indication to the patient that his current activities are harmful and must be stopped at once, or death will ensue. But there remain a few patients whose sufferings are so severe that relief at any cost seems desirable.

Numerous operations on the cervical nerves and ganglia have been performed with the object of severing the sensory communications between the heart and the brain ; but so far as our knowledge goes these operations are based upon erroneous theories. The sensory tracts run into the upper dorsal segments of the spinal cord, and not along the neck. It is known that left-sided pain is referred from the heart to the upper five or six segments, the chief pathway being along the inferior cardiac nerves, the stellate ganglion, the vertebral sympathetic ganglia, and the white rami communicantes to the spinal cord. Subsidiary pathways may exist along the middle cardiac nerves and the lower cervical sympathetic trunk to the stellate ganglion ; and directly from the heart to the upper dorsal vertebral ganglia[6] (Fig. 2).

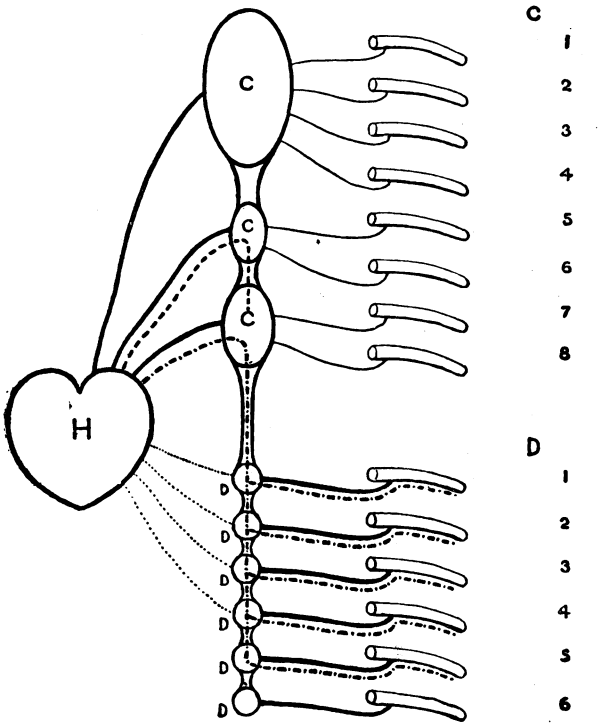

FIG. 2.—Diagrammatic scheme of the sensory nervous connexions of the heart. C, Cervical sympathetic ganglia ; D, Dorsal sympathetic ganglia ; D, Dorsal nerve roots ; — - — - — - — - —, Main route of sensory impressions ; - - - - - - - - - -, Secondary route ; . . . . . Direct route.

The pathways might be blocked by : (1) removal of the stellate and the upper dorsal vertebral ganglia ; (2) section or block of the rami communicantes ; (3) section or block of the posterior nerve roots.

The least dangerous procedure seems to be alcohol injection of the rami communicantes, of which favourable results have been reported.[7] James C. White has now operated upon 17 patients who were subject to severe and frequent attacks of angina which resisted medical treatment. All recovered from the operation without serious trouble, the only unfavourable sequels being attacks of pleurisy in three cases, which rapidly subsided. In 7 cases complete relief from the left-sided pain followed, and in 5 the relief, while not complete, was considerable. In 3 cases improvement was slight, and in 2 cases no improvement resulted. Five patients have been able to return to work. He states that shortness of breath, peculiar sensations, without pain, in the region of the heart, or mild attacks of right-sided angina, have always afforded sufficient warning to the patient that the danger zone of exertion was being approached. The upper dorsal ganglia were removed in 3 patients whose general condition permitted an open operation by Henry's route. All these patients made good recoveries, and the pain was completely checked.

Eight of these patients have died, seven of them within a year of the operation, one from an empyema, the others from cardiac causes. One patient is alive three years after operation, and two patients two years after operation. Such results must be expected, for the operation is merely palliative and in no way curative. But relief from severe recurrent pain, even if of short duration, may be an inestimable boon to some patients.

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THE DEVELOPMENT OF THE SCIENCE OF NUTRITION IN RELATION TO DISEASE*

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In the last twenty years there have been rapid developments in our knowledge of animal nutrition. This knowledge continues to accumulate at an increasing rate ; it has such a direct and important bearing on the prevention or cure of disease that nutrition may now be regarded as a new branch of medical science.

HISTORY

It is interesting to contrast the outlook of last century with that of the present day. At the beginning of the period our ideas were little in advance of those held by the Greeks. Writers still believed that there was only one nutrient substance common to all foodstuffs. Early in the century it was established that heat and muscular energy had their origin in a process of oxidation, and calorimetric studies had shown that the human body obeyed the law of conservation of energy. By the middle of the century, chemists had differentiated food constituents into three "proximate principles"—proteins, fats, and carbohydrates—all yielding energy. At the end of the century, the energy values of different foodstuffs, and the energy requirements of the human body under different conditions, were fairly well known, and the position of the calorie as the symbol of nutrition was well established. Proteins were recognized to be of special value, being necessary for construction in growth and repair of "tear and wear" of the tissues. Dietaries were calculated in terms of calories and protein, and studies in the physiology of nutrition were concerned mainly with metabolic processes involving exchanges of energy, and with the metabolism and chemistry of the proteins and their derivatives, and to a lesser extent of

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the fats and carbohydrates. With knowledge at this stage it was inevitable that workers should tend to over-emphasize the analogy between the body and a machine as energy converters, and to regard the provision of sufficient fuel for energy and material for repair as the only aspects of nutrition which were of practical importance. Although the limitations of this view are now recognized, we must not underestimate the importance of the work done in the nineteenth century. The succession of investigators from Lavoisier to Fischer established the main principles and laid the foundation of the science of nutrition. Nor can we assume that the research on energy exchange and protein metabolism is finished. Although at the present time popular interest has moved to the newer aspects of the subject dealt with here, there is still work of great scientific interest and practical importance being done on energy exchange and the metabolism of the proteins, fats, and carbohydrates.

The main feature of the work of the present century has been the shift of the centre of interest in nutrition from quantity to quality. The epoch-making experiments on vitamins, and the tardy recognition that a diet may be adequate in calories and protein, and still deficient in some of the inorganic constituents, opened up new fields of research. The discovery that a slight difference between two diets, which could neither be detected by the eye nor determined by chemical analyses, might mean the difference between life and death, completely altered our point of view, and of necessity our methods of work. In addition to chemistry and mathematics we had to resort to the biological test to determine the value of foodstuffs. Calculations based on the results obtained with the calorimeter and the test tube have been supplemented by clinical observations; the adequacy or inadequacy of a diet is now judged by observations on the state of health, the presence or absence of symptoms of disease, the rate of growth, and powers of reproduction. In this way, modern nutritional studies are tending more and more to become of the same nature as clinical studies, and so the gap that existed at the end of last century between the biochemical laboratory and the hospital ward is now being bridged.

Results of Modern Investigation

Let us review briefly the main results obtained in experimental work on animals by these newer methods of investigation. The spectacular effects in diseases arising from vitamin deficiency, such as scurvy, beri-beri, and rickets, are so well known that they need not be further discussed. It is completely established that these diseases can be produced or prevented at will in experimental animals by introducing or withholding certain nutrients from the ration. The work on diseases due to mineral deficiencies which has been done on the larger domestic animals is not so well known to the medical profession. Owing to the very rapid rate of growth of modern improved breeds the mineral requirements of the larger domestic animals are relatively high, and consequently the effects of deficiency are easily demonstrated. Rickets and osteoporosis can be produced by deficiency either of calcium or of phosphorus. In cattle, a condition characterized by inco-ordination of movement, and later by paralysis accompanied by the usual signs of malnutrition, is produced on a phosphorus-deficient diet. In certain districts, goitre accompanied by a high mortality rate in the young occurs, and is prevented by the administration of iodine. Anaemia, which can be prevented by administration of iron, is found both in cattle and pigs on certain diets. All these diseases in domestic animals, which have been produced and studied under experimental conditions, are known to occur, and in some cases to be common under ordinary conditions.

The discovery that these deficiency diseases are due to the lack of specific nutrients, whether vitamins or minerals, was in itself a great achievement, but the practical importance of this work is much greater than the mere cure or prevention of these pathological conditions. In experimental studies with animals it has been observed that there are all stages of malnutrition ranging from what we regard as normal health to that in which the gross and terminal symptoms appear. The signs of minor degrees of deficiency are now well known, and need not be enumerated. Some of the signs are common to, and occur in, the early stages of nearly all deficiency diseases. Generally they are indications of lowered vitality. Young animals have a slower than normal rate of growth, the reproductive powers of adults are defective, the coat is dull and lustreless, appetite is decreased, and the animals show, instead of the *joie de vivre* of the perfectly healthy animal, lethargy and other signs of premature senility. A point of practical importance which should be emphasized is that when these diseases occur under ordinary conditions the number of animals suffering from minor degrees of deficiency usually far exceeds the number showing the gross signs of disease.

Increased Susceptibility to Infections

There is another result of dietary deficiency which is equally far reaching in its practical importance. It has been noted by many workers that susceptibility to certain infectious diseases is definitely greater in groups of animals on deficient diets than in comparable animals on complete well-balanced diets. Classical examples of this are the development of xerophthalmia in rats, and epithelioma contagiosum in fowls, in deficiency of vitamin A. It has been repeatedly noted that animals on diets deficient in the fat-soluble vitamins have a high proportion of deaths from respiratory and alimentary infections. It is believed by some (though we lack definite data on the subject) that in deficiency of calcium and iron there is increased susceptibility to pulmonary infections, and recent work on cattle in South Africa seems to indicate that deficiency of phosphorus increases the death rate, apart from the deaths due directly to styfsiekte or lamsiekte, the direct or indirect cause of which is phosphorus deficiency. The information obtained from these observations warrants us accepting, as a working hypothesis, the view that in animals suffering from even minor degrees of deficiency, resistance to organisms normally present in the body may be reduced, and hence bacteria, which, in an animal on a perfect diet might remain non-pathogenic, find in the abnormal tissues and fluids of the host a favourable medium in which their activities can give rise to the specific signs of infection. This aspect is only beginning to be explored. It is an intricate subject to study, because there are involved such a large number of factors, some of which are difficult to control.

It is impossible here to do more than indicate the nature of the work being done in this field of research. There are three important lines: attempts are being made to ascertain (1) the changes which occur in the composition of the blood under different dietary conditions; (2) the effect of diet on immunological reactions; and (3) the effect of diet in altering either the nature of the flora or the pathogenicity of the existing flora in the respiratory, intestinal, and other areas in the body.

Diet and the Composition of the Blood

Biochemical examination of the blood of experimental animals has shown that the level of some of the mineral elements is by no means so constant as was at one time thought. For example, it has been shown that the feeding of a diet low in calcium and high in phosphorus results in a lowering of blood calcium and a rise of blood

inorganic phosphorus to an extent which was thought impossible a short time ago. In an experiment on sheep at present being carried out, it has been found that the blood calcium has been nearly halved, and inorganic phosphorus more than doubled. On the other hand, in cattle suffering from aphosphorosis, the inorganic phosphorus in the blood may be less than half the normal. These results in large animals are on the same lines as those which have been previously noted in rats. Studies are also being made on the influence of the diet on the alkali reserve of the blood, which, as is well known, can be altered within fairly wide limits by medication.

These experimental studies in which workers are seeking for a correlation between composition of diet and composition of blood are already giving fairly definite results in so far as the inorganic constituents are concerned. Comparatively little headway has been made, however, with the organic constituents, though observations on these are being carried out.

Diet and Immunological Reactions

Side by side with this inquiry by chemical methods, investigations are proceeding on the effect of diet on immunological reactions. Here, also, positive results are being obtained. Thus, in observations on agglutinin formation in guinea-pigs and rats inoculated with *B. typhosus*, it has been noted that there is a significantly low titre in animals on a diet deficient in phosphorus, and both agglutinins and bacteriolysins against *B. typhosus* in rats are reduced on diets deficient in vitamins A and D, or B and E. In work on sheep very marked changes have been found in animals transferred from deficient experimental rations to pasture feeding.

Diet and the Flora

The effect of diet on the flora in different areas of the body has been studied in the case of the intestine for many years. It is well known that the reaction of the intestinal contents can be altered by the food, and that such alterations cause changes in the bacterial flora. Of special interest are some observations on the effect of changes in the reaction of the blood. Most bacteria flourish best in a slightly alkaline reaction. It has been observed that treatment which tends to alter the *p*H of the blood to the acid side, or which lowers the alkali reserve, reduces antibody formation in response to infection. Reduction of bactericidal power has been obtained by an administration of hydrochloric acid, and by section of the spinal column, which causes a fall in blood alkalescence. On the other hand, a directly reverse effect has been noted in a recent study of wound infections. In controlled experiments in which alkali reserve, *p*H of blood, and *p*H of wound exudate were estimated, it was found that a rise in the alkali reserve above normal was associated with an increase in the number and virulence of the bacterial flora, and that a shift to the acid side resulted in a reduction of the number of infecting organisms. If these results be confirmed they show that the alkali reserve, which can be controlled by the diet, is an important factor in resistance to infection, and that changes in its level affect differently the individual types of bacteria.

Even this brief consideration of work along these three lines is sufficient to show that we have here a most promising field of research. The scrappy data which we have already obtained prove that the nature of the diet affects the powers of the body fluids to deal with infection, and, what is equally important for the success of further work, that chemical analyses of the blood and serological tests give us a means to make a quantitative assessment of the effect.

In view of the vast extent of this field, however, we cannot claim to have done more, so far, than make a few preliminary observations. Even the meagre results obtained have not yet been all confirmed, nor is their full significance clear. More experimental work is needed before we can begin to link up the biochemical, immunological, and clinical data to see what correlation exists between different dietary factors, the chemical composition of the blood, its immunological reactions and susceptibility to different pathogenic organisms. When we *do* reach that stage we will have greatly increased our powers to prevent and cure disease. We will be able, by dietary measures, to keep animals in such a state of health that when invasion by organisms takes place the *vis medicatrix naturae*—the only therapeutic agent of any real value—will be able to exert its full beneficial influence, unhampered by abnormal conditions of body fluids and tissues due to faulty diet.

NUTRITION AND THE HUMAN BEING

So far we have confined the discussion almost exclusively to the results of experimental work on animals. Let us consider to what extent our findings are applicable to human beings. We know that deficiency diseases such as scurvy and rickets occur in the human being, and are cured by the same dietary manipulations as are found to prevent or cure them in animals, and there is abundant evidence to show that when these diseases appear, minor degrees of malnutrition are prevalent among the whole population living under the same dietary conditions as those suffering from the gross symptoms of disease. Thus it is now recognized that beri-beri is but the terminal gross manifestation of deficiency disease, the actual outbreaks being merely superimposed on a condition of chronic ill-health.

We cannot put groups of human beings under experiment to test directly the effect of diet on the chemical composition and serological reactions of the blood and on resistance to disease. Recently, however, observations have been made on two tribes in Africa, living under conditions almost as favourable for the study of this problem as if the diets had been prearranged. The diet of one of the tribes consisted chiefly of cereals, and was found to be deficient in calcium, and almost certainly in vitamins A and D. The diet of the other tribe, consisting largely of milk, meat, and raw blood, though defective in other respects, was rich in those nutrients deficient in the former tribe. Unfortunately, samples of blood could be obtained only from members of the cereal-eating tribe, but the incidence of disease was studied in both. It was found that the average calcium content of the blood serum in the tribe on the cereal diet was only 9.4 mg., compared with an average of 11.4 mg. for Europeans living in the same district. A survey of the incidence of disease showed that in the tribe with the cereal diet, pulmonary conditions, bronchitis, and pneumonia accounted for 31 per cent. of all cases of sickness, tropical ulcers 33 per cent., and phthisis 6 per cent., compared with a percentage of 4, 3, and 1 respectively in the tribe with the meat, milk, and raw blood diet. In the latter tribe the chief disease was rheumatoid arthritis. There is obviously in these two tribes a correlation between the nature of the diet and the resistance to disease.

Some surveys on the incidence of disease in this country show a social distribution which indicates a possible connexion with diet. In a recent study in which the population was divided into five social classes, ranging from the professions and higher ranks of business to unskilled labour, it was found that at ages between 20 and 65 the death rate from respiratory diseases was 3.3 times, from heart disease 2.24 times, and from cancer

1.54 times as high in the fifth class as in the first class. There are here other environmental factors which complicate the issue, but the fact that the diets of the professions and higher ranks of business life are so much more varied and better balanced than the cheaper, carbohydrate-rich diet of unskilled labour, suggests that diet may be a factor, and warrants further study.

If malnutrition with increased susceptibility to certain diseases commonly exists, it should be possible to show that dietaries in common use are faulty. Unfortunately, we have too little information on the requirements for either vitamins or minerals, the two classes of nutrients to which our discussion has been limited. Nor have we much exact information as to the amount of intake of these nutrients. We have had many dietary surveys of the protein, fat, and carbohydrate intake, but very few on those dietary factors which we are finding of so much importance for health. One such survey, recently completed in Scotland, has yielded results which suggest that in a large proportion of families the diet does not supply a sufficiency of certain minerals to maintain the maximum rate of growth. In 607 families in the seven largest Scottish towns it was found that in only two cases was the energy value of the diet below 2,000 calories per man. There was thus no indication of any gross undernutrition. If we take Sherman's figures, however, which are almost the only reliable data we have on the subject, as a true indication of the requirements of the growing child for calcium and phosphorus, we find that there was a deficiency of calcium in 24.5 per cent. and of phosphorus in 23 per cent. of the dietaries. The position was worse in the case of iron. In 61.6 per cent. of families the amount of iron in the food was below that regarded by those who have worked on the subject as the optimum intake. In 41 per cent. of the families the protein intake, though sufficient for adults, was below the optimum requirement for growth in children.

We must not place too much importance on these findings, since far too little work has been done to enable us to know, with any degree of certainty, the requirements of the child for these food constituents. The results, however, appear to be of some significance when they are considered in the light of a test on the value of an increased consumption of milk in children drawn from the households of which the survey was made. In that test it was found that the addition of milk, either whole or separated, during a seven months' experimental period was accompanied by a rate of growth as indicated by increase in both height and weight about 20 per cent. greater than that in the children not receiving the extra milk. Clinical examination of the children showed that the increased rate of growth was accompanied by an improvement in the general condition. The improvement could not have been due to an increase in the number of calories, because it was found that in different groups of children who received carbohydrate and fat-rich biscuits of equal caloric value to the milk, there was no improvement in condition or increase in rate of growth. This is in accordance with the finding of the survey that the calorie intake was, on the whole, ample. It may be assumed that the effect of the milk was due to the fact that it supplied nutrients which the survey showed to be otherwise deficient.

CONCLUSIONS

We have here brought together some of the more striking results of experimental studies on animals and of observations on human beings, to illustrate the nature of the recent developments of our knowledge of nutrition in its relation to disease. It is obvious that the progress already made in this new field of study is of great importance in both preventive and therapeutic medicine. The principles of some of the results have been applied in stock farming, and have led to a reduction in disease and to increased output by farm stock. In human medicine the effects of their application on children, who are more likely to suffer from deficiencies than adults, are well known, especially as regards the cure and prevention of rickets and scurvy. The spectacular results obtained in the United States and Switzerland in the prevention of endemic goitre and cretinism by iodine medication, and such facts as the prevention of beri-beri by the improvement of rations through the substitution of unpolished for polished rice, are now common knowledge. The recent work on the influence of the acid-base ratio of the diet on chronic nephritis gives an interesting example of the application of nutritional science to therapeutic ends.

The potential value of the information acquired from the research work we have described, as well as the practical results, give every encouragement to extend our studies. Some of the lines along which work should be conducted are clear. We need more information dealing with the amounts of different nutrients required for optimum growth in children, and for the maintenance of health, and also as to the amounts of these nutrients present in dietaries in common use. A concerted international effort to elucidate whether there is a correlation, and, if so, to what extent, between dietary habits, physique, and incidence of disease in the different populations throughout the world would yield results of fascinating interest. The League of Nations has recently carried out a survey of the diet of Japan in relation to beri-beri. The wider problem of the world correlation between diet and health appears to be of sufficient importance to warrant the attention of that council.

In addition to such dietary studies, an urgent need exists for more clinical research on nutritional lines. There are a number of diseases of which the main symptoms are those of disturbance of the normal digestive or metabolic processes—for example, gastric and duodenal ulcers, constipation and its sequelae, rheumatism, anaemias, high blood pressure, and cardiac and nephritic disorders. The etiology of these remains obscure. It has been suggested that they originate in long-continued errors of diet. As a matter of fact, we have very little definite evidence to show to what extent hereditary, nutritional, and other factors are involved. An extended series of studies of previous nutritional histories, of the condition of the circulating fluids, and of the influence of dietary factors on the course of these diseases might throw much-needed light on their etiology.

Future advances in the study of nutrition as applied to human medicine will undoubtedly be made through team work, especially of biochemist, immunologist, and clinician. An essential feature of such work should be the co-ordination of research on the larger domestic animals with that on human beings. The main problems are essentially the same in both fields, and, indeed, some of the diseases on which more work is urgently required are common to man and the higher mammals. For example, osteoarthritis is as common in the horse as in man, and simple goitre appears to occur in all mammals in certain areas where its distribution is coincident with that of endemic goitre in the human population. The nutritional factor in resistance to tuberculosis, which is now recognized as being of importance in human medicine, is equally important in the dairy cow. It is to be hoped that, in the future, in those comprehensive studies which are initiated or supported by the State, there will be co-operation, not only between individual workers in different branches of science, but also between medical and veterinary research institutions and organizations.