a high carbohydrate lunch (carbohydrate 92, protein 6, fat 2) and another group received an equicaloric (total—1,000 C.) low carbohydrate lunch (carbohydrate 21, protein 43, fat 36). By reversing the groups on two of the days, more consistent data were obtained than when the entire squad was given the same type of lunch.

The high carbohydrate meals held their advantage for approximately 6 hours, covering the normal interval between successive meals. Some of the tests showed slightly more and others less impairment during the 6- to 7-hour period of testing, in comparing the two types of meals, but none of the eight subjects showed a distinct tendency toward impairment as a result of the preceding meal being low in protein and fat. The average results from tests of visual field, block placement, pursuitmeter, addition, self-rating and experimenter's rating were nearly equal for the two test meals at the last period of testing.

It has been our experience and it has been demonstrated in tests conducted by the armed services that it is practical, when maximal altitude tolerance is desired, to provide attractive and satisfactory meals from regular food supplies, such as the "B" ration, having a protein content in the range of 8 to 12 per cent. of the total calories.

Preflight and inflight meals relatively high in carbohydrates, which afford increased altitude tolerance, can be followed by meals correspondingly high in protein, to provide an over-all food intake of high nutritive quality and excellent acceptability.

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STUDIES IN MECHANISMS OF PENICILLIN ACTION. I. PENICILLIN EFFECTS ON BLOOD COAGULATION

IN the course of studies on the blood levels attainable with varying dosages of penicillin given both by the oral[1] and intra-muscular routes, it was ob-

[1] L. F. Moldavsky and Wm. B. Hesselbrock, "Oral Penicillin" (in press).

served that within minutes after administration of the drug there was a marked increase in the speed with which the blood clotted. In some instances so marked was this phenomenon that coagulation occurred in the syringe before the blood could be expelled. This finding, together with the known tendency towards thrombosis when penicillin is given intravenously, led us to measure this phenomenon more quantitatively by the simple laboratory determinations of the clotting and bleeding time.

The data obtained so completely affirmed this incidental observation that, although these studies are in their early phase, a preliminary note seemed justifiable.

As part of the analysis of this effect prothrombin time determinations have already been begun and serum calcium studies are planned.

EXPERIMENTAL DATA

In 20 patients to whom both oral penicillin (enteric coated capsules—each containing 100,000 units) and intra-muscular penicillin were given, the concentration of penicillin in the blood, at the same time the clotting time, bleeding time and prothrombin time, was measured. The determinations were made before penicillin was given, than at 15- and 30-minute intervals after its administration. The experiments were begun each morning and food and water withheld to maintain uniform conditions for the duration of the experiment. Determinations of clotting time, bleeding time and prothrombin time were also carried out in a group of controls under the same conditions.

Clotting time was determined both by the use of the capillary tube and by the method of Lee and White. Duke's method for bleeding time and Howell's method for prothrombin time determination were utilized for the data obtained concerning these variables. It is recognized that Howell's method for prothrombin time estimation is of limited value and no attempt is made to draw any conclusions from these determinations. It is planned to repeat these prothrombin determinations by the use of more accurate laboratory methods.

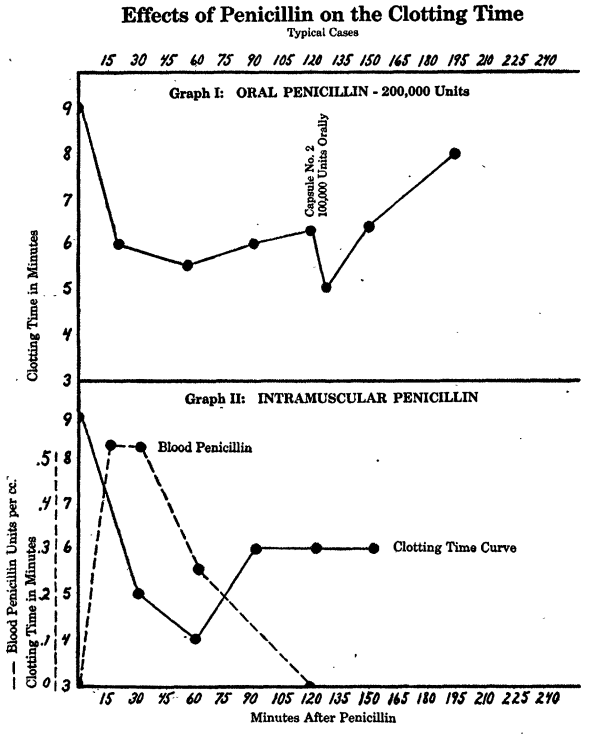
RESULTS

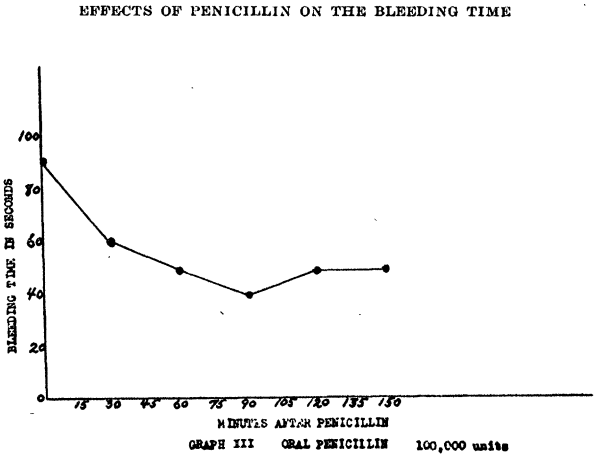
The absence of change in the clotting time exhibited by the control group sharply contrasted with the sharp fall shown when oral penicillin (Graph I) or intra-muscular penicillin (Graph II and Table 1) was given. It was found (Graph II) that as the concentration of penicillin in the blood rose, the clotting time fell, and persisted at a depressed level even after penicillin had completely disappeared from the

TABLE 1

EFFECT OF PENICILLIN (INTRAMUSCULAR) ON CLOTTING TIME; A TYPICAL CASE

	Capillary-tube method	Test-tube method
Control	4 min. 30 sec.	17 min.
PENICILLIN—50,000 UNITS INTRAMUSCULARLY		
After 10 minutes	2 min. 40 sec.	8 min.
After 25 "	1 " 30 "	6 " 30 sec.
After 40 "	1 " 50 "	6 " 20 "
After 1 hour	2 " 40 "	6 " (slightly less)
After 1 hour 40 min.	2 "	6 "
After 2 hours	1 " 55 "	6 "
After 3 "	1 " 30 "	7 " 10 sec.





blood. In several of the experiments this depression persisted for as long as an hour after penicillin had been completely excreted from the blood, on others there was a more rapid return to the control value for that particular patient.

The bleeding time, which in the control group also remained constant, fell when penicillin was given (Graph III). The curve of descent was not quite so marked, and from these early results seemed more transient.

The prothrombin times have so far not shown a characteristic uni-directional change.

DISCUSSION

This consistent, penicillin-evoked alteration of the blood possesses two components. The first one, the hastening of the coagulation of the blood, has already been described. The second is an even more startling change in the nature of the clot itself. There is produced, as a result of the increased penicillin level in the blood, a non-retractile clot; the blood is dark and exceedingly viscous in its flow, and when coagulation is complete it appears solidified. The appearance of the coagulated blood is that of an artificially produced solid thrombus. The mechanism of this peculiar clotting response is deserving of complete analysis, and such studies are planned.

There is a twofold clinical significance to be attached to these findings. First, they serve to emphasize the danger of thrombus formation with penicillin administration. This becomes more important with the newer tendency to increase dosages employed to augment clinical effect. Second, they suggest investigative studies to test the value of the drug as a coagulant in hemorrhagic disorders.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

STANDARDIZATION OF STREPTOMYCIN[1]

IN the isolation and purification of antibiotic substances, the bacteriologist has to depend upon biological assays. Until the chemical nature of the active agent has been established and until a suitable chemical test has been developed, the chemist, as well, has to depend upon such methods. This is true also of the pharmacologist and of the clinician, who study the effectiveness of such materials *in vivo*. The unit of measurement adopted for a certain purpose, however, may not be suitable or may prove too small when applied to a totally different problem or use. As a result of such different applications, new units of measurement of the antibiotic substance may have to be introduced.

In the case of penicillin, for example, the dilution unit originally employed for measuring the activity of this material using a standard test organism, namely, *Staphylococcus aureus,* was later replaced by the Oxford unit.[2] This unit represented "that amount of penicillin which, when dissolved in 50 ml of meat extract broth, just inhibits the growth of the test strain of *Staphylococcus aureus.* Thus material containing one unit of penicillin per mg just inhibits the growth of *S. aureus* at a dilution of 1 to 50,000." When crystalline penicillin was finally obtained, the value of the Oxford unit was adjusted to the weight of the product, 1 unit corresponding to 0.6 micrograms of the crystalline material.[3]

A similar situation has now arisen in establishing standard units for another antibiotic substance, streptomycin. The previous method for measuring the antibacterial activity of this material was based upon its bacteriostatic effect against a given strain of *Escherichia coli.*[4] A unit of streptomycin was thus defined as that amount of material which will inhibit the growth of the particular strain of *E. coli* in 1 ml of nutrient broth or other suitable medium. This unit proved to be satisfactory for production and isolation studies of streptomycin;[5] it appeared to be satisfactory also for pharmacological investigations, especially when small animals were used.[6] For clinical purposes,

[1] Journal Series Paper, New Jersey Agricultural Experiment Station, Rutgers University, Department of Microbiology.

[2] H. W. Florey and M. A. Jennings, *Brit. Jour. Exp. Path.,* 23: 120–123, 1942.

[3] M. V. Veldee, R. P. Herwick and R. D. Coghill, *chairman,* SCIENCE, 101: 42–43, 1945; P. Hartley, *ibid.,* 101: 637–638, 1945.

[4] A. Schatz, E. Bugie and S. A. Waksman, *Proc. Soc. Exp. Biol. and Med.,* 55: 66–69, 1944.

[5] S. A. Waksman, E. Bugie and A. Schatz, *Proc. Staff Meet. Mayo Clinic,* 19: 537–548, 1944.

[6] H. J. Robinson, D. G. Smith and O. E. Graessle, *Proc. Soc. Exp. Biol. and Med.,* 57: 226–231, 1944.