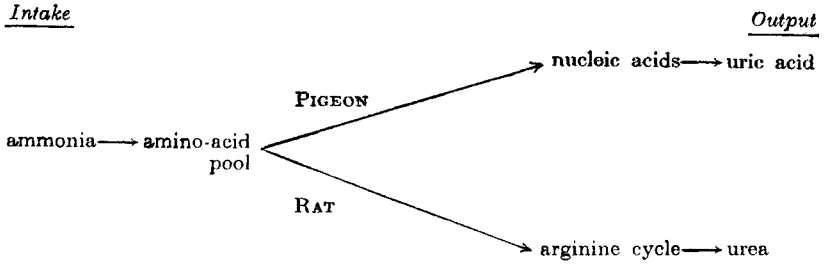
but not to any great extent in the muscle adenylic acid, and in the excreted uric acid (Barnes and Schoenheimer, 1943). It appears that the pathway from ammonia to uric acid in the bird passes through the purines and pyrimidines of the tissue nucleic acids. The following scheme shows the metabolic pathways in the rat and in the pigeon:



The use of N^{15} has also revealed that the pigeon does not employ urea, arginine or histidine in the synthesis of purines (Barnes and Schoenheimer, 1943), nor can dietary purines be used in nucleic acid synthesis. When isotopic guanine is fed to pigeons the isotope appears in the uric acid excreted but not in the tissue nucleic acid (Plentl and Schoenheimer, 1944). The nucleoproteins therefore appear to be built up from smaller molecules in the general metabolic pool, and not from dietary purines or pyrimidines, although there is some evidence that the latter may be utilized if they are supplied as nucleosides or nucleotides, instead of as free bases.

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Discussion

Dr. I. Leitch (Imperial Bureau of Animal Nutrition, Bucksburn, Aberdeen): I have recently read an interesting paper which suggested that in the organisms studied, all mutations were characterized by the loss of power to synthesize one or other complex chemical compound. Some of these were essential to survival, some not. If this is true and if evolution is by selection of successive mutations then the higher the stage in evolution, the more dependent the organism must be for survival on the diet available.

I have pleasure in asking Captain Stevenson of the Canadian R.A.M.C. to describe his experiences in the field of protein metabolism during the war.

Captain J. A. F. Stevenson (McGill University, Canada and C.R.A.M.C.), opener: I might refer to some recent work on protein metabolism carried out by myself with particular reference to the treatment of extensive war wounds and burns. I can confirm what Dr. Cuthbertson has said about a marked increase of protein loss in burns with resultant negative nitrogen balance. Protein catabolism is followed by protein anabolism. When N intake is raised during the catabolic phase N output also is increased so that N balance is not much affected, but there is rapid storage in the anabolic phase. This is true for whole protein given by mouth as well as for protein hydrolysates given intravenously. My experience with "Amigen," as supplied by the makers, has been very satisfactory, with no pyrogenic reaction or thrombosis, but an attempt to use "Amigen" prepared in my own laboratory was much less satisfactory owing to the presence of pyrogens. As regards diet in convalescence I would suggest a complete change of view. The usual diet considered adequate for a patient in bed is about 70 g. protein with some 1500 to 2000 Calories per day. I might refer to the case of two R.A.F. pilots suffering from 15 to 20 per cent. third degree burns who lost 40 lb. weight in 6 weeks. On a diet of approximately 100 g. protein and 2700 Calories per day they gained $\frac{1}{4}$ lb. in ten days. When given a diet of 180 g. protein and 3500 to 4000 Calories per day they started to put on $\frac{1}{2}$ lb. a day, their general condition improved, burns healed and skin grafts took well. There may be some initial difficulty with such an ample diet, but patients very soon take to it. It is important to start early, at first with protein hydrolysates if necessary. In ill nourished persons, there is often a marked diminution of liver function, especially after operation. Finally, it is important to ensure that patients are really getting the diet prescribed.

Dr. E. C. Owen (The Hannah Dairy Research Institute, Kirkhill, Ayr): I wish to call attention to yet another method of studying the metabolism of proteins and amino-acids.

The method is illustrated by an experiment of White and Jackson (1935). The growth of rats can be slowed down or completely arrested by adding certain substances to the diet, bromobenzene for example. If, to the diet containing bromobenzene, cystine or methionine is added, growth is resumed. The explanation of these phenomena is that in the body of the rat, or rabbit, pig, or dog, the bromobenzene is detoxicated largely in the form of S-*p*-bromophenyl-N-acetylcysteine (parabromophenyl-mercapturic acid) and the cysteine for this synthesis is provided either by cystine or by methionine in the diet. Part of the bromobenzene is detoxicated as *p*-bromophenyl-sulphuric acid, so that when bromobenzene is fed the neutral sulphur and the ethereal sulphates of the urine are increased while the inorganic fraction diminishes.

Other phenyl halides act similarly to bromobenzene.

Nakashima (1934) showed that naphthalene when fed to rabbits caused a large increase in the excretion of ethereal sulphate and neutral sulphur, and Bourne and Young (1934), and Ing, Bourne and Young (1934)

showed that, in this case also, the increased excretion of neutral sulphur was due to formation of a mercapturic acid, *l*-(S-α-naphthyl)-N-acetyl-cysteine. It may be mentioned here that naphthalene causes cataract in the rabbit, that cysteine deficiency causes cataract in the salamander and that the proteins of the lens of the eye are rich in cysteine.

Anthracene has been added by Boyland and Levi (1936) to the list of compounds which are detoxicated as mercapturic acids.

Other substances which generate a sulphur deficiency in the body and thus inhibit growth are iodo-acetate, cholic acid, and methyl cholanthrene (White and White, 1938).

Cholic acid is particularly interesting, for it combines with taurine (2-amino-ethane sulphonic acid) to form the bile acid, taurocholic acid. White (1936) has demonstrated that the growth of rats is inhibited by ingestion of cholic acid. Growth is resumed when extra *l*-cystine, or *dl*-methionine, but not when taurine, is added to the diet.

These functions of cysteine in detoxication and in forming a bile acid may be added to Dr. Stewart's list of special functions of amino-acids and they serve to support his conclusion that an amino-acid may be dispensable from the diet and yet have a special function in the body. A further well known example is the detoxication by glycine of the benzoic acid occurring in stone fruits.

Note added in proof. In a paper published after this meeting, Elson, Goulden and Warren (1945) reported experiments on the effect of nine aromatic hydrocarbons on the partition of sulphur in the urine of the rat. With the carcinogens, 1 : 2 : 5 : 6-dibenzanthracene and 3 : 4-benzpyrene, they found inhibition of growth but no evidence of extra excretion of neutral sulphur. They therefore questioned the validity of White's (1936) hypothesis that retardation of growth by aromatic hydrocarbons is causally connected with the excretion of mercapturic acids.

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Dr. H. W. Kosterlitz (Physiology Department, University of Aberdeen): The quantity of non-glycogen, non-lipoid solids present in the rat's liver expressed in mg. per 100 g. bodyweight depends on the quality and quantity of the dietary protein. An attempt was made (Kosterlitz and Campbell, 1945) to utilize this phenomenon for the determination of the biological value of proteins. It was found that the non-glycogen, non-lipoid liver solids were directly proportional to the logarithms of the protein intakes expressed in mg. N per 100 g. bodyweight per 24 hours. There was no significant difference between the regression lines constructed for casein and for egg albumin. Very low values for non-glycogen, non-lipoid liver solids were obtained for zein and for zein supplemented with *l*(+)-lysine, low values for zein supplemented with *l*-tryptophane,

and normal values for zein supplemented with both *l*(+)-lysine and *l*-tryptophane. The feeding also of acid-hydrolysed casein, which was deficient in tryptophane, resulted in very low values; if the hydrolysate was supplemented with 1 per cent. *dl*-tryptophane, normal values were obtained. When an enzymic digest was fed, normal quantities of non-glycogen, non-lipoid liver solids were found.

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Professor J. R. Marrack (London Hospital, Whitechapel, London, E.1): In early days hydrolysates were so unpleasant to take that patients often said they would prefer to die. As regards intravenous administration, this was no doubt useful *in extremis* but I am sure that as long as patients are able to ingest and digest, the natural route is best. As regards the treatment of babies with gastro-enteritis, intravenous treatment is in some cases not undertaken until patients have recovered to some extent from dehydration, for fear of renal complications. These patients, however, are already probably on the road to recovery. Did Dr. Anderson refer to these? In other cases the treatment was probably of no use anyhow.

Mr. E. M. Bavin (c/o Genatosan, Ltd., Loughborough): With reference to the unpleasant taste of a hydrolysate, it is my experience that if patients are encouraged in the beginning, they quickly acquire a taste for it and afterwards take it readily. In patients with chronic tuberculosis as much as 50 to 150 g. per day have been given. Probably the best flavouring to mask the taste and odour is peppermint or aniseed.

Dr. C. P. Stewart replied: As regards *Dr. Leitch's* reference to the power to synthesize our own requirements as an index of the level of evolutionary progress, I would point out that birds require two essential amino-acids additional to those required by man.

Captain J. A. F. Stevenson: With reference to the use of hydrolysates in oedema, those in crystalloid solution would tend to increase the oedema. One must first look for an osmotic effect, not for an immediate nutrient effect. Elman has shown that the proportion of blood plasma protein to tissue protein is 1 : 30 so that from 50 g. protein something less than 2 g. plasma protein would be expected and this would not greatly affect the oedema.

I should like to ask Mr. Bavin how he got so much protein into his patients. The intake was practically doubled. Could not that have been done by ordinary feeding?

Mr. E. M. Bavin (in reply): In our experience 70 to 80 g. per day, given as "medicine", are taken quite readily.

Captain J. A. F. Stevenson: In my opinion there is no need to resort to protein hydrolysates in the treatment of tuberculosis. The protein intake could, I think, easily be doubled by ordinary diet and in more palatable form.

Mr. H. C. H. Graves (Vitamins, Ltd., 23 Upper Mall, Hammersmith, London, W.6): With reference to methods of studying the biological value of proteins, it appears that we are now moving away from the old conception of biological values, which ignored calorie requirements. The method outlined by Dr. Kosterlitz does take into account calorie intake. Clinicians also seem to appreciate the necessity of carbohydrate additions to hydrolysates, as Dr. Anderson has mentioned. The ignoring of calorie requirements has, in the past, led to difficulties of interpretation of experimental results.

Dr. A. B. Anderson: The chief obstacle to the use of hydrolysates is their unpalatability, but in my experience they can be rendered more palatable by being neutralized and flavoured with aniseed.

As regards *Professor Marrack's* enquiry about gastro-enteritis, we have not had much experience in Glasgow. Clinicians are not satisfied with results, but administration has been mostly by mouth.

Concluding Remarks

Dr. D. P. Cuthbertson: I would remind the meeting of Rubner's remark that "Protein contains the magic of life, ever newly created, ever dying". Much that has been said by Dr. Stewart, Dr. Davidson and Mr. Griffiths, and much of the discussion at this meeting has emphasized this viewpoint.

Dr. Anderson and Captain Stevenson have dealt with certain clinical aspects, and more particularly with the use of protein hydrolysates. When the Medical Research Council were set the problem of advising on the preparation of hydrolysates for use in Western Europe they expected to have to treat patients with a great diminution of digestive enzymes, and often in a semi-comatose condition. This opinion was based largely on descriptions of the condition of the starving destitutes of the Bengal famine. As it turned out, the clinical picture was different, and the chief problems were largely those of administration and of combating the distressing psychological state of the victims.

In India, the starving subjects were frequently in a state of coma, whereas in Holland patients were often alert until death supervened quite suddenly. Intravenous methods were fraught with difficulty owing to the large volumes of dilute solution which had to be used and on account of which oedema worsened. Further, such methods were associated in the minds of the unfortunate patients with the Nazis' methods of extermination. Oral hydrolysates were unpalatable, and in any case were not required as the patients could use intact protein. Indeed, treatment with skim milk and glucose was much the most effective method.

If a perfectly safe hydrolysate of protein can be obtained and administered in sufficient amounts to spare body protein, then there is no doubt that it might prove a life saving measure in certain conditions where there is a marked defect in the ability to ingest, digest or absorb sufficient protein.