MAMMALIAN PROTEIN METABOLISM

H. N. MUNRO
and
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Volume I

MAMMALIAN PROTEIN METABOLISM

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Preface

Shortly after World War II, an international meeting was convened to consider nutritional deficiencies affecting populations in the post-war world. The agenda did not include protein deficiency. Since then, a revolution in outlook has taken place, so that in 1960 the Director of the Nutrition Division of the Food and Agricultural Division of the United Nations stated that, in the view of his organization, protein malnutrition is without doubt the most compelling nutritional problem in the underdeveloped countries today (M. Autret, 1961, *in* "Progress in Meeting Protein Needs of Infants and Preschool Children," National Academy of Sciences–National Research Council, Washington). In the more highly developed countries interest in the role of dietary proteins in the promotion of health has also quickened during the past few years.

The past decade has witnessed a revolution in a different aspect of protein studies. In less than ten years, the study of protein biosynthesis has progressed from a state of unproved and contradictory hypotheses to become the seat of intense and fruitful activity. When the dust of battle has settled, current work bids fair to resolving problems as varied as the nature of the inheritance mechanism and the genesis of the malignant cell.

These investigations into the importance of proteins in nutrition and into the mechanism of protein formation have each produced an abundant and specialized literature in which it is difficult for anyone other than the specialist to evaluate recent advances. In consequence, a barrier of non-communication has arisen between experts in each field of inquiry, although in reality they are but opposite sides of the same coin: the doctor faced with a case of protein malnutrition is observing a natural experiment in the inhibition of protein synthesis. Other areas of protein metabolism present a similar rapid growth of knowledge. Changes in protein metabolism are now known to be involved in the action of many hormones. In the field of medicine, the physician observes an expanding series of errors in the metabolism of individual amino acids, and the surgeon continues to explore the significance and the repair of the large dissipation of body protein resulting from injury.

It is thus difficult nowadays for the research worker in any one branch of the subject to comprehend the advances which are taking place on all fronts in protein metabolism. The objective of this treatise is to provide an up-to-date account of current thought in all areas of protein metabolism which will meet the needs of specialists in nutrition, biochemistry, clinical chemistry, medicine, and indeed in all aspects of biology in which mammalian protein metabolism is studied. We are not aware that this has been done in recent years.

The contents of the treatise are presented in three parts. After a short historical account of early studies on protein metabolism, the first part provides a picture of the biochemical mechanisms involved in protein metabolism, the second part deals with the place of proteins in nutrition, the third part gives an account of protein metabolism in diseased states. Although written as a multi-author text, the book is designed to be read in continuity by those who have only a general knowledge of the outlines of protein metabolism, as presented in textbooks of general biochemistry. In order to emphasize this continuity, each main part—biochemical, nutritional, and pathological—is introduced by a short general survey of the area covered. It is hoped that, in this way, the treatise will serve as a source-book for the graduate student who requires an advanced survey of the whole subject, and, at the same time, will interest the specialist who needs an authoritative account of selected areas of protein metabolism.

As editors, we should like to say how fortunate we have been in securing as authors many of the leading investigators in the field of protein metabolism, and we are deeply conscious of the honor they do us in participating in the writing of this book. We should also like to acknowledge with gratitude the help and encouragement of many colleagues and friends who have advised us during the assembly of this book. In particular, it is a pleasure to thank Professor D. McKie of the Department of the History and Philosophy of Science at London University for the advice on the historical introduction; Dr. L. Fowden of University College, London, for information on the amino acids found in plants; Dr. J. G. Black of Unilever for providing us with a survey of literature on protein metabolism in the skin; and Dr. G. Leaf of the University of Glasgow for much general advice on protein metabolism. Dr. Renwick of the Genetics Department at Glasgow University kindly gave advice on some of the genetic points in abnormalities of protein biosynthesis, discussed in the introductory material to Part III, and Mr. Robin Callander, Medical Artist at Glasgow University, provided a number of excellent illustrations. We are much indebted to these and many other friends for the help they have given us.

H. N. MUNRO

October, 1963 J. B. ALLISON

Mammalian Protein Metabolism

Volume II

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Historical Introduction: The Origin and Growth of Our Present Concepts of Protein Metabolism

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The man of science ought to realise the factors which have given him the vantage which he holds. But there are textbooks on the animal mechanism which do not even mention the name of Liebig. This anomaly is possibly only for those who do not understand history and hold only the new to be worthy of consideration.—Carl Voit, 1865 (cited by Lusk, 1928).

I. Discovery of Nitrogen and Its Biological Consequences: The Age of Black, Rutherford, and Lavoisier

Protein is the most abundant nitrogenous compound in the diet and in the body. Consequently, the early history of protein metabolism is linked to the discovery of nitrogen and its distribution in nature.

The identification of nitrogen was a product of the revolution in scientific thought from which modern chemistry arose in the second half of the eighteenth century. The initiator of the new chemistry and one of its chief architects was Joseph Black (1728–1799), who was lecturer in chemistry in the University of Glasgow from 1756 to 1766, and subsequently Professor of Chemistry and Physic in Edinburgh (Kent, 1950). To Black can be attributed the discovery of carbon dioxide ("fixed air") which was published first in 1756 in an expanded form of an address given the year before to an Edinburgh literary society (Black, 1756). In his lectures on chemistry, Black is quoted (Robison, 1803) as saying: "In the same year, however, in which my first account of these experiments was published, I had discovered that this particular kind of air, attracted by alkaline substances, is deadly to all animals that breathe it by mouth and nostrils . . . and I convinced myself that the change produced on wholesome air by breathing it consisted chiefly, if not solely, in the conversion of part of it into fixed air." This was the first of the gases to be discovered. (Hydrogen was identified as a separate substance by Cavendish in 1766 and oxygen by Priestley in 1774–1775.) Black comments in the same lecture about his discovery: "Here a new and boundless field seemed open before me. We do not know how many different airs may thus be contained within our atmosphere nor what may be their separate properties."

Although Black published no further experiments on the gases, one of his pupils, Daniel Rutherford (1749–1819), obtained his doctrate in Medicine in 1772 from the University of Edinburgh for his "Dissertatio inauguralis de Aere Fixo Dicto, aut Mephitico" (Rutherford, 1772). Among the experiments recorded in this thesis, Rutherford noted that, when an animal is made to respire in a closed container, it eventually dies and the air left can no longer support life or the combustion of a flame. If the fixed or mephitic air (carbon dioxide) is now removed with alkali, the residual gas is still incapable of supporting respiration or fire. Rutherford thus recognized that yet another entity was present in air, and he named it "aer malignus" or noxious air. Rutherford then went on to argue that "aer malignus" is compounded of atmospheric air saturated with phlogiston.

Rutherford's thesis is dated September 1772. In March of that year, Priestley had presented experimental evidence similar to Rutherford's before the Royal Society of London without, however, drawing definite conclusions regarding the nature of the residual gas (Priestley, 1772). Two years later, Priestley (1774) gave a more extensive account of these studies and came to the conclusion, like Rutherford, that the residual gas was air saturated with phlogiston, and he proposed the term "phlogisticated air." The question of priority in the discovery of the new gas has been discussed in considerable detail by McKie (1934), who favors the view that Rutherford has some claim to being the first investigator to recognize nitrogen as an independent substance. He was certainly the first to provide it with a name, "aer malignus." As noted above, Priestley later called the new gas "phlogisticated air" and in 1777 Scheele referred to it as "vitiated air" ("verdorbene Luft"). The French school of chemists, engaged in the revision of chemical nomenclature in 1787 (de Morveau *et al.*, 1787) indicated the inability of the gas to support life by calling it "azote," a name which it still retains in France. The name "nitrogen" was given to it by Chaptal in 1790 in a French text on chemistry which was translated into English in 1791. The name was intended to express "the characteristic and exclusive property of this gas, which forms the radical of the nitric acid," and thus be chemically more specific than "azote."

The next stage is described in a correspondence which can no longer be traced but was fortunately published in 1871 by the British Association for the Advancement of Science. One of the foreign students attracted to Edinburgh by Black's international reputation brought with him a letter dated September 19, 1789, from the French chemist Antoine Lavoisier, in which Lavoisier acknowledges the inspiration given him by Black's researches and sends some views of his own on oxidation. He encloses, he states, "un exemplaire d'un ouvrage que je vien de publier; vous y trouverez une partie des idées dont vous avez jetté le premier germe." In a later letter to Black dated November 19, 1790, Lavoisier describes experiments on the respiration of human subjects in which he shows that oxygen is consumed and carbon dioxide evolved during this process, that the quantity of oxygen used increases by some 50% above the basal level after a meal (the modern specific dynamic action of food) and that in severe exercise, oxygen consumption can increase by as much as three-and-a-half times. The actual data are not very different from those currently accepted for oxygen consumption of man under these various conditions. Part of the letter states: "Le gaz azote ne sert absolument à rien dans l'acte de la respiration et il ressort du poumon en même quantité et qualité qu'il y est entré." This experiment, described a mere 18 years after the discovery of nitrogen, may be regarded as the first metabolic experiment with nitrogen, and appears (D. McKie, personal communication, 1962) to have been based on studies made by Fourcroy in the late 1780's, using gasometric methods which were published in 1791 by Séguin. The findings were negative and, although from time to time investigators have claimed that some nitrogen is lost from the body during respiration, most scientists of the present day would subscribe to Lavoisier's view that gaseous nitrogen plays no part in the nitrogen metabolism of the mammalian organism.

Lavoisier not only introduced order into the study of the new chemistry. He also left behind him a vigorous school of chemists, some of whom turned their attention to the study of organic compounds by procedures in which gas was either evolved or removed. In 1810 a system of organic analysis was worked out by Gay-Lussac (a pupil of Lavoisier's collaborator, Ber-