The Oliver-Sharpey Lectures

ON

THE BEARING OF METABOLISM EXPERIMENTS UPON THE TREATMENT OF SOME DISEASES

Delivered before the Royal College of Physicians of London on April 3rd and 5th, 1906

BY

EDMUND I. SPRIGGS, M.D. LOND., F.R.C.P. LOND.

ASSISTANT PHYSICIAN TO ST. GEORGE'S HOSPITAL AND TO THE VICTORIA HOSPITAL FOR CHILDREN.

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LECTURE I.

Delivered on April 3rd.

INTRODUCTION.

MR. PRESIDENT AND FELLOWS,—The true basis on which the knowledge of medicine rests is exact observation. Of all the processes of nature those which are concerned with the maintenance of life are the most illusive to the observer. Problems are presented which make great demands upon the resources of mechanical, physical, and chemical science. The inquiry into the source of the energy of the living body and into the forms in which its energy is manifested has occupied some of the greatest researchers of the last century, and not until recent times have chemical and physical methods been applied to the more difficult task of the measurement of these forces. More than commensurate with the difficulty of the subject, however, has been the brilliancy of the results obtained. The principle of the conservation of energy has been applied to living structures. The various forms of living activity have not only been correlated to their source, the potential energy of the food, but measured. Rübner, Laulanie, and a host of untiring workers have been able to show that in animals there is an absolute balance between the energy taken in as food and that used by the body and given out as heat and the chemical energy in the excreta. In order completely to estimate these metabolic processes as a whole it is necessary, not only to analyse the food and the liquid and the solid excreta, but also to ascertain the amount of oxygen taken in and carbon dioxide and water given out by the lungs. This has been done in man in a limited number of cases. On the other hand, a very large number of metabolism experiments has been carried out in which, although the respiratory analyses are wanting, the food and excreta have been daily examined over long periods, both in health and disease. In this way a mass of facts has been accumulated concerning nutrition which cannot fail to be of paramount importance to medicine and the principles upon which diets are constructed have been put upon a sure foundation.

Our present object is to examine the results of metabolism experiments with reference to their bearing upon the treatment of disease. In many cases we shall find nothing that is new. The medical observation of the past and experiment at the bedside have often pointed to the truth and this indication has been acted upon with good results and thus a line of practice has come into use which the exact observation of scientific method has later confirmed. But those who have laboriously carried out accurate experiments have put medical knowledge upon firmer ground by transferring some statements from the list of what we think to that of what we know. We speak of the science and art of medicine. Such researches confer a great benefit upon the science by relieving it of some of the oscillations of opinion and practice which only too frequently obscure the art. It is probable that I shall say nothing that is not known to my audience. My endeavour is rather to fulfil the design of the distinguished founder and to show some points in which practice is supported by "observation and experiment on man himself" and some perhaps in which it is not.

Since the intention of these lectures is specifically to "encourage the application of physiological knowledge to the prevention and cure of disease and the prolongation of life" I shall devote the first lecture to the consideration of the principles upon which our knowledge of the nutrition of the body depends and to their general application, and the second to the application of these principles in the investigation of some pathological conditions. I shall constantly be referring, from the point of view of the experimental evidence only, to matter which is daily familiar to every medical man.

Preliminary Considerations.

The food supplies the elements necessary for the structure of the body and also energy for the various bodily activities. The elements are mainly supplied by proteids and salts. The energy is conveyed in different chemical substances, proteid, carbohydrate, and fat. The heat produced when these foods are oxidised in the body is the same as that given off when they are burnt outside the body, and can be ascertained for each foodstuff by combustion in a special calorimeter. The average figures from one gramme of the food substance used in the body have been found to be: for proteid, 4·1 Calories; carbohydrates, 4·1; and fat, 9·3. In a metabolism experiment the proteid, carbohydrate, and fat in the fæces must be subtracted from those in the food, the difference being the quantity absorbed from the intestine. The carbohydrate and fat absorbed are wholly oxidised; not so, however, the proteid, for its nitrogen is excreted as urea and other substances which are not fully oxidised and therefore still possess some chemical energy. So that in estimating the total energy supplied by the food to the body we must also subtract this value from that of the absorbed food. The energy value of the urine is most accurately determined by direct estimation of the dry residue in a bomb calorimeter; it can be calculated approximately, however, if the amount of nitrogen in the urine and fæces be known. The oxygen taken in and the carbon dioxide given out by the lungs should also be measured. The respiratory quotient thus obtained varies according to which foodstuff is being oxidised and from its value we may gain information on this point.

The Conservation of Energy.

The proof of the law of the conservation of energy has been supplied in the case of man himself by Atwater and his fellow-workers. A chamber was constructed in which a man could remain for days at a time. The walls were fourfold and the spaces containing air were kept at the same temperature as the chamber by means of a thermo-electric apparatus. Thus no heat was lost to or from the chamber through the walls. Tubes led warm dry air to the chamber and the products of respiration were conducted away through a meter which measured the air and automatically took a sample for analysis at regular intervals. The heat produced by the individual was taken up by a kind of inverted radiator in the chamber, through which water flowed continually. The difference between the temperature of this water on leaving the chamber and that on entering it and the volume flowing through being known, the heat given off could be calculated. The evaporated water in the air leaving the chamber was also estimated and the heat lost from the body in converting this from the liquid to the gaseous state could then be calculated. The food was measured and analysed and its caloric value determined and the urine and fæces were treated in the same way. These experiments were more complete than the previous ones on animals referred to in that the subject could do muscular work in the chamber. The muscular work of the body is of two kinds, internal and external. The internal work is that done by the circulatory, respiratory, and visceral muscles. The energy thus set free is, like that produced by the activity of the living cells of the body other than those of the muscles, discharged as heat. The external work is that portion of the energy liberated during the contraction of the skeletal muscles which is manifested as work done—e.g., when a weight is raised. In treatment we can control the external completely; the internal partially. In these experiments the subject worked a stationary bicycle and the bicycle was connected with a dynamo and the electrical current generated carried through a glow-lamp in the chamber and thus converted into heat and measured together with that given off from the body. The amount of work done and converted into heat was also separately measured by registering the electrical current produced. The potential energy of the substances actually oxidised in the body was thus compared with the kinetic energy produced, either as heat when the body was at rest or as heat and external muscular work, which was measured as heat. The experiments, which were 45, lasted several days, usually four, the total number of days observed being 143. The results were a complete confirmation in man of the above-mentioned work in animals, both when the subject was at rest or doing work. During complete rest, therefore, in the recumbent position no external work is done and the internal work done by the circulatory and respiratory muscles is at a minimum.

We know therefore, not by inference but by direct experiment, that in health the body produces no form of physical energy which is not derived from, and cannot be directly traced to, the chemical energy of the food or of its own tissues. Although the same complete prolonged experiment has not been done in disease, yet the results of a number of metabolism experiments, including calorimetric observations, furnish us with evidence, if such be wanted, that the same is true in disease. With this foundation to work upon, the carrying out of observations upon nutrition in man becomes a much more simple matter. Such detailed experiments as those of Atwater required an extremely costly apparatus and the services of about 12 skilled workers. But since the relation of the food energy to that evolved from the living organism is now definitely known we can calculate from the food consumed the energy which the body uses without making a calorimetric experiment. An ordinary metabolic experiment with a nitrogen balance-sheet will tell us whether nitrogenous food be laid on as proteid tissue and not burnt at once. Also, if respiratory analyses be made in a suitable chamber, such as is constructed in a number of laboratories, the determination of the respiratory quotient will enable us to conclude, in the case of tissue other than proteid being used up, whether it is carbohydrate or fat.

In order to form clear ideas as to the management of disordered states of nutrition we must consider briefly the uses to which the different foodstuffs are put in the body.

Proteids.

Proteid food contains those elements of which the essential tissues and organs of the body are made, since these consist of protoplasm. It is therefore an essential foodstuff. The manifold activities of living protoplasm are only equalled by the bewildering complexities of the molecular groups composing it, now being daily unravelled by many workers. These groups are separated from each other by digestion and such as are needed for the reconstruction of tissue are built up again into protoplasm, while any excess taken is converted into urea and excreted within a few hours. The work done by the digestive organs in dealing with proteid is, as we shall see, considerable. We have to ask ourselves the question, Can we, in diseased conditions of the digestive system, or in those diseases, such as fevers, where the stomach certainly, and the whole alimentary canal probably, share in a general depression of function, carry out with advantage part of this work beforehand. To answer this we must know first whether the hydrolytic products of digestion of proteid can replace proteid in the diet and supply the needs of the body for nitrogenous tissue; and secondly, whether, if this be so, there are any disadvantages attached to their use. The reply to the first question is an affirmative. Albumoses, peptones, and even the groups of fractions obtained by prolonged pancreatic digestion, amido-bodies and their congeners, no longer proteid in nature, have been shown to be capable of keeping the animal body in nitrogenous equilibrium. The albumoses form the major part of some prepared foods, such as somatose. Metabolic experiments show, however, that these substances are far from being desirable, from a dietetic point of view, either in health or disease. True, they are normal products of digestion, but an examination of the intestinal contents shows that under normal conditions they are only present at any one time in minimal quantities. Each step in the disintegration is rapidly succeeded by the next, or by the removal through absorption of the product formed. But albumoses when given in bulk in the food are shown to possess irritative qualities which cause increased secretion, diarrhœa, and lessened absorption. For instance, Hildebrandt showed in a man by analyses of the fæces that 87 per cent. of proteid given (which contained 23 grammes of nitrogen per day) was absorbed. On replacing about a quarter of this proteid with somatose the absorption sank to 73 per cent. On replacing two-thirds with somatose only 67 per cent. was absorbed. Still less favourable figures have been obtained by Neumann, Salkowski, Bornstein, and Ellinger. Small quantities added to the diets are better used, though by no means so well as ordinary proteid. These substances are, therefore, less acceptable to the alimentary canal than the original proteid. The same is true of sugar as compared with starch.

the natural form in which carbohydrate is taken. We may seriously question whether peptonised milk has any advantages as a nutriment. The mixed products of digestion introduced into the stomach call forth gastric juice and ordinary milk calls forth less than any other food. Since in disease milk is digested normally, there seems to be no need to substitute for it a partially digested fluid which will increase the gastric activity unnecessarily without any corresponding benefit to nutrition and with the possible disadvantages mentioned above. Peptonised milk does not clot in the stomach like ordinary milk; but the formation of a hard clot from natural milk can be prevented by dilution or by adding 20 cubic centimetres of 25 per cent. sodium citrate to each litre, or to some degree by thickening it. We must also remember that if albumoses or peptone be present in any considerable quantity in peptonised milk their bitter taste comes noticeable.

Fate of Proteid.

When any quantity of proteid has been digested there is an early excretion of urea—i.e., within 24 hours an amount of nitrogen corresponding to that ingested appears in the urine, except in such cases as are laying on flesh. Panum showed that half of this urea excretion may occur within seven hours and in some cases the elimination is more rapid still. This fact suggests that the proteid taken in has not been built up into body tissue and thus the view has forced itself upon observers and has especially been urged by Folin, that this rapidly excreted nitrogen is not needed by the body for structural purposes and hence the proteid containing it is hydrolysed and the nitrogen excreted. The rapidity with which the elimination of nitrogen takes place is explained when we consider the probability that proteids are absorbed not as peptone but as amido-bodies and such simpler derivatives, the hydrolysis referred to above taking place chiefly in the intestine, and that such a proportion of these absorbed substances as is not needed to build up tissue is not reconverted into proteid at all but turned at once, as regards its nitrogenous moiety, into urea, and excreted in the urine. The fate of the non-nitrogenous carbon-containing moiety is not definitely known, but it is no doubt oxidised to furnish energy in the same way as carbohydrate and fat. The hydrolysis of proteid involved in splitting off its nitrogen may take place with very little loss of energy, leaving most of the available energy of the original proteid in the carbonaceous part. The suggestion naturally follows that this excess proteid may be replaced by carbohydrate or fat which, while serving equally well for the production of heat and energy by oxidation, would not throw upon the excretory organs the work of eliminating nitrogenous material. Experiment bears this out.

Hirschfeld, Landergren, Sivén, Kumawaga, and others have shown that nitrogen equilibrium can be maintained at a low level of proteid ingestion—e.g., even at 15 grammes of proteid per day for a time if abundance of carbohydrate and fat be taken. More convincing, however, are the observations of Chittenden on different classes of men, scientific workers, soldiers, and athletes, extending over long periods. These observations proved that about 50 grammes of proteid per day, or half the amount usually recommended, sufficed to keep these individuals in nitrogenous equilibrium and in health, without any increase of, indeed with even a diminution in, the total caloric value of the food taken. Other observers have fixed from 0·5 to 0·6 gramme of proteid per kilogramme per day as the lowest limit advisable, which in a man of 70 kilogrammes is from 35 to 42 grammes. On the one hand, then, the theoretical reasoning from the fact that an excess of nitrogen is so rapidly eliminated from the body, and on the other the practical result of experiment, substantially agree that more than 50 grammes of proteid is not necessary in health to supply the needs of the body, and increases the work of nitrogenous excretion with no apparent advantage.

Chittenden's results must remind everyone of acquaintances whose consumption of proteid is exceedingly small. They also suggest that many workers in the poorer classes are not so underfed as regards proteid as they are supposed to be, but that rather the richer classes are overfed. Caspari and Glaessner investigated the metabolism of a married couple who lived upon a vegetable diet. The daily consumption of proteid was represented by from 5·3 to 7·8 grammes of nitrogen. On this not only was nitrogenous equilibrium attained but some proteid was laid on. The absorption of proteid was only from 74 to 76 per cent., but that of the other food-stuffs was above normal, for of the total energy of the food from 90 to 92 per cent. was utilised, these figures being as good as those for an ordinary diet.[1]

Schryver and Hamill have recently brought before the Physiological Society evidence that the physiologists working in a London laboratory utilised on the average 9·6 grammes of nitrogen a day. Hence large quantities are obviously unnecessary for most individuals. Are they desirable from any point of view? We must remember that we are dealing with average figures and people of large bulk will require more and this is important when fixing standards which are to apply to a number of people. Again, none of the physiologists above referred to, though living active lives, were doing hard muscular work. It is true that Chittenden's subjects were some of them athletes and some soldiers, but none were doing active continuous

[1] Atwater found that on a mixed diet there was absorbed from the food 90 to 93 per cent. of the energy, 89 to 93 per cent. of the proteid, 95 to 96 per cent. of the fat, and 97 to 98 per cent. of the carbohydrate.

muscular work[2] such as thousands of workmen perform for from eight to 12 hours a day. Although, as we shall see in a few minutes, the energy for muscular work is not supplied from proteid when other foods are available, yet the wear and tear of muscular tissues is supplied from proteid and we should expect that a fairly liberal supply of it would be an advantage to hard workers. It is to be noted that in Atwater's experiments the subjects were excreting in the urine and therefore metabolising on an average from 15 to 18 grammes of nitrogen in the rest experiments with a diet worth about 2700 Calories and were practically in nitrogenous equilibrium. In the work experiments there was a daily loss of nitrogen in the urine in 19 experiments out of 23 with a similar amount of proteid in the food and a caloric intake averaging 4340 Calories. This does not prove that they could not have adjusted themselves to a lower standard, but they were evidently not perfectly adjusted even to the higher one when doing hard work. It is stated that coolies work continuously through the day on a diet which contains from nine to ten grammes of nitrogen, of which from eight to nine grammes would be absorbed from the bowel. This being so, it is necessary to ascertain whether they do as much work as a European would in the time and also how their body bulk compares with that of our workmen. Kumawaga used 2478 Calories, of which 6·3 per cent. was derived from proteid and 93·7 from carbohydrate—i.e., 50 grammes proteid were taken, of which 38 were used, equivalent to six grammes of nitrogen. He was not, however, doing hard continuous muscular work. It is possible that more than the minimum requirement of proteid is a benefit to a race, but this only long-continued careful observation can decide. The fiercest animals are carnivorous and take an excess of proteid according to our standard, but this is perhaps because courage as well as cunning is necessary to enable them to obtain their food. There are certainly herbivorous animals, such as the horse, which in sagacity, endurance, and strength are not inferior to the carnivora. This question is not one of vegetarianism, for it is possible to take an excess of nitrogen on a vegetable diet, and this is often done.

Whether the optimum amount of proteid in a diet be as low as has been claimed there is no doubt that many people eat a great deal too much of this form of food and the above results strengthen the hands of the medical man in his crusade against an excessive nitrogenous diet. We have before us definite proof that 60 grammes or two ounces of proteid—i.e., 300 grammes or ten ounces of meat—is a sufficient proportion for an ordinary diet in health, and in conditions such as chronic granular kidney, arterio-sclerosis, and gout we may keep this figure before us as the total quantity to be allowed in the

[2] See Physiological Economy in Nutrition, p. 135.

various foodstuffs. In diseases involving the kidneys and digestive organs we can therefore limit the proteid to this amount with the full assurance that we are not in any way handicapping the nutrition of the body, but, on the contrary, lessening the demands upon the digestive and secretory organs.

Reference may be made to Hopkins's suggestion that proteid food is not only required to form proteid tissue, but also to furnish certain molecular groupings necessary for the formation of some substances in the body, such as adrenalin and pigments, which exist in small quantities but are of great importance.

Fat and Carbohydrate.

Fat and carbohydrate are used to supply energy for all the bodily activities, whether manifested as heat or movement. Fat is weight for weight much the more valuable, but both are necessary; of the two carbohydrate is the more necessary (Kumawaga). The total caloric value of the diet must be made up to from 35 to 40 Calories per kilogramme—i.e., about 2000 to 3000 Calories for an adult who is doing moderate work. Chittenden's men used less but they all lost weight, and this part of his results is not so well supported by the evidence of other workers as is the reduction of proteid. It follows from the principle of the conservation of energy that with hard work the caloric value of the diet must be much increased. We shall see that in some of Atwater's observations as much as 1000 Calories of heat were recorded as given off from the body in two hours in working a bicycle hard against resistance.

Rest in Bed.

We may now consider the food requirements of those who are not working. The effect of resting in bed was shown clearly by Atwater's experiments; he found that the energy given off by his subject during sleeping hours was nearly half that used when he was up and about in the chamber without doing any serious work; the figures show that the demand is 80 per cent. more in the latter case. This exact measurement is a striking example of the difference between stopping entirely in bed and being up, leaving external muscular work out of the question. In such diseases as anæmia, heart disease, respiratory disease affecting the circulation, fever, or any disease endangering nutrition, and in which the demands made upon the body are not balanced by its resources, it is clear that complete rest in bed is nearly 80 per cent. better than being kept in one room and not in bed. I say nearly 80 per cent. because the subject was not at this time taking food. Patients kept in bed, of course, require food and we shall see that digestion increases the oxidation processes in the body; we shall also see, however, that the work done in digestion varies considerably with the kind of food given and may be kept low. Internal work is done in the body by the circulatory and respiratory muscles, by those of the alimentary canal and by the striated muscles in preserving their tone. Zuntz calculated that the respiratory and circulatory work represents about from 10 to 20 per cent. of the total Calories of the fasting body. Johannsen found that by controlling his involuntary muscular activity he could reduce his excretion of carbon dioxide by nearly a third. Speck has shown how quite inappreciable movements greatly increase the oxidation processes. Light increases the metabolism, doubtless through causing muscular movement. In treatment we can considerably reduce these demands upon the individual by complete rest in the recumbent position. When digestive activity is absent, as in fasting with complete rest, the energy used by the body is at its lowest and we can trace the influence exerted by food.

Effect of Food.

Atwater's figures show that in a resting experiment the carbon dioxide excretion was greater on the feeding days by 24 per cent. (33·8 : 27·3). The effect of an individual meal is also very noticeable when the oxygen as well as the carbon dioxide is measured. Both the intake of oxygen and the output of carbon dioxide show a rise of oxidation after taking food. There is much evidence that this is largely due to the muscular and secretory activity of the alimentary canal. The same increase of oxidation takes place in colic, as shown by Lehmann and Zuntz in the fasting man Cetti. It also occurs after a saline purgative has been administered. It is, however, probably not entirely due to the alimentary canal activity but also to an increase in the general metabolic activity of the body.[3] Nevertheless, such observations may yield useful information as to the degree of oxidation called forth by different foods which, with the above reservation, we may look upon as indicative of digestive work. It is interesting to note that this rise of oxidation after food is contemporaneous with the flow of tissue lymph demonstrated by Dr. George Oliver. It is often desirable in disease to feed the patient upon a food which will yield a maximum of energy to the body with a minimum of expenditure in its elaboration. The work of Speck in 1874[3] and of Magnus-Levy (1893) has shown that more demands are made upon the digestive activity with a proteid diet than with any other, and also that this increase of internal muscular and secretory work lasts a longer time than with carbohydrate and fat. I may suggest here that it is possible that the prolonged rise

3 Pembrey and Spriggs: Journal of Physiology, vol. xxxi., p. 333, 1904.

of oxidation processes which follows the ingestion of proteid may be associated with the rapid breakdown of unneeded nitrogen and the conversion of the non-nitrogenous moiety into carbohydrate for future use. A meal of proteid produces a rise in the respiratory exchange of from 30 to 50 per cent. above that of the fasting animal.[4] Speck and Magnus-Levy found that in man the oxidation after taking meat is 30 per cent. higher than after taking sugar and butter and the increase lasts about four hours. It also increases with the amount of meat taken. This oxidation begins before there is time for any appreciable amount of absorption to have taken place; it is not caused by injecting food substances into the blood directly (although the excretion of carbon dioxide is increased under this condition) and, as above mentioned, it may be imitated by producing activity of the intestine by means of purgatives. Here, again, we have unequivocal evidence in favour of limiting in diseased states the proteid in the food as far as may be without prejudice to nutrition, and especially in alimentary diseases, since it requires more digestive work than other foodstuffs. We can therefore lessen the internal work of the body by (1) rest in bed and avoidance of all excitement and (2) limiting the digestive work by not allowing too much proteid.

Exercise: External Work.

Exercise involving the performance of external muscular work increases the metabolism of the body very greatly, but not that of the proteid tissues, unless it be excessive, when there is a slight addition of excretion of nitrogen in the urine for a day or two after. Atwater's figures showed that a man during the night gave out 150 Calories in two hours, 500 Calories in the same time during moderate work, and when a muscular man was working hard 1000 Calories were used in two hours. The actual external work done is about a fifth of the energy discharged or even less. This is rather better than the yield of a steam engine, which gives about 15 per cent. of its total discharge of energy as work and the rest as heat. It is often necessary to prescribe exercise of a moderate nature and it is obvious that a more liberal diet is required, just as in health when muscular work is done. In some diseases, as, for instance, in those of the kidneys, we must know what kind of food must be added. Experiment shows plainly that it is not necessary to add proteid, for when other material is available the body tissues are not used up to furnish muscular energy. During rest one of Atwater's subjects gave out in a given period 436 Calories; of this 40 were derived from proteid and 296 from fat or carbohydrate probably from fat. When the same individual did muscular work the discharge of energy rose to 772 Calories in the same

[4] Pembrey: Recent Advances in Physiology.

time. That from proteid, however, only increased from 40 to 60, while 712 were derived from fat. Again, on one day 543 Calories were discharged as external work; this necessitated an increase in the production of energy of over 2000 Calories. Nevertheless, the heat given off from proteid oxidised, as shown by the nitrogen balance, was substantially the same as on a rest day, being 434 Calories as against 429. Hence the whole of the 2000 Calories was supplied by the oxidation of non-nitrogenous substances.

Of course, if neither carbohydrate nor fat is available for the production of the energy required in muscular work proteid is used, but the proof that there is any advantage in using it is wanting, while we know that extra work devolves upon the alimentary canal and the kidneys in dealing with the excess of nitrogen and it is also probable that the carbohydrate required for muscular contraction has to be made from the carbonaceous moiety of the proteid. Since, then, a man taking exercise does not require a corresponding increase in his nitrogenous food, carbohydrate or fat should be freely given. Metabolism experiments here give definite proof that either of these foodstuffs is available. Carbohydrate may have a slight advantage over fat but there is practically no difference between them. Fat furnishes more energy per gramme given and when we desire to keep the bulk of the food as low as possible it is convenient to use it in abundance, for one gramme of fat is equivalent to more than two of carbohydrate. Again, when carbohydrate is not utilised in the body or only partially utilised, as in diabetes, we are forced to rely mainly upon fat and proteid as energy furnishers. Carbohydrate food is almost invariably well digested by the stomach when given in simple form, such as arrowroot. Even in the case of dilated stomach when fermentative changes are especially liable to occur, if lavage be carried out, this food is well borne and has, like fat, in cases of gastric ulcer the advantage over proteid of not stimulating the secretion of gastric juice.

Fasting.

A large number of diseased persons are suffering from partial inanition. There are also cases in which abstinence from food is adopted as a therapeutic means, notably in gastric ulcer. A consideration of the processes of nutrition during fasting will be of help in dealing with such conditions. In the first place we may, I think, start with the premiss that it is *a priori* desirable to feed the patient, except in specially selected cases of those diseases in which the taking of food seriously favours the progress of the morbid condition. Fasting has been advocated as a universal system of dietetics, especially in acute illnesses.[5] But we

[5] The Lancet, Feb. 3rd, 1906, p. 311.

know that fasting animals are more liable to contract acute infections to which they are exposed and less liable to resist the infectious process when contracted and must conclude that the same applies to man. And this is certainly confirmed by experience. When an individual is obliged to go without food for a longer or shorter time, the point of greatest importance is the quantity of storage material contained in the body, and especially of fat. The body uses as little of its actual—i.e., proteid—tissue as possible. For instance, von Noorden calculated that a man on the second day of fasting oxidised proteid and fat to the value of 1897 Calories. Of this, only 10 per cent. came from proteid and the remaining 90 per cent. from fat. Cetti, who was not a fat man, used on the second day of a fast 1595 Calories, of which 18 per cent. came from proteid and 82 per cent. from fat. Further, as the fasting days proceed the body uses less energy and the proteid excretion, which is usually about from nine to ten grammes per day, may sink as low as from three to four grammes of nitrogen per day after three weeks. The amount of energy used per kilogramme does not fall much, but as the body loses in weight the total energy used falls regularly. After a certain time the proteid tissues are called upon to supply all the energy needed, for the fat becomes used up or else the body loses the power of oxidising it, for some fat usually remains in the body even after death from starvation. In this case the nitrogen in the urine represents—1. The unavoidable tissue breakdown, probably equivalent to from three to four grammes of nitrogen. 2. The proteid used in producing energy; this is increased after the fat is gone. 3. The proteid broken down to form carbohydrate.

Towards the end of a hunger period, acetone, diacetic acid, and oxybutyric acid appear in large quantity in the urine. It is noteworthy that acetone has been regarded as arising from fat, but that it appears in greatest quantity when that substance is present in least amount and when most of the energy is being furnished from proteid. This, together with the fact that it may arise when abundance of fat is available, suggests rather that a deficiency of carbohydrate is the accompaniment of the formation of this substance. The suggestion of Embden and von Noorden that acetone may arise as a disintegration product of leucin, the remainder of the molecule, containing the lactic acid group, being synthesised to form carbohydrate, would also accord with this view. We should then suppose that proteid forms the carbohydrate and that acetone is a biproduct and the appearance of this substance with diacetic acid in the urine in fever and wasting diseases would indicate that carbohydrate is required.

Since most of the observations on the metabolism of fasting people have been made when the patients were up we should expect that a fasting period would be much better endured with a subject in bed, for the demands made upon the body are in this case much less as shown above, firstly because the internal work of the muscular, circulatory, and respiratory system is at a minimum owing to the absence of exertion ; secondly, because the internal work accompanying digestion is absent ; and thirdly, because the oxidation in the muscles necessary to maintain the body temperature is less owing to the body being warmly clothed. This is found to be the case, for fairly nourished women suffering from gastric ulcer bear easily a fasting period of three weeks or more, fluid being supplied by mouth or by rectum. The secretion of gastric juice ceases and the ulcer is under the most favourable conditions for healing.

In treating such cases with injections of albumin water and sugar we must remember that the patient is very nearly completely fasting. For instance, a patient at present in St. George's Hospital took per day by the rectum 45 ounces of albumin water, each pint of which contains the white of two eggs (26 Calories), one teaspoonful of sugar (14 Calories), and a teaspoonful of salt. This was given in three doses of 15 ounces each. Each enema was equivalent to about 30 Calories and the total energy supplied per day was less than 100 Calories, even supposing that the albumin was fully absorbed.

The facts which have been observed upon fasting men and animals show that in such conditions careful attention must be paid to the following points.

1. The weight ; the loss must be carefully observed and should not be more than from 1 to 1·5 per cent. of the total per day. As to the total loss, it is said that a man cannot survive a reduction of more than a third of his weight in acute hunger. Such a statement is of no clinical value, but any increase in the rate of loss is an indication to supply nourishment.

2. A fall of temperature below the normal limits is of sinister significance. This is a sign which is well known in cases of pathological starvation, such as that of œsophageal stricture.

3. A rise of the temperature above the normal contra-indicates fasting for more than a short time. Fever has been found in animals to lessen considerably the power of resistance to inanition. The nitrogen breakdown is never so little as in fasting without fever.

4. Sufficient fluid must be supplied. The body can only survive the deprivation of water for a short time. In the condition of which we are treating at present fluid is usually given by the rectum in an isotonic solution, such as normal saline solution. The quantity of urine should be watched and if it fall below the preceding average and become concentrated and the patient feel thirsty more fluid should be administered, if necessary by subcutaneous injection. Less water is necessary than when food is taken.

Partial Inanition.

With partial feeding the period of resistance is much longer; indeed, in such a condition of subacute starvation the body may survive the loss of a much greater proportion of its weight than in complete hunger, and has been known to become reduced by nearly half. We may class with this condition the treatment of enteric fever with whey. König's analyses of milk give the following percentages: casein, 3·02; albumin, 0·53; fats, 3·69; and sugar, 4·88; the heat values of these substances being 5·86 (casein), 5·74 (albumin), 9·23 (fat), and 3·95 (lactose), in one litre we should get a heat value of 740 Calories. This is a high figure. The average for cow's milk obtained by direct estimation is about 670 Calories (Langstein) per litre. Taking the higher value we see that the constituents of the whey, the albumin and the lactose, give 30·42 and 102·76, that is 223·18 Calories in a litre or 1·76 pints. Making the necessary deductions for imperfect absorption, &c., we must conclude that a litre of whey cannot furnish more than 200 Calories. So that two pints of whey a day at most mean a furnishing of about 240 Calories per day, a nutritive value of a little more than half a pint of milk (212 Calories).

Nutrient Enemata.

Turning now to the metabolism of patients receiving nutrient enemata, it is important to remember that we are dealing with a condition of partial starvation; the enemata usually given contain a fuel value of not more than 200 kilo-calories in each enema. We must inquire how much food and of what kind is likely to be absorbed and what relation the quantity bears to the actual needs of the body. A fasting man (Cetti) used up tissue to the extent of about 30 Calories per kilogramme per day. During sleep and with as complete rest as possible the figure may be as low as 25 Calories per kilogramme. Even if only a portion of this be supplied it is of great value, as we have seen that a man can survive very much longer if a part of his energy be furnished than in fasting. In such conditions as gastric ulcer, when it may not be desirable to supply food by the mouth, this question is of importance. Voit and Bauer, and Eichhorst showed that the absorption of albumin is aided by salt. A 1 per cent. saline solution is isotonic with the intestinal wall and forms a suitable medium for the conveyance of foods. Leube carried out experiments in which meat and pancreas were mixed and concluded that a considerable quantity could be taken into the body in this way. But in this case food was also given by the mouth. Boyd and Robertson do not recommend this enema as they find the putrefaction in the bowel is excessive. Ewald showed that peptone and eggs were well absorbed. His observations were made for the most part on a neurotic woman who was also receiving food by the mouth. Brandenburg concluded that only one-third of the casein of milk was absorbed, and other observers have also reported unfavourably on casein. In 1903 Ehrström investigated this point afresh. He points out that O. Cohnheim has shown that casein can be directly broken down by the erepsin of the intestinal juice without previous peptonisation, while other proteids cannot. On the other hand, it is probably more easily acted upon by bacteria. The following enema was administered two or three times a day to a patient with carcinoma of the cardiac orifice: 50 grammes of dextrose, 150 grammes of warm milk, and 15 grammes of proton (a combination of soda with caseinogen). This has a heat value of 350 Calories. No abnormal fermentation was observed. An analysis of the fæces showed that 80 per cent. of the nitrogen was absorbed. He believes that the caseinogen was really broken down—that is, digested—in the bowel. If this substance be introduced into the blood directly it appears in the urine, but a frequent examination of the urine showed that this did not occur. Bial mentions a research by Zehmisch, which I have not read, in which enemata were given consisting of milk, eggs, sugar, and salt. The proteid and fat were very badly absorbed, the figures for absorption being: 1·5 per cent. proteid, 6 per cent. fat, 67 per cent. sugar, and 31 per cent. salt. These results are exceedingly unfavourable except as regards the sugar. Bial made one-day observations upon himself on two occasions with a 10 per cent. solution of Witte's peptone. He found that 50 per cent. was absorbed and if alcohol were added 66 per cent., and recommends the following enema: peptone, lactose, and absolute alcohol, of each 25 grammes; tincture of opium, ten drops; and water up to 250 cubic centimetres; to be given three times daily. The enema contains no fat.

Boyd and Robertson have recently carried out some very useful observations. Six patients were observed for six days each and different enemata were given, six hourly, no food being taken by the mouth, and the urine and fæces being analysed daily. They found that very little proteid in the form of milk and eggs is absorbed from the bowel. From 30 to 70 grammes were given and from 4 to 14 were absorbed. In two cases when the white of one egg was given just as much was absorbed, 9 and 16 grammes, as in four cases with the whites of two eggs in which 4, 7, 10, and 11 grammes were absorbed; therefore no definite relation existed between the amount given and that absorbed. The highest caloric value obtained in the day from proteid was 56 Calories.

With fat results much more favourable were obtained than by previous workers. We have seen that Zehmisch reported an absorption of 6 per cent. only and Munk and Rosenstein in their observations on a patient with a lymphatic fistula reckoned that about the same proportion was taken up when lipanin was introduced into the rectum. Boyd and Robertson found that from 12 to 51 per cent. of fat was retained from milk, the yolk of egg, and in one case from cod liver oil. The absorption was absolutely greater when more fat was given. In four enemata for the one day of two eggs, 47 grammes of dextrose, ten cubic centimetres of cod liver oil, with saline solution, there were 103 grammes of fat, of which 46 were absorbed, having a heat value of 426 Calories. In others 24 and, as I have already mentioned, 51 per cent. was absorbed. Such a utilisation of fat in these emulsified forms is of great importance and exerted, as might be expected, a distinct proteid-sparing action, much less nitrogen being passed in the urine. Hausmann has recently found that of a 15 per cent. solution of grape sugar 60 per cent. is absorbed in two hours, of cane sugar 51 per cent. at most, and of milk sugar 37 per cent. 10 per cent. alcohol delays absorption but its caloric value more than makes up for the delay. Sugar is more easily absorbed from 1 per cent. saline solution than from water.

We see therefore that sugar is well taken up from the rectum. To exclude the possibility of its being simply broken down by bacterial action these observers applied to it an experiment previously used in the case of caseinogen. Dextrose was digested with fæces in an incubator and it was found that less than 1 per cent. was broken down in four hours. From the enemata 37 to 81 grammes of dextrose were taken up in the day, furnishing from 150 to 330 Calories in fuel value. No glycosuria was observed.

It follows from the consideration of the above figures that the feeding was effective. They recommend an enema of the yolks of two eggs, 30 grammes of dextrose (pure), and pancreatised milk to 300 cubic centimetres (ten ounces). In the experiments the caloric value actually taken up varied from 240 to 645 Calories in a day. The average was 389. The enema here recommended contains 300 Calories. Therefore four enemata in the day contain 1200 Calories, and probably about 500 will be absorbed. The authors lay stress on the smallness of this value, and state on the authority of Umber that gastric juice is secreted into the stomach during rectal feeding, which would be prejudicial to an ulcer.

I think nevertheless that these results are encouraging to this method of feeding. 500 Calories is nearly half the need of a woman of 50 kilogrammes lying in bed. At 25 Calories per kilogramme she would require 1250 Calories, and it is obviously very much better to supply 500 Calories if the patient is in any danger of malnutrition than that she should break down more tissue still to furnish it herself. For instance, if she excreted ten grammes of nitrogen in the urine this means that 62·5 grammes of proteid would be broken down, or 330 of actual flesh, and this would furnish 256 Calories of the 1250 and the remaining 994 Calories would need the oxidation of

107 grammes of fat—that is, about 150 grammes of fatty tissue. But the 500 Calories absorbed from the rectum would save a good proportion of the fat breakdown and although very little proteid is absorbed the other food-stuffs will still spare the tissue proteid, as, indeed, the figures in the above research show. Thus, although we must be perfectly clear that rectal feeding, even under the most favourable conditions, cannot supply the caloric need of the body, it is shown to be a means by which we can introduce a valuable amount of food. The prospect of supplying any useful quantity of proteid is regarded by Boyd and Robertson as slight and indeed the quantity taken up in their experiments was very small. But Ehrström's results with milk and proton and Bial's with peptone are suggestive that more success might be attained with those substances. Since 10 or even 20 per cent. of dextrose is taken up it is clear that it is not necessary under suitable conditions to have a fluid isotonic with the rectum, but the more nearly this is attained the more likely are the enemata to be borne for long periods. Dextrose, unless pure, contains irritating substances. The rectum must always be washed out daily and it is very important that sufficient fluid should be given. Experience is showing that enemata of ten or 15 ounces can be retained if slowly given and they have the great advantage of needing less frequent administration. Cannon showed that in the cat an anti-peristalsis of the large intestine is a normal occurrence and is also set up when a nutrient enema is passed into the rectum, carrying the material to the cæcum, and may force fluid through the ileo-cæcal valve, but only when sufficient bulk is present. We may conclude from this that there is much more chance of the contents of an enema reaching the upper part of the large intestine and even the small if a good quantity be given.

Feeding after Inanition.

Under normal conditions if the food taken into the body be in excess of that required there is a storage of energy in the form of fat. Although carnivora easily lay on proteid tissue this is not the case with man. In special circumstances, such as the provision of an excessive diet, enormously rich in proteid, given for short periods only, nitrogenous tissue may be laid on. But, generally speaking, this is not so, except when the muscular tissue is growing in bulk under the influence of constant exercise. After a period of fasting, however, the condition is different and proteid is laid on rather than fat, just as during the fast fat is broken down rather than proteid—that is to say, when the body is from any cause below its weight or increasing in weight proteid is laid on. The retention of nitrogen is not a function of the amount of food but of the body cell.

We may recall that the same is true of the use of oxygen by the body. The supply of oxygen in the lungs is in almost all cases sufficient, and increasing it does not increase the oxidation processes, since these depend solely upon the needs of the tissues. Von Noorden points out that after fasting the body will retain proteid from a diet which in the well nourished would lead to a loss of nitrogen. A girl who had suffered from an œsophageal stricture retained a quarter of the nitrogen given. Bleibtreu's hysterical patient laid on over four grammes of nitrogen per day for 14 days, on a diet containing 30 grammes. The observations of Popov also showed how well nitrogenous tissue can be laid on and nutrition improved. Dr. Hale White and I investigated the metabolism of a woman whose weight had fallen to 39 kilogrammes. She was confined to one room for eight weeks, massaged, and fed on an exceedingly liberal and varied diet. She illustrated well the amount of food which can be taken in such circumstances. Its energy value per day was over 5000 Calories and more than 110 Calories per kilogramme. After the first week from 35 to 46 grammes of nitrogen were taken daily and between 200 and 300 grammes of fat. The quantities of fat and proteid were thus approximately equal, the average proteid intake being 244 grammes and the fat intake 252 grammes. Abundant carbohydrate was also supplied in the form of bread, potatoes and other vegetables, puddings, milk, &c. The absorption was astonishingly complete, 96 per cent. of both nitrogen and fat being utilised. There was no diarrhœa, vomiting, or disturbance of digestion. A large amount of the nitrogen was retained and the case showed with what avidity the tissues retain this kind of food in inanition, as has been demonstrated by other workers. The weight increased from 39 to 52 kilogrammes—that is, she added a third of her original weight—in the eight weeks.

After fevers the same is true. Abramovitch in 1888, for instance, in a case of pneumonia after the fever had come to an end, found that a man, aged 22 years, weighing 54 kilogrammes, retained 7·2 grammes of nitrogen per day. This is equivalent to 238 grammes, or about half a pound of proteid tissue a day. The diet contained 550 grammes of bread, 150 grammes of meat, and about a litre of soup. This was not excessive in heat value; the bread and meat would come to about 1650 Calories. We cannot make a calculation for the soup and bouillon but these would not add much fuel value. Other observers have since confirmed these results in convalescence after acute illness.

The factors favouring the putting on of weight, including proteid and fat, after inanition from any cause, are :—

1. Feeding at frequent regular intervals.

2. A varied diet.

3. The removal of all causes of loss of energy—that is to say, all sources of unrest.

From observations upon animals it is probable that flesh would be still better deposited if short fasting periods were intervened from time to time.[6] Even on an excessive diet, no fear need be entertained of producing any harmful retention of purin bodies in the organism if food be chosen with this object in view.[7]

[6] Pembrey and Spriggs: Journal of Physiology, vol. xxxi., p. 335, 1904.
[7] Spriggs: Guy's Hospital Reports, vol. lvii., 1902.

LECTURE II.

Delivered on April 5th.

Fever.

Mr. President and Fellows,—The treatment of fever is of the greatest importance. Such cases form a large part of medical practice. They are, moreover, in the majority of instances capable of recovery and the course of the disease may be profoundly modified by rational treatment. That a disturbance of metabolism is a prominent feature is obvious to every observer. An investigation into the nutrition of patients suffering from fever shows at once that a great increase in the excretion of nitrogen in the urine is present as compared with that of a healthy individual on the same diet. This phenomenon may begin early in the disease, even before the pyrexia, but usually does not, and it reaches its maximum much later, often after the crisis. Naunyn,[2] for instance, found on the tenth day that a patient was excreting 10·7 grammes of urea, on the eleventh day the pyrexia subsided and 45·4 grammes were excreted, and on the next day 91·9 grammes. In another case the fever was falling on the twelfth day and the excretion was 54·4 grammes, on the thirteenth 54 grammes, and on the 14th, the day of disappearance of the pyrexia, 90·4 grammes. Garratt found in scarlet fever and measles, however, that the excretion of urea reaches its maximum usually before the temperature returns to normal. When the excretion occurs late it is not due to retention of nitrogenous matter, because analysis of the tissues shows that there is no excess of urea in patients dead from fevers. Also, urea administered to febrile dogs is quantitatively excreted by them. The nitrogen arises from the breakdown of proteid tissue, chiefly muscle. This is shown by the facts that there is a corresponding increase in the output of potassium salts, sulphuric acid, and neutral sulphur and creatinin. The amount of breakdown is much greater than ever occurs with muscular work, and, indeed, in any circumstances except the taking of large quantities of proteid food. It is not due to starvation, for the excretion of nitrogen and the loss of weight is much greater in a fever patient than in a healthy man on the same diet.[3] A similar excretion of nitrogen, though

[2] Archiv für Experimentelle Pathologie, 18, 49, 1884.
[3] Vide Pembrey, Allbutt and Rolleston's System of Medicine, vol. i., p. 823, 1905.

less in degree, is observed after the administration of certain poisons, such as phosphorus, and in conditions of deficient oxidation.

It is important to know the cause of this breakdown of tissue and the possibility of its being due directly to the pyrexia suggests itself. Hot baths, sufficiently prolonged to cause a rise of temperature, give rise to increased oxidation, as shown by the respiratory exchange, and also to a rise in the amount of urea in the urine, occurring on the following and the third day. Predtetschenki found that the carbon dioxide might be even 70 per cent. above normal, and the nitrogen excretion from 50 to 100 per cent. (Speck, Winternitz). Muscular exertion, if carried on under conditions leading to a rise of temperature, such as in unsuitably clothed soldiers marching in hot weather, may also cause a delayed increase in the urea (Zuntz und Schumburg, Speck). But the facts that (1) the excretion of nitrogen in fever is not proportional to the pyrexia and bears no constant time relation to it, and (2) that septic infection may cause a similar rise in the nitrogen without any pyrexia (Simanowsky) are against this view that the pyrexia is the sole cause of the nitrogenous breakdown.

Again, is the tissue breakdown causally connected with increased oxidation? The determination of the oxidation going on has been made by many observers through estimations of the oxygen used and the carbon dioxide given out. The results show that, on the whole, more oxygen is generally used;[1] the excess is usually not more than 10 per cent. and seldom more than 20 per cent. above the normal (Lœwi, Langlois, Babák); there may be no increase in oxidation, and when it does occur it shows no parallelism with the excretion of nitrogen, or with the height of the temperature. Calorimetric experiments on man by Nebelthau showed that there may be an increased production of heat but the prominent factor is the inconstancy of the production. The variability and lack of decision of these results suggest that the larger use of oxygen in fever which may take place is not due to the breakdown of nitrogenous tissue at all, but to other causes, one of which is the muscular movement resulting from the restlessness which accompanies the febrile state. The patient is uncomfortable and slight movements are constantly being executed. We have seen in discussing the question of the effect of rest on metabolism how definite an effect upon the oxidation processes even inappreciable activities occasion. Atwater's subjects produced more carbon dioxide when their sleep was restless. That muscular activity is a cause of the greater use of oxygen is also supported by the observation of Zuntz that the consumption of oxygen is normal in curarised animals rendered septicæmic, since in this case no impulses can reach the muscles and cause them to contract. The non-muscular tissues are

[1] Vide Pembrey: loc. cit.

also believed to take part in the increased oxidation of fever.[5] It appears, therefore, that the breakdown of nitrogenous tissue is in some cases independent of any increase in the oxygen used, and it is probably due to the action of poisonous substances produced from the micro-organisms which give rise to the pathological process. The pyrexia is a concomitant effect of the poison acting upon the mechanism which regulates the temperature in such a way that the balance between heat production and heat loss is no longer accurately maintained. The loss is usually relatively diminished as compared with the production.

We may sum up then by saying that so far as the evidence at present leads us the products of bacterial infection cause: (1) a disturbance of the heat regulatory mechanism, resulting in instability of regulation; a febrile temperature is more easily altered by hot or cold baths than the normal; (2) a disintegration of the nitrogenous tissues, especially the muscles; and (3) the pyrexial condition is usually accompanied by increased oxidation. This is probably chiefly due to subconscious muscular movements, brought about reflexly from subjective sensations of discomfort.

We have now to ask how far and in what way these processes can be modified by treatment. It is obvious that the first thing to do is to attack the cause by means of anti-toxins or any anti-bacterial substances that may be available. In addition to this method, or failing it, every means should be taken to make the patient comfortable, because the more at ease he is the less will be the reflex involuntary movements which may make a considerable demand upon his store of available energy and which in so doing shorten the length of time during which he will be able to resist the infection. Also, we can supply food to make up for energy lost. Although we usually cannot remove the cause of the fever we can diminish some of its effects by adopting measures for the reduction of the temperature. If the temperature be not dangerously high the condition of the patient as to restlessness is a useful guide in considering whether bathing or sponging should be carried out or not in order to increase the heat loss and cause a fall of temperature.

Effect of baths in fever.—The effect of cool baths upon the metabolism is shown in the results of Sassetzky (1883).[6] Nine cases of typhoid fever were observed. In each case a three-day period during which baths were administered was compared with a three-day period without baths and with the same length of time, about four weeks, after the subsidence of fever in eight of the cases. The food during the observations was milk and water. During the bath

[5] Pembrey, loc. cit.

[6] A Digest of Metabolism Experiments, p. 209; see also Virchow's Archiv, 94, p. 533.

periods four baths a day were given at a temperature of 22·5° C. The patient sat up to the neck in the water and water was poured on to the head. The beneficial effects of the treatment were distinctly shown in the nitrogenous metabolism. If we take the average of the figures for all the bath periods we arrive at the result that the excretion of nitrogen was less in each case during the bath periods and the loss of nitrogen over the intake was less by 2·7 grammes per day than in the periods without the baths. This is not an average of conflicting figures, for the same effect was seen in each case. 2·7 grammes of nitrogen are equivalent to 16·8 grammes of proteid and to about 89 grammes of flesh. This comes to 267 grammes of flesh, or over nine ounces in the three days. We may assume that the fat in the body would also be spared to a considerable degree. The analysis of the fæces showed that the nitrogen excreted in this way was also less and therefore a more perfect absorption of the proteid of the milk took place during the bath period. The same observer gave quinine in three cases for a similar period and sodium salicylate in two cases for two-day periods. These drugs caused an improvement in the same way. This was more marked with quinine but in neither case was it as great as in the bath observations. Deucher[7] also found that antipyretics, which lower the temperature in typhoid fever, also lessened the loss of nitrogen. Actual nitrogenous equilibrium, however, could not be attained.

These observations seem to show that tepid or cold baths exert an influence upon the proteid breakdown in the direction of lessening it. The amount of milk supplied was two litres or more, which would give a caloric value of 1400 calories; since this would barely supply the needs, the body might have been calling upon its own proteid for energy needs for muscular movement, secretion, &c. We cannot exclude, therefore, the possibility that the baths really produced their effect upon metabolism by diminishing the subconscious movements with the fall of temperature and thus lessening the call upon the body tissue, and this might explain the results without calling in any effect of the treatment upon the direct poisoning action of the toxins on the proteid constituents of the body. Indeed, we know that cold baths do not shorten the period of the disease in typhoid fever and may conclude from this that they do not intrinsically affect the bacterial process.

In connexion with the question of baths in typhoid fever it is of interest to compare a series of metabolism observations made for other purposes with a series in which baths were given. In the "Digest of Metabolism Experiments," if we compare the figures of the excess of nitrogen in the urine over the intake in the experiments of Diakonov (1890), undertaken to investigate the

[7] Zeitschrift für Stoffwechsel, 1906, p. 122.

action of alcohol, with those of Matzkevich (1890), undertaken to ascertain the effects of copious water-drinking but in which each patient received two or three baths per day, we see a marked difference. Each worker observed several cases; the diets are not identical but roughly alike, the amounts of nitrogenous food being similar; but whether we look at the periods with or without alcohol, or with plentiful or restricted water, the most noticeable point is that in Matzkevich's cases, in which baths were used, the loss of nitrogen is usually several grammes a day less than in those of Diakonov. I need hardly remind you that there is strong evidence of a statistical nature that the prognosis in this disease is better under the bath treatment. This beneficial result may be ascribed to the fall of temperature produced. I have already mentioned that experiments on animals have shown that the resistance to a state of inanition is much lessened when the temperature is raised, and though, as we shall see, much may be done in the direction of supplying food to such cases, in most instances we are dealing, nevertheless, with a condition of partial inanition.

Food in fever.—Coming now to the problem of the feeding of fever patients it is obvious from what we have seen of the pathology of this condition that in circumstances in which the proteid tissues of the body are being continually broken down by the action of a poison, while at the same time the needs of the body as shown by the oxidation—that is to say, the ordinary running expenses—are commonly greater than usual, it is desirable to supply to the organism what energy we can, provided that the course of the disease is not thereby adversely influenced. "One of the dangers of prolonged fever is the general failure seen in starved animals."[8]

The absorption of food.—The first question to be answered is, If food be given, is it absorbed from the intestine? Huppert (1869) found but little deficiency in the absorption of nitrogen in recurrent fever.[9] Abramovitch (1888) in seven cases of croupous pneumonia found that the absorption of proteid from bread and milk was sufficiently good during the fever as compared with that after the crisis and in convalescence. It is true that he states the opposite but an examination of the figures shows no difference great enough to have any bearing upon the point at issue. From five to eight grammes of nitrogen were given per day. Pipping[10] (1891) found that in diphtheria with moderate fever in children on a mixed diet the absorption was as good as in health unless the temperature was exceptionally high.

[8] Pembrey: Allbut and Rolleston's System of Medicine, vol. I.
[9] A Digest of Metabolism Experiments, p. 240.
[10] Ibid., p. 206.

Von Noorden found absorption good in two cases of pneumonia and in one of tuberculosis, both for proteid and fat. Hoesslin (1882) in 19 cases of typhoid fever found that the digestion and absorption of a mixed diet were, in respect to proteid, carbohydrate, and fat, very little inferior to those in health. These patients were suffering from diarrhœa which does not seem to affect the utilisation of the food unless it be excessive. Khadgi (1886) found that the assimilation of meat, bread, and milk was almost as good during typhoid fever as in convalescence. Tschernoff showed that the absorption of milk fat was almost normal; from 88 to 93 per cent. was used. We find, then, that in a number of fevers if food be introduced into the alimentary canal it is made use of. The point of difficulty is that the patient has no desire for it. Appetite is wanting because it depends upon the integrity of the stomach and this organ shares in the general depression of function of the whole body. The hydrochloric acid is usually deficient, though not commonly absent. Pepsin may generally be found to be present. Food introduced into the stomach is in most cases passed on into the intestine and though we should expect that in the absence of hydrochloric acid from the stomach the stimulus to the secretion of pancreatic juice would be wanting, nevertheless experiment shows that the nutriment is not usually discharged from the intestine. It does not, however, necessarily follow that it is made use of for purposes of nutrition because we might suppose that it is broken up by bacterial action and its energy lost to the body. The excretion of aromatic sulphates gives a guide to the putrefactive processes going on in the intestine and we find that these bodies are not necessarily increased in the urine in fevers, although this may be the case. The best answer to this doubt is that in fever it is possible to feed the patient so that the body weight is kept up in some cases and in others so that the loss is very much less than it otherwise would be. This fact proves that the food is utilised. There is, of course, no doubt that the putrefaction in the gut is often greater than normal in this condition and carbohydrate and fat may be to a considerable extent broken down into substances which would escape recognition in the analysis of the fæces. Any unabsorbed nitrogen, however, would be recognised as such, while in the putrefactive processes resulting in the formation of tryptophane and its aromatic derivatives it is possible that other amido-bodies formed can be absorbed and made use of, just as they generally are when the proteid is disintegrated by the action of the normal ferments, without an excess of bacterial growth.

In connexion with the question of digestive disturbances due to putrefaction we may notice that proteid is the food-stuff from which the aromatic portion of the molecule of the ethereal sulphates is derived and that consequently the determination of these substances in the urine only gives us information concerning the bacterial action upon proteid in the intestine. But it is important to know what foods favour or hinder this process. Analyses show that a rich diet of proteid with but little of other foodstuffs is likely to undergo more putrefaction than when abundance of carbohydrate is present. This is believed to be because from carbohydrates weak acids are produced which restrain the action of putrefying organisms. The addition of much fat, on the other hand, increases the ethereal sulphates in the urine. So that a diet of all three foodstuffs in the proportions generally used in health—that is, with only a moderate amount of proteid or of fat—is indicated when it is thought that the patient is suffering from the effects of harmful substances absorbed from the intestine. Constipation is favourable to excessive bacterial growth and the removal of this condition when present is often of more importance than the alteration of the diet.

The quantity and kind of food.—We must now inquire what information we may get from metabolism experiments as to the quantity of food which should be given in febrile states. The needs of the body are as great as, or greater than, usual and if possible it would be desirable to meet them with food. This is a counsel of perfection and in many cases will not be attained but, nevertheless, should always be aimed at. We have seen that in starvation, when the body is living upon its own tissues, about 25 Calories per day are used for every kilogramme of body substance; fat people requiring somewhat less, since a good proportion of their weight consists of fat, and this does not undergo constant metabolic changes as does all the more living proteid tissue. We should endeavour therefore, unless there is reason to believe that the fever is likely to be of extremely short duration and the individual is well nourished, to give sufficient food to supply at least 25 Calories per kilogramme of bodyweight. This is of the greater importance because, as we have already seen, the condition of inanition is far worse sustained with pyrexia. That it is possible to keep the weight from falling during fever is shown by the experiments of von Noorden in a case of typhoid fever. Some other cases quoted by him, such as those of phthisis and chronic sepsis, are less convincing as regards acute fevers. To expect to prevent the toxic breakdown of proteid by means of food is in most cases probably more than is reasonable, but it is essential to supply the energy which the body needs and thus to ward off the addition of inanition to the other dangers of the disease.

Fluid food has the advantage that it satisfies thirst but its energy value is correspondingly low. Three pints of milk contain about 1150 Calories. In a man of 70 kilogrammes 25 Calories per kilogramme come to 1750 Calories. Milk calls forth less gastric juice than other proteid foods, but if it curds must be diluted, peptonised, or decalcified with sodium citrate, as suggested by Professor Wright. It is not within the scope of my subject to discuss the various ways in which the diet may be varied, except in so far as metabolic experiment is concerned. Has such observation shown that any foodstuff has an advantage? Since much proteid is being broken down it seems desirable, even if we do not hope to prevent the breakdown, to supply enough to replace it. An examination of the figures shows that this is not to be expected. In most recorded experiments the amount of proteid given is low, but in those in which it is not, nitrogen equilibrium is not usually attained. In those of Puritz (1893) a diet of over 2500 Calories was given, amounting in some of the patients to more than 42 Calories per kilogramme per day, and containing proteid corresponding from 20 to 26 grammes of nitrogen per day, and yet in the observations upon six cases of typhoid fever extending from nine to 27 days in the different cases, in none was nitrogenous equilibrium attained. We may therefore ask if there be any advantage in giving such large quantities of proteid food. The observations of Moraczewski[11] in 18 cases of pneumonia show that although nitrogenous equilibrium is not to be looked for, yet the loss of nitrogen from the body—i.e., the output minus the intake—may be much lessened by furnishing a plentiful supply of proteid. He also claims that convalescence is much shorter when this has been done. This we should expect, for the poorer the body is in proteid at the end of the fever the longer would the period of convalescence be. The same has been found to be the case in enteric fever. One way of furnishing a fair quantity of proteid is to add proton or plasmon to the milk.[12]

With the object in view of contriving that nourishment of a sufficient caloric value shall be provided, as much fat as can be taken without exciting distaste for food should be given. This quantity is not great. In addition to the fat in milk, that of cream and butter is of most value in fevers. One ounce of cream gives about 89 Calories[13]; four ounces of milk about 95. So that a quarter of a pint of cream added to the day's feeds of milk adds 356 Calories. Butter contains about twice as much fat as cream, and therefore two ounces of butter a day will add another 356 Calories to the value, and this is likely to be nearly all absorbed. Hence a quarter of a pint of cream and two ounces of butter introduced in the milk, or upon bread, together add 712 Calories to the value of the diet in an absorbable form. This is more than half the need of a woman of 50 kilogrammes, and even two ounces of cream and two of butter add over 500 Calories. It is not so neces-

[11] Zeitschrift für Klinische Medicin, Band 39, S. 44, 1900.
[12] Benedikt: Münchener medicinische Wochenschrift, 1899, S. 220.
[13] Hutchison: Diet and Dietetics, p. 134.

sary to give fat to patients who have a large share of this substance in the body.

Carbohydrate should never be omitted from a diet unless, as in certain severe cases of diabetes, this may be necessary for a time. We have seen that it is very probable that it is the absence of this foodstuff which leads to the appearance of acetone and its congeners in the urine in inanition and other conditions, and there is reason to believe that proteid is broken down to furnish carbohydrate. The experiments of May on rabbits showed that dextrose has a considerable sparing power on proteid in fever just as in health, and that 25 per cent. of the nitrogenous output was diminished by giving dextrose. Moraczewski [14] and others have found the same to be true in man. Our object is to give carbohydrate and fat so as to insure that no proteid need be broken down to supply the energy needs of the body, since we cannot prevent proteid breakdown from toxic action. Starch is probably the best form in which to give these foods. Failure of the amylolysis in the intestine must be a very rare phenomenon and since this process takes place gradually the sugar is probably absorbed at once and the risk of fermentation is less than if a quantity of absorbable sugar is introduced at one time. Such forms of starch as arrowroot, or that in bread, or in biscuit eaten with the milk, are usually well taken. Neither carbohydrate nor fat makes demands upon the digestive activity of the stomach. Since we know, however, from the work of Pawlow that the appetite is much keener when gastric juice is called forth, it is often desirable, whatever the nature of the meal, to cause a flow of this secretion, and this may be done by the use of some form of meat extract, home-made or otherwise. No bulky foods should be used, or the patient will take an insufficient quantity.

Water must be abundantly supplied in all cases of fever. An estimation of its intake and output shows that a smaller proportion of it appears in the urine than in health, as is indeed obvious. The experiments of Matzkevich, already referred to,[15] show that water drinking carried to excess increases metabolism in typhoid fever. Some of his patients took as much as six litres of fluid altogether in the 24 hours. Eight series of exhaustive experiments were carried out and no harmful effect other than the above, which was not constant, was observed. Gruzdiev [16] also found copious water drinking (from five to 13 litres) increases nitrogen loss somewhat. The absorption of food is much the same. The author says it improves secretion from the skin and advises it. The tissues contain more water in fevers, perhaps because the number of nitrogenous molecules is increased.

[14] Loc. cit.
[15] 1890, A Digest of Metabolism Experiments, p. 135.
[16] Ibid., p. 133.

Typhoid fever.—The feeding of patients suffering from typhoid fever has a special interest apart from general considerations concerning metabolism, in that the intestine is ulcerated, and it has been the general custom to give the food, whatever it be, in fluid form. A growing school of opinion regards this as unnecessary and it adds materially to the difficulty of getting a sufficient amount of fuel into the body, a matter of great importance in this fever from the beginning owing to the prolonged period of partial inanition which is likely to ensue. Also, a fluid diet, usually milk, soon becomes distasteful. In the decision of this question copious clinical statistics must prove a prime factor but it is germane to our subject to see what metabolic observations have been made which throw light upon it. In a number of the Russian experiments referred to when we were discussing the assimilation in fever, bread was taken in quantity with milk and other fluid foods, and in some meat. In those of Hoesslin at Munich, published in 1882, such articles of diet as porridge, rice, and ham formed part of the ration.[17] The foods were chopped and given in frequent meals. He found that the temperature was not harmfully affected. The danger of inanition, he concludes, is a much greater one than that produced by a mixed diet and gastric disturbances and vomiting are much less likely to occur than with the same foodstuff time after time. The observations of Puritz were made upon six soldiers, lasting from five to 29 days in each case. I have mentioned above the sufficiency of the diet in these cases; it amounted to at least 42 calories per kilogramme and often more. Proteid was in excess, nearly three grammes per kilogramme per day, the diet consisting of meat, bread, and milk, with tea, coffee, and port wine. He reports that no albuminuria or rise of temperature was caused by the diet and no complications, relapse, or lengthening of the fever period were observed, that the patients were comfortable, and that the convalescence was shorter.

It is interesting to remember that it is possible that the changes in the tissue-lymph circulation described by Dr. George Oliver, the founder of these lectures, which follow a meal may possibly exert, both in disease and in health, a beneficial effect upon metabolism.

Pulmonary Tuberculosis.

In pulmonary tuberculosis we are dealing with an infective process which may or may not be pyrexial. Suitable material must be furnished to the cells of the body (1) to enable them to provide energy for their usual needs; (2) to provide any extra energy they may require in opposing the bacillary

[17] Virchow's Archiv, Band 89, S. 106, S. 320.

growth and withstanding toxins; and (3) to replace any tissue which may be broken down by toxic action. In the pyrexial cases there is often in addition a want of appetite to deal with just as in the shorter fevers. In this condition the motor and secretory functions of the stomach have, nevertheless, been frequently found to be normal. With respect to the toxic breakdown we have seen that it occurs in other infections even without pyrexia. Duclaux[18] ascribes the loss of organic substance to the agency of a ferment-like substance of a tryptic nature derived from the bacillus. The wasting of pulmonary tuberculosis is not due to deficient absorption of food, for many analyses have shown that it is usually normal. For instance, in 1894 Blumenfeld and Spirig found that when from 84 to 168 grammes of fat were given in the form of butter and a mixture of olive oil and oleic acid assimilation was normal. Goodbody, Bardswell, and Chapman found that from 87 to 98 per cent. of the fat given in a mixed diet was utilised, a considerable quantity being given in the day, the averages in each period ranging from 123 to 231 grammes. Proteid is also well absorbed (Mitalescu, Mircoli and Soleri, Goodbody, Bardswell and Chapman, Ott, and older workers) except when a great excess is given, and so is carbohydrate.

Mircoli and Soleri[19] compared the needs of a phthisical patient with those of a normal man. The subject had lost 10 kilogrammes in a year and weighed 77 kilogrammes. The sputum contained a large number of bacilli. There was no pyrexia. A normal individual took a diet of 35 Calories per kilogramme containing 14 grammes of nitrogen per day. But this did not suffice for the patient, who only maintained his weight and nitrogenous equilibrium when 50 Calories per kilogramme were given and 29 grammes of nitrogen. Each was fed until he felt fully satisfied. He took then 30 per cent. more caloric value and 100 per cent. more proteid than the healthy man. They express the view that the excess of proteid is necessary owing to the direct action of the poison upon the tissues. On such a diet a little proteid was laid on. Ott has also shown that even with complete rest a phthisical patient will not only lay on fat but tissue proteid.

I have already referred to a diet of 50 Calories per kilogramme as one found essential to maintain equilibrium in a phthisical patient. Goodbody, Bardswell, and Chapman in their researches found that from 50 to 70 Calories could be given with advantage. Taking the average, 60 Calories, this comes to just over 4000 Calories a day in a man of 68 kilogrammes. They found also, as we have seen in the case of normal metabolism, that an excessive diet is very much better borne by patients who are below their usual weight and that it must be relaxed when the weight has passed above the normal figure. If too much food be given,

18 Traité des Microbiologie, tome ii.
19 Berliner Klinische Wochenschrift, 39, 1902.

although some of it may be laid on for a time, intestinal and gastric disturbances set in, putrefaction takes place in the intestine to an excessive degree, as was shown by the more than doubling of aromatic sulphates in the urine, and distaste for food soon follows. It is interesting to note that a boy, aged 13 years, whose metabolism was investigated, took and assimilated 3500 Calories per day; as his weight was 35 kilogrammes this is over 100 Calories per kilogramme per day. A growing individual uses relatively more food, both on account of the growth and of the larger surface loss of heat relatively to mass, and also probably on account of greater activity. The amount of food taken per kilogramme by this boy approaches that used in the case of a woman undergoing a rest cure above referred to (Hale White and Spriggs) who was taking and assimilating well a diet of over 110 Calories per kilogramme per day.

With regard to the constituents of the diet Goodbody, Bardswell, and Chapman recommend 120 grammes of proteid, 140 of fat, and 300 of carbohydrate as average figures for an adult. The amount of proteid here is moderate. In this respect we may ask ourselves whether in the light of the recent movement in the direction of diminishing proteid in ordinary diets we have sufficient evidence that such large quantities are necessary in phthisis, since extra work is thrown upon the digestive organs and the kidneys. I do not know whether careful experiments have been done in which the proteid has been replaced by a sufficient caloric equivalent of other food over a considerable period. That the output of nitrogen of the body can be diminished in tuberculosis as in health by carbohydrate and fat has been shown by Laufer, who found that sugar was much more efficient than an equivalent weight of fat and still more so if the caloric equivalents be given, as 94 grammes of sugar correspond to 50 of fat. A similar investigation was made by Bockarev (1893) who investigated the effect of adding malt extract to a liberal diet. From 50 to 100 grammes were given in milk daily. Dry malt extract contains 76 per cent. of maltose and 16 per cent. of dextrin. A teaspoonful containing four grammes gives about 16 Calories and a tablespoonful 60 Calories, almost as much as an egg.[20] Bockarev's figures show a slight proteid sparing effect such as is to be expected from the addition of a small amount of sugar to the food.

We have seen that a phthisical patient requires more proteid than an ordinary individual according to Mircoli and Soleri, in addition to a diet of greater fuel value. In one mode of treatment extra proteid has been supplied in the form of meat powder. Kurlev (1886) carried out experiments on five cases in which there was forced feeding by means of a stomach tube with a meat powder and

[20] Zeitschrift für Stoffwechsel und Verdauungs-Krankheiten, March, 1904.

milk, and the metabolism during the feeding was compared with the period before and after. Only two of his experiments are of real value, since in the remainder the patient had been fasting. As much as 52·6 grammes of nitrogen (i.e., 52·6 × 6·25 proteid) was given per day for three days. An enormous quantity of nitrogen was laid on in each of the cases. In the one quoted, for instance, 12·8 grammes per day. We may probably assume that their weights were below normal. The heaviest was 54 kilogrammes. Absorption was fair, 3·9 grammes of nitrogen appearing in the fæces. The caloric value of this diet was about 3510 Calories. The patients put on weight, the appetite improved, their temperature fell, the dyspnœa, perspiration, cough, and expectoration were less, and sleep was better. Experience, however, shows that with such forced feeding the weight put on above the normal weight is usually lost again,[21] and also causes deterioration in health.

In the system known as zomotherapy the object is not so much to introduce a quantity of proteid into the body as that raw meat or raw meat juice shall be taken. Héricourt and Richet[22] have published some striking experiments upon dogs rendered tuberculous, which seem to show a marvellous effect from this treatment, those animals fed upon raw meat withstanding the infection, whilst others fed upon cooked meat or other food did not do so. It should be borne in mind that raw meat is the natural food of the dog. Beneficial results have, however, been reported with other animals. R. W. Philip in favourably commenting upon the results of this treatment in man[23] mentions a metabolism research conducted by Galbraith upon patients undergoing it. Food was given of a constant nitrogenous content, but for a period raw meat was substituted for other nitrogenous food. The retention of nitrogen was increased, also the amount of hæmoglobin rose above normal, these results being coincident with a general improvement in the condition of the patient.

The value of rest, as employed in the treatment of pyrexial phthisis, has been discussed under the heading of fever. In this disease, in which it is necessary to husband all the chemical resources of the body, the conclusions we have drawn from a consideration of the metabolic circumstances apply with force.

Nephritis.

The object of the physician in treating diseases of the kidneys is to maintain the nutrition of the body while keeping the excretion of nitrogenous matter, of salts, and of fluid,

[21] Goodbody, Bardswell, and Chapman, Journal of Physiology, vol. xxviii., p. 257, 1902.

[22] Comptes Rendus de l'Académie, 130, 1900.

[23] Practitioner, vol. lxxiv., p. 14, 1905.

at such a level as shall not act harmfully upon these organs. The number of metabolism experiments in cases of kidney disease has been great during the past few years and patients suffering from acute and parenchymatous nephritis and from granular kidney have been subjects of investigation.

Absorption of proteid.—The absorption of nitrogenous food is reported to be not so good as in health[24]; from 10 to 15 per cent. of the nitrogen taken escapes in the fæces. On examination of the figures of the above workers, however, it will be seen that the amount of nitrogen discharged daily in this way is seldom more than two grammes and often less than one. The high percentage reported is due to the fact that the quantities of proteid given were small and when we remember that even when no food is taken nitrogen is excreted by the bowel we see that the percentage test is not a fair one. In general the nitrogen in the fæces is normal or nearly so. Higher figures have been many times recorded[25] but are exceptional. In such cases there may be as much as five grammes of nitrogen in the fæces in the day. With diarrhœa, such as is not uncommon in kidney disease, there is naturally a greater loss from the bowel and this is usually a coincident symptom in those cases in which an increase in the loss is reported. In Butler and French's case[26] in four out of the five days in which the fæcal nitrogen was more than two grammes there was excessive action of the bowels. It is clear that we have no means of distinguishing what part of the loss is truly unabsorbed proteid and what part is cellular and secretory detritus or even compensatory excretion by the gut. If such true excretion exist it is clear from the above results that it can only reach a useful figure when there is diarrhœa extending over a considerable period and even then there is the possibility that the nitrogen in the fæces has never been absorbed. In this case the same result would be more intelligently and less harmfully attained by giving a little less proteid in the food. There is more ammonia in the fæces in nephritic than in other diarrhœas, but I do not know that this points to excretion from the gut, for the more recent analyses show that ammonia is not in excess in the blood in these diseases.

The excretion of nitrogen.—In acute nephritis with suppression, partial or complete, of the urine the kidney temporarily does not secrete either water or solids and it is reasonable to give what nourishment can be taken in

[24] Garine, a Digest of Metabolism Experiments, p. 145, 1887; Prior, Ibid., p. 225, 1890; Müller, Ibid., p. 256, 1891; von Noorden and Ritter, Zeitschrift für Klinische Medicin, Sup. 1891; Mann, Ibid., 20, 114, 1892; Kornblum, Virchow's Archiv, 127, 416, 1892.

[25] Strauss, von Noorden and Ritter, Ascoli und Licci, p. 975; Lehrbuch der Pathologie des Stoffwechsels von Noorden. 1906.

[26] Transactions of the Pathological Society, vol. liii., 1902.

such forms as will throw no work on this organ at all. Fats and carbohydrates answer this requirement and should for a few days be supplied in the form of dextrin, dextrose, rice, cream, and butter (von Noorden). In the more chronic forms the excretion of nitrogenous material from the kidneys is variously reported upon. Bartels (1877) in granular kidney found that the excretion of urea was normal. Fleischer (1881) affirmed that in chronic as well as in acute Bright's disease there may be retention of nitrogen even to seven grammes per day. Von Noorden and Ritter found both in parenchymatous nephritis and in granular kidney that in some cases there was retention and in others nitrogenous equilibrium and showed that there is frequently an oscillation of excretion, normal periods alternating with periods of retention. A woman with granular kidney took 15·5 grammes of nitrogen per day in the food. The urine contained 20·1 grammes—that is, 4·6 grammes more than that taken in was given out. Four days later the condition was reversed and for five succeeding days she retained 4·9 grammes per day. Again, observation of Mann's figures[27] shows the same thing. A man on a diet containing 17·5 grammes of nitrogen for two days retained 0·5 gramme and for three subsequent days ten times this amount. Similar variations were observed in other patients. Emerson[28] noticed the same phenomenon, a periodic increase of the nitrogen, albumin, and the total quantity of the urine taking place. A comparison is suggested with the spontaneous diuresis which occurs from time to time in diabetes. It is evident that with these alternations to reckon with none but observations extending over several days can guide us. Müller[29] found that if more than nine or ten grammes of nitrogen per day were given there was liable to be retention. This observation is fully confirmed by other workers. For instance, Kornblum's figures show that a patient weighing 62 kilogrammes for 11 days on 13·9 grammes of nitrogen retained 1·3 grammes per day, but on a diet containing 15·3 grammes retained three grammes per day for four days. Emerson's figures also showed delayed excretion of nitrogen on adding eggs to a milk diet in parenchymatous nephritis. We have seen that in normal metabolism this does not usually occur. There seems to be no essential difference between chronic parenchymatous nephritis and granular kidney in this respect, except that the granular kidney can often gradually adapt itself and excrete a larger amount of nitrogen daily. The striking unanimity of experimental results makes it clear that in chronic diseases of the kidney a certain amount of nitrogenous food can be satisfactorily dealt with but that an increase is followed by an excretion which is much more

[27] Loc. cit.
[28] Johns Hopkins Reports, 10, I. 323, 1902.
[29] Loc. cit., 1891.

delayed than in health—that is, by retention for a longer or shorter period. The quantity which the kidney does excrete is about nine or ten grammes of nitrogen or about 60 grammes of proteid. This is about the same amount that we have seen a healthy adult has been shown to be able to subsist on, together with other foods. It is contained in one and a half litres of milk, or two and a half pints. When more proteid is given and retention occurs this is not necessarily followed by uræmia; neither, when uræmia occurs, has there necessarily been a preceding retention. Butler and French's figures show well that during a period of subacute uræmia the excretion of nitrogen in the urine may remain fairly constant, as compared with the periods before and after. On the nitrogen balance there was a greater excretion than intake, but this was no doubt due to the fact that the boy during the attack of subacute uræmia took so little food—less than half a litre of milk—that he was living partly upon his own tissues.

Baginsky came to the conclusion that the kidneys of children with albuminuria did not excrete nitrogen as well as did those of children in health. This is no doubt true, but the amounts given by Baginsky were excessive. In one case he gave a child of 21·8 kilogrammes 12·5 grammes of nitrogen, which is more than 0·5 gramme per kilogramme. We know that children take proportionately more food than adults, because their surface is relatively greater and also they have to grow, but with such figures as those above it is not surprising that there was a retention of 1·6 grammes of nitrogen.

It follows that in treating these complaints this limitation of excretion must be recognised and that from both directions. The diet should not contain much more than 70 grammes of proteid, of which about 60 will probably be absorbed, and it is clear that it should not contain much less, for the minimum necessary for the needs of the body lies not far below this figure. Secondly, not only should the average proteid content of the diet be low but it should be constantly so from day to day. Thirdly, according to Ernberg it is advantageous to withhold proteid almost entirely from the diet for a day or two occasionally.

Allowance must be made, as we shall see shortly, if there is loss by albuminuria of appreciable amounts of proteid. Gumlich in 1892 found the proportion of the urea in the urinary constituents was a normal one, from 83 to 87 per cent. In some cases with accumulating œdema the proportion was somewhat less, even down to 72 per cent. Butler and French estimated the urea as well as the total nitrogen and the albumin and found, excluding the albumin, an average of the nitrogen in the form of urea of 83 per cent. and this average did not vary appreciably during an uræmic attack. There were individual variations of from 71 to 94 per cent., such as are found in normal urines. It is probable that the methods used to estimate urea may include other amides. Von Jaksch[30] states that in many diseases, including those of the kidneys and typhoid fever, from 20 to 25 per cent. of the total nitrogen in the urine may be present in the form of amido-acids or allantoin. Perhaps any accumulation of disintegration products prevents the tissues from being able to build up proteid from the amido substances formed during digestion or, on the other hand, from oxidising the products of break-down to urea as completely as usual. These variations in the amount of urea are not such as could be recognised by the ordinary hypobromite method and it follows that the testing of urine by this method to find the percentage of urea is fallacious as a guide to the excretive capacity of the kidney. Such a test is only valuable when the whole day's urine is collected and its content of nitrogen compared with that of the food. In nephritis patients are usually kept on a low diet and therefore they excrete but little urea. In ordinary cases, not upon a proteid rich diet, the nitrogen of the urine, together with that in the fæces, equals that in the food.

Albuminuria.

Albumin in the urine is a direct loss to the body of material which could be used, just as is sugar in diabetes. The quantity of proteid lost in this way is usually small but if it be considerable may lead to a diet, which would otherwise suffice, being deficient in proteid. If we exclude from consideration acute nephritis or an acute process temporarily superimposed upon a chronic one, we may lay down as a rule that it is more important to feed the patient than to get rid of the albumin in the urine. Von Noorden gave a patient with albuminuria for three weeks a diet of milk containing 15·2 grammes of nitrogen; the patient remained in nitrogenous equilibrium, excreting 1·3 grammes per day as albumin and 1·9 in the fæces, therefore using 12 grammes per day. On reducing the nitrogen in the food to 10 grammes, keeping the caloric value (32 calories per kilogramme) and the quantity of fluid constant, 1·1 was lost as albumin and 2·5 in the fæces, leaving 6·3 to be used; on this diet 8·3 grammes was the daily average in the urine and so two grammes were lost daily, or 66 grammes of flesh. If sufficient food be given, with due regard to the dangers of excess which we have discussed, nitrogenous equilibrium may be maintained with large losses of albumin. I have mentioned from nine to ten grammes of nitrogen as being a desirable upper limit in the diet of a chronic nephritic, about 60 grammes of proteid. When the patient is constantly excreting a considerable quantity of albumin, proteid must

[30] Berliner Klinische Wochenschrift, 1902, 39, 1013.

be cautiously added to this, raising the maximum to from 85 to 90 grammes.

The estimation of the percentage of albumin in a single specimen of urine is liable to fallacy, for the amount of albumin is not constant during the 24 hours. Nevertheless, if the whole day's urine be collected and the albumin estimated daily variations in the percentage of albumin may form a valuable guide to the progress of the case, as Emerson has shown,[31] more so, indeed, than the total quantity in the 24 hours. The actual amount of albumin in chronic nephritis, if it be constant, though of use, as we have seen, in constructing the diet, is of little prognostic value. Emerson's experiments upon metabolism in albuminuria showed that as a case becomes chronic the percentage of albumin tends to become regular.

Important results have been obtained by metabolic experiments comparing the effect of the amount and nature of the diet upon the albuminuria. The proteid in the urine is, in the main, body proteid derived from the blood serum, as shown by precipitin tests. Food proteids, such as egg albumin, beef proteid, and lactalbumin, may be found in the urine when these foods are taken, but only in small quantities. If, as appears probable, the food proteids are completely broken down in the intestine to non-proteid substances, to be subsequently built up again into body proteid, we should only expect food proteid to occur in the urine when some of it had been absorbed in an undigested form from the alimentary canal.

The effect of food upon albuminuria.—The evidence goes to show that in granular kidney the nature of the food makes but little difference to the albuminuria, if its amount be regulated by the above principles, and no definite relation is found between the albumin and the food if the observations be carried on for fairly long periods. In acute nephritis and acute exacerbations of chronic nephritis this is not so. A rise in the amount of proteid given is usually followed by a rise in the albuminuria. Emerson's observations upon acute and subacute cases made over considerable periods with determinations of the total nitrogen metabolism are of interest. He found a parallelism between the percentage of albumin and the temperature, both tending to rise with an unsuitable diet or with an increase in the inflammatory process or with exercise. The third important symptom going with these is a diminution in the quantity of the urine. The nature of the food was of greater importance than its amount—for instance, the same percentage of albumin as before was excreted in a case of amyloid disease when the milk was reduced by half, but a sweatbread sent up both the percentage and the temperature. Perhaps the liver was also

[31] Emerson: Loc. cit.

diseased in this case. Even starvation did not affect the albumin percentage to any degree. Raw eggs given with a milk diet sent up the albumin but this is an unfair test, for the same may occur in health from direct absorption. In severe parenchymatous nephritis the albumin was lowest with milk and rose when other articles were added. Milk alone has the disadvantage that a greater amount of proteid than necessary is given if more than from two to two and a half pints be taken by the patient. But cream or sugar or arrowroot may be added to this quantity without giving more nitrogen and thus the caloric value be raised.

Actual metabolism experiments as to the effect of different meats in chronic nephritis have been made by several observers. Prior[32] found that the addition of boiled eggs to the diet did not increase the albumin in the urine, neither did raw eggs when consumed with other food, but only if taken alone—i.e., under conditions which cause albuminuria in health. Offer and Rosenqvist[33] found no difference between red and white meat. Pabst's experiments[34] were not, strictly speaking, metabolism experiments, but he found that mutton, beef, veal, lamb, or fowl produced no effect on the microscopical characters of the urine as regards the number and nature of the casts present when compared with milk of the same proteid content. Kaufmann and Mohr investigated two cases of chronic parenchymatous nephritis and three of granular kidney. For five-day periods they gave a diet of 200 grammes of bread, 100 grammes of potatoes, 100 grammes of butter, 500 grammes of soup, and 325 grammes of either beef or veal to compare the effect of red or white meat. In each case there was slight loss of nitrogen but the albuminuria and the œdema were less with the beef. These periods were rather short and the proportion of nitrogenous food was too high, from 15 to 20 grammes of nitrogen appearing in the urine. In another case excreting from 12 to 13 grammes of nitrogen in the urine no difference in metabolism could be detected between diets of constant nitrogen and caloric content supplied by means of milk, beef, veal, and milk again in five-day periods, one after the other. In older experiments, such as those of Gregoriev,[35] similar observations with milk and meat lead us to no definite results, because the amount of nitrogen in the different diets varied and the caloric value was often too low.

DIURETICS.

Since the urea in the blood has been found to be increased both in nephritis and in uræmia and since we know that this substance is an excellent diuretic, one would suppose that

[32] Prior, 1890, loc. cit.
[33] Berliner Klinische Wochenschrift, 1899. [34] Ibid., 1900.
[35] A Digest of Metabolism Experiments, p. 249.

the administration of diuretics other than water would not be likely to produce much effect. Diuretin was given in the course of Emerson's experiments and was followed by an increase in the urine, which was more dilute, though the total albumin in the urine in the 24 hours was increased. Grünwald[36] also reports that diuretin causes the excretion of a more dilute urine, with less albumin.

Decapsulation.

The metabolism of two patients before and after decapsulation for acute parenchymatous nephritis was observed by Emerson. The period of observation was too short to give definite results, since in cases reported to have been benefited by this operation, results such as disappearance of albumin and casts have been delayed as long as a year. In a few weeks during which analyses were made the metabolism of nitrogen showed the usual features of subacute nephritis becoming chronic with oscillations of excretion. The patients reported that they felt much better and the excretion of albumin became less.

Elimination of Nitrogen by the Skin.

Perspiration in health contains a small quantity of nitrogenous substances, of which over two-thirds is in the form of urea (Argutinsky). This quantity is increased by profuse sweating and as much as 0·76 gramme and even 1·36 grammes have been found in the day in a hot climate (Eijkmann, Java). Atwater found that the mean amount in 68 experiments with muscular work was 0·29 gramme of nitrogen. With conditions in which the proportion of urea and other non-proteid nitrogenous substances in the blood was increased we should expect that the quantity in the sweat would be larger. Strauss[37] has recently found that the proportion of nitrogenous substances which are neither proteid nor urea is greater in nephritic perspiration than in healthy blood serum and may, especially in uræmia, reach a similar value to that in the serum and serous effusions of nephritis. These observations strongly support the practice of producing sweating, as do actual metabolic experiments with baths of hot water or hot air.

Baths.

Very many observations have been carried out as to the effect of baths upon metabolism in nephritis. Korkounov[38] found that the dropsy diminished and

[36] Zeitschrift für Stoffwechsel und Verdauungs-Krankheiten, 1906, p. 90.
[37] Ibid., 1904. [38] A Digest of Metabolism Experiments, p. 249.

the weight with it. The diet was milk and for from three to five days two baths per day at 40° C. and of from 15 to 20 minutes' duration were given. At the same time nitrogen was retained in the body but an examination of the figures shows that this was probably because more milk was taken during the bath period, owing presumably to thirst induced by sweating. Evdomikov[39] found in acute parenchymatous nephritis that the absorption and excretion of nitrogen were definitely improved by sweating. This was induced by enclosing the subject in a rubber bag up to the neck. A blanket was wrapped round the bag and the sweating lasted from one and a half to two hours. Improvement also followed in a second case of nephritis and cirrhosis of the liver as regards absorption. Hot air baths lasting from 20 to 25 minutes from 40° to 60° C., on a mixed diet containing an excess of nitrogen (from 20 to 40 grammes) were also given by Garine in 1887 in two cases of acute interstitial nephritis. Here again the excretion of nitrogen was improved during the bath periods (five days) and for the five subsequent periods, during which analyses were carried out, as compared with five days before the baths.

Water and Sodium Chloride.

Since the constituents of urine are all dissolved the amount of water available is a matter of importance and it is desirable to get what information we can as to what quantities should be allowed.

We must remember that in kidney disease the blood usually contains a larger proportion of water than in health[40] but this appears to be due to poverty of proteid, while smaller molecules, such as salt ions and the non-proteid nitrogenous substances, of which urea forms from one-half to four-fifths, are usually increased.[41] Thus, since the osmotic pressure of a solution depends on the number of molecules and not upon their size such hydræmic blood may, and often does, have a greater osmotic value than normal blood. According to Strauss, to whom we owe much work upon this subject, there is a parallelism between the amount of these nitrogenous substances and the degree of œdema, though none is established with the quantity of urine excreted (Brunner) or with uræmia. Now it is clear that the accumulation of fluid in the tissues may be due to a loss of power of the excretion of water by the kidneys or to a retention of water by the tissues. In the former case the drinking of an extra quantity of water would lead to œdema and no

[39] 1887, Ibid., p. 143.
[40] Honigmann: Ergebnisse der Pathologie, viii., 1904.
[41] Lindemann, Hermann, Strauss, und Bickel. See Honigmann loc. cit.

increase in the urine. In the latter if water be held by the tissues owing to the osmotic pressure of these electrolytes and of the saline molecules, additional water taken would cause increased secretion of urine. Experiment shows that in the acute form of nephritis an addition of water increases the œdema usually and does not appear in the urine,[42] though some cases of nephritis after the infectious fevers with hæmaturia prove exceptions.

In parenchymatous nephritis many cases react to water by passing it in the urine. Only experiment can ascertain whether this be so or not in the individual instance. The presence of œdema seldom means inability on the part of the kidney to secrete more water. Hence, in the treatment of such cases when œdema supervenes it is desirable to add water to the daily diet and to find out whether it be excreted in the urine or not. If it be, this most valuable of all diuretics will enable a portion of the substances to be excreted, which by their osmotic pressure may be holding fluid in the tissues and causing the œdema. The experiments upon granular kidney with abundant urine show that additional water is usually excreted in the urine. But Kövesi and Rothschultz state the amount of solid constituents is not increased, that is, a more dilute urine is passed. Von Noorden has found that the granular kidney can secrete urine of a normal specific gravity if water be restricted, and he is an advocate of such restriction, holding that thirst arises from some undetermined cause, but that the satisfaction of it by drinking is harmful, especially to the vascular system.

We must remember, however, that the secretion of a dilute urine more nearly isotonic with the blood than normal urine involves less work on the part of the kidney cells.[43] Galleotti found that after the injection of sodium chloride into a dog the osmotic pressure of the blood was not normal for 46 hours and the work done by the kidney was exceedingly large, but that if the dog were given water to drink the same result was produced in half the time with half the expenditure of work. Again, in Bradford's experiments[44] when the total kidney tissue was much reduced, the animals secreted a large amount of dilute urine and, at the same time, the blood became more watery and contained more urea, a condition strikingly similar to that in granular kidney. The production of dilute urine in large quantity, therefore, in this disease is, as experiment would lead us to expect, the way in which solids can be removed from the blood with the least performance of work by the kidney. Indeed, Beddard's reference[45] to the experiments of Bradford and of Ribbert applies equally well to the case of

[42] Kövesi und Rothschultz, 1904; vide Lehrbuch der Pathologie des Stoffwechsels, von Noorden, 1906.
[43] Galleotti, vide Beddard: Recent Advances in Physiology, p. 717.
[44] Ibid., p. 721. [45] Ibid., p. 722.

granular kidney when he remarks that the "change in the character of the urine observed in these experiments is probably to be explained in the light of Galleotti's results as the effort of the reduced kidney substance to excrete the maximal amount of material with a minimal expenditure of energy." The fact that the granular kidney may be able to produce urine of a high specific gravity does not show that it is desirable to perform this experiment upon every case of the disease.

The harm which von Noorden supposes is done to the vascular system by dealing with large quantities of fluid is also somewhat problematical or its results would be more often seen in diabetes insipidus and mellitus, in which much more water is drunk and excreted than is usual in chronic disease of the kidney.

The metabolism of water in nephritis is closely connected with that of sodium chloride and many observers have ascribed the œdema and many of the symptoms of nephritis, including the terminal uræmia, to the non-elimination of salt. It is improbable in the light of many facts that the pathology is as simple as this, but from the point of view of treatment we may look at the metabolism of chlorides in this disease. The excretion of chlorides in nephritics may follow the normal course and be equal in amount to that taken in with the food. On the other hand, a large number of analyses have been made which show that this is frequently not so. Many conflicting results are probably due to the observations not having been sufficiently prolonged, for the excretion of chlorides often oscillates, and while for a time there may be less in the urine, later in the case the retention may be corrected by a larger excretion. Such oscillations are also characteristic of the excretion of water and nitrogen in kidney disease, and the excretion of salt is usually, but not always, parallel to that of nitrogen. This variation explains those instances in which more chlorides appear in the urine than were in the food, as in a case observed by Halpern in which in 16 days the excess of chlorides in the urine was 208·69 grammes. A similar phenomenon is the delay in the excretion of added salt. A healthy individual excretes an extra dose of salt in from 28 to 48 hours, while in kidney disease the whole of the salt may not appear for some days. This is similar to what we have seen in the case of the nitrogenous substances.

Most striking are the cases with definite retention of salt, associated with œdema. This condition is usually found in acute nephritis and severe chronic parenchymatous cases, not so commonly in cases of granular kidney, except during exacerbations of a superimposed acute or subacute process, and also when the heart is failing. In cases of one-sided disease less salt has been found in the urine from the affected kidney. The two kidneys, however, do not always excrete the same amount of salts in health. The quantity of sodium chloride in the urine in 24 hours may be less than one gramme and Bing[46] has reported two cases of achloruria, in which hypersecretion in the stomach occurred, with vomiting of salt and water, a condition which he designates as one of chronic sodium chloride poisoning. This would certainly suggest failure of excretion. Apart from diarrhœa no increase in the fæces accompanies diminished excretion in the urine. The retention of chlorides is connected with œdema, and in some instances this relation is very marked. Diminishing the amount of food has been found to be followed by less œdema, while adding salt again is accompanied by increase of the fluids retained (Javal and Widal). A similar phenomenon is observed when sodium bicarbonate is given in large doses in diabetes. While such cases are very striking we can hardly suppose that salt is the only sinning material, but may regard it as an electrolyte whose accumulation in the tissues is accompanied by fluid as a natural result of the osmotic pressure of the salt. Maries regards the tissues as the element holding the salt, either in a free condition when fluid is attracted or combined with the protoplasm as fixed salt, a hypothesis which would account for the observations of salt retention without œdema. The fact that the chlorides are reported to be present in greater quantity in œdema fluid than in blood serum is perhaps in favour of Maries' view that the tissues attract and hold the salt, but whether this be so or whether the kidney cannot excrete it, it is important to know what indications for treatment have been afforded by the workers in this field.

It has been shown that in cases of retention if the salt in the food be diminished the body soon comes into salt equilibrium.[47] About from two to six grammes a day may be allowed. There need be no fear of doing harm, for a normal individual can subsist on this amount without losing more than the intake in the urine. With this small quantity of salt the œdema and the general condition of the patient improve. Since salt in the tissues attracts water by withdrawing it from the food we are practically giving the patient water. We may also conclude that in ordinary cases of granular kidney which are doing well there is no need to reduce the salt below a moderate amount, but that this should be done when any signs of an exacerbation present themselves.

In conclusion, Mr. President and Fellows, I may express the hope that further research upon the processes of nutrition in disease may be ardently prosecuted in this country. Only by fuller knowledge can the art of healing be advanced.

It is important to remember that the information acquired by means of experimental investigations must be combined with the wisdom of clinical experience and that the means

[46] Zentralblatt für Stoffwechsels und Verdauungs-Krankheiten. 1906, S. 90.

[47] Claus, Plant, Beach. 1905. Vide Lehrbuch der Pathologie des Stoffwechsels, von Noorden, 1906.

employed for the relief of illness must be adapted to the bodily state and to the circumstances of the individual. I cannot do better in this connexion than read to you the words of Bacon: "Physicians are some of them so pleasing and conformable to the humour of the patient, as they press not the true cure of the disease; and some other are so regular in proceeding according to art for the disease, as they respect not sufficiently the condition of the patient. Take one of a middle temper; or if it may not be found in one man, combine two of either sort ...."

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