evidence of irritation or allergic reaction for a treatment period which varied from 4 to 11 months. In order to make certain that these were not temporary remissions, one year was permitted to elapse before the clinical report was made, the first patient having healed by February 1945 and the last by November 1945.

It is hoped that this preliminary communication will stimulate further exploration of the treatment of tuberculous lesions with glycerol peroxide solutions.

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Depletion of Vitamin A Reserves in the Livers of Cattle

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In a recent publication (*2*) the writers reported on the depletion of vitamin A reserves in the livers of steers while in the feed lot. One-hundred twenty Hereford steers, about 18 months of age, were taken from native grass pasture and placed on a fattening ration consistent with good feeding practice. Table 1 gives the slaughtering data and the average vitamin A content of the livers. Vitamin A was determined by the method of Davies (*1*).

TABLE 1

Days in the feed lot	No. of animals slaughtered	Vitamin A reserves (μg. vitamin A/gram liver)
0	22	51.4
41	19	23.7
76	20	11.9
119	19	5.3
166	40	1.9

A relationship in the above data has recently been pointed out by Norris Embree, of Distillation Products, Inc. It was mentioned (*2*) that the curve obtained by plotting the data in Table 1 shows a decreasing rate of loss of vitamin A reserves throughout the experimental period. Dr. Embree cited an article by K. C. D. Hickman (*3*), also of Distillation Products, Inc., which appeared while the above publication was in press and in which Dr. Hickman proposed the hypothesis that the rate of depletion of the body reserves of a vitamin are directly proportional to the total reserves of that particular vitamin in the body. Further, when an animal is subjected to vitamin therapy, it should be possible to calculate a period of half adjustment.

To determine the validity of Dr. Hickman's hypothesis, the data in Table 1 were subjected to analysis. Vitamin A reserves were plotted against days in the feed lot and vitamin A values determined at intervals of 40 days. Table 2 gives the values obtained.

TABLE 2

Days in the feed lot	Vitamin A reserves (μg. vitamin A/gram liver)	Drop in 40 days (%)
0	51.4	—
40	24.2	47
80	11.1	46
120	5.2	47
160	2.2	42

It will be observed that the percentage drop in vitamin A reserve in the liver at the end of each 40-day period is practically constant. This supports Dr. Hickman's hypothesis as regards the rate of depletion of body reserves of a vitamin.

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Thromboplastic Properties of Penicillin and Streptomycin

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Moldavsky, Hasselbrook, and Cateno (*6*) have described some interesting findings with the blood of patients receiving parenteral injections of penicillin. In a series of human subjects studies on the clotting of blood before and after administration of penicillin revealed that the clotting time was much shorter after injections of the antibiotic than the normal clotting time was before injection. In connection with a study of blood in hemophilia the present writer and Dr. Marcus Ostro repeated the above observations on normal clinical subjects and confirmed the findings made by Moldavsky and his associates, but, curiously enough, when injections of penicillin were given to two patients suffering from hemophilia, no shortening of coagulation time was produced by the drug (*5*).

Inasmuch as it has been discovered experimentally on animals and confirmed by clinical observations that drugs belonging to the digitaloid group show a definite tendency to promote coagulation of blood (*2*, *3*), and inasmuch as more recently certain widely employed mercurial diuretics have also been found to produce such a thromboplastic effect leading occasionally to fatal thrombotic accidents (*4*), an extensive investigation was undertaken to ascertain the frequency and degree of the thromboplastic effects of penicillin on the blood of higher animals. For this purpose not only the ordinary

[1] Grateful acknowledgment is made to the Commercial Solvents Corporation and its medical director, Dr. Lawrence Smith, for valuable aid in carrying out this research.

amorphous penicillin available on the market but also the more recent crystalline sodium salts of penicillin were examined, and, still further, the isolated crystalline penicillin principles as well as the newer antibiotic streptomycin were tested.

Method

Over 200 experiments on blood coagulation were performed. These studies were confined to the clotting of *whole blood* as studied by the original Howell Method or, as it is sometimes known, the Lee and White Method. One cc. of whole blood is drawn and immediately put into a homeopathic vial 1 cm. in diameter, and the clotting time is measured with a stop watch, the end-point being taken when the vial can be inverted without flowing of the blood. The majority of the experiments were made on rabbits and cats; a few were also made with dogs' blood and still others with human patients' blood. In obtaining blood from lower animals, as in the case of rabbits, the samples were drawn by heart puncture. In the case of cats, nembutal anesthesia was first produced and blood drawn either directly from the heart or from the carotid arteries. In making these coagulation studies a good deal of experience is required to avoid complications such as admixture of tissue juices, etc., which may produce abnormal changes in coagulation time.

The earlier studies, begun in the summer of 1945, were made with sodium salts of amorphous penicillin, a dozen or more brands of such penicillin on the market being used. Later, with the development of more reliable therapeutic products, the colorless and more stable crystalline sodium salts of penicillin were employed and compared with the amorphous variety. In these studies the crystalline sodium penicillin of the Commercial Solvents Corporation was used for the most part. Later, through the courtesy of the same concern and also partly by courtesy of Dr. Harry Eagle, of the Johns Hopkins School of Hygiene and Public Health, small quantities of the four crystalline active principles of penicillin were studied separately and in combination with each other. The streptomycin employed in this present work was obtained through the courtesy of Dr. C. S. Keefer, of the Evans Memorial Hospital, Boston.

Results

Amorphous penicillin of every brand examined produced marked acceleration of clotting time, whether injected intravenously or intramuscularly and even when administered by stomach tube mixed with amphogel. The onset of this property can be noted usually within 15 or 20 minutes after injection but in some cases is most marked about one hour after. The effect persists usually for several hours.

When the newly produced sodium salt of crystalline penicillin (C.S.C.) was examined, however, the thromboplastic effect was much less striking. According to the scientists in charge of preparing the crystalline substances, this preparation consists almost entirely of penicillin G. For this reason it was deemed very desirable to secure and examine the comparative effects on coagulation of the four crystalline penicillin principles. Penicillin G (benzyl penicillin) and penicillin F (pentyl penicillin) were much less thromboplastic in their efficiency than penicillins X (hydroxy benzyl penicillin) and K (heptyl penicillin). The most potent in this respect was X. Next in order came K, followed by G and F. It was found, furthermore, that a small dose of penicillin X added to penicillin G produced a synergistic effect and hastened coagulation much more than a large dose of G alone.

Streptomycin was found to be also markedly thromboplastic for blood of rabbits and cats.

Discussion

In the light of these experiments and the results outlined above, there can be no doubt as to the accuracy and importance of the observations first reported by Moldavsky and his associates.

The author was also impressed by the interesting fact that when rabbits were repeatedly used for the above experiments, the coagulation time of those animals was permanently shortened for long periods of time, so that for examination of new preparations fresh animals had to be employed. It was also interesting to learn that this shortening in coagulation time in rabbits and cats could be antagonized and canceled by suitable doses of dicoumarol administered by stomach. It is the opinion of the present writer that, next to the chemotherapeutic properties of penicillin and streptomycin and their low toxicity, the most important pharmacological finding is their thromboplastic activity, which at first impresses the clinician as a very dangerous factor to be considered in their therapeutic use. Fortunately, however, nature has provided such generous checks and balances as well as compensatory and reserve faculties to the higher animals that thrombotic accidents in medical practice after the use of penicillin are extremely rare. Nevertheless, such clinical reports are already cropping up, as, for instance, that by G. Frada (*1*), who reports four patients with embolic accidents attributed by him to increased coagulability of the blood due to penicillin. The complete details of the present research will appear in the *Archives Internationales de Pharmacodynamic et de Therapie.*

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Activity of Protein Synthesis by the Intestine

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In a recent paper (*1*) Bloch reported that the proteins of the intestinal wall of an animal fed arginine labeled with N^{15} had the highest isotope concentration. He advanced two alternate explanations to account for his finding: (1) If the bulk of the absorbed amino acids is carried by the portal vein, arginine enters the internal organs only after passage through the liver, where arginase and the ornithine cycle cause the replacement of the isotopic amidine nitrogen by ordinary nitrogen; thus, the proteins in the liver and those poured out by the liver have a low isotope concentration if compared to the