SOME RECENT ADVANCES IN PHYSIOLOGICAL CHEMISTRY AND NUTRITION

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It is a most difficult task to attempt such a brief review of recent advances in physiological chemistry and nutrition. Last year (1945), even after a succession of war years, 8,137 abstracts on biochemical subjects appeared in *Chemical Abstracts* in the Sections on Biochemistry and Foods alone. Also, we have the further evidence of the tremendous activity in this field in the appearance each year of the *Annual Review of Biochemistry*, the most recent volume of which (for 1944) comprised 856 pages. Accordingly, the material presented here will be quite general and will be illustrative of trends of development over the past few years rather than an attempt to cover any field in detail.

The Carbohydrates.

The three most important polysaccharides in nature are cellulose, starch and glycogen. The structures of these compounds are similar in that they are made up of glucose units bound together between the 1-C of one glucose molecule and the 4-C in the next. The view that this 1–4-linkage is the one always elaborated by natural synthesis has been contradicted in recent years by the discovery of carbohydrates with 1–2-, 1–3-, and 1–6-linkages. Starch is believed to be a molecule made up of ***repeating units***, each consisting of from 24 to 30 glucose molecules (1), and combined by cross linkages to form a molecule of about 200,000 molecular weight. Most natural starches contain at least two components, designated as amylose and amylopectin. Thus, corn starch (2, 3) contains 10–20 per cent of amylose of unbranched chains of molecular weight 10,000 to 60,000 and 80–90 per cent of amylopectin with highly branched chains of 50,000–1,000,000 molecular weight. The most important polysaccharide in the human body is glycogen, the molecule of which is considered to be spherical in shape and to which a weight as high as 4,000,000 has been assigned (4). Such a molecule would contain nearly 23,000 glucose units.

The role of phosphoric acid in nearly all of the phases of carbohydrate metabolism has now been well established, beginning with the phosphorylation of absorption and ending with its various functions in the utilization of carbohydrates in the tissues. A most interesting achievement is that of Green and Cori (5) who isolated phosphorylase from rabbit muscle. One of the components of this enzyme is a crystalline euglobulin of molecular weight 400,000. This enzyme catalyses the formation of glycogen from glucose-1-PO_4, and presumably also the breakdown of glycogen. By studies with deuterium labelled compounds Stetten and Boxer (6) showed that 69 per cent of liver glycogen (in rats) was turned over daily but only 19 per cent of carcass glycogen. Labelled CO_2 has been shown to appear in both liver and heart muscle glycogens (7). The course of intermediary metabolism of carbohydrate, leading to its final oxidation, is still the subject of active research and rapidly changing views with practically no final answers to the problems raised. In this connection the Krebs tricarboxyllic acid cycle is most often mentioned (8).

The Fats and Oils and Other Lipids.

Methods for studying the glyceride structure of the fats and oils and of their component fatty acids are being continually improved. It is now possible to evaluate the fatty acids of these lipids with a high degree of accuracy, and in many instances to discover new fatty acids, hitherto not believed to be present. Thus, a few years ago hexadecenoic acid was a rare compound in fat chemistry. Now, as a result of refinement in distillation and other procedures (9) it has been found in most animal fats examined, including human fat (10) and human milk fat (11), the latter containing 2.6 per cent of this acid.

The separation of fatty acid mixtures by low temperature crystallization from organic solvents (12) and the development of spectrophotometric procedures for the estimation of unsaturated acids with more than one double bond have proved to be important methods of study. Several reports have already noted the occurrence of fatty acids with conjugated unsaturation in naturally occurring lipids. The significance of these compounds in fat metabolism has not been studied.

More and more attention is being paid to the lipo-proteins (13). The lipid components of these compounds are usually not extractable from tissues without being previously diassociated from the proteins by hydrolysis (HCl), by extraction with methanol or ethanol, or by such a mild treatment as freezing at —25° (14), this last treatment having been shown to release the bound lipids of blood plasma.

An interesting development in fat metabolism is the view expressed by Frazer (15) that glycerides can be absorbed as such. Thus the classic concept of the necessity of complete digestion to fatty acids and glycerol preliminary to their absorption seems to be seriously questioned. Depancreatized dogs absorb up to 75 per cent of ingested fat (16). Other developments in fat metabolism have been due in no small part to the use of tagged molecules, especially the deuterium, used first by Schoenheimer and coworkers (17). Thus, the processes of desaturation of fatty acids, of interconversion of one fatty acid with another in the tissues, and of new functions of depot fat have been experimentally demonstrated. The fat depots seem to be one of the important destinations of dietary fatty acids, even when they are fed to a partly starved animal. Depot fat, long considered to be an inert storage material, has now assumed the role of a rapidly changing, functioning organ. In fact, the half-life periods of the fatty acids of various tissues have been actually determined (18, 19). Likewise, we are seeing rapid changes in the theories of fat utilization. The classic beta-oxidation theory is now scarcely recognizable, although it still accounts for a considerable part of the oxidation mechanism. The production of ketones is considered to be a normal process, largely resulting from recombination of the acetate residues or "active acetyls" produced by beta-oxidation. Incidentally it has been suggested that acetoacetate, or some other similar product of fat metabolism, enters the scheme of carbohydrate metabolism by conversion to oxaloacetic acid which is one of the compounds of the citric acid cycle (20). In this sense fat and carbohydrate metabolism merge into each other, and the fat does indeed burn in the flame of the carbohydrate, as we were teaching twenty years ago.

The Proteins.

Two recent volumes on "Recent Advances in Protein Chemistry" have reviewed progress in this field (13). All crystalline enzymes so far isolated have been found to be proteins. In the pituitary gland alone at least six hormones of a protein nature have been demonstrated and their properties described. In the later aspects of this work the Tiselius electrophorometer has been especially useful, as well as in extensive work on the patterns of the plasma proteins. The plasma proteins have been the subject of a most extraordinary series of fractionations by the Harvard group, headed by E. J. Cohn (21). From human plasma several simplified protein fractions have been prepared, studied, and adapted to specific uses in medicine. Thus, the gamma-globulins possess an antibody titer approximately ten times that of pooled plasma and can be used to confer passive immunity against measles, infectious hepatitis, and the like. Albumin of over 98 per cent purity is available in 25 per cent solution for use against shock and for many other purposes.

Incidentally, the albumins and globulins are heterogeneous in composition, and are usually associated with lipid and with glucosamine,—thus in fact being conjugate proteins. The viruses, which are found in the border zone between bacteria and non-living protein molecules, have been shown to be nucleoproteins of very high molecular weight and to possess the unique property of reproduction.

Study of protein metabolism with isotopic N^{15} has demonstrated the rapid interchange between dietary nitrogen and the nitrogen of the amino acids in the protein molecule of the living tissue; this isotope has also been employed in studying the intermediary metabolism of the individual amino acids. By this method, creatine has been shown to be derived from three sources, glycine, arginine and methionine, each of these amino acids contributing specific fragments to the creatine molecule.

Hydrolysates of complete proteins such as casein and lactalbumin are coming into use in medicine in the treatment of hypoproteinemia and other disorders; some of them are suitable for parenteral administration. According to the newer views the plasma proteins are in dynamic equilibrium with the proteins of the tissues. Theoretically, at least, the total protein nutrition of an individual can be adequately supported by administration of the plasma proteins.

General Trends in Nutrition.

The last ten years of research in nutrition have seen the field develop from a qualitative to a fairly quantitative science. Most of the better known vitamins have been identified chemically, many of them are prepared synthetically so that they are very inexpensive, and accurate methods for their quantitative estimation have become available. We now have accurate tables of analysis of the several vitamins, which suffice for many nutrition studies without actual food analyses. From such data it has been possible to evaluate quantitatively the diets of population groups and to compare their dietary habits with the standard requirements.

In the two or three years before the war our government became nutrition conscious as a consequence of many of these population studies, as a result of which the Surgeon General came out with the statement that nearly half of the American people were living on diets which were deficient in one or more items. The committee on Foods of the National Research Council was formed, one of its important contributions being to set up a list of recommended dietary allowances which have served as standards during the war both for this country and others. This has been a powerful influence toward better nutrition throughout the world, although the present food shortages are working in the other direction. The recommended allowances may be higher than necessary in some instances, as subsequent work is now showing.

It is true that deficiencies of clinical severity are rare in this country, but there is adequate evidence that pre-clinical inadequacies are relatively common. Incidentally the exigencies of war and its concurrent incidence of severe starvation of peoples in the occupied nations and in prison and concentration camps have for the first time given many of our doctors first hand experiences with the classic diseases of nutrition.

A great deal of important work relative to the vitamins during the past few years has been concerned with the further study and isolation of the lesser items of the vitamin B-complex, as for example, folic acid, pantothenic acid, choline and numerous others. The recent finding that folic acid will cause remission of certain types of anemia and the importance of choline in preventing fatty liver are examples of developments in this direction which have proved to be of use in medicine. Most of these newer B-complex vitamins have not as yet been applied to human nutrition, and undoubtedly research in the near future will add most interesting chapters to the story of this science.

BIBLIOGRAPHY

1. **Bawn, C. E. H.**, **Hirst, E. L.**, and **Young, G. T.** Trans. Faraday Soc., 36, 880 (1940).
2. **Meyer, K. H.**, and **Bernfeld, P.** Helv. Chim. Acta, 23, 845 (1940).
3. **Meyer, K. H.**, **Bernfeld, P.**, and **Wolff, E.** *Ibid.*, 23, 854 (1940).
4. **Meyer, K. H.** Advances in Enzymology, 3, 109–35 (Interscience Publishers, Inc., New York (1943)).
5. **Green, A. A.**, and **Cori, G. T.** J. Biol. Chem., 151, 21 (1943).
6. **Stetten, D., Jr.**, and **Boxer, G. E.** *Ibid.*, 155, 231 (1944).
7. **Evans, E. A., Jr.**, **Vennesland, B.**, and **Slotin, L.** *Ibid.*, 147, 771 (1943).
8. **Krebs, H. A.**, and **Eggleston, L. V.** Biochem. J., 37, 334 (1943). Also, **Krebs, H. A.** Advances in Enzymology, 3, 191 (1943).
9. **Baldwin, A. R.**, and **Longenecker, H. E.** Oil and Soap, 22, 151 (1945).
10. **Cramer, D. L.**, and **Brown, J. B.** J. Biol. Chem., 151, 427 (1943).
11. **Brown, J. B.**, and **Orians, B. M.** Arch. Biochem., 9, 201 (1946).
12. **Brown, J. B.** Chem. Rev., 29, 333 (1941).
13. **Anson, M. L.**, and **Edsall, J. T.** Advances in Protein Chemistry. Vols. I and II (1944 and 1945). (Academic Press, Inc., New York.)
14. **McFarland, A. S.** Nature, 149, 439 (1942).
15. **Frazer, A. C.** J. Physiol., 102, 329 (1943–44).
16. **Vermeulen, C.**, **Owens, F. M., Jr.**, and **Dragstedt, L. R.** Am. J. Physiol., 138, 792 (1943).
17. **Schoenheimer, R.** The Dynamic State of Body Constituents. (Harvard Univ. Press, Cambridge (1942)).
18. **Stetten, D., Jr.**, and **Grail, G. F.** J. Biol. Chem., 148, 509 (1943).
19. **Salcedo, J., Jr.**, and **Stetten, D., Jr.** *Ibid.*, 148, 633 (1943).
20. **Lynen, F.** Ann., 552, 270 (1942).
21. **Cohn, E. J.** Medicine, 24, 333 (1945).