Although penicillin can now be expected to control the infection in about 90% of patients, a closer inspection of our results shows several features which are far from satisfactory and which reveal our ignorance of several important aspects of this disease: (a) In the majority of patients who relapse no good reason can be given for the failure of penicillin; in only a few could it be explained on the basis of a highly resistant organism. (b) The remarkably high incidence of heart failure, both during and soon after apparently effective treatment, is not explained. (c) The presence in the heart valves of what appeared to be living organisms in about one-third of patients who died after apparently effective treatment suggests that dormant infection may be an important sequel of treatment with penicillin.

For these and other reasons we believe that further intensive research on this disease is indicated, with particular emphasis on higher dosage and on careful analysis of post-mortem material. The following centres are continuing this work, and it is hoped that an adequate number of patients will be referred to them: Belfast (Queen's University, Institute of Pathology). Birmingham (Professor Wilkinson, Queen Elizabeth Hospital). Bristol (Professor Bruce Perry, Bristol Royal Infirmary). Edinburgh (Dr. A. R. Gilchrist, Royal Infirmary). London (Sir Alexander Fleming, St. Mary's Hospital; Professor Christie, St. Bartholomew's Hospital; Dr. G. E. S. Ward, Middlesex Hospital). Manchester (Professor Crichton Bramwell, Royal Infirmary). Leeds (General Infirmary).

Conclusions

The administration of 500,000 units of penicillin a day for 28 days can be expected to control the infection in about 90% of patients suffering from subacute bacterial endocarditis, but about 35% of these die of heart failure and other complications.

Larger doses should be given for a longer period of time to patients who relapse and to patients in whom the infecting organism is more than eight times as resistant as the Oxford staphylococcus.

Of the relapses 90% occurred within a month of treatment, but a danger of relapse persists after a year or more of good health.

Evidence of heart failure or of poor nutrition is of great importance in prognosis. The duration of infection and the nature of the primary cardiac lesion are also of some significance.

What appear to be viable organisms are not infrequently found in the heart valves of those who have died after the infection has apparently been controlled.

This report is made on behalf of a large number of clinicians and bacteriologists who have taken part in this investigation. Dr. J. E. Cates and Dr. P. J. N. Cox have also assisted in the analysis of results. Mr. J. A. Heady and Professor Bradford Hill have given valuable help and advice on statistical analysis.

One of the special duties of the local health department is to disinfect verminous properties and persons. *Insect Pests*, by W. C. Harvey and H. Hill (2nd ed., pp. 347, 14s.; H. K. Lewis and Co., London, 1947), is a useful handbook for the medical officer or sanitary inspector, particularly for its account of practical procedure and legislative control. The biological data about the various pests form the weakest section of the book; there are also some errors and misspelt specific names. The quality of the illustrations varies: about half are photographs which, for such difficult subjects, are fairly good; the rest are drawings and are rather poor. The authors have enlarged this edition to include information about mosquitoes and moths (clothes moths), which for some mysterious reason they discuss in the same chapter. There is an informative chapter on the new insecticides, such as D.D.T., and the authors have taken pains to describe the practical applications of these materials.

INTRAVENOUS ALIMENTATION*

BY

H. E. MAGEE, M.B., D.Sc.

The proper functioning of the body in all or any of its parts demands a sufficiency of all essential nutrients. I mention this obvious fact merely for emphasis. When injury or disease of an incapacitating degree occurs nutrition is nearly always interfered with and malnutrition may be said to have begun. The two main causes are: (a) the direct effect of the disease or injury leading to destruction of tissues and loss of nitrogen, and (b) inability (or disinclination) to take and retain food. If destruction of tissue continues unchecked malnutrition becomes progressive and a vicious circle begins; the disease causes digestive upsets or anorexia, or both, which in turn aggravate the disease. The clinician then has on his hands the original, diseased state complicated by starvation or semi-starvation. He will attempt to break the vicious circle by removing the cause of the tissue destruction or by checking it, and he will probably try to supply nutrients to the tissues so as to combat the malnutrition and assist the body to overcome the primary condition. In chronic conditions, too, these considerations are relevant, and superadded infections, bed sores, or hypostatic pneumonia may develop and make further contribution to the vicious circle.

By malnutrition I mean derangement of the physiological processes concerned in the supply of essential nutrients in sufficient amounts to any and every part of the body and with their metabolism. Although it includes in the broad sense the effects of excess of some or all nutrients, such considerations are not germane to this paper, and I therefore restrict the meaning of the term to the effects of failure of all nutrients or of some to reach the tissues in sufficient quantities. Malnutrition in this sense might be caused by inability to swallow food—e.g., in stenosis of the oesophagus and comatose states; by inability to retain and digest food—e.g., in cyclic vomiting; by failure of absorption—e.g., in persistent diarrhoea. In infective states of long duration, happily less common now than before the introduction of the sulphonamide drugs and penicillin, malnutrition is a prominent feature, partly because of anorexia and partly because of impaired digestion and assimilation; and if stupor and the "typhoid state" supervene inanition becomes absolute and a fatal issue is a matter of time. If the clinician were able to supply nutrients to the body, not merely to stave off starvation but also to supply the elements to reconstruct the damaged tissues and to form antibodies, the outlook would at once be transformed.

Thanks to researches in recent years, we are now able by means of intravenous alimentation to meet such situations with much greater confidence than formerly. Hydrolysates of protein suitable for intravenous use were first prepared about seven or eight years ago. Before that time intravenous alimentation was confined to the use of saline and glucose solutions, the value of which is strictly limited because of the absence of protein.

Protein Requirements

In the conditions we have been considering it is protein that is specially required.

Metabolizable Proteins.—The intestinal villi cannot absorb proteins until they have been hydrolysed by digestion

* Substance of a lecture given to the North of England Branch of the British Medical Association on May 8, 1947.

to amino-acids and peptides. The body is intolerant of foreign proteins, and if they get into the blood they cause reactions of an anaphylactic type. Human blood proteins can, however, be given by vein with impunity, and there is evidence, provided mainly by Madden and Whipple (1940), that blood proteins can supply the "building stones" required for the construction of the body's tissues. For long it was assumed that the amino-acids, after being absorbed, went via the portal vein to the liver, where those not wanted by the body were de-aminized and the non-nitrogenous residue used for energy, while those required for growth or repair by any organ or tissue were taken up from the general circulation. Whipple, on the basis of much experimental evidence, has advanced an attractive theory about the fate of absorbed amino-acids (and peptides). It is that (a) the amino-acids are changed, mainly in the liver, into plasma proteins; (b) there is a constant ebb and flow between plasma and tissue proteins; (c) in the tissues there is a reserve store of protein for emergency use; and (d) normally a state of dynamic equilibrium exists between the plasma proteins, the reserve proteins, and those ingested.

Blood Proteins.—It would follow from Whipple's theory that we have had, since blood transfusion became perfected, a means of supplying by vein all the proteins the body requires; but it is doubtful if supplies of human blood available, or likely to be available in the near future, would suffice for the very many uses to which human plasma could be put in intravenous alimentation. Moreover, we do not know whether plasma proteins can be used for energy purposes. As I point out later, a large proportion of the energy needs of the patient treated by intravenous alimentation must, in the present state of knowledge, come from the proteins injected. The use of plasma is therefore likely to be confined to the purposes for which it was originally intended—namely, to combat shock and the effects of haemorrhage and of certain diseases.

Protein Hydrolysates.—Loewi in 1902 was evidently the first to show that nitrogen equilibrium and weight could be maintained by administering protein digests by mouth. He fed dogs on pancreatic digests of protein, plus starch and fat. In 1913 Henriques and Andersen kept goats in N and weight equilibrium for twenty days with intravenous protein digests, sugar, and salts. In 1938 Rose showed that ten of the thirty or so known amino-acids, given by mouth as the only source of N, sufficed for maintenance of N balance and weight in rats. The practical significance of these findings did not become apparent until Elman and Weiner (1939) reported the successful administration of protein digests by vein to human patients. Since then increasing attention has been given to the subject, and there are at present on the market American and British hydrolysates of proteins, which can be given to human patients day after day in substantial quantities without reaction and often with striking success. The subject has been reviewed by Elman (1944), Cuthbertson (1944), and Gaunt (1944).

Hydrolysis of protein can be effected by acids or by enzymes, but enzymic preparations have been found to be the more successful. The earlier preparations often provoked reactions which were caused, as animal experiments showed, either by toxic substances produced by bacteria or by large polypeptide aggregates. The enzymic preparations now used very extensively in North America seem to be practically free from such risks and less prone than acid digests to cause thrombosis. An enzymic preparation made in this country, and at present being submitted to extensive trial under M.R.C. auspices, appears

also to be giving satisfactory results, but further experience must be gained before its full therapeutic value can be stated.

Amino-Acids

Madden and Whipple (1946) have done much experimental work on dogs to ascertain whether solutions of pure amino-acids given parenterally could maintain the animals in N equilibrium. The work of Rose (1938), showing that only ten amino-acids are essential, simplified the trials of Whipple's school. He was able to secure substantial quantities of these amino-acids, most of them synthetically prepared, and showed that, when given by mouth, skin, vein, or peritoneum along with glucose, they sufficed for N equilibrium, but weight was not wholly maintained. Whipple, when I saw him in his laboratory in October, 1946, expressed the opinion that another protein element, perhaps a peptide, is essential for health, and it may well be the strepogenin of Woolley (1946); I will take this up later.

All synthesized amino-acids are in racemic form—i.e., a mixture of the natural and unnatural isomers. The animal body can make use of only the natural isomers, and the unnatural forms, which Madden and Whipple (1946) and Madden *et al.* (1946) found to be non-toxic to man, however administered, are excreted unchanged by the urine. The ten essential amino-acids are: threonine, valine, leucine, isoleucine, lysine, tryptophan, phenylalanine, methionine, histidine, and arginine. The use of mixtures of these on an extensive scale is out of the question; they are difficult and very costly to manufacture.

Rose *et al.* (1942, 1943), who maintained young men for several weeks on a diet of which the N was in the form of amino-acids, are of the opinion that arginine and histidine are less essential for man than for the other animals tested. Madden, Whipple, *et al.* (1945) have always incorporated glycine in the amino-acid mixture given to human patients because this seems to make it better tolerated. They have reported the maintenance of, and even gains in, weight of several patients suffering from various diseases with mixtures of the ten essentials and glycine given by vein, skin, or mouth, plus small amounts (about 7 g.) of protein by mouth. It may well be that the protein consumed by mouth filled the part of strepogenin in the animal experiments. One patient suffering from ulcerative colitis was kept going in this way for 100 days, during which a gain in weight of 11 kg. occurred (Madden *et al.*, 1946).

Strepogenin.—Woolley (1946) found that a peptide which he isolated from certain crystalline proteins, including insulin, and which is essential for the growth of haemolytic streptococci, is necessary also for the growth of mice in addition to the ten essential amino-acids plus glycine. He called the peptide "strepogenin." Strepogenin is present in enzymic hydrolysates but not in acid ones.

Urinary Leakage after Injections

Whipple and his colleagues found that, soon after giving amino-acids intravenously, substantial amounts were rapidly excreted in the urine; the excretion was less when they were given by the skin and least by mouth. Clinicians here and in America have found that large amounts of N are lost in the urine in the first half-hour or so after giving hydrolysates by vein. The losses can be detected even by the appearance and smell of the urine. This raises the important question whether, in normal absorption from the intestine, amino-acids undergo any change in physical or chemical properties in passing through the intestinal wall and the liver. It may be that the epithelium

renders the amino-acids more easily metabolized or convertible into plasma proteins. Kotschneff (1926) claims to have found in dogs an increase in polypeptides in the portal vein during absorption of protein meals and of amino-acids. The findings of Madden and Whipple (1946), showing that amino-acids given orally result in better production of blood proteins than when given by vein, support Kotschneff. He used the technique of London (1927), which enables blood to be drawn from the deep blood vessels in unanaesthetized animals. Analysis of blood samples from the portal and hepatic veins of dogs before and after protein meals by modern biochemical methods would be worth while.

There is an important difference between the routes followed by amino-acids absorbed in the ordinary way and by intravenously injected amino-acids or hydrolysates. Normally, of course, all the amino-acids pass via the portal vein to the liver, and, as we have seen, the great bulk of them are apparently changed into polypeptides and proteins. Small amounts of amino-acids are, however, found in the general circulation, but evidently not in such high concentrations as after injections of amino-acids or protein digests. The injected hydrolysates go in the venous blood to the right heart, the lungs, the left heart, and thence in the arterial blood all over the body. If, according to the older theory, the amino-acids were straightway used by the tissues of the body, leakage by the kidney would probably not be as great as it is, but if they must first be changed into blood proteins by the liver, according to Whipple's view, then the dispersal of the material through the circulation would make the necessary transformation in the liver and removal of amino-acids from the blood a very gradual process. The kidney threshold for the separate amino-acids may thus be exceeded. This, it seems to me, is the main reason for the losses of N by the kidney after intravenous infusions. There are clearly many gaps in our knowledge, and it is important that steps should be taken to fill them.

Clinical Experiences

Notwithstanding our lack of knowledge, there is no doubt that protein hydrolysates have provided much success, even where their use has been very limited, as in this country. Very few cases have, however, been published. Two interesting ones came under my observation (Magee, 1946). Both were cases of homologous serum jaundice and were *in extremis* before treatment began; the response and recovery were spectacular. They were given 5% acid hydrolysate in amounts up to 1,000 ml. in twenty-four hours (50 g. of protein and 200 calories) at the rate of 500 ml. in about three hours. The hydrolysates were usually preceded and sometimes followed by 500 ml. of 5% glucose given in amounts up to 1,600 ml. (320 calories) in 24 hours. The rate of administration in North America varies from 350 to 600 ml. an hour of a 5% solution each of digest and glucose, and about 4 litres is apparently the maximum that can be given with impunity in twenty-four hours (200 g. of protein and 1,600 calories). Experience there indicates that it would be difficult to exceed this amount because of the care and attention required for the infusions and because of the risk of reactions and extensive thrombosis.

The conditions in which protein hydrolysates have been used with success include hepatitis, injury or disease of the bowel, intestinal obstruction, severe typhoid state, enteritis, colitis, severe burns, cyclic vomiting, peptic ulcers, and after operations. The most striking case I know of was reported by Brunschwig *et al.* (1945). The patient was kept alive for eight weeks entirely by venous infusions of protein hydrolysate plus glucose, and during this time

he had two severe operations—one for removal of a tumour and the other a bowel resection. Brunschwig, when I saw him in October, 1946, informed me that the man was enjoying a normal life about two years after his discharge from hospital.

Thrombosis

Thrombosis has occurred in every case treated with acid preparations that I know of in this country, but it would seem that it is less likely to occur with enzymic preparations. Although they have rarely reported thrombosis in their papers I found that the Americans have also been bothered with it. Brunschwig told me that in his famous case so many superficial veins were affected that he had difficulty in giving injections towards the end of the treatment. The Americans are now combating this complication with fair success by using different veins and giving no more than 500 ml. at a time by the same vein. Joliffe showed me in a New York hospital a novel method of infusion in an emaciated patient—through a cannula tied into a vein. He treated this patient with blood, then protein hydrolysate for a week, and later with a 25% solution of albumin. The improvement in the patient was remarkable. She had had a large intestinal resection and was in desperate plight before the treatment was started.

Energy Requirements

The energy requirement of an adult male confined to bed is probably not much less than 2,000 calories daily, and may be 2,400 or more in febrile states. If the maximum we can give by vein is substantially less than this, then we run the risk of the hydrolysates being used largely for energy purposes, so that nothing would be left over for reconstruction of damaged tissues. It is to avoid this that glucose is given immediately before or in solution with hydrolysates. To what extent this succeeds is unknown, but the question would not arise if we were able completely to satisfy the energy needs from non-protein sources and have, say, 70 g. of protein for reconstruction. This cannot be done with any combination of hydrolysates and glucose because stronger solutions are excluded owing to the risk of extensive thrombosis and losses via the kidneys, and with solutions of the present strengths the bulk of fluid which would have to be given would be too great.

Fats

As we have seen, the maximum energy we can hope to give by vein day after day is only 1,600—i.e., 400–800 calories less than requirements. There can be little doubt, therefore, that a large proportion, maybe all in many cases, of the injected hydrolysate is oxidized for energy, thus frustrating its primary purpose—namely, tissue reconstruction. Now that we have succeeded in making digests of proved value on a commercial scale, the problem remaining to be solved is how to “protect” the protein hydrolysates by sufficient non-protein energy-giving materials so that the bulk of the amino-acids and peptides will be spared for tissue-building. To do this we would require to give 2,000 calories or more a day in non-protein form.

At present we have no means of giving fats and are therefore restricted to glucose, but the maximum energy we can provide in this form is only about 800 calories a day. The energy problem then becomes one of incorporating fat in usable form in the injections. If this were possible we could reduce the protein hydrolysate to about 75 g. more or less—i.e., to 1,500 ml. of a 5% solution. It would, however, be better to increase the fluid to 2,000 ml. and reduce the concentration of digest to 3.5%, thereby lessening the risk of leakage by the kidney.

With glucose in a concentration of 5% this would give 400 non-protein calories, leaving 1,600 to come from fat in order to reach the 2,000 target. About 170 g. of fat would be required.

So far it has not been found possible to give to human subjects fats in amounts that matter, but research is proceeding. Hegsted, Hay, and Stare (1945) have got so far as to risk giving small amounts to patients, but reactions, none serious, have followed in several instances. Dunham and Brunschwig (1944) have also busied themselves on the subject, experimenting with dogs, but apparently with little success. The main difficulty seems to be to get an emulsion stable enough to stand sterilization. Ivy has been working vigorously on the subject, and he informed me at the International Physiological Congress in Oxford in July, 1947, that he had succeeded in making a stable emulsion with which he has kept dogs in N balance, constant weight, and good health by exclusively venous feeding for 42 days. Since then he has been good enough to send me the following particulars of his emulsion.

Preparation of the Emulsion

1. 50 g. of butter oil refined.

2. 2 g. of lecithin "purified."

3. 2.5 g. of "span 20" (a wetting agent).

Mix thoroughly and heat and mix on a steam bath. Then add, stirring, to:

4. 445 ml. of either 5% or 10% glucose solution made in triple-distilled water and containing 0.1% sodium cholate.

Homogenize five times at a pressure of 3,000–4,000 lb. per square in. (210–280 kg. per cm.²) in a Cherry-Burrell viscolizer (junior model) or its equivalent. Autoclave twice at 10 lb. for 10 minutes within 24 hours.

This yields a mixture of: 10% fat by weight, 0.4% lecithin, 0.5% span 20, 0.1% sodium cholate, 5% glucose.

1. The butter oil is refined by melting and removing curd and water. Then the oil is washed with three or four volumes of hot freshly distilled water three times. Highly refined oil may also be used, though most experiments have been done with butter oil.

2. The "purified lecithin" is a soya-bean lecithin prepared by the "Lecithin" Products Co., Elmhurst, New Jersey. If the lecithin is not purified, or even if a 1% concentration of this lecithin is used, anaemia results.

3. Span 20 is a sorbitan wetting agent made by the Atlas Powder Company, Wilmington, Delaware. It is the best (non-toxic) of numerous wetting agents so far used.

4. Sodium cholate is obtained from Breon and Co., of Kansas City, Missouri, or G. D. Searle and Co., of Chicago.

The emulsion is infused slowly intravenously so that the total calorie and nitrogen requirement is given in six to eight hours. Various protein hydrolysates have been used (one by Mead Johnson and Co., Evansville, Indiana, and another prepared by Cutter Laboratories, Berkeley, California). Enough of the hydrolysate is given to keep the dogs in N balance. It can be used separately or mixed with the emulsion.

The total daily mineral and vitamin requirement may be added to the solution. Calcium and iron may disturb the emulsion; these should be given separately.

There can be no doubt that if we succeed in making a preparation suitable for human intravenous use and containing about 75 g. of protein hydrolysate and 2,000 non-protein calories in 2 litres or so we shall have a therapeutic agent of great possibilities. This work of Ivy and his colleagues is an important step in that direction.

Summary

Until recent years we had no adequate means of combating the malnutrition which complicates many diseases, especially

those directly hindering the ingestion, digestion, absorption, or metabolism of food. A preparation of protein suitable for intravenous use and metabolizable by the body was required. Although there is evidence suggesting that the plasma proteins can supply the elements for tissue growth and repair, it is doubtful if transfusion with human plasma is the solution of the problem; sufficient human blood might not be obtainable for such extensive use.

Enzymic hydrolysates of protein suitable for administration by vein have been prepared in U.S.A. and Great Britain and have been used with impunity and success in a wide variety of conditions in which secondary malnutrition is a prominent feature. They include acute hepatitis, comatose states, typhoid state, infantile diarrhoea, and post-operative conditions. The hydrolysates are usually given in 5% solution with 5% glucose at about 500 ml. an hour to a maximum of about 4 litres (200 g. of protein and 1,600 calories) in twenty-four hours. Thrombosis can be lessened by using different veins and giving no more than 500 ml. at a time by the same one.

A defect in the present procedure is that a large proportion of the injected hydrolysate is oxidized to supply energy and is thus diverted from its intended purpose of tissue-building, because it is not yet possible to incorporate enough non-protein calories in the infusion fluid.

It is desirable to administer up to 2,000 calories as glucose and fat emulsion; the hydrolysate could then be reduced to about 2,000 ml. of a 3.5% solution (70 g. of protein) and the bulk would probably be used for tissue repair.

It has not yet been possible to make a fat emulsion suitable for human use; but dogs have been kept in N equilibrium for six weeks by intravenous feeding on protein hydrolysates and glucose-fat emulsions which withstand sterilization.

An important problem remaining to be solved is to check the urinary leakage of hydrolysate which occurs in the first thirty minutes or so after starting infusions.

I am indebted to Prof. Himsworth and Dr. Stannus for comments on the paper, and especially to Prof. Ivy for his great courtesy in allowing me to publish for the first time the details of his fat emulsion.

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The number of technical dictionaries available to the medical worker interested in foreign languages is very limited, and any reliable addition to their number is welcome. The *English-Spanish Chemical and Medical Dictionary*, by Morris Goldberg (pp. 692, 50s.; McGraw-Hill, New York, 1947), will be of more use to Spanish-speaking medical men than to their English-speaking colleagues and should provide them with a fairly complete guide to British and American technical terms. The dictionary is up to date and includes such newcomers to medicine as streptomycin and thiouracil. Definitions of words are given in Spanish. It is inevitable that in a new book there should be a number of relatively important omissions. For example, the author has omitted the names of some muscles while including others less commonly referred to. Nevertheless, he has prepared the dictionary as a whole with care, and we can recommend it not only to those interested in medicine and the allied sciences but also to chemists and biologists.