A METHOD OF COMBATING INFECTION

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In spite of all the anti-infection agents available at the present time, patients still occasionally die from the results of infection, and these failures are customarily attributed to the development of drug resistance by the infecting organisms. It seems that this explanation is incomplete, and that the quality of nutrition of the victim might be at least as important a factor in the failure. Further, a person who has had an adequate quantity of food, even to the point of being obese, might have reduced resistance to infection through eating an unbalanced diet; this concept is not generally accepted at the present time, as the prevailing feeling is that only gross degrees of malnutrition, particularly undernutrition, reduce resistance to infection.

The method of combating infection to be described can hardly be claimed as new. Some of the details could possibly be claimed as original, but the broad principle has been known for many years. It is basically the method which was used by medical practitioners to combat infections before the advent of sulphonamides and antibiotics, but unfortunately it was insufficiently understood, and so it was considered inadequate.

Earlier physicians were well aware of the importance of the factor of nutrition, and to this end they examined much more attentively the state of the patients' teeth, tongue, mouth, skin, thyroid gland, etc., than we do today. But having made these careful observations, the said physicians had, unfortunately, insufficient knowledge of nutrition to make the necessary corrections; they were correct when they advised the patient to eat a well-balanced diet, but they did not have the knowledge to explain in sufficient detail how the well-balanced diet is achieved. Because of this, incapacitating infections continued to be commonplace, and so when sulphonamides, and later antibiotics, made their appearance they were hailed. Further, some of the 'nature cure' fraternity have had for many years a better, though still inadequate, understanding of the principle, than the orthodox medical practitioners. Gayelord Hauser[1] states that many years ago his chronic tubercular hip-joint disease began to heal after he commenced eating the 'living foods' which an old man at his breakfast table had advised him to eat.

The literature dealing with the effect of the state of nutrition on resistance to infection by bacteria, viruses, parasites, etc., is extensive and adequate reviews of the literature have been given by Howie,[2] Gallagher,[3] and Scrimshaw;[4] but these reviews deal mainly with the effects of *undernutrition*. However, some of the work done on the effects of *unbalanced* nutrition on resistance to infection will now be described.

Cl. welchii Type D-Enterotoxaemia of Sheep

Bullen[5] performed his classical work on *'Cl. welchii* type D-enterotoxaemia of sheep' at the Rowett Research Institute in Aberdeen. He states that all forms of enterotoxaemia have the following characteristics in common:

1. The bacteria are often normal inhabitants of the intestinal tract.
2. The disease is initiated by a variety of predisposing causes, some known, some unknown, which precipitate a rapid multiplication of *Cl. welchii* in the intestine.
3. Death is due to absorption of soluble toxins produced by the rapidly growing organisms. (Epsilon-toxin can be demonstrated in the intestine.)

The importance of diet in the pathogenesis of enterotoxaemia. Bullen[5] found that enterotoxaemia could not be produced in normal animals fed on hay and small amounts of concentrates even with very large oral doses of a culture of *Cl. welchii* type D. Experimentally it became clear that the bacteria were not growing fast enough to maintain their numbers even though there was normal flow of the intestinal contents.

As natural outbreaks of enterotoxaemia are often associated with a change in feeding habits, especially from poor to rich diets, Bullen decided to compare the effect of introducing cultures directly into the duodenum, the animals being fed either on hay or wheat. On hay diets, the organisms multiplied fairly well, but toxin production was poor and none of the sheep died. When the diet was suddenly changed to wheat, it was found that the rumen flora was temporarily disorganized and this resulted in large quantities of partially-digested food, especially starch granules, escaping into the ileum. Under these conditions, *Cl. welchii* type D introduced into the intestine, grew extremely rapidly in spite of the development of copious mucoid diarrhoea. High concentrations of epsilon-toxin appeared in the intestine which resulted in the death of 10 experimentally infected animals within 27 hours after the start of the experiment.

This demonstrated the importance of diet in the pathogenesis of enterotoxaemia of sheep caused by *Cl. welchii* type D, and suggested that sudden changes in feeding habits should be avoided, and this, in fact, is well recognized by good shepherds.

Primary E. coli Infections in Man

Cleave and Campbell[6] offer evidence that primary *E. coli* infections are manifestations of 'the saccharine disease', i.e. the disease resulting from eating large quantities of refined carbohydrates. These authors consider such infections to play the dominant role in appendicitis, cholecystitis (with or without gallstones), pyelonephritis and symptomless bacilluria, and diverticulitis. The infection stems from the presence of a quite abnormal number of these organisms in the intestine, due to an 'unnatural food surplus' occurring there, which provides their sustenance. They further argue that food surplus arises partly from the eating of food that is not truly desired, but mainly from the consumption of refined carbohydrates. 'The refining of the carbohydrates leads to deception of the instinct of appetite and overconsumption; and hence to the

presence in the intestine of the food surplus just described, with its inevitable effect on the bacterial population', and its delaying effect on the emptying time of the organ concerned, i.e. gallbladder, appendix and colon.

An example of the effect of artificial feeds is provided by infants. The stools of breast fed infants are acid in reaction, with the *Bacillus bifidus* predominant, and smell like 'bread in the oven', while those of infants fed on artificial feeds with much sucrose are alkaline in reaction, with the *E. coli* predominant, and have a putrefying smell.

The evidence offered by Cleave and Campbell[6] for believing that primary *E. coli* infections are manifestations of 'the saccharine disease' is as follows:

(*a*) *Racial considerations.* These infections, i.e. appendicitis, cholecystitis, and diverticulitis, are known to be rare in primitive peoples. But when the latter adopt the so-called 'civilized diet' these diseases are frequently seen, e.g. in the United States Negro.

(*b*) *Historical evidence.* There has been a great increase in incidence of primary *E. coli* infections, e.g. appendicitis, in Westernized countries over the last century or so, during which time a great rise in sugar consumption took place.

(*c*) *Association with other manifestations of 'the saccharine disease'.* It is well known that gallstones are commonly associated with diabetes, obesity and coronary artery disease.

(*d*) *The results of treatment.* Using unprocessed carbohydrate foods, the motions and flatus lose any offensiveness. Cleave and Campbell[6] find that the basic treatment of all primary *E. coli* infections, when not calling for urgent operation, lies in starving out the abnormal number of these organisms in the gut by attacking the food surplus sustaining them.

Effect of Non-deficient Diets (or Seemingly Non-deficient Diets) on Resistance of Mice to Staph. aureus Infection

Nutini and Berberich[7] describe the effect of a non-deficient (or apparently non-deficient) diet in lowering the resistance of mice to infection. In their experiment, the control animals were maintained on 'Rockland mouse diet', while the experimental animals were maintained for 6 - 8 weeks on a diet which previously had been found adequate for the growth requirements of mice (i.e. corn 83·15%, casein 16%, DL-methionine 0·85%).

In the case of the experimental animals an infecting dose of staphylococci of concentration 3·2 x 10^5 organisms in 0·5 ml. produced 100% mortality, whereas in the control animals, an infecting dose of 25·0 x 10^5 organisms per 0·5 ml. resulted in only 60% mortality.

From these experiments it appears that in commercial mouse diets there are substances referred to by these authors as 'tissue factors' which increase the natural resistance of these animals to staphylococcal infection ('tissue factors' because nearly all commercial diets contain a moderate proportion of materials derived from 'tissue material').

THE PRESENT STUDY

Material and Method

After considerable preliminary experimentation the following experiment was carried out, using laboratory mice. Male mice were used in order to eliminate the possible influence of pregnancy on resistance to infection. All the mice were approximately the same age and were reared under identical conditions. None of them had shown any obvious previous signs of infection. From birth to the age of 10 weeks they were reared at the animal house of the Faculty of Agriculture at the University of Natal in Pietermaritzburg. The diet used was the stock ration for rats, made up as shown in Table I.

TABLE I. STOCK RATION

	Pounds
Yellow maize	292½
Milk powder (whole milk)	40
Milk powder (skim milk)	40
Fish meal	40
Peanut oil meal	30
Fermivite	12½
Carcass meal	20
Lucerne meal	15
Bone meal	5
Salt	2½
Lime	2½
Total	500 lb.

At the age of about 10 weeks, 32 male mice, weighing about 24 G each, were transferred to an improvised animal room in order to prevent spread of infection to the stock colony. The 32 mice were randomly split into 2 groups, A and B, of 16 mice each, and housed in 2 separate cages.

Group A—16 mice—were fed on stock ration (Table I) *ad lib.*, together with Scotch shortbread biscuits and lemon-cream biscuits, *ad lib.* This diet was so arranged that it bore some resemblance to the usual diet of modern human beings, especially in relation to the consumption of processed foods.

Group B—16 mice—were fed on stock ration (Table I) *ad lib.*, together with mixed whole grain *ad lib.* and greens (usually lettuce leaves). Also parboiled unmilled rice was given daily during 2 periods of 12 and 5 days respectively. The mixed whole grain was made up as shown in Table II. This diet was

TABLE II. MIXED WHOLE-GRAIN RATION

Sunflower seeds	2 parts by weight
Yellow mealies (grain)	1 part by weight
Oats	1 part by weight
Mabela grain	1 part by weight

TABLE III. RECOMMENDED DIET FOR HUMANS OF UNREFINED (OR SLIGHTLY REFINED) FOODS

1. *Protein foods*:	Meat, fish (especially sea fish), liver, kidneys, poultry, etc.
2. *Carbohydrate foods*:	Brown or whole-grain bread or biscuits, whole-grain cereals only (e.g. whole-grain mealie meal or mabela porridge), potatoes preferably cooked in jackets, lightly milled rice correctly cooked.
3. *Fats*:	Butter, cheese, cream, vegetable oils, ice-cream made from evaporated milk and honey.
4. *Milk and eggs*:	Total of about 1 pint of milk per day (or more during pregnancy). About 1 egg per day.
5. *Vegetables*:	In season.
6. *Salads*:	Assorted, in season, daily.
7. *Fruits*:	Assorted, in season, daily (only fresh fruits—if forced to eat canned fruits, wash off the syrup).
8. *Liquids*:	Unadulterated fruit drinks (with or without added water), tea, milk, water, occasional coffee.
9. *Sweetening*:	Honey only.
10. *Eat only these foods*:	This means avoiding all sugar, and foods, jams and drinks containing added sugar, sweets, chocolates, toffees, biscuits (other than whole-grain), cakes, pastries, cornflakes and other refined breakfast cereals, highly polished rice, commercial ice-cream, alcohol.

arranged so as to bear some resemblance to that considered to be a good balanced diet for humans (Table III).

The mice were fed and watered daily according to this plan for a period of 7 weeks and 2 days, after which they were about 17 weeks old. A schedule of the weights of each group

TABLE IV. COMPARATIVE WEIGHT GAINS FOR EACH GROUP OF MICE

Date	*Weight of group A (stock ration + biscuits)*	*Weight of group B (stock ration + mixed whole-grain + greens)*
27/10/65	13⅛ oz.	13½ oz.
3/11/65	13⅝ oz.	13⅞ oz.
17/11/65	15⅛ oz.	15⅛ oz.
28/11/65	15⅞ oz.	16⅛ oz.
9/12/65	16⅞ oz.	16½ oz.
15/12/65	17 oz.	17⅛ oz.

of mice is given in Table IV. It will be seen that the over-all gain in weight of group A on stock ration and biscuits was slightly more than that of group B on stock ration plus mixed whole-grain plus greens diet.

Observation of the food selection by the mice showed that in group A the mice ate roughly as much of the stock ration as they did of the biscuits, while in group B the mice appeared to eat about 3 large lettuce leaves per day, and about 4 times as much mixed whole grain as stock ration. Of the mixed whole grain, the mabela and sunflower seed were consumed in roughly equal quantities, while about half as much oats were eaten, and one-tenth as much mealies. Thus the great majority of mealie grains were left untouched. The sunflower seed kernels were eaten. Only the germ of the mabela and mealies was eaten. The oats were consumed without the husk. The whole unmilled rice grain appeared to be eaten, and about ¼ oz. rice was eaten per day when it was given.

On 15 December 1965, when the mice were about 17 weeks old, they were all inoculated intraperitoneally with coagulase-positive *Staphylococcus aureus*, strain M.F. 31. A 24-hour broth culture of this organism was prepared; 12·5 ml. of the suspension was centrifuged at 2,950 r.p.m. for 15 minutes, and the sedimented bacteria were then suspended in 30 ml. sterile normal saline. Each mouse was subjected to an intraperitoneal inoculation of 0·5 ml. of this suspension, using a 1 ml. tuberculin syringe (with a 1-in. 24-gauge hypodermic needle) to ensure accuracy of dosage to 1/100 ml.

Results

Nineteen hours after the inoculation, 4 of the 16 mice in group A (stock ration and biscuits) were dead, while all 16 mice in group B (stock ration plus grain plus greens) were alive and healthy.

From previous experience it is assumed that none of the deaths were due to trauma. All the mice appeared to be alive and well when observed 6 hours after the inoculation. The mice were kept on the same rations for 30 days following the introduction of the infection and no further mice died or fell ill.

Statistical analysis of these results. The exact probability that out of 4 deaths all should be among animals on diet A (stock ration plus biscuits), when diet B (stock ration plus mixed whole grain plus greens) is expected to be beneficial (i.e. in a single-tail test), was calculated according to the method of Fisher,[8] and found to be 0·0506. This means that for all practical purposes the difference between the diets is significant at the 5% level.

Conclusion

As far as can be judged from this preliminary experiment, there is evidence that a diet of unprocessed foods (i.e. standard ration plus mixed whole grain plus greens) resulted in the mice having a higher resistance to staphylococcal infection than found in those mice on a diet of processed foods (i.e. standard ration plus biscuits). This conclusion is in accordance with clinical experience over the past year or more.

It is suggested that the diet of unprocessed foods constitutes a balanced diet and so results in optimum cell nutrition and increased ability of the cell to defend itself against infection.

DISCUSSION

With this diet it is unnecessary and unwise to take any vitamin or mineral supplements or fortified foods or drinks as these will have the deleterious effect of unbalancing the diet (except that, during pregnancy, it may be necessary to take iron tablets in small doses daily, depending upon the blood haemoglobin level). It is likely that nuts will not be tolerated except in small amounts, possibly because of the high content of B-group vitamins.

If a change in diet is to be made, it is wise to undertake this gradually, as sudden major changes in the diet may reduce resistance to infection. It usually takes weeks or even months for the individual to adjust to this diet. The foods, being unrefined, give the body the full complement of nutriments, vitamins, and minerals, so that any imbalance will show up relatively quickly, e.g. by onset of symptoms such as dyspepsia, headache, undue tiredness, photophobia, abdominal cramps.

Clinical experience suggests that this diet greatly increases the natural resistance at least to the common types of bacterial infection, and also affords significant protection against virus and fungal infection. This protective effect may be influenced adversely by obesity or underweight, smoking, inadequate exercise, insufficient sleep, and by helminthiasis. (Worms, by selective absorption of nutriments in the lumen of the gut, have the effect of unbalancing the diet, resulting in faulty nutrition of the host.)

SUMMARY

Some of the literature relating to the effect of qualitative differences of nutrition on resistance to infection is reviewed.

Experimental evidence is provided which suggests that a diet of unprocessed foods, especially mixed whole grain and greens, raises the resistance of mice to artificial infection with *Staph. aureus*, and this is in keeping with recent clinical experience.

We thank the following staff members for their valuable and enthusiastic assistance: Prof. G. V. Quicke, Department of Biochemistry; Mr. R. Stead, Professional Officer, and the Department of Agricultural Technical Services; Mr. P. Clark, Department of Dairy Science; Miss Marion Abbott, technician; Mrs. M. Stephenson, technician, Department of Biochemistry; and Miss A. Mays and her staff, Samuel Zondi and Simon Ncobeni, who reared the animals for the experiments. We also thank Mrs. N. Ward for facilities and Mrs. F. Davies, for secretarial assistance.

REFERENCES

1. Hauser, G. (1952): *Diet Does It*, p. 11. London: Faber & Faber.
2. Howie, J. W. *in* Cuthbertson, D. P., ed. (1963): *Progress In Nutrition and Allied Sciences*, p. 357. Edinburgh: Oliver & Boyd.
3. Gallagher, C. H. (1964): *Nutritional Factors and Enzymological Disturbances in Animals*, 1st ed., p. 117. London: Crosby Lockwood.
4. Scrimshaw, N. S. *in* Brock, J. F. (1961): *Recent Advances in Human Nutrition*, p. 375. London: J. & A. Churchill.
5. Bullen, J. J. *in* Cuthbertson, D. P., ed. (1963): *Progress in Nutrition and Allied Sciences*, p. 272. Edinburgh: Oliver & Boyd.
6. Cleave, T. L., and Campbell, G. D. (1966): *Diabetes, Coronary Thrombosis and the Saccharine Disease*, p. 121. Bristol: John Wright & Sons.
7. Nutini, L. G. and Berberich, N. J. (1965): Appl. Microbiol., **13**, 614.
8. Fisher, R. A. (1946): *Statistical Methods for Research Workers*, 10th ed., p. 96. Edinburgh: Oliver & Boyd.