A THEORY OF PROTEIN METABOLISM: THE TRANSFORMATION OF PROTEINS

THE current view of protein catabolism is that proteins are hydrolyzed to their constituent amino acids, and these, in turn, are deaminized and the carbon-containing residues are then oxidized or converted into other substances. The particular reaction involved depends on the chemical nature of the amino acid under consideration. It is not the purpose of the present article to deny that some breakdown of proteins may occur in this manner. It is, however, our object to point out that this is not the only possible way whereby proteins may be catabolized. Likewise, although it is possible for the animal organism to synthesize tissue proteins from the amino acids that enter the circulation, it appears to us that synthesis of proteins can take place in the body by the transformation of existing proteins into others without first being broken down to amino acids.

Proteins consist of amino acids that are chemically bound by means of peptide linkages. The side groups are generally free. Among these are the guanidino group of arginine, the hydroxyphenyl group of tyrosine, the phenyl group of phenylalanine, the imidazole ring of histidine, the indole ring of tryptophane, the ε-amino group of lysine, the methylthiol group of methionine, the pyrrolidine ring of proline, the hydroxypyrrolidine ring of hydroxyproline, the carboxyl or acid amide groups of the dicarboxylic amino acids, the methyl group of alanine, etc. Special chemical tests for many of these groups have been devised.

In vitro it is easy to introduce acetyl groups, nitro groups or iodine, etc., into proteins that possess the necessary groups or rings. In fact, it has recently been shown that under appropriate conditions addition of iodine to a number of proteins leads to the appearance of thyroxine in these molecules.[1] Thyroxine is a dispensable amino acid. This is also true of diiodotyrosine. These amino acids are present in proteins of the thyroid gland.[2] Synthesis of the iodine-containing amino acids must then take place *in vivo*. It is not illogical, in view of the *in vitro* experiments, to conclude that thyroglobulin and other iodine-containing proteins are synthesized from proteins that are present in the body rather than built up *de novo* from the appropriate amino acids after synthesis of thyroxine or diiodotyrosine. The latter possibility is not wholly excluded, however, and it may even be possible that the synthesis of the iodine-containing proteins follows both reactions.

Evidence is at hand which shows quite definitely that urea may be formed from proteins by treating them with arginase.[3] It has not yet been found possible, in most instances, to convert all the guanidino groups of proteins into urea in this manner. Krebs and Henseleit[4] report that they were unable to obtain urea from liver slices by the action of arginase. It is quite possible that the optimum conditions for the action of arginase on proteins have not yet been found. The fact that some urea was obtained is significant. The guanidino groups that participated in the reaction have been changed into the δ-amino group of ornithine and thus, by enzymic means, one protein has been converted into another. There is no experimental evidence at hand to indicate that the ornithine-containing protein may be reconverted into the original arginine-containing protein, but this possibility is not excluded. It may perhaps be necessary to postulate such a cycle in the body, especially in view of the fact that, from a quantitative standpoint, it has not been shown that a sufficient amount of free arginine is present in the liver to account for the comparatively large amounts of urea synthesized daily. On the other hand, there is no doubt that there is an ample amount of "potential" arginine in liver proteins.

Tarver and Schmidt[5] have recently advanced the hypothesis that a necessary condition for the conversion of methionine to cystine is that the amino and probably also the carboxyl group of methionine be not free. The attack is then on the distal end of the methionine molecule. The conversion of methionine to cystine evidently takes place when the methionine is contained in a peptide or a protein or both. If the conversion takes place in the protein molecule, then from a methionine-containing protein a cystine-containing protein is obtained, and this is another instance of the transformation of one protein into another.

Since cystine is a dispensable amino acid, it is not unreasonable to conceive that the cystine-containing proteins of animals that were maintained on a cystine-free diet, but did receive methionine, at one time contained only the latter amino acid. Some of the methylthiol groups were subsequently converted to the sulfhydryl groups of cysteine or the dithio groups of cystine.

In fact, the chemical changes that take place in pro-

[1] W. Ludwig and P. v. Mutzenbacher, *Zeits. physiol. Chem.*, 258: 195, 1939.

[2] G. L. Foster, *Jour. Biol. Chem.*, 83: 345, 1929; W. T. Salter and O. H. Pearson, *Jour. Biol. Chem.*, 112: 579, 1935–36.

[3] K. Felix and H. Schneider, *Zeits. physiol. Chem.*, 255: 132, 1938; I. Kraus-Ragins, *Jour. Biol. Chem.*, 123: 761, 1938.

[4] H. A. Krebs and K. Henseleit, *Zeits. physiol. Chem.*, 210: 60, 1932. See also, R. Schoenheimer, S. Ratner and D. Rittenberg, *Jour. Biol. Chem.*, 130: 703, 1939.

[5] H. Tarver and C. L. A. Schmidt, *Jour. Biol. Chem.*, 130: 67, 1939.

tein molecules during denaturation are indicative that transformation of one protein into another takes place without the intervening stage of amino acids.

Recent evidence points to the likelihood that some breakdown of fatty acids occurs by ω-oxidation.[6] It is not inconceivable that the straight side chains of amino acids in the protein molecule may be similarly oxidized.

Indole is easily oxidized, and it is well known that, unless special precautions are taken, tryptophane, when wet or in solution, turns brown on exposure to air. This is also true of some proteins under appropriate conditions. It is difficult to conceive that a necessary condition for the breakdown of the indole ring of tryptophane is that the amino acid be in the free state and not combined in peptides or proteins.

The point that we desire to emphasize, and to which careful consideration should be given in future studies dealing with protein metabolism, is that it may be quite possible that some transformation or breakdown of the free groups in proteins occurs before hydrolysis of the peptide linkages. By such changes one type of protein may be transformed into another. From a thermodynamic view-point such a reaction is probably more efficient than one that requires hydrolysis to amino acids and resynthesis from the selected amino acids.

Finally, it does not appear to us impossible that the immune bodies that are commonly found in the globulin fraction of blood serum are not synthesized *de novo* but by modification of existing globulins. The upset of the normal albumin-globulin ratio by the injection of non-antigenic substances into animals[7] may possibly be another example of the transformation of proteins by slight modification rather than *de novo* synthesis from amino acids.

Our visualization of protein anabolism and catabolism is that not only free amino acids are concerned in the reactions, but also peptides and proteins. It is admitted that experimental evidence in support of the latter concept is still meager. However, but little thought has been given to this idea, and it is the purpose of this article to stimulate interest in this field so that eventually we may have a thorough and adequate knowledge of protein metabolism.

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[6] P. E. Verkade and J. van der Lee, *Biochem. Jour.*, 28: 31, 1934. See also, M. Jowett and J. H. Quastel, *Biochem. Jour.*, 29: 2143, 1935.

[7] E. S. Schmidt and C. L. A. Schmidt, *Jour. Immunology*, 2: 343, 1917.

THE TREATMENT OF EXTREME CASES OF "SNIFFLES" IN THE RAT WITH SULFAPYRIDINE

SULFANILAMIDE, though very helpful as a counter-irritant in the lighter attacks of "sniffles" in the laboratory rat, apparently does little more than slow the progress of the disease in cases where the infection is more extreme and deep-seated.

In such cases we have employed sulfapyridine with much success. The dosage used is 1 mg per gram body weight of rat mixed with a small quantity of food. If the animal will not eat, a 2 cc concentrated solution of *sulfanilamide* injected abdominally gives the animal a respite from the disease which is accompanied by a return of appetite. *Sulfapyridine,* in the meantime, is mixed with a small quantity of food, preferably cow's milk (18 per cent. butter fat). Ingestion of the sulfapyridine obviates further use of sulfanilamide.

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SOVIET COSMOLOGY

THE following is a translation of resolutions that were adopted by the section of astronomy of the Academy of Sciences of the U.S.S.R. in December, 1938, and printed in Volume 16, No. 2, of the *Astronomical Journal of the Soviet Union:*

Having heard the papers of Eigenson, Zelmanoff, Bogorodsky and Krat, the meeting adopts the following:

1. Modern bourgeois cosmogony is in a state of deep ideological confusion resulting from its refusal to accept the only true dialectic-materialistic concept, namely, the infinity of the universe with respect to space as well as time.

2. The hostile work of the agents of Fascism, who at one time managed to penetrate to leading positions in certain astronomical and other institutions as well as in the press, has led to revolting propaganda of counter-revolutionary bourgeois ideology in the literature.

3. The few existing Soviet materialistic works on problems of cosmology have remained in isolation and have been suppressed by the enemies of the people, until recently.

4. Wide circles interested in science have been taught, at best, only in the spirit of indifference toward the ideological aspect of the current bourgeois cosmologic theories. . . .

5. The exposé of the enemies of the Soviet people makes necessary the development of a new Soviet materialistic cosmology. Already there are a few pioneer Soviet specialists in this subject. . . .

8. It is deemed necessary that Soviet science should enter the international scientific arena carrying concrete achievements in cosmologic theories on the basis of our philosophic methodology.

ASTRONOMER