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HUMAN NUTRITION AND THE SOPHISTICATION OF FOODS AND FEEDING HABITS*

SOME OBSERVATIONS, IMPLICATIONS, AND SPECULATIONS*

BY

B. S. PLATT, C.M.G., Ph.D., M.B., Ch.B.

Human Nutrition Research Unit, M.R.C. Laboratories, London, N.W.3

In the Constitution of the World Health Organization health has been defined as a state of complete physical, mental, and social well-being. Good nutrition undoubtedly contributes to the attainment of this state, so "food and health" would be a happier theme than "food and disease." Unfortunately, we are not so accustomed to measure healthiness as we are to recognize the signs of illness, so that for the most part the effects of food have been analysed in relation to evidences of ill-health and the occurrence of diseases.

Failure to feed properly—overfeeding, underfeeding, or taking a diet in which the proportion of nutrients is imbalanced—leads to primary malnutrition; nutritional disorders may also be secondary to infections and infestations (Platt, 1954a). Since these aspects of malnutrition are now familiar, I shall consider food and disease in a context which is perhaps not so well known and which may be of special interest to the general practitioner of medicine in the years to come.

SOPHISTICATION OF FOODS

Sir Edward Mellanby (1951), commenting on the increased incidence in the past fifty years of certain morbid conditions, said that he found it "difficult to avoid the conclusion that some at least of these increases in disease are due to errors in living recently introduced or greatly expanded in modern times," and that "it may be that one of these errors is the ingestion of food treated by unnatural chemical substances." In the past, chemical manipulation or, as I shall call it, sophistication of foods was, apart from gross adulteration amounting to fraud, largely concerned with preservation, but there is now a formidable array of chemical and other treatments for a variety of purposes; these provide "at least a subject worthy of inquiry" and one which "might well be considered whenever a disease commonly found in countries which use these methods has resisted all efforts of the investigator to find a satisfactory aetiological basis" (Mellanby, 1951).

Examples of the deliberate introduction of chemicals into food for human consumption and their accidental occurrence are included in the accompanying Table,

which also gives references to some sources from which further information may be obtained. It will be clear, even from this limited bibliography, that the subject is so extensive that it will be possible here to make only brief comments on some selected aspects. These are dealt with in the same order as followed by the sections set out in the Table.

Unintentional Chemical Additives

The report of a Working Party on Toxic Chemicals in Agriculture and Residues in Foods (Ministry of Agriculture and Fisheries, 1953) contains a list of more than a hundred preparations, and these include some of the most powerful known poisons. The seriousness of the hazards to agricultural workers and others handling these aids to food production is recognized; but the Working Party, like a number of other authorities, reports that it has "been unable to discover any specific instances of illness which have resulted" from eating food treated with or exposed to some toxic chemical. "The position," it concludes, "does not therefore appear to have been *established*" (my italics) "as one of immediate danger." On the other hand, it does not consider that "it is one which allows of complacency."

I would be the last to deny the need for measures towards increasing crop production and preventing losses in storage, particularly in those parts of the world where food supplies are short. We have, however, to recognize in this, and indeed in the whole field of food technology, the possibility of a conflict of interests in which, as the *British Medical Journal* (1954) remarks, "It is doubtful if the influence of any such reformer [posing as a champion of the individual safety and protector of the public welfare] would ever equal or exceed that of a powerful commercial interest anxious to introduce a new material or technique into food production." The need for a strong and well-informed body of opinion is indeed well illustrated by an observation of the Working Party, commenting on the employment of bacterial rodenticides.

"The Public Health Laboratory Service and the Medical Research Council consider that the risks are such that the use of bacterial rodenticides should be discouraged with a view to their discontinuance. The Ministry of Agriculture's Infestation Control Division advise that immediate policy

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should concentrate on ensuring proper care and attention in the preparation and use of these cultures and that any hasty action against these methods might lead to a serious dislocation in commercial rat destruction services." (Ministry of Agriculture and Fisheries, 1953.)

It is specially important to realize that much more is known about the hazards to health of these bacterial preparations than about many of the chemicals used in food whose presence may be difficult to detect and whose

effects on the human body may be subtle, insidious, and long-delayed. The problem is not so difficult when, as in the case of D.D.T., evidence has been obtained of the effects of acute poisoning in man. It is much more difficult to decide whether the occurrence of D.D.T. in the milk of cows and in a number of staple foodstuffs treated with this insecticide may have insidious and possibly long-delayed effects on the human body (House of Representatives, 1952).

Illustrations of Various Treatments Employed at Different Stages in Food Production and Technology, with some Possible Hazards

Stage	Purpose	Agent or Treatment	Examples	Possible Hazards
Production	Increase of yield	Insecticides, fungicides, herbicides, rodenticides ^{1 2}	D.D.T. Organic phosphorus compounds—e.g., parathion ¹ ; thiourea; arsenic compounds Salmonella rat bait ¹ "Aureomycin" in chick foods Oestrogen implanted in cockerels	? Residues in cows' milk and on foodstuffs ^{3 4 5} Toxic residues on fruit, skin-nerve poisoning ⁶ ? Bacterial food-poisoning ¹ —
		Antibiotics ^{7 8} Hormones ⁹		
Processing	Enhanced acceptability	Refinement	Low extraction wheat-flour Highly milled rice Sugar Salt Flour "improvers"	Reduced dietary B-vitamin/calorie ratio ¹⁰ — Manifested as fits in dogs fed on agenzized bread ¹¹ Carcinogenic action of butter yellow ¹² Liver tumours with dulcin and kidney lesions with P4000 ¹³ —
		Addition of chemicals	Colouring agents—e.g., dyestuffs Flavourings—e.g., artificial fruit essences Sweeteners—e.g., saccharin, dulcin, and P4000 Anti-oxidant ¹⁴ , anti-browning, and anti-staling agents ^{15 16} Emulsifiers, fat extenders, and hardening agents (hydrogenation of oils and fats)	Renal calculus with polyoxy-ethylenemonooleate ⁴ Vitamin B imbalance ^{10 19} — —
		Addition of synthetic nutrients	Some B vitamins to refined cereal products ^{17 18} Ascorbic acid to fruit preparations ²⁰ Ergosterol to margarine Amino-acids—e.g., lysine to cereals flours ²¹	— — — —
		Addition of mineral salts	Calcium carbonate and/or iron salts to wheat-flour ¹⁷ Iodides—iodates—to common salt ²² Fluorides to drinking-water ²³	Mineral imbalance ¹⁰ — — —
	Increased nutritive value (enrichment, fortification, ennoblement)	Addition of food concentrates	Fish-liver oil to margarine Skimmed-milk powder ²⁴ and fish meal to bread ²⁵ Yeast to various food preparations ^{26 27}	— — — —
		Fermentation	Cheese Bread Many traditional preparations ²⁸ —e.g., nuocmam ²⁹	— — —
		Chemicals: Artificial	Benzoic acid, sulphur dioxides, and nitrites ³⁰	SO ₂ destroys vitamin B ₁ , and sulphites cause haemorrhagic diathesis ³¹ —
		Natural	Salt Sugar Vinegar	Dietary imbalance —
	Preservation	Heating (including pasteurization)		Loss of some amino-acids by heating and in Maillard reaction ^{32 33 34 35} — —
		Physical means	Drying Freezing Canning and bottling	— — —
Storage	Packaging and transport	Detergents	Quaternary ammonium compounds ³⁶	Dermatitis ³⁷
		Newly developed wrappings, etc. Gas storage	Plasticizers ³⁸ For fruit, dried milk, and eggs	See ³⁸

¹ Ministry of Agriculture and Fisheries (1953). *Report of the Working Party on Precautionary Measures against Toxic Chemicals used in Agriculture*. H.M.S.O., London.

² World Health Organization (1953). *Bull. Wld Hlth Org.*, 8, 535.

³ Pottenger, F. M., and Krohn, B. (1952). *Hearings before the Select Committee to Investigate the Use of Chemicals in Food Products*, p. 954. U.S. Government Printing Office, Washington.

⁴ Lehman, A. J. (1950). *Ass. Food Drug Officials U.S. Quart. Bull.*, 14, 82.

⁵ Laug, E. P., Kunze, F., and Prickett, C. S. (1951). *Arch. indust. Hyg.*, 3, 245.

⁶ Barnes, J. M. (1953). *Bull. Wld Hlth Org.*, 8, 419.

⁷ Porter, J. W. G. (1953). *Vet. Rec.*, 65, 288.

⁸ *Nutr. Rev.*, 1954, 12, 166.

⁹ Bird, S. (1948). *Official Report 8th World Poultry Congress*, p. 131.

¹⁰ Elvehjem, C. A., and Krehl, W. H. (1947). *J. Amer. med. Ass.*, 135, 279.

¹¹ Mellanby, E. (1946). *British Medical Journal*, 2, 885.

¹² Greenstein, J. P. (1954). *Biochemistry of Cancer*, 2nd ed., p. 89. Academic Press Inc., N.Y.

¹³ Fitzhugh, O. G., and Nelson, A. A. (1950). *Fed. Proc.*, 9, 272.

¹⁴ Lehman, A. J., Fitzhugh, O. G., Nelson, A. A., and Woodward, G. (1951). *Food Res.*, 3, 197. Report of Food Standards Committee on Antioxidants: Revised Recommendations Relating to the Use of Antioxidants in Food (1954). H.M.S.O., London.

¹⁵ Joslyn, M. A., and Ponting, J. D. (1951). *Ibid.*, 3, 1.

¹⁶ Stadman, E. R. (1948). *Ibid.*, 1, 325.

¹⁷ Ministry of Food (1945). *Report of the Conference on the Post-War Loaf*. Cmd. 6701. H.M.S.O., London.

¹⁸ Horder, T. J., Dodds, E. C., and Moran, T. (1954). *Bread*, p. 159. Constable, London.

¹⁹ Richards, M. B. (1945). *British Medical Journal*, 1, 433.

²⁰ Bauernfeind, J. C. (1953). *Food Res.*, 4, 359.

²¹ *Nutr. Rev.*, 1954, 12, 70.

²² Murray, M. M. (1953). *Bull. Wld Hlth Org.*, 9, 211.

²³ Ministry of Health (1953). *The Fluoridation of Domestic Water Supplies in North America as a means of controlling Dental Caries*. H.M.S.O., London.

²⁴ Henry, K. M., Houston, J., Kon, S. K., Powell, J., Carter, R. H., and Halton, P. (1941). *J. Dairy Res.*, 12, 184.

²⁵ Latsky, J. M. (1954). *Report of the 2nd Inter-African Conference on Nutrition*, p. 277. H.M.S.O., London.

²⁶ Medical Research Council (1945). *War Memorandum, No. 16*. H.M.S.O., London.

²⁷ Platt, B. S. (1946). *Nutrition in the British West Indies*. Colonial No. 195. H.M.S.O., London.

²⁸ — (1954). *Report of the 2nd Inter-African Conference on Nutrition*, p. 271. H.M.S.O., London.

²⁹ Van Veen, A. G. (1953). *Food Res.*, 4, 209.

³⁰ Statutory Rules and Orders, 1925 No. 775 and 1940 No. 633.

³¹ Lepkovsky, S. (1953). *Food Res.*, 4, 105.

³² Morgan, A. F. (1931). *J. biol. Chem.*, 90, 771.

³³ — and Kern, G. E. (1934). *J. Nutr.*, 7, 367.

³⁴ Rice, E. E., and Beuk, J. F. (1953). *Food Res.*, 4, 233.

³⁵ Lea, C. H., and Hannan, R. S. (1952). In *Food Science*, edited by E. C. Bate-Smith and T. N. Morris. Cambridge Univ. Press.

³⁶ Dunn, C. G. (1949). *Food Res.*, 2, 117.

³⁷ Hodgson, G. (1953). *Practitioner*, 170, 166.

³⁸ House of Representatives (1950). *Hearings before the Select Committee to Investigate the Use of Chemicals in Food Products*, p. 71. U.S. Government Printing Office, Washington.

Intentional Additives

Many chemicals are added to foods in an attempt to satisfy the supposed desire of the consumer for uniformity of certain qualities of food products; for example, it is said that a large well-piled loaf of bread is demanded. Uniformity can be carried too far, and sometimes we have to deplore the success of the caterer in producing a sameness of taste whatever the dish. Those of us who are concerned with the application of the principles of nutrition do not want to conflict with the efforts of the food technologist and caterer; in fact, we believe that our interests are, or could be, in many respects identical, and often the methods of preparation of food by which the best flavours are secured are also those which retain or enhance the biological value of foodstuffs. The next section in the Table is concerned with increasing the nutritive values of foods by methods known as enrichment and fortification.

The fortification of foods is now a well-known procedure; however, the wisdom of removing a number of naturally occurring nutrients from wheat-flour and replacing them by a limited number of synthetic substances is open to question. It has been shown (Richards, 1945) that an animal given an imbalanced mixture of synthetic B vitamins may show no signs of deficiency, but if the animal bears young her offspring may show signs of deficiency of one of the factors which has not been restored to the mother's diet. When a dietary deficiency develops it would seem to be obvious that the diet should be improved—for example, by adding natural concentrates. In medicine, developments in bacteriology since Pasteur have been almost exclusively concerned with the study of micro-organisms pathogenic to man, but in food some micro-organisms may be not only non-pathogenic but actually beneficial to mankind. I would regret the passing of fermentative procedures, a natural way of improving the value of food which I have called "biological ennoblement" (Platt, 1946).

The conventional preservatives in current use are the successors of the spices of earlier days, which were used to disguise the flavours of food which had 'gone off'; some of these spices also had bacteriostatic or fungistatic properties. To-day the microbiologist is wisely directing his efforts towards eliminating the contamination of food products with pathogenic organisms so that chemical preservatives should not now be so necessary.

Chemical substances added to food may not only be toxic themselves but may also destroy, alter, or interfere with the absorption or utilization of nutrients, and the altered nutrients and their decomposition products are themselves sometimes harmful: for example, the effect on flour of agene is to convert the essential amino-acid methionine into a substance, methionine sulfoximine (Bentley *et al.*, 1950; Campbell *et al.*, 1951), which has a striking effect on the behaviour of some animals. This compound belongs to a fascinating group of substances known as anti-metabolites (Woolley, 1952).

Physical Treatment

As well as the problems associated with the addition of chemicals to food there are also problems which result from the physical treatment of foods by such methods as cooking, heating, drying, canning, and freezing (Lepovsky, 1953). Although, by definition, cooking is heating, the word does imply much more than this: its aim should be to retain or enhance flavours and to make the food appetizing and palatable. It is well known that flavours and food values are lost when the art of cooking is lost; in particular, the loss of ascorbic acid has been thoroughly examined (Stewart, 1946). In some respects the retention of ascorbic acid is a guide to good cooking, as flavours, colouring agents, etc., are dependent on the presence of chemical substances which, like this vitamin, may be leached out or destroyed in the course of many cooking methods.

It has been known for some years that fats and oils decompose on heating, fortunately at temperatures which

are high compared with those normally employed in cooking, and that carcinogens are produced (Peacock *et al.*, 1953). The phenomena of denaturation of proteins and the "browning" or Maillard reaction between proteins and carbohydrates have also been familiar to biochemists for many years; they have now been associated with the lowering of the biological value of protein; there is evidence that in these changes the essential amino-acids lysine and methionine may be destroyed. With the rapidly increasing interest in protein malnutrition (*British Medical Journal*, 1952) which is now known to be prevalent in so many parts of the world these effects are likely to receive increasing attention. Are there any reasons for believing that they are relevant to unsolved problems in medicine in this country?

Lysine we know to be required for growth and for maintaining a normal blood picture; methionine and the other sulphur-containing amino-acid, cystine, are important in the nutrition of skin and hair (Platt, 1953). A relative methionine deficiency has been shown (Mann *et al.*, 1953) to be in monkeys a factor in the production of hypercholesterolaemia and atherosclerosis. The aetiology of a number of disorders of the blood, skin, blood vessels, and eyes is still in question; a case might be made out for investigating these in relation to recent developments in food technology. I want to stress the point that there may not necessarily be merely deficiency of a nutrient following destruction during some process, but this insufficiency may be combined with the effects of the altered nutrients behaving, for example, like the anti-metabolites.

Technical Difficulties

Attempts to assess the effects on the consumer of all these procedures raise great technical difficulties. Barnes (1951) states that "any substance added to food must display no demonstrable toxicity for animals and must satisfy rigorous standards of purity," but this toxicologist concludes that "the problem of the adulteration of food by chemical substances will come to lie within the field of nutrition rather than in the more strictly limited one of toxicology." It is difficult to reconcile with this the views of a pharmacologist who, for reasons which are by no means clear, would exclude nutritional and palatability effects from those used in determining an effective dose level, though he concedes that "it seems advisable that the effect of food additives on the nutritional value of the diet should be known" (Frazer, 1953). Animal experiments may afford some help, but we must face the conclusion that "it is impossible to conceive of animal experiments which will provide complete information about the toxic effects of chemicals on human beings" (Barnes, 1951). The demonstration by experimental or other techniques of the dangers to human health of a procedure introduced into food technology may follow its introduction only after a long lag period. We may note here that agene was in use in the flour-milling industry for 30 years before its toxic effects, even in animals, were recognized and explained.

If there are hazards, then I consider that they may be relatively greater if exposure occurs during the period when biochemical changes are most intense—that is, during growth; and the clinical results may appear only with advancing age. As in industrial medicine, so in food technology, each new development may raise new medical problems. The onus of assessment of hazards to the health of the consumer must be accepted by the medical profession, which must lose no opportunity to obtain, scrutinize, and weigh the evidence before countenancing existing practices in food technology and sanctioning new developments in this field.

SOPHISTICATION OF FOODS AND FEEDING HABITS

Changes have occurred and others are still occurring which affect the foods and feeding habits of mankind; prominent in the dietary history of this country are the results of the introduction of potatoes and, earlier still, the

change in the meat supply consequent on the provision of root crops for livestock. Alternating periods of shortage and comparative plenty, markedly seasonal variations in the diet, and very localized peculiarities of taste and custom are still to be found in many primitive communities. In sophisticated communities feeding now is generally characterized by an evenness of supply throughout the year and a uniformity of diet amounting often to monotony; this has been the result of advances in agriculture, food technology, and modern methods of transport. The health of the community may be affected, for better or for worse, to the extent to which these developments affect the predominating foodstuffs and influence feeding habits. I shall now discuss only one such development—the artificial feeding of infants with some form of cows' milk.

Infant Feeding

Two centuries ago, in this country, breast-feeding by the mother or wet-nurse was almost universal and was probably continued for two or even three or more years, as it still is in many parts of the world to-day (Platt, 1954b). In Western countries nowadays, however, the child is often artificially fed from its earliest days or is weaned from the breast at 6 to 9 months of age. It must be admitted that until quite recently there has been no very convincing evidence for the superiority of human milk to cows' milk (Platt and Moncrieff, 1947), and the preference for the feeding of human infants at the breast instead of with cows' milk has been almost entirely a matter of faith. Such differences as a calcium content five to six times greater in cows' milk than in human milk have been overlooked. However, the curves showing the relation between the calcium content of the infant and the duration of feeding on cows' milk and human milk are reminiscent of those mentioned below relating nitrogen content of the body to age. After six to ten months' feeding on cows' milk the proportion of calcium in the infant's body is more than half as much again as that in the infant fed on human milk (Stearns, 1939).

The fact that so few infants show gross clinical, pathological, and biochemical changes in the early months of life is a comment on the point made below about the differences that are likely to occur between individuals; there are here, however, grounds for apprehension about the possible delayed effects of excessive intake of calcium in artificial feeding. It has been stated (Lancet, 1954) that hypercalcaemia "must be quite a common disorder, for 42 cases have been reported in this country alone in the last year and many more have been recognized." The frequency with which a history of feeding on cows' milk is reported suggests that the practice is an important if not a determining factor in the causation of the condition.

I want now to offer some observations which have led me to speculate about the possibility that modern infant-feeding practices may be concerned in the causation of certain diseases which we associate with modern conditions of life and living, and for the occurrence of which we have as yet no satisfactory explanation. I have found (Platt, 1954c, 1954d) that milk in the infant rat's stomach separates into curds and whey. The curds, which are laid down in successive layers, are slowly digested and normally do not leave the stomach for 15 hours or more. The whey, however, leaves rapidly, and the greater part of it passes through the pylorus in 30 to 40 minutes. The casein of the curds appears to be broken down into its constituent amino-acids, but there are some grounds for believing that the components of the whey not only behave differently in the stomach, but may not be completely broken down before absorption. We do not know if milk behaves in a similar way in the human baby's stomach; indeed, very little appears to be known about this subject. It is customary, in the study of gastric function, to start by ensuring that the stomach is empty. If the infant animal takes milk into a stomach which has been empty for some time, an undifferentiated clot forms which contains pockets of air and mucus, and only after several hours is the usual pattern of

layers restored. I suspect (Platt, 1954b) that there may be physiological as well as psychological grounds for a return to the recently reinstated system of feeding "on demand."

Since 1892 it has been known from Ehrlich's work on mice (Ehrlich, 1892) that antibodies can be transmitted in colostrum or milk from mother to offspring. Similar observations on the transference of immunity factors have been made on calves (Howe, 1921; Orcutt and Howe, 1922; Smith and Little, 1922), and these have been confirmed by electrophoretic methods for the pig (Foster *et al.*, 1951) as well as for the calf (Smith, 1948). The low serum cholinesterase of newborn puppies has been shown to be increased (McCance *et al.*, 1949) when they were fed on bitches' milk containing this enzyme, but not when they were fed on cows' milk or human milk. There is also an interesting observation made by Rutman (1950) on rats; he found that the infants of one strain, in which a poor ability to incorporate methionine into protein was demonstrated, acquired this ability when fed by mothers which had an efficient capacity for this process; presumably this was acquired by transference of some factor in the foster-mother's milk.

The importance of the protein components of colostrum and early milk may not be so great for the human infant as it appears to be for many species of animals. However, on the basis of the evidence available, I have wondered whether we should regard the mother during lactation not merely as a provider of food but also as a supplier of substances ready made for use by the infant until such time as he can synthesize them for himself. Is breast-feeding, therefore, a device by which provision is made for a transition between complete dependence on the mother before birth and complete independence after weaning from the breast?

Galactose and Myelination

A main component of whey is milk sugar—lactose—which is entirely contained in the whey. It is a disaccharide which is made up of glucose and galactose. As well as being present in milk as lactose, which is in part combined with neuraminic acid (Trucco and Caputto, 1954; Heyworth and Bacon, 1954), galactose is known to be a component of several substances found in the mammalian body. It is found in the cerebrosides of the central nervous system and in mucopolysaccharides in connective tissue (references to the occurrence of these are given below), in a galactan (Wolfrom *et al.*, 1947; Wolfrom *et al.*, 1952), and in the protein-bound carbohydrates of seromucoid, certain serum globulins (glycoproteins), and the carbohydrate of chorionic gonadotropin (Werner and Odin, 1949). We do not know if the human infant is able, in his early life, to synthesize galactose; indeed, we do not know if galactose can be synthesized in any human tissue at any age except in the mammary gland (Reiss and Barry, 1953). Galactose, therefore, may be a substance for which the human infant is dependent on his food—that is, in this case it would be an "essential" nutrient in the sense that some amino-acids and the accessory food factors are "essential" and the origin of any galactose laid down in later life is quite obscure.

The cerebrosides are the principal lipids of myelin, most of which, as is well known, is laid down after birth (Johnson *et al.*, 1949). Myelination continues until perhaps the fifth to sixth year of life (Kennard, 1952), and the progress of myelination of nerves may well be determined by the activity of the muscles with which they are connected. In this connexion I wish to draw attention to an observation (Stearns, 1939) the significance of which has not, so far as I know, been explained. This is that an infant fed on cows' milk stores nitrogen at a much greater rate than one on breast milk, and that at 6 months of age the percentage of nitrogen in the bodies of infants fed on cows' milk is about twice that in the bodies of those fed on human milk. Presumably most of this nitrogen is stored as muscle protein, and we may infer that in the cows'-milk-fed infant the rate of muscle development may be more rapid than in the breast-fed infant. If this also entails more rapid myelination of the appropriate nerves, and if the galactose for the

synthesis of myelin must come ready synthesized from the food, we have to take account of the fact that the cows'-milk-fed baby gets only two-thirds of the amount of lactose which he would receive if he were being fed the corresponding amount of human breast milk. Does this possible extra demand, coupled with the reduced supply of galactose, have any adverse effect on the subsequent health of the individual?

We know that when unusually large quantities of cerebroside are synthesized, as in Gaucher's disease, those from the spleen and from the brain may contain glucose (Woolf, 1954). There was a report last year (Montreuil *et al.*, 1953) that glucose occurs along with galactose in the cerebroside of normal brain. It has been reported that in mammals there is a positive correlation between the percentage of lactose in the milk of the species and the cerebroside content of the brain (Brody and Sadhu, 1947). On feeding dextrose to young pigeons, glucocerebrosides were found to constitute one-third of the total cerebroside, there being none in the brain of the normal birds (Sadhu, 1953a). Changes in the proportion of cerebroside to other lipids have been observed when weanling rats are fed whole milk as compared with skimmed milk (Sadhu, 1953b). It would seem from these observations that an investigation of the composition of the cerebroside of myelin of the human infant's nervous system should be made with a view to determining whether the substitution of cows' milk for human milk has any effect on it. I suspect that the effect on the composition of myelin may be particularly profound when an infant is artificially fed on a "humanized" cows' milk preparation which may supply as little as one-third of the lactose obtainable from human milk.

If glyocerebroside occurs as a substitute for part of the galactocerebroside, does it persist into adult life? We do not know the answer to this question. It might at first be thought, in view of the dynamic equilibrium of substances in the human body, that glucose would ultimately be replaced by galactose. This would depend on whether galactose could be synthesized in the brain or elsewhere in the body, and, if outside the central nervous system, could it pass through the haemocephalic barrier, which seems to be more difficult to cross in the mature than in the growing subject (King, 1939)? There is some evidence from isotope studies that metabolically the brain is somewhat isolated from the rest of the body. Thus there appears to be no significant turnover of C^{14} in rat-brain protein after the isotope has been incorporated in the organ during its period of growth (Schubert and Armstrong, 1949), and the general conclusion has been expressed that "there seems to be in the brain a degree of spatial permanency" (Folch-Pi, 1951). It may then be that, like proteins, the brain lipids remain throughout adult life within the brain metabolic pool.

Possible Consequences of Imperfect Myelination

If abnormal cerebroside occur and persist, do they have any adverse effect on the subsequent health of the individual? In my contribution to the symposium on Food and Disease (Platt, 1954e) I contented myself with asking whether, if the composition of myelin is affected as a result of the sophistication of a feeding habit, this might have some possible relation to the prevalence of disseminated sclerosis. I shall now, so far as I am able, discuss this possibility in more detail.

Lumsden (1951) suggests two alternative views of the causation of disseminated sclerosis, one of them being that it is "a specific form of reaction on the part of the nervous system peculiar to certain individuals and, within limits, independent of its immediate precipitating cause." May the presence of an abnormal cerebroside determine the occurrence of this specific form of reaction? If this were so, it would fit in with a restatement of the meaning of the haunting term "abiotrophy" introduced by Sir William Gowers and defined as a primary nervous system disorder in which local tissue resistance is overcome, with consequent disintegration of that tissue. In a recent study of a familial

myelinating disease it has, however, been stated that "there is more than suspicious evidence that the term primary is misleading, and that actually one deals with a primary disorder of metabolism with a secondary nervous system disorder" (Stadler *et al.*, 1954). There is, it seems, an important and relevant conclusion to be drawn from the study of the pathology of disseminated sclerosis—namely, that "some property of myelin determines the localization of the pathology" (Adams and Kubik, 1952).

If a poor supply of galactose in the infant's diet contributes to this specific form of reaction, then it might well be expected that disseminated sclerosis might be even more common than it is. There are, however, two possible considerations which might account for a comparatively low incidence: (a) the occurrence of the postulated "immediate precipitating factors," and (b) individual differences in rates of development of muscle and nervous system. Lumsden offers the hypothesis that, whatever the precipitating factors may be, the pathological changes may result from the action of a myelinolytic ferment; could it be that this is a cerebroside and that the glyocerebrosides may be more readily hydrolysed than the normal compound, or that there is no anti-enzyme for this reaction? These points are now being investigated.

So far as development of muscular and nervous systems is concerned there is now good evidence of quite remarkable differences in the ages at which various behaviour patterns are seen in infants (McGraw, 1943). How far these are associated with differences in the extent of myelination does not appear to be known, nor does there seem to have been any investigation of the possible relationships between the methods of feeding infants and their rates of maturation. There is evidence that there are differences for certain forms of behaviour up to 3 to 4 years of age (McGraw, 1943), that myelination may not be complete till 5 to 6 years of age (Kennard, 1952), and that breast-feeding is uncommon nowadays beyond 1 year.

Douglas (1950), in a survey in the United Kingdom, found, out of over 40,000 infants, only nine who were breast-fed up to 2 years of age. If the amount of galactose supplied to the infant is crucial then obviously the amount of breast milk taken, the duration of breast-feeding, and the amount of galactose obtainable from other dietary sources are all important. Materials containing galactose are known to come from plant sources (Black and Cornhill, 1954), but there is no evidence that they are assimilated; galactose-containing substances are also found in snails and slugs, and it is known that small "dew slugs" were at one time recommended for the nourishment of backward children (Hartley, 1954). In communities where breast-feeding is usual, and is continued for two to three years, disseminated sclerosis is rare and the cases reported are often unconfirmed by pathological evidence. Also, in other communities where feeding with carbohydrates, including cane sugar, is common in infancy—for example, in the West Indies—a syndrome with the features of a transverse myelitis is not uncommon and is suspected to be of nutritional origin. Inquiries are being made about the precise nature of this condition.

Dietary Damage in the Young

There may be some difficulty in accepting the hypothesis of a dietary defect in infancy resulting in a disease whose earliest clinical manifestations may be delayed till the second decade in life, or later. It is, however, being increasingly recognized that dietary damage in the young—or even prenatally (Giroud, 1954)—may have effects only late in life. Acute choline deficiency in the young rat may result in hypertension, but only in later life (Hartroft and Best, 1949) and after a period equivalent in man to about 20 years. Similarly, the development in a strain of mice of a type of arthritic degeneration occurring in older animals has been shown (Silberberg and Silberberg, 1952) to be strikingly affected by the nature of the diet throughout life. There is a good deal of evidence of the occurrence of a lag between a biochemical disturbance and the appearance of

pathological and clinical manifestations: one of the longest intervals is that recorded (Henry, 1946) in the development of epitheliomata of the scrotum and penis many years after exposure to the carcinogenic agent.

Most of the evidence that disorders in early life may produce tissue changes at an advanced age is derived from observations on animals, and, whilst it may be misleading to apply inferences from experiments in animals to the explanation of disease processes in man, it is obviously convenient to study such changes in animals with a short life-span. In the human species the period of growth is uniquely long in proportion to the life-span (Brody and Ragsdale, 1922-3), and in the study of human disease, therefore, we must be particularly concerned about disturbances during growth, neonatal as well as post-natal, and be on the look-out for sequelae in the adult. Thus the possible effects of artificial feeding of infants may not be seen for many years, and perhaps only after the tissues have been exposed to stresses or the effects of noxious agents. We may indeed be reaping in medical practice and in the post-mortem room to-day the results of methods of feeding infants and young children which were prevalent 20 to 30 years ago.

A conclusion about disseminated sclerosis on which there seems to be agreement is that "the major histopathologic changes seem to conform to those seen in degenerative diseases of the central nervous system" (Davison, 1950). The phylogenetically newer systems—the pyramidal tracts and the proprioceptive system—commonly suffer permanent damage (Martin and Elkington, 1946). These observations are of interest, since presumably the maturation of the neuromuscular mechanisms of the older systems is completed early in infancy; the swimming behaviour of the newborn infant, one of the oldest phylogenetic functions (McGraw, 1943), disappears in most infants in the first few weeks of life. Many disorders of nutrition and metabolism have clinical features in common with those of old age; and it has been stated that during "the involutionary period, the individual loses his capacity for homeostasis as if involution were a mirror image of adolescence with senescence as a return to the physiological instability of infancy" (Frank, 1946). It might be, though I am not sufficiently well informed to do more than make the suggestion, that in the clinical signs of disseminated sclerosis may be found the mirror image of development, but as reflections which are revealed early and distorted as a result of imperfect myelination.

"Collagen Diseases"

Galactose is, as mentioned above, a constituent of some components of extracellular material (ground substance) and connective tissue. There has in the past been an almost exclusive interest in the biochemistry, physiology, and pathology of the cell, and until recently little consideration has been given to the nature and functions of the extracellular structures and substances. The concept of an "extracellular space" is being replaced and some of the properties hitherto attributed to the membrane of the cell are being ascribed to the extracellular matrix. One suggestion made recently is that the blood-brain barrier may be due to the existence of ground substance (Woollam and Millen, 1954).

The possibility that galactose might be a constituent of the mucopolysaccharides of the cornea was suggested by Suzuki (1939) and confirmed recently by Woodin (1952) and Meyer *et al.* (1953); its presence in connective tissue (Conden and Bird, 1954) and in human subcutaneous tissue (Conden and Bird, 1954) has now been established. Several times has the presence of galactose in collagenous material been reported, and Glegg *et al.* (1953), who review these observations, have evidence that it is the reticular fibres of connective tissue which appear to have the sugars galactose, glucose, and mannose as integral constituents. During some work on wound healing Penney and Balfour (1949), in my unit, demonstrated the importance of mucopolysaccharides in skin for healing, and they associated this substance with

the formation of reticulin fibres, an observation which is supported by the recent demonstration of Glegg *et al.* (1953) on the composition of these fibres.

Interest is growing in a group of disorders of connective or mesenchymal tissue which have been called "collagen diseases," and Robb-Smith (1952) has claimed that there is quite a lot of evidence that the mechanisms of formation of abnormal glycoprotein are associated with the morphogenesis of these diseases. I want to do no more here than to suggest that the supply of galactose—or substitution of glucose for this sugar—in the feeding of the infant and young child may affect the nature, composition, and reaction to stress in later life of the extracellular matrix and connective tissue, and may thus be a factor in the occurrence of a number of diseases which might be identified with the sophistication of living. I would add to Mellanby's suggestion, quoted at the beginning of this paper, a plea for a study of the effects of changes in feeding habits consequent on the various methods of sophistication of foods, and conclude with the support of a pathologist (Robb-Smith, 1952) that "yet more profit may be gained by considering the biochemical morphogenesis of which something is known and more can be learnt than by restricting oneself to aetiology of which almost nothing is known."

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TREATMENT OF SCHISTOSOMIASIS WITH "NILODIN"

BY

B. A. KING, M.B., B.Ch.

(From the Witpoort Native Hospital, Brakpan, Transvaal)

A mine medical officer in the Union of South Africa has undeniable advantages in assessing the effects of treatment of schistosomiasis. In the first place, the mines of the Witwatersrand and Orange Free State are situated in "clean" areas, whereas the labour force is to a large extent drawn from heavily infested areas; therefore once the disease has been successfully treated the question of reinfection is not likely to arise to cloud the issue. In the second place, a wholly adequate follow-up of cases is possible, as natives recruited from the infested areas do not sign labour contracts for periods of less than nine months, and furthermore any mine employee can be recalled for re-examination at any time. Thirdly, a very large percentage of the tropical labour force, especially the Portuguese East African contingent, is infected with both *Schistosoma haematobium* and *S. mansoni*, so that an adequate number of cases are available for treatment and assessment.

At the Brakpan Mines in the Transvaal a trial was made of the use of "nilodin" brand of lucanthone hydrochloride (1- β -diethyl-aminoethylamino-4-methylthioxanthone hydrochloride; "miracil D") in the treatment of both urinary and rectal schistosomiasis. In the former the infecting organism was *S. haematobium*, and in the latter *S. mansoni*. In reporting the results certain aspects, such as the clinical diagnosis, presenting symptoms, tribal incidence, and haematology, have been omitted for the sake of brevity.

In both forms of infection the diagnosis was based on laboratory examination of specimens of urine and faeces respectively for the presence of viable ova. Ova are considered to be viable if free-swimming miracidia are present or there are active movements of miracidia within the ova. Occasionally an ovum remains motionless after exposure to water in high dilution, but the flame cells can be observed beating in the organism and the cilia may be moving. An ovum with none of the above signs but morphologically normal is referred to throughout this paper as "inert." After treatment ova are passed which can be referred to only as "macrated." They contain an amorphous mass; no movement or "pulse" of flame cells can be observed. Some ova are shrunken, while others appear to have swollen and burst. It is

common to observe "globules" within macrated ova which are not seen in normal ova.

The nilodin used throughout the trial was in the form of tablets each of which contained 200 mg. In these circumstances it was usually impossible to adhere strictly to a particular scheme of dosage based on body weight. No patient was started on less than the specification decided upon, and when part of a tablet was indicated a whole tablet was given. Thus when the dosage was 20 mg. per kg. of body weight a day, a patient weighing 56.5 kg. would actually receive six tablets=1,200 mg. daily instead of the 1,130 mg. indicated by his weight.

URINARY SCHISTOSOMIASIS

Results of treatment in a total of 46 cases of infection with *S. haematobium* are presented. These are divided into two series in which the dosage, the course of treatment, the method of follow-up, and the method of urine collection differed.

Series 1

This series originally consisted of 37 cases, but 13 of these were excluded from the investigation for various reasons: in 9 cases the follow-up was inadequate, 3 proved to be cases of rectal schistosomiasis, and in the other case no viable ova were demonstrable before treatment. The remaining 24 cases were followed up for at least three months. Cases were re-examined once a week for the first three months and thereafter at monthly intervals.

Laboratory Examination

In most of these cases viable ova or miracidia were found in the first (casual) specimen of urine passed. In no case were more than three specimens required to make a positive diagnosis. The technique of urine examination used for both diagnostic and follow-up purposes is as follows.

The conical glasses of urine are allowed to stand for a variable period after collection, but not less than 15 minutes. The supernatant urine is then decanted; the remainder is well stirred, poured into a centrifuge tube, and spun down at 3,000 r.p.m. for three minutes. The supernatant urine is now discarded, and the centrifuge tube filled with tap water and again spun down. The supernatant water is discarded and the sediment shaken up in the few drops remaining. With a clean pipette in every instance the remaining drops are placed on a slide and examined. The search for ova can be made very satisfactorily with the low-power objective of the microscope, but to establish viability of an ovum the high-power lens ($\times 800$) is required. It is of the greatest importance that the complete sediment—that is, four drops as a rule—be examined at every re-examination. Each centrifuge tube as used contains 14 ml. of urine.

The great advantage of this technique for follow-up purposes is that the viability of ova can be established almost at once, it being common to find miracidia swimming in the drops upon examination immediately after preparation of the slide. The World Health Organization Expert Committee on Bilharziasis (1953) recommends that centrifuging be limited to 1,000 r.p.m. to obviate the risk of ova disintegrating. I have never, however, found excessive centrifuging, either for too long a time or at too high speed, to cause disintegration of ova.

Dosage

The dosage of nilodin was worked out to give 20 mg. per kg. of body weight per day divided into three equal doses. However, as explained above, the strength of the tablets made it impossible to conform exactly to this amount; consequently, and taking into account reduction of dosage because of toxic symptoms, the average daily dose received by these patients was 22 mg. per kg. No case received less than a 12-day course of treatment, and in one case the treatment extended over 13 days.

Toxicity

Of the 37 cases in which treatment was started 21 (56.7%) had toxic symptoms. These were easily controlled and in no case was it necessary to discontinue treatment, although