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

Felix Friedberg

Division of Biochemistry, University of California Medical School, Berkeley

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

proteins of the intestinal wall. Or (2) the amino acids are utilized while they are being absorbed, and thus the arginine would be incorporated into the protein of the intestinal wall without having been exposed to dilution.

Bloch's first explanation cannot account for the observation that orally administered methionine (labeled with S^{35}) shows the highest incorporation in the proteins of the intestinal mucosa, as reported by Tarver and Schmidt (*2*). Bloch's second explanation was tested in our laboratory by injecting labeled methionine *by way of the jugular vein.* (Bloch administered the amino acid orally.) Again the protein of the intestinal mucosa showed the highest isotope concentration. The same result is obtained when tyrosine (labeled with C^{14}) is injected intravenously.

The interesting finding that the intestinal mucosa has the highest specific activity is explained by us as being due to actual increased protein synthesis rather than to the conditions of the experiment. The intestinal wall secretes enzymes and mucous-proteins which are lost in enormous quantities (unlike other enzymes and proteins within the body). To compensate for this loss the intestinal wall may be more active in protein synthesis than other organs.

If this explanation is correct, then the pancreas should also show a high turnover rate; pancreatic juice contributes many enzymes needed for digestion. Actually Tarver and Schmidt (*2*) found that the pancreas has the second highest specific activity among the organs of animals treated with isotopic methionine.

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Lipoid Substance in the Cells of Proximal Convoluted Tubules of the Kidneys of Young Rats on a Choline-deficient Diet

W. Stanley Hartroft and C. H. Best

Banting and Best Department of Medical Research, University of Toronto, Canada

Descriptions of the histological changes in the acute "hemorrhagic" kidney of young choline-deficient rats make little, if any, mention of the appearance in frozen sections of any demonstrable fat (*1*). In a series of such sections stained with Sudan IV, from kidneys of rats three to four weeks of age and weighing 35–45 grams, fatty droplets have been consistently observed in the cells of the proximal convoluted tubules. The animals were killed at daily intervals after being placed on a choline-deficient diet. These fatty changes were usually first seen on the third day, but in one instance were observed as early as the second day. The droplets of fat increased in size and number, reaching a maximum on the sixth or seventh day, when congestion, hemorrhage, and cortical necrosis were readily demonstrable.

The appearance of this fat may be secondary to degenerative changes in the tubular epithelium resulting from dietary lack of the lipotropic factor, choline; but the possibility that it may be important in the production of the other lesions of the "hemorrhagic" kidney is being investigated. The fatty droplets are observed before the onset of congestion, necrosis, hemorrhage, or cast formation. It has already been demonstrated (*3*) that the lipase content of the proximal convoluted tubule is diminished or absent in such kidneys. Reduction of the ratio of the phospholipid fraction to the total lipid content has also been established (*2*). Further biochemical and histochemical investigations of the nature of the histologically demonstrable fat are being undertaken to determine its relationship, if any, to the kidney lesions which result from choline deficiency.

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Quick Decline of Orange Trees—A Virus Disease

J. M. Wallace and H. S. Fawcett

University of California Citrus Experiment Station, Riverside

Recent results of experimental tests set up in southern California in June 1945 have shown that the highly destructive quick-decline disease of oranges is infectious, and these new results, now viewed in connection with other experiments, indicate that it is a virus disease. Quick decline, known only since 1939, is similar in many respects to the disease known in Brazil as *tristeza*, which, within the last 8 or 9 years, is reported to have almost completely destroyed all orange trees on sour orange root stocks in Argentina and Brazil. The quick-decline disease has been known to occur only on sweet orange varieties on sour orange root stock. Consequently, a test was made with 200 one-year-old healthy Valencia orange trees grown on sour orange stock. Live buds from quick-decline trees were placed in 100 of these healthy trees, and 100 trees were used as checks. Healthy buds were placed in 50 of the latter group, and 50 remained unbudded.

In September 1946 a few trees into which diseased buds had been inserted began to show symptoms. On November 11, 1946, 36 per cent of the trees in which diseased buds had been inserted showed symptoms; only 2 per cent showed disease in each of the two groups of the check trees. Since all these test trees were healthy trees that had originated in a non-diseased area and were planted in a quick-decline area in the open, the 2 per cent was presumably caused by natural infection.

A description of the transmission tests and of many other experiments planned for investigation of other phases of the quick-decline problem will be found in the April, October, and December 1946 numbers of *California Citrograph.* The more detailed evidence on which this preliminary statement is made will appear later.

The great preponderance of diseased trees in the inoculated