Section of Comparative Medicine

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DISCUSSION ON NUTRITION AND ITS EFFECTS ON INFECTIOUS DISEASE

Dr. Stuart J. Cowell: It is notoriously difficult to establish the truth regarding the effect of individual hygienic factors on the health and well-being of mankind, one reason being that, in large-scale observations, it is virtually impossible to exclude the influence of factors other than the one which is being deliberately varied. While it is fairly generally agreed in the medical profession that some connexion exists between imperfect nutrition, or faulty feeding, and susceptibility to infectious disease, the actual evidence relating specific variations in diet to changes in resistance to definite types of infection is extremely conflicting.

There is no cause for complaint about the quantity of evidence on this subject, and only a fraction of the recent contributions can be referred to in this discussion. These contributions can be grouped in more or less distinct categories, and I propose to deal with some of the more important of them.

(1) *Attempts to correlate the incidence and course of infections with the characteristic diets employed by different races, social groups, or institutions.*

In this group would be included studies such as that of Nicholls, who in 1936 published a dietary survey of Ceylon and attempted to relate the effect of the very imperfect dietaries common among certain classes of the population to the distribution of the malaria epidemic which ravaged the country in 1933–34. His conclusion was that " even if the masses had been well-fed there would have been an epidemic—but the vicious cycle of malaria and destitution acting and reacting on one another would not have been established—the mortality rate would have been lower and convalescence would have been shorter ". In the same group would be placed the observations of Orr and Gilks on the diets and health of the Masai and Kikuyu tribes in East Africa. There were far more admissions to hospital for bronchitis, tropical ulcer, and malaria among the latter, who subsisted largely on cereals, than among the Masai, who lived chiefly on meat, milk, and raw blood. Spence compared the incidence of such infections as bronchitis and pneumonia among poor and well-to-do children in Newcastle. Such infections were about eight times as common among the poor children, a great many of whom showed some evidence of being imperfectly fed. McGonigle, who has made similar studies in Stockton, did not find any close correlation between unsatisfactory diets and the incidence of bronchitis in children. The frequent occurrence of certain infections in institutions has been

studied in relation to possible dietary faults. Thus the high death-rate from dysentery in some prisons in East Africa a few years ago was apparently related in part to the very ill-balanced rations of the prisoners. A striking reduction in the mortality rate from this disease followed improvement of the dietaries. Rather similar observations have been reported from asylums in our own country.

In many of the studies belonging to this group it is difficult to decide how far bad diets alone were responsible for the increased incidence of infections, for obviously many racial, social, and other environmental factors must have varied, as well as dietary habits. Nevertheless, the evidence obtained along these lines does suggest that grossly defective diets diminish the resistance of human beings to certain kinds of infection.

(2) *Attempts to determine the effect on the incidence of infectious diseases of changes in the diets of a whole population or of an isolated section of a community.*

There seems a fair measure of agreement that the increased incidence of tuberculosis in Central European countries towards the end of the Great War was due at least in part to the severe quantitative and qualitative food restrictions which were imposed on the inhabitants. From time immemorial famine has been regarded as bringing pestilence closely in its train. On the other hand, the great influenza pandemic of 1918–19 appeared to ravage the comparatively well-fed troops as severely as the less well-fed civilian populations. The effects of less drastic dietary changes have been followed by Dr. Friend at Christ's Hospital. He could observe no clear relation between the dietary changes which he instituted in the school from time to time and the incidence of colds and febrile chills, though he did find an indication that septic infections of the skin were more common when the diets contained more sugar.

(3) *Attempts to define the part played by individual food constituents in determining resistance to infections.*

Many of the observations in this category have been made as the result of experimental work on laboratory animals. I propose to deal in turn with some of the evidence concerning the possible relation of the supply of individual vitamins and mineral elements to infections in man.

Vitamin A, which has been called the anti-infective vitamin, will be considered first. No one questions the fact that severe degrees of deficiency of this vitamin are practically always associated with bacterial invasion in all species of laboratory animals. Most observers who have studied vitamin-A deficiency in man on any large scale have also reported an increased susceptibility to certain kinds of infection. The question which has aroused the most attention in recent years, however, is whether a liberal supply of this vitamin confers increased resistance to infections on individuals who do not show obvious signs of this particular deficiency. Many studies have been published in which the incidence of special types of infection among individuals who have received some preparation of vitamin A or carotene has been compared with the incidence among a control group to whom the preparation has not been given. The duration of illness, the frequency of complications and, with serious infections, the death-rate, have also often been compared in such tests. In some studies the aim has been limited to determining the effect of large doses of vitamin A on the clinical course of established infections. These tests have, on the whole, yielded negative results. A positive result obtained on one occasion has usually been followed by a negative result obtained by a different set of observers studying the same kind of infection. Many series of observations have been reported in connexion with the common cold, perhaps with rather more positive than negative results. The incidence of puerperal infections and the course of puerperal fever have been studied in relation to the provision of extra supplies of vitamin A ; again both positive and negative results have been obtained. Mortality rates from pneumonia have been studied in South Africa ; in one series this vitamin seemed to

have exerted a distinctly favourable effect, while in another it was without any effect. The clinical course of measles in fever hospitals has been the subject of two investigations in our own country in recent years. In the first it appeared that a concentrate of vitamins A and D was responsible for a significant reduction in the mortality rate. In the second test, carried out in much the same way, no reduction in the mortality rate was found in the group which had been given the supplement of vitamins A and D. In the only two investigations on this subject with which I personally have been concerned, negative results were obtained. One was concerned with the effect of a vitamin-A concentrate on the winter sickness rate of Royal Air Force recruits and the other with the effect of the same concentrate on the occurrence of otitis media as a complication of scarlet fever.

Such results cannot be interpreted as proof that vitamin A plays no part in determining the resistance of human beings to infections, but they do suggest that no dramatic effects are to be expected as the result of giving supplements of vitamin A to those whose diets may already contain a sufficiency.

It has been much debated whether vitamin D is concerned with maintaining the resistance of human beings to infections. Clinicians have for a very long time stressed the tendency of children with rickets to develop respiratory disorders, such as bronchitis and pneumonia, though in one or two careful studies made in children's institutions, it has been found that pneumonia attacked as many children with well-calcified bones as children with radiological evidence of rickets. It is very widely believed, however, and it is probably true, that children with active rickets succumb more readily to pneumonia, partly no doubt, on account of the mechanical obstruction to respiration provided by the deformed and yielding chest wall. Clinical trials of the effect of irradiated milk and ergosterol and of irradiating the skin have yielded conflicting results in studies concerned with resistance to the common cold and with the healing of tuberculous lesions.

There is some evidence that deficiency of the vitamin-B complex may be related to increased susceptibility to certain kinds of infection. Among the recorded observations bearing on this point are those of Bray, who found severe infections common among infants whose mothers were getting an insufficient supply of vitamin B complex. When measures were taken to guard against this deficiency the frequency and severity of infections among the infants fell dramatically.

Vitamin C has been shown to play an important part in determining the resistance of guinea-pigs to tuberculosis, but the evidence regarding its effect in human tuberculosis is indecisive. Observations have been made on the state of saturation with vitamin C of human beings suffering from a great variety of acute and chronic infections. In some of these observations the storage of vitamin C has been found to be reduced, whereas in other observations normal storage is the rule. The special case of rheumatic fever may perhaps be mentioned. It was suggested a few years ago, on the basis of experiments with guinea-pigs, that rheumatic lesions might be caused by a combination of vitamin-C deficiency and a specific infection.' This view has not so far been substantiated by observations on children, though it does appear that there is some disturbance in the storage or metabolism of this vitamin in children who show signs of the active rheumatic process.

The only specific mineral deficiency I shall mention in relation to diminished resistance to infection is that of iron. Dr. Helen Mackay found, in her study of nutritional anæmia in infancy, that the incidence of infections of the respiratory tract was almost twice as high among infants who had not been protected from this anæmia by some additional source of iron.

The general impression which one obtains from the kind of evidence outlined here—and I hope that the selection of observations may be regarded as a fair one—is that it is exceedingly difficult to prove definitely the relation of any particular food factor to resistance to infections in man. One is left with the feeling that in so far

as the state of nutrition is connected with resistance to infection, the connexion is rather that good nutrition may determine the course an infection will take than that it will decide whether infection will occur. The evidence available at present in the case of man does not seem to warrant the view that one isolated food constituent is responsible in any specific way for maintaining the resistance of the body to infection in any general sense. On the other hand, there is suggestive evidence that gross malnutrition in a broad sense of the term, or individual states of specific food deficiency, may lower the resistance to established infections. The possibility will have to be considered that an optimum state of nutrition, lasting for a longer time in the life of the individual than has been aimed at in most of the tests so far reported, may be necessary to secure the maximum degree of resistance to infections.

Dr. Harriette Chick: Although famine and pestilence have always been associated with one another in history and there is a widespread conviction that defective nutrition increases susceptibility and lowers resistance to infection, absolute proof of this has been difficult to obtain. The reason for this failure is chiefly that observations on the human subject are complicated by so many variables that it is only by a lucky chance that the effect of one factor only can be studied. Thus, in considering the spread of infectious disease in a community, in addition to (1) the nutritive state of the individual, depending on the dietary, other factors, (2) such as chill, anxiety, and bodily or mental fatigue, will affect the susceptibility of the individual. The chance that infection will take place will also depend on (3) the dose, and (4) the virulence, of the infective agent.

In an epidemic of acute infectious disease, factor (1) will be relatively unimportant in comparison with factors (2), (3), and (4). With a slow and more chronic type of infection, the longer time taken for the inception of the disease renders factors (2), (3), and (4) of relatively less importance. In studying the more chronic infective diseases, therefore, one might expect to trace the effect of nutrition more successfully, and this in fact has been the case.

For example, in epidemics of influenza the richer and poorer classes are alike affected. A disease like measles will sweep through a school of boys from prosperous families as well as through a school run on cheaper lines for poorer children.

With more chronic infections the experience is different. The chronic infective conjunctivitis which was rarely observed among well-situated children was formerly a common occurrence among children in residential Poor Law Schools, but now, under better conditions of diet and management, is rarely seen in these institutions.

The best example perhaps is tuberculosis, the incidence of which is known to be greatly increased by poverty and poor diet. A striking example was afforded by Austria during and immediately after the Great War. In Vienna, where the food deprivation, both quantitative and qualitative, was very severe, the death-rate from tuberculosis was doubled in the period from 1915–1918/19. In the province of Salzburg, on the other hand, where during the same period such important foods as milk, butter, meat, and vegetables were relatively abundant, the tuberculosis death-rate showed little change. It seems probable that infection with tuberculosis is common among all classes but, because of their greater resistance, is more successfully fought by well-nourished people.

TABLE I.—MORTALITY FROM TUBERCULOSIS IN AUSTRIA (ALL AGES).

	Vienna City		Salzburg Province	
Year	No. of deaths	Per 1,000	No. of deaths	Per 1,000
1913	5,937	3·0	527	2·4
1915	6,873	3·4	539	2·5
1917	8,548	4·2	549	2·5
1918	11,531	—	588	2·7
1919	11,490	—	670	—

The above conclusions are well summed up by Clausen at the end of his critical review of the subject (*Physiological Reviews*, 1934, **14**, 244): "Susceptibility to infection is not, as a rule, affected by diet; resistance to infection, on the other hand, may be greatly reduced by deficient diet."

In experimental nutrition work with animals, it is possible to arrange for all variables except one, the diet, to be eliminated. Vitamin A has been considered to possess special anti-infective properties. In severe deprivation of this factor, the mucous membrane undergoes such severe structural degeneration that the entrance of infective organisms is facilitated, and after long periods of such deficiency experimental animals invariably show an infective condition of some part of the respiratory system. The work of Dr. Harris suggests that vitamin-C deficiency may also be associated with many infective conditions.

The truth would seem to be that deficiency of any essential dietary factor may predispose to infection by lowering resistance. Mackay, studying anæmia in infants, found that the incidence of infective disease in those medicated with iron was about one-half as great as in untreated control infants.

An interesting demonstration of the influence of the nutritional state upon resistance to infection has occurred in the course of some experiments with pigs, carried out at Cambridge in the Department of Animal Pathology, in collaboration with Sir Charles Martin and Dr. T. A. Birch, who have kindly given permission for publication of the results. The experiments formed part of an investigation of the nutritive value of maize, the aim being to throw light upon the ætiology of human pellagra.

Young pigs, weanlings, and litter mates 30–40 lb. in weight, received one of the following three diets :—

	Group I	Group II	Group III
Maize meal	83	—	76
Wheat	—	20	—
Barley	—	63	—
Pea meal	11	11	10
Casein	4·4	5·3	2·2
Cod-liver oil	3	3	3
Salts	2·5	2·5	2·5
Yeast	—	—	8

After three weeks on the unsupplemented diet the pigs in Group I began to fail in growth, became anæmic, developed diarrhœa sometimes accompanied by vomiting, and rapid loss of weight; they died unless the diet was changed. On post-mortem examination these animals showed a condition of necrotic enteritis with an inflamed and ulcerated colon. All attempts to isolate pathogenic organisms of the Salmonella group from blood and stools were unsuccessful.

The pigs in Group II, receiving barley wheat in place of maize, also developed diarrhœa at the same time as those in Group I, but they recovered and growth was resumed. The pigs in Group III, receiving yeast in addition to the maize diet, showed no sign of illness and developed normally and remained in perfect health. The sick pigs in Group I showed a dramatic recovery when yeast was added to their diet.

In this instance one might suppose that the whole series of pigs had a latent infection which could only develop on an unfavourable diet, or that some harmless organism inhabiting the alimentary tract acquired powers of invading the tissues, in other words became virulent, under conditions of malnutrition of the host.

Dr. Leslie Harris referred to some experimental observations made by his colleagues and himself on the relation of vitamin C to infection. A year or two ago some measurements were being made on the excretion of vitamin C in the urine as influenced by the amount in the diet. Some of the experimental subjects happened to develop sharp colds or an attack of influenza and the amount of vitamin C excreted in the urine showed a sudden and marked drop.

This led to extended observations on the effect of different infectious diseases on the excretion of vitamin C. The " usage " of vitamin C seemed to be influenced by infection ; in other words, there was an apparent extra need for vitamin C in infections.

Dr. Harris reminded his hearers how, in control subjects *without infection*, the excretion of vitamin C varied according to the amount which had been present in the diet. The more the vitamin C in the past diet, the more was excreted daily in the urine and the greater the state of " saturation ". The degree of " saturation " was measured by the amount of vitamin C which overflowed into the urine after a series of large daily test doses had been given. An " unsaturated " subject retained more of the vitamin in his depleted tissues and in consequence less of it appeared in the urine. Intermediate degrees of saturation showed intermediate responses.

Among the " infective " conditions examined were the following: Acute rheumatism, surgical and pulmonary tuberculosis, osteomyelitis, rheumatoid arthritis. Some account had already been published of the results with acute rheumatism and surgical tuberculosis, but the remainder were still in the press.

It would be recalled that Rinehart in the United States had produced in guinea-pigs, by means of a diet deficient in vitamin C plus a superimposed infection, an experimental condition bearing some resemblance to acute rheumatism in man. Rinehart supposed that rheumatic fever in man might have its origin in a state of vitamin-C deficiency combined with infection. Their own observations (Abbasy, Gray Hill, and Harris) related more to the *effects* of rheumatic infection than to its origin. Both in juvenile rheumatism and in surgical tuberculosis in children their results showed that there was a greatly diminished excretion of vitamin C. The response to test doses confirmed the conclusions to be drawn, that in these conditions the body tissues were " unsaturated ", and much more vitamin C was used up than normally. (In all these surveys dietary conditions had been standardized by the provision of an adequate fixed amount of vitamin C in the diet for some weeks before the test ; and non-infected control subjects on the same diets were always examined simultaneously for comparison.) The same conclusion was reached by further tests when the effect of a constant increased intake of vitamin C in the diet was examined : more vitamin C was used up in the body by the infected children and less was excreted in the urine. (As would appear presently, they had also been able to establish the fact that in infection less vitamin C was present in the body-tissues of experimental animals. This was confirmed by actual analysis, post mortem, of the tissues of infected guinea-pigs.)

A special feature of juvenile rheumatism was that even when the child had become convalescent, and showed no symptoms, and clinically appeared normal, the excretion of vitamin C still remained low and the child could be shown to be relatively unsaturated. This appeared to indicate a condition of latent infection in the convalescent rheumatic. It was evident that the urine test might have diagnostic uses in this direction therefore. This conception of the presence of a latent infective state accorded with clinical experience that a child who had had acute rheumatism was liable to suffer a relapse.

The conclusion to be drawn from these tests seemed to be that, as extra vitamin C was used up in the body, so additional provision of it should be made in the diet. He understood from Dr. Gray Hill that the exhibition of vitamin C in massive doses, in the attempted curative treatment of juvenile rheumatism, had not been found effective. On the other hand, he believed that preventive treatment might offer greater hopes. He suggested that a trial should be made of the prophylactic use of

vitamin C after scarlet fever and streptococcal pharyngitis with the aim of lessening the incidence of subsequent rheumatic complications. In a number of public institutions, for example, it seemed to him that sufficient was known about the average rate of incidence of such complications, and there were sufficient numbers of cases available to make such an investigation probably worth while.

Surgical tuberculosis: osteomyelitis.—With Drs. Abbasy and Gray Hill he had examined children with surgical tuberculosis, and here too urinary excretion of vitamin C was diminished and the patients were below standard in their "reserves". In contrast with juvenile rheumatism, however, there was no evidence of a latent infection, for when convalescent patients were examined they were found to be normal in their vitamin C levels. Similar conditions were found for osteomyelitis.

Pulmonary tuberculosis.—Among the various diseases investigated the most extreme effect, with regard to the vitamin-C "deficit", was met with in pulmonary tuberculosis. The state of unsaturation generally found was very great, and even when the diet had been specially supplemented for some time past the excretion of vitamin C and the response to test doses still stayed very low. These tests and the observations on rheumatoid arthritis were carried out in conjunction with Dr. Philip Ellman.

Rheumatoid arthritis.—The deficit in vitamin C was also striking in rheumatoid arthritis, and gave some evidence of the importance of the much-discussed underlying infective process in this disease. It was instructive to find that as the blood sedimentation rate falls to normal, so the urinary excretion of vitamin C tends to be restored to normal.

Animal experiments.—Tests had been made with Dr. Passmore and Dr. Pagel to examine the state of the "reserves", or the amount of vitamin C in the tissues, of experimental animals as influenced by infection. In such varied infections as tuberculosis, pasteurellosis, and mouse typhoid, and after the injection of diphtheria toxin, the amount of vitamin C in the suprarenals had been found to be diminished. These results confirmed the conclusion drawn from the observations on human beings, made by the more indirect method of urine analysis, that a state of diminished "saturation" of the body tissues existed.

The role of vitamin C in infection.—It was generally agreed that a deficiency of vitamin C reduced the resistance of guinea-pigs to infection. In man also it had been stressed by Hess and others that one of the special characteristics of the "prescorbutic" or "subscorbutic" state was the increased liability to infection, and Helen Mackay had concluded in her review on diet and infection, that a case had been made out for vitamin C being involved in combating infection. The experiments described here indicated (1) that there was an increased destruction of vitamin C as the result of the infective process, and (2) that the tissue stores of vitamin C (as in the suprarenal) were diminished in experimental animals in infections. Other workers had stated that vitamin C might have an "anti-toxic" action, for example on diphtheria toxin, both *in vitro* and *in vivo*.

When one came to consider the mechanism by which vitamin C exerted its action one could do little more than speculate, but it might well prove to be of significance that vitamin C was found to be essential for the proper activity of formative cells and for the production of new tissue. In the absence of the vitamin, scar tissue failed to form, and (as he had recently noted) even the hair ceased to grow. Without adequate vitamin C there was degeneration of odontoblasts, ameloblasts, osteoblasts, etc. (Fish and Harris). It might reasonably be supposed, therefore that vitamin C was needed for the formation of blood-cells, and perhaps of antibodies. It should be remembered in this connexion that there was a remarkably high concentration of vitamin C in the leucocytes, and perhaps this might furnish one reason for its increased need in infections. Several workers had pointed out that administration of vitamin C was able to bring about a reticulocyte response.

Finally, Dr. Harris said that he thought the evidence was still inconclusive as to

whether vitamin C in massive doses would help an adequately nourished subject once an acute infection had got a hold. Although claims had been made recently for vitamin C therapy in pneumonia, herpes, and some other conditions, the prospect in prophylaxis seemed more hopeful.

Dr. J. T. Edwards: *A summary of work done on this relationship while working under the Foot-and-Mouth Disease Research Committee, at the Lister Institute and the Pirbright Experimental Station.* A full report of most of the findings has been published in the Fifth Progress Report of the Committee. A review of the statements made by previous workers that size, age, nutrition, and race have a marked influence on the lesions in experimental animals is given in that Report.

White rats.—Systematic investigation was begun early in 1932, following the observation of irregularities in the appearance of lesions in white rats inoculated into the skin of the feet with foot-and-mouth disease virus. Individual animals varied greatly in their susceptibility and it was noted particularly that it was difficult to infect rats which had been kept some time in the laboratory. These rats were fed on a diet of bread and milk, on which they seemed to remain in good health though they did not usually gain in weight. In a preliminary experiment, to see whether more severe lesions could be produced in better-fed rats, Wistar rats were divided into two groups, namely, (i) a well-fed group, fed on a theoretically complete paste diet (Diet N, Korenschevsky, 1922), and (ii) an under-fed group, fed on the bread and milk. Fourteen days later they were all inoculated with virus into the skin of the hind feet. All rats in the well-fed group showed fairly uniform lesions, well-marked local lesions appearing in forty-eight hours, and generalization in three days. The results in the under-fed rats were irregular, varying from no visible lesions, or slight local lesions only, to moderate local lesions and generalization; the lesions were slower in development than in the well-fed group. It appeared that the better-nourished the rats, the more severe the lesions.

A confirmatory experiment was then carried out, placing in the under-fed and well-fed groups, respectively, litter mates from rats specially bred for nutrition experiments. Freshly weaned rats from different litters were placed in the two groups, the sexes being kept separate. At the time of inoculation, seventy days after weaning, the males in the well-fed group had gained on an average 65 grm. more than those in the under-fed group; the females, however, showed a much smaller average difference, namely 23 grm. According to Hutchison and Mottram (1936), the basal metabolism of the adult human female is 83 per cent. that of the adult male, and therefore the bread-and-milk diet may have more nearly satisfied the metabolic needs of the females than those of the male rats. The results of inoculation of virus were very different in the two groups. The greatest difference in severity of lesions was between the under-fed and well-fed males. Those in the under-fed group showed hardly any trace of lesions, whereas, in the well-fed group, all showed severe local lesions and severe generalization. In most of the litters the difference between the corresponding groups of females was not so striking, though still quite well marked. Those from the same litter, when kept under the same conditions, showed lesions almost identical in extent and distribution. Those belonging to different litters reacted differently; this would indicate a familial or hereditary difference in susceptibility.

Susceptibility to infection therefore seems to be influenced by the following factors:—

(1) Diet: That susceptibility is influenced by the nature of the diet, irrespective of its growth-promoting qualities, was suggested by the results obtained in the females of some litters, e.g. in one litter the average weight difference was 22 grm. between the two groups, but the lesions in the two groups were almost the same; in another litter the average weight difference was less, namely 20 grm., but there was a pronounced difference in the lesions. Experimental animals, especially hedgehogs

placed on a good diet, may display great physical activity and fail to gain in weight in the same way as more lethargic individuals. These active animals show a high susceptibility to foot-and-mouth disease infection.

(2) Age.

(3) Heredity.

(4) Sex : The difference in the metabolic needs of the sexes may account largely for the differences in susceptibility between males and females. The observed greater rapacity of males and the greater fastidiousness of females may also influence nutrition, so that the males would be more likely to eat plentifully the paste diet fed to the well-fed groups.

Another experiment confirmed these results. Freshly weaned rats, before inoculation with virus, were specially fed for a short period, namely, eighteen days, upon the " complete " rat diet of basal and supplementary portions described by Korenschevsky, Dennison, and Kohn-Speyer (1932). Two control groups of litter mates were fed respectively on the basal portion only, and on the bread and milk only. A test upon very young rats after this short period of special feeding was considered to be a very severe one for differences in susceptibility. The results showed clearly that the rats fed on the complete diet were the most susceptible ; there was hardly any trace of lesions in those fed on the basal portion only. The factor, or factors, promoting increased susceptibility therefore appear to be present in the supplementary portion of the diet.

Rate of onset of increased susceptibility in response to good feeding.—When placed on a good diet (Diet N), after a period of under-feeding, white rats responded very quickly—the males in five days—by showing increased susceptibility to infection. The response was slower in females.

Rate of onset of decreased susceptibility in response to under-feeding.—After several weeks on a good diet, white rats changed to a poor diet (bread and milk) were found to retain their high susceptibility for a long time. After three months the differences observed between litter mates (*a*) changed to the poor diet and (*b*) kept on the good diet were very slight, but after five months there was a clear difference in susceptibility, more striking in the female litter mates. The males therefore seem to retain their high susceptibility, after change to the poor diet, longer than the females.

No difference was found between wild rats and tame (white) rats when both had been kept for some time on a good diet before being tested for susceptibility.

Whether any component of the diet was particularly concerned with causing increased susceptibility to foot-and-mouth disease infection had not been determined. Rats with very severe symptoms of vitamin " A " deficiency did not become completely insusceptible to infection. The addition of raw liver and carrot to the bread-and-milk diet produced a distinct and rapid increase in susceptibility, which acted in a few days. The decreased susceptibility of rats placed on an inadequate diet was found to be associated with the constant symptom of anæmia. It is possible that the addition of raw liver to the bread-and-milk diet prevented the occurrence of anæmia and it may have also been an important factor in producing increased susceptibility to foot-and-mouth disease. The impression gained from observations upon the smaller experimental animals has been, however, that susceptibility to infection is influenced, not so much by any specific ingredient in the diet, but by the degree to which nourishment promotes metabolism generally in the animal body.

Guinea-pigs.—It is a common observation that guinea-pigs, which have been inoculated in large numbers in foot-and-mouth disease research laboratories for diagnostic and other tests, present considerable differences in susceptibility, small guinea-pigs and those in a poor state of health being much less likely to develop lesions. Guinea-pigs are, however, much less satisfactory than white rats for determining the effects of variation in nutrition upon susceptibility to infection. They are naturally herbivorous and refuse food and starve when there is any considerable

departure from their ordinary diet; the effects therefore tend to become those of simple starvation. With sudden change in feeding, or bad feeding, however, they become resistant. For example, on one occasion at Pirbright, the supply of cabbage and carrots ran out, and the stocks of guinea-pigs were fed on green weeds, mostly dandelion leaves and roots; these caused diarrhœa and a high death-rate. The animals showing these symptoms were resistant to inoculation.

Hedgehogs.—Whereas guinea-pigs and rats can be infected with the foot-and-mouth disease virus by inoculation only, hedgehogs can be readily infected with this virus by contact with diseased hedgehogs also, and the disease is more severe and fatal than in any other species known to be susceptible. Stocks for research are captured wild, and so it is difficult to carry out any satisfactory experiments to find out the effects of nutrition upon susceptibility to infection. Bodily condition is, however, a most important factor in determining susceptibility, and this factor renders foot-and-mouth-disease research in these animals particularly difficult. Severity of the disease in inoculated animals has been found to correspond closely with bodily condition. The better the condition the more severe the disease.

When first brought into captivity, hedgehogs, particularly the larger, and presumably older, ones, often refuse food for long periods, which may extend to nearly two months, lose weight rapidly, and many die from starvation. While they are losing weight, they always show a high resistance to infection, and artificially set-up outbreaks die out rapidly when such animals are used for transmission of the disease. On arrival, each hedgehog is caged separately, because they are likely to attack each other and cause fatal sores when they are first brought in and are in falling condition. The following diet has been found from experience to be most suitable and maintains them in the good bodily condition necessary for ensuring uniformly high susceptibility to infection with the virus of foot-and-mouth disease.

ROUTINE HEDGEHOG DIET

Minced meat	11 lb.
Suet	2½ ,,
Liver	3 ,,
Root vegetables { potatoes	8 ,,
Root vegetables { carrots or swedes	8 ,,
Wholemeal biscuit	8 ,,
Skimmed milk powder	1½ ,,
Frozen egg	1 ,,
Salt mixture	2 oz.

Steam together until cooked (*a*) suet and minced meat, and (*b*) chopped potatoes and roots. Pass potatoes and roots through mincer. Mix milk powder with 2 quarts of water, add to wholemeal biscuit; steam together until soft. Dust salt mixture into mixed food. Add minced raw liver and frozen egg. Mix together all food ingredients thoroughly. Feed once daily *ad lib.* in the evening; fresh water daily *ad lib.*

When hedgehogs hibernate their metabolism is greatly lowered and they become completely resistant to infection. If, however, the virus has already begun to multiply in them when they enter this state, it remains dormant in their tissues for as long as two months and probably longer. When they become active again, the virus multiplies and sets up the clinical disease, and this has been found to be transmissible to healthy hedgehogs by contact. To obtain regular severe infection in hedgehogs experimentally it is therefore necessary to use only such as are feeding well and showing a normal, warm-blooded, temperature, that is, those in which metabolism is most active.

Concurrent bacterial infection.—A preceding or intercurrent bacterial infection renders all these small animals highly resistant to foot-and-mouth disease infection. This resistance is probably caused by the state of under-nourishment produced. In hedgehogs, on the other hand, infection with the virus of foot-and-mouth disease,

especially a severe infection contracted naturally by contact, causes, as in several other virus diseases of animals, serious secondary multiplication of bacterial invaders, e.g. *Salmonella enteritidis* (Gaertner) in the alimentary tract, and *Brucella bronchiseptica*, pasteurella and streptococci in the respiratory tract.

Age.—The fact that the small animals dealt with in this paper can be infected with the smallest dose of virus and show the most severe lesions when they are presumably fittest, namely, when they have nearly finished, but not completed, their stage of growth, suggests that the animal body becomes more and more susceptible to infection with the virus of foot-and-mouth disease when healthy metabolism or physical fitness is increased. Very young and old animals are relatively resistant.

Cattle and other large animals.—Experimental work to determine the relation between the state of nutrition and susceptibility to foot-and-mouth disease infection has not yet been carried out upon the larger, naturally susceptible, animals. It has often been noticed, however, that when cattle and other larger animals are in low condition they do not react well to inoculation with the virus. The records of field observations in temperate countries give little information upon the relationship, although it is often observed in outbreaks that high-class stock, fed and kept in the best conditions, suffer more severely than lean beasts when the disease is allowed to run its course. According to Hutyra and Marek (1920), foot-and-mouth disease spreads on the Continent of Europe with particular rapidity during the warmer period of the year, while in the winter it does not occur so extensively. They attribute this increased prevalence in warm weather to the greater traffic in cattle.

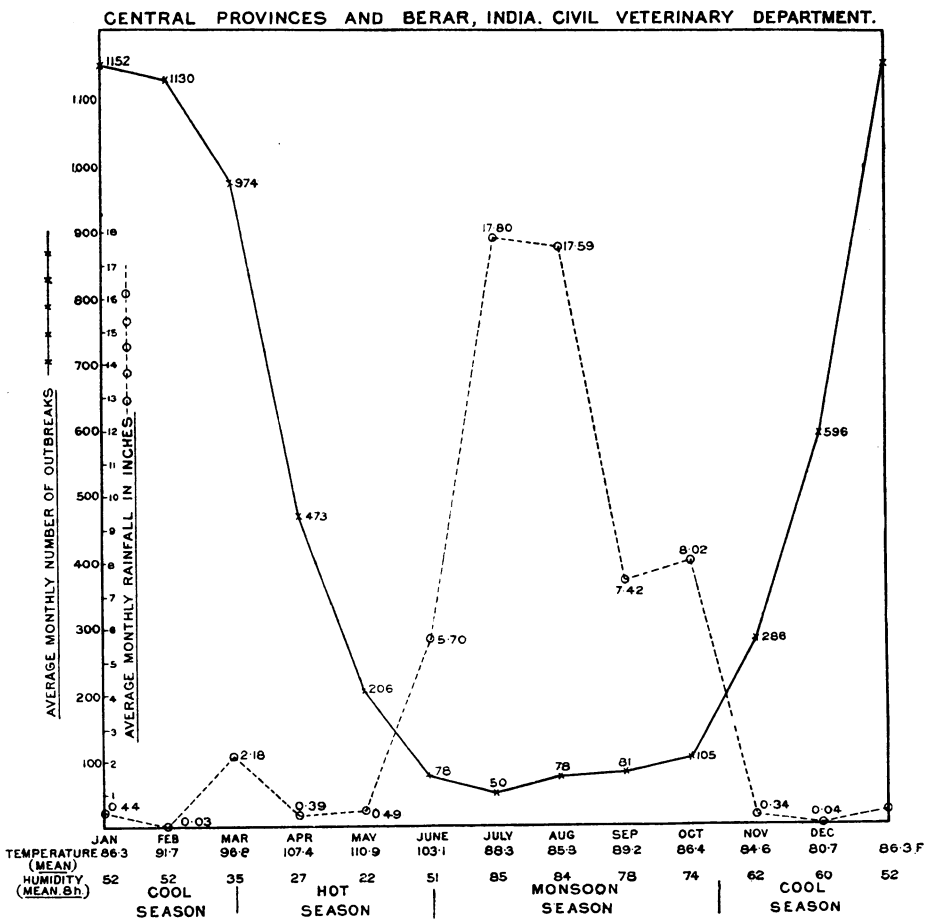
In hot climates, where there is little or no fodder storage and where there are great seasonal fluctuations in the natural food resources dependent upon the annual monsoon, with consequent cyclical fluctuations in the bodily condition of the cattle, one expects to find the most striking evidence of the relationship between foot-and-mouth disease susceptibility and the state of nutrition of the animals. Bevan (1932, 1933) described a very mild form of foot-and-mouth disease which occurred in Southern Rhodesia in 1931, which spread slowly and could only be transmitted with difficulty. This form occurred in the dry season, but became more active and severe after the rains. It seems probable that its mild character was in part determined by the scarcity of fodder and that the more severe phase of the epizootic reappeared when the pasture had improved.

Records showing the prevalence of foot-and mouth disease and its epizootic course in India at different seasons are shown in the chart (p. 48). This gives a composite curve showing the average monthly returns of outbreaks of foot-and-mouth disease in the Central Provinces and Berar, India, for the six years 1926–31 inclusive, in relation to a curve showing the average rainfall during the same period ; other meteorological data are given below (compiled from data collected by the late Director of the Civil Veterinary Department, the late Major R. F. Stirling). It was thought that the records of disease incidence in this province, which is just south of the Tropic of Capricorn, would be particularly valuable, because there is very little variation in climatic conditions from year to year, and every year there is a very striking alternation of " hot weather " and " cold weather " conditions. It will be seen that foot-and-mouth disease becomes very prevalent, as it does elsewhere generally in India, during the " cold weather " season of the year, when the cattle are in their best condition, owing to climatic and pastoral conditions. Afterwards, with the coming of the " hot weather " season, from March to the middle of June, through tropical heat and lack of rain, the fodder resources disappear to such a degree that a very large proportion of the cattle experience great shortage and many die from starvation. At the same time, foot-and-mouth disease disappears to such an extent that rare mild outbreaks only are reported.

The records of other countries which experience annually regular profound climatic variations need to be examined in order to ascertain whether these related

phenomena of seasonal periodicity in foot-and-mouth disease and the nutritional state of the cattle can be correlated.

Conclusions.—The conclusions to be drawn from the evidence presented are opposed to much current opinion regarding infectious diseases in general. The view commonly held, and apparently more widely applicable, is that low physical condition, such as that found in the under-nourished, the very young, the old and



Composite chart showing curves of the average monthly number of outbreaks of foot-and-mouth disease during the six years 1926-1931, inclusive, and of the average monthly rainfall during the same period. The monthly returns for the average mean temperature and relative humidity (8 h.) are also given below the chart.

sickly, makes them an easy prey to any current infection. The facts presented in this contribution can be paralleled, however, to some extent by experience with other diseases in veterinary medicine and pathology. It is generally accepted that strong, well-grown young cattle are more susceptible to blackleg and anthrax than lean cattle, and perhaps in some infections of sheep, such as braxy, there is a similar tendency.

The experiments upon small animals described in this paper confirm the observations of others that foot-and-mouth-disease infection is most severe in well-grown and well-nourished animals. In fact, they are most susceptible when they are in prime condition and at the prime of life.

REFERENCES

BEVAN, LL. E. (1932), *Tr. Roy. Soc. Trop. Med. and Hyg.*, **26**, 89; *ibid.* (1933), **27**, 105.
HUTCHISON, R., and MOTTRAM, V. H. (1936), "Food and the principles of dietetics", 8th ed. London, p. 71.
HUTYRA, F., and MAREK, J. (1920), "Special pathology of the domestic animals", Trans. Mohler and Eichorn, I, 360.
KORENCHEVSKY, V. (1922), Med. Res. Counc. Spec. Rep. Ser., No. 71, p. 7.
KORENCHEVSKY, V., DENNISON, M., and KOHN-SPEYER, A. (1933), *Biochem. J.*, **27**, 557.

Dr. H. Warren Crowe said that some experiments which he conducted a few years ago might be of interest, and perhaps throw light on this question of nutrition in relation to infection. In experiments in the production of arthritis in rabbits by injections of arthrotropic streptococci, the appearance of arthritis in all rabbits injected became quite regular as the technique became standardized. Professor H. A. Harris suggested that the effects might be more obvious and rapid if the rabbits had been previously fed on a non-vitamin dietary. For this experiment thirty-six rabbits were fed exclusively on a certain cereal prepared for consumption by cooking in super-heated steam, so that all vitamin content was destroyed. After a month or six weeks these rabbits had lost weight, the fur was roughened, and they appeared fairly sick. The rabbits fed in this way were then injected three at a time, three healthy rabbits in each case being used as controls. The latter developed arthritis in the expected manner, but the non-vitamin rabbits, broadly speaking, developed no arthritis at all. The reason for that should be clear when one realized that rheumatism and arthritis were diseases of tissue reaction. If the tissues did not react, there would be no arthritis. If, as the result of malnutrition, the tissues failed to react, then arthritis would not develop.

Possibly, then, the experiments quoted by Dr. Edwards in regard to foot-and-mouth disease had the same explanation. If the symptoms of this disease were due to tissue reaction, under-nourished animals would not be so likely to show lesions.

With regard to the epidemic of influenza of 1918 referred to by previous speakers: The same explanation would account for the fact that it was the young, strong, healthy soldiers who died so rapidly and in such large numbers, rather than the under-nourished civil population. He (Dr. Warren Crowe) had had to perform several post-mortem examinations, and the cause of death in every case had been mechanical; owing to the intense reaction the patients had been drowned in their own secretions.

Mr. A. L. Bacharach called attention to the fact that the total effect of several food constituents affecting resistance to infection was integral rather than a sum. The effect of one addition, or subtraction, might well be masked by the limiting effect of shortage of another substance. This principle, it seemed to him, was not always borne in mind in interpreting results of investigations falling into Professor Cowell's third category, in which it had been attempted to examine the effect of specific dietary conditions on infections in a group of human subjects. Ascorbic acid (vitamin C) appeared to be utilized at above the normal rate, as evidenced by a condition of sub-saturation, not only in the febrile conditions described by Dr. Harris, but also in benzene poisoning, as well as during lactation and pregnancy. The amount secreted in the milk was, apparently, not sufficient to account for the extra utilization. Any physiological or biochemical explanation of the role of ascorbic acid in fevers must take into account these other observations if, as he believed they would be, they were confirmed and generally accepted.

Dr. Curjel Wilson referred to the nutritional research aided by the Royal Society which was being carried out in India. Six thousand nutritional examinations (on the lines of those recently carried out in Britain under Sir John Orr and Dr. Magee), were made on children between the ages of 5 and 15 years, among wheat-eating races—Hindu, Muslim, and Sikh—in Northern India.

In addition, in view of Dr. Aykroyd's recent publications (*Indian J. M. Research*, January 1937) on the frequent occurrence of signs of deficiency disease in Southern India, the signs of deficiency disease were sought for among these northern children and a diet survey carried out on 120 families among these races living both under urban and under rural conditions. The results of the research were in course of publication.

With regard to malaria: Over 2,000 children were examined in areas recognized by the Malarial Survey of India to be highly infected. The signs of diet deficiency, phrynoderma, angular and buccal stomatitis, and eye conditions were practically absent. He understood that similar observations had been made by Dr. Nicholl on malaria in Ceylon.