

## INTERMEDIARY PROTEIN METABOLISM \*

OTTO FOLIN, PH.D.

BOSTON

The subdivision of protein metabolism into intermediary metabolism and tissue metabolism indicates that we to-day are in possession of a much more detailed and accurate knowledge concerning animal metabolism than was available a few years ago. The controversy between Voit and Pflüger and their followers of the past generation as to whether the protein of the food must be incorporated in the protoplasm of the tissues before it is oxidized was an unprofitable and useless controversy, because it was too far in advance of the experimental knowledge of that period. We still do not know the spatial relationship between protoplasm and food materials at the moment of oxidation. On the other hand, we no longer speak of protein metabolism as being an oxidation process at all in the sense understood by Pflüger and Voit. While protein materials like other carbonaceous food materials are of course finally oxidized in the body, we now believe that the nitrogenous foodstuffs first undergo changes and chemical transformations involving the loss of all protein characteristics before they are completely destroyed by the oxidation processes involved in the production of heat and energy. Through the investigations of Kutscher (1898), and more recently of Abderhalden and his associates, it has been made clear that protein materials are completely decomposed into simple crystallizable products, the amino-acids, as a result of digestion. This discovery is fundamentally important for it has necessitated a complete revision of the earlier ideas and doctrines as to the nature of the metabolic processes involved in the utilization of protein as food. The old, burning question as to whether protein must be incorporated in the living tissue protoplasm before it is oxidized we now know was a false question, because the food protein has been altered beyond recognition even before it leaves the digestive tract and many of us no longer believe that protein as such is ever oxidized in the body.

The discovery that protein materials are split up into the simplest possible component parts during the digestion suggested two new fields for metabolism investigations. The first of these is the question as to whether simple amino-acids can be substituted for ordinary food protein, and which if any of the amino-acids are most indispensable for the maintenance of the animal organism. Much interest and important work has been done in this field, and it has become quite clear that some amino-acids are indispensable while others appear to be less necessary constituents of the food. The importance of all these data to the science of metabolism, if not to medicine, is self-evident in view of the fact that practically all the amino-acids can be manufactured. The second metabolism problem which required renewed investigations when the deep-seated character of protein digestion became clear concerns the subsequent history of the digestion products, and inasmuch as my own investigations lie in this field, I shall confine myself to a discussion of this problem.

Formerly it was generally believed that protein materials were but little altered by the digestion, and the protein of the food was supposed to pass into the blood-stream without any material alteration. Since no peptones were found in the blood the peptones formed during the digestion were supposed to be regenerated into more complex albuminous materials while passing through the mucous membrane of the intestinal wall just as fatty acids and glycerin are believed to be transformed into neutral fats during the absorption. This hypothesis seemed plausible, because it agreed with the experimental observations and because the animal organism was supposed to be dependent on the complex kind of proteins found in the blood. Many investigators, including Kutscher and Abderhalden, adhered to this explanation of what happens to the nitrogenous food in the intestinal wall even after it became certain that amino-acids and not peptones were the chief end-products of the digestion. Many physiologists, however, abandoned the protein regeneration hypothesis about ten years ago. To them it seemed highly improbable that the proteins should first be completely split up into amino-acids only to be immediately recombined into albumin and then again immediately broken down so as to give the urea, the elimination of which is greatly increased three or four hours after the intake of protein food.

In place of the protein regeneration hypothesis these dissenting physiologists assumed that the transformations of nitrogenous materials which take place in the intestinal wall are of a destructive rather than of a constructive character. Just as the digestive ferments convert the proteins into amino-acids within the digestive tract, so by a continuation of the digestive or hydrolytic processes most of the amino-acids immediately lose their nitrogen while passing through the intestinal wall and the liver. The prompt formation of urea, the supposedly large amount of ammonia in the portal blood, and many other features of the nitrogen metabolism were explained in a fairly plausible fashion by this hypothesis.

There remained, however, another possibility, namely, that the intestinal wall does nothing to the amino-acids but simply lets them through. From a theoretical aspect, this point of view has been the most plausible, and notwithstanding numerous early failures, the efforts to prove that the amino-acids are absorbed from the intestine without change have been continued, and now there is no longer any doubt about the fact that the end-products of protein digestion, the amino-acids, are quickly and easily absorbed. In fact, the speed of the absorption and the speed with which the amino-acids are distributed to all the different tissues in the body is one of the reasons why the earlier investigators failed to find the digestion products in the blood.

By means of the quantitative colorimetric methods devised in my laboratory, by means of Van Slyke's micro method, and by means of Abderhalden's qualitative ninhydrin test it is now easy to show that the amino-acids are absorbed. We have therefore now not the slightest reason for believing that the amino-acids formed during the digestion undergo any change while passing through the walls of the intestine.

The essentials of the story of protein digestion and absorption appear to be very clear indeed, and can be stated in two or three sentences. In the stomach the greater part of the protein is dissolved and much of it is converted into albumoses and peptones. In the

\* Read before the joint meeting of the Section on Practice of Medicine and the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, June, 1914.

intestine the dissolved products as well as the remaining undissolved residues are attacked by the trypsin and are thereby split up into amino-acids. The intestinal wall yields another ferment, erepsin, which, so to speak, prevents the absorption of albumoses and peptones by converting such as may escape the action of the trypsin into amino-acids—and the amino-acids as fast as they are formed are absorbed and transported by the blood to all parts of the body.

The absorption of amino-acids from the blood by the different tissues and organs is extraordinarily rapid, but is not complete. The communication between the blood and the tissues appears to be about equally good in either direction, and the accumulations of the nitrogenous digestion products in the blood and in the tissues reach therefore substantially the same level. This is, I think, true for the nitrogenous waste-products as well as for the digestion products, and if correct is important, for it means that by analyses of the blood we determine also the concentration or accumulation of the same products in the tissues.

The speed of the absorption is not the same for all tissues. The liver, for example, according to Van Slyke, absorbs amino-acids from the blood more rapidly than do the muscles even when the amino-acids are injected into the general circulation, and similar though smaller variations will doubtless be found in the speed of absorption revealed by different muscles; but such variations are probably only temporary, so that on the whole it will be found true, I think, that the concentration of a given nitrogenous product in the blood is the same as in such general tissues as the muscles.

In view of the established fact that the muscles absorb the greater part of the amino-acids coming from the digestive tract, it is no longer permissible to regard the liver as the chief seat of the urea formation. The greater part of the urea formation represents nothing but the removal of the nitrogen from amino-acids which are not needed for the rebuilding of new tissue material, and there is in my judgment no reason to doubt that the muscles which absorb the greater part of the amino-acids also form from them the greater part of the urea. Dr. Denis and myself have repeatedly emphasized this point of view, and recent studies made in the Harvard Medical School by Drs. Fiske and Sumner on the urea formation have clearly indicated that this process is not localized in the liver.

In its broad outlines the intermediary protein metabolism appears now comparatively simple and clear. The blood gets amino-acids from the digestive tract and all the tissues get them from the blood. From the amino-acid mixtures thus received each tissue rebuilds itself, and the amino-acids which are not needed for such synthesis are converted into urea and carbonaceous remainders. The latter are either converted into carbohydrates or are otherwise oxidized for the production of heat and energy. When protein materials from within the body are broken down, as in fasting and in fevers, these are in all probability digested in the tissues down to the stage of amino-acids, and from that stage on undergo the same transformations as do the amino-acids derived from the food.

According to this view it is to be noted that the specialization of functions which characterizes the higher animals does not extend very far into the field of general protein metabolism. All the tissues prob-

ably take part in this process roughly in proportion to the weight of living protoplasm contained in them. We cannot therefore expect to find the general protein metabolism materially or specifically altered because of this or that disease in any particular organ. I feel it incumbent on me to emphasize this aspect of the case, for we laboratory workers are often expected to elucidate diseases by metabolism studies when no such elucidation is possible on the basis of the available fund of knowledge of metabolism processes.

## THE SPECIFIC DYNAMIC ACTION OF THE FOODSTUFFS \*

GRAHAM LUSK

NEW YORK

The conclusions to be reported in this paper are based on results obtained from 250 experiments on dogs. The animals rested quietly in a respiration calorimeter, at an environmental temperature of 26 C. (78.8 F.), and were subjected to different dietary conditions. Under these circumstances the simplest nutritional elements can be given and their effect on the heat production can be noted in hourly periods. This gives an idea of the interplay between the nutrient particles and the oxidizing tissues.

Dr. Du Bois will present the story from the point of view of investigations made with a similar though larger respiration calorimeter devised to determine the nutritional condition of the human being in disease.

All nutrient proteins, starches and compound sugars undergo fragmentation in the intestinal tract into simple chemical substances which are soluble in the fluids of the body. A polysaccharid like starch is broken up into glucose molecules; a disaccharid like cane-sugar (sucrose) is split into a molecule each of glucose and fructose, and lactose undergoes similar transformation into a molecule of glucose and one of galactose. Glucose, fructose and galactose are sugars which may be absorbed and carried to the living cells by the blood-current that bathes them. In similar fashion, the protein molecule is demolished in the intestine and broken into units such as glycocoll (amino-acetic acid), alanin (aminopropionic acid), glutamic acid, which is a dibasic amino-acid with five carbon atoms, and there are many others. These amino-acids are absorbed into the blood-stream and are carried to all the living cells of the body.

The result of the ingestion of food in any quantity is to increase the amount of heat production in the body. The extent to which the increase in metabolism occurs depends not only on the quantity, but also on the kind of food introduced into the blood-stream. Since the power to increase heat production exerted by protein, carbohydrate and fat is different for each substance, Rubner has defined this power as the specific dynamic action of the substance. The term is technical and cumbersome, yet the meaning is perfectly simple.

Every one has experienced the increased feeling of warmth after a hearty meal, and no one eats largely of meat in midsummer, for it increases heat production and consequently increases sweating.

\* Read before the joint meeting of the Section on the Practice of Medicine and the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, June, 1914.

\* From the Physiological Laboratory of the Cornell University Medical College, New York.