On the Role of Antibiotics in Nutrition and Metabolism

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THE role of antibiotics in nutrition is centered —if not exclusively, then certainly with obvious preference—around the intestinal flora and specifically around the interaction between antibiotics, intestinal flora, and the host organism.

Man and animals live in symbiosis with microbes; in particular, the intestinal flora may act as a modifying environmental factor, and as such may influence growth, development, and the metabolic processes of the host organism. It was Escherich[1,2] and his followers[3] who first established the fact that the composition of the intestinal flora is primarily influenced by the food ingested and in the final analysis by the milieu in the intestinal lumen, acting as culture medium, with selective capacity for bacterial inhabitants of the intestinal tract.

On the nutrition and metabolism of the host organism the intestinal flora may exert its effect in different directions: (a) Beneficially such as through synthesis of essential nutrients (mainly of micronutrients) or through transformation of undigestible or poorly digestible food constituents, for example, cellulose and other polysaccharides, especially in ruminants; (b) in a more harmful direction, as by utilizing nutrients and thus withholding them from the host organism, or by the formation of toxic metabolites which adversely effect the host organism.

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INTESTINAL FLORA AS SOURCE OF VITAMINS

Intestinal flora as a possible source of vitamins, synthesized by bacteria, was first discussed by Cooper as early as in 1914.[4] The first most convincing proof for the synthesizing ability of the intestinal flora for a vitamin in man was furnished by the study of prothrombin levels as an index of vitamin K activity in the newborn infant.[5] Prothrombin levels in the serum, after an initial drop following delivery, show a sudden increase, after the first three to five days of life apparently synchronized with the establishment of a functioning bacterial flora in the intestine.

There exists a wide literature on the synthesis of vitamins by the intestinal flora in experimental animals. It is outside the scope of this presentation to review the extensive experimental material in detail. It should suffice to call attention to a few basic observations gained by experiments on animals. Fridericia[6] described spontaneous recovery in rats kept on a diet deficient in the vitamin B complex without the addition of vitamin-containing supplements. The exact nature of this phenomenon, called refection, is not yet determined. It is still an open question whether it is due to intestinal absorption of vitamins synthesized by the bacteria or to coprophagy. The best and unequivocal evidence, not only for the role of intestinal bacterial synthesis of vitamins, but also for their nutritional efficacy, was first furnished by experiments on rats and later on other animal species fed purified diets supplemented with various sulfonamides.[7–11] In addition to vitamin K, biotin, folic acid, and to some extent perhaps nicotinic acid, may be furnished by intestinal bacteria and their intestinal syn-

thesis be suppressed by sulfonamides. Experiments with sulfonamides on human volunteers[12–15] seemed to indicate that such synthesis of various vitamins or vitamin-like compounds may occur also in man through the metabolic activity of the intestinal flora. However, these observations were largely inconclusive with regard to the availability of these bacterial products for the host organism.

The first observation on the beneficial effect of antibacterial substances for the nutritional state of animals was first reported by Moore and co-workers in 1946. They found that succinylsulfathiazole and streptomycin increased the growth of chicks on a purified diet.

ANTIBIOTICS

Growth Promoting Effect

Greater and general interest in antibiotics as useful dietary supplements in practical animal husbandry was stimulated and spread widely only later, since 1950, through the studies of Jukes and his associates on the growth-promoting effect of antibiotics in animals.[16] At present antibiotics, such as penicillin, the tetracyclin group, and others, are widely used as supplements in commercial animal feeds. A very extensive literature on antibiotics as growth stimulants and dietary adjuvants has accumulated during the last eight or nine years.[16,17] Nevertheless, the mechanism by which the antibiotics produce their effects on nutrition is still an open problem. It is generally related to the action of antibiotics on the intestinal bacteria. "When antibiotics are administered, the total numbers of bacteria in samples of the intestinal contents characteristically decrease for a few days and then increase above the original levels. Perhaps antibiotics suppress certain bacterial forms which are inhibitory not only to the growth of the host, but also to the growth of some of the other intestinal bacteria."[16]

Seen from this angle it is not surprising that observations on the nutritional effect of antibiotics vary widely not only in different laboratories, but often in the same laboratory at various times. It has been claimed that the intestinal flora may show equal variations. Growth promotion by antibiotics would then occur only when bacteria are present in the gut which in themselves retard growth of the host and may be eliminated under the influence of antibiotics.[16,17] It was in accord with this assumption that the growth-promoting effect of antibiotics was found to disappear or be diminished when chicks were raised in clean quarters.[18] In addition, the promotion of growth in animals under the influence of particular antibiotics may be related to the relief of subclinical or clinically mild intestinal infections. Clostridium has been widely named[17] as the bacterial species around which the growth-promoting effect may be centered. A particular strain of Clostridium has recently been isolated in the National Institute for Research in Dairying in Reading (England) which was found to be present in chicks which responded with enhanced growth to the administration of antibiotics and was found to be absent in refractory animals.[19]

As expected, germ-free animals have shown no positive response to antibiotics. The absence of any growth-promotion in germ-free turkey poults, compared with the conventional controls fed the identical ration, was especially conclusively demonstrated by Forbes, Supplee and Combs in yet unpublished experiments carried out in the Germ-Free Research Laboratory of the Walter Reed Army Institute of Research and the University of Maryland.

Difficulties of proper controls have made studies on the growth-promoting effect of antibiotics in infants and children even less easy to assess than those carried out on animals. The most impressive positive results were reported by Scrimshaw and his associates[20,21] on Mayan children 7 to 12 years of age living in the Guatemalan highlands and subsisting on diets low in animal protein. Chlortetracycline exerted a pronounced effect on the increases in height of the children. This effect was observed in the spring months and was related to the suppression of seasonal infections in the children. The response to penicillin was variable and not as consistent as with tetracycline.

Use in Elimination of Toxic Factors

Antibiotics may exert their effect on the intestinal flora either through elimination of

toxic factors or by sparing beneficial nutrients. Suppression of infection is considered in this context as tantamount to the elimination of toxic factors. More conclusive evidence for the harmful role of toxic metabolites produced by intestinal bacteria was furnished by clinical observations on patients with severe liver disease, near decompensation. In such patients Sherlock and her associates found methionine given in very high doses orally (8–20 g/day) to be distinctly toxic. Chlortetracycline given together with methionine to the same patients prevented the development of toxic manifestations.[22] The development of coma in patients with hepatic decompensation following a high-protein diet has been generally related to the absorption of nitrogenous toxic metabolic products of bacterial action.[23] Hence, the recommendation of antibiotics in the treatment of hepatic coma.[24]

Sparing Effects

The sparing effect by antibiotics concerning a beneficial nutrient is well demonstrated in animal experiments in which antibiotics, such as chlortetracycline and penicillin were used to delay the development of experimental dietary necrosis of the liver.[25]

In one experiment (Table I) 40 rats received first only the basal experimental diet. A second group of 20 rats received chlortetracycline (5 mg daily) and a third group of 20 rats penicillin, in form of a basic, poorly soluble compound (Bicillin 5 mg daily) as supplements to the basal experimental diet. At the end of 26 experimental days ten rats in the control group died from acute massive necrosis. Of the remaining 30 rats in this group, 11 animals received Bicillin® (5 mg daily) from the 26th experimental day on. Eleven animals starting on the same day received chlortetracycline (5 mg daily). The remaining eight rats in this group were left on the unsupplemented basal diet.

Rats receiving supplements of chlortetracycline or Bicillin from the start were subdivided into two groups each. One subgroup originally receiving chlortetracycline was shifted after 44 days to Bicillin, the other subgroup was kept on chlortetracycline. The same scheme was applied to the group receiving Bicillin, with the difference that the change took place on the 42nd experimental day.

The results obtained seem to indicate (Table I) that the effect of antibiotics is not simply antibacterial, and further, that the development of bacterial resistance may not play, at least in this particular case, an important role if any in determining the duration of the prevention of massive hepatic necrosis.

These conclusions are best supported by the beneficial results of Bicillin and chlortetracycline which are significantly more impressive when administered during the whole duration of the experiment. This is in contrast with the group of animals (C, D, Table I) in which the supplemented diet was begun after the rats were kept for about four weeks on the unsupplemented basal experimental diet. These observations are in closest accord with the hy-

TABLE I

The Effect of Continuous, Delayed, or Alternating Administration of Antibiotics on the Development of Massive Dietary Hepatic Necrosis

Group	Supplement	Number of rats	Died with hepatic necrosis	Average survival time *days*	Survived 150 days without hepatic necrosis
A	None	10	10	32±0, 8	—
B	None	8	8	34±1, 3	—
C	Nothing for 26 days, then Bicillin	11	10	44±7, 6	1
D	Nothing for 26 days, then chlortetracycline	11	9	50±9, 0	2
E	Chlortetracycline	10	4	54±8, 5	6
F	Chlortetracycline for 44 days, then Bicillin	10	4	63±5, 0	6
G	Bicillin	10	2	42±0, 0	8
H	Bicillin for 42 days, then chlortetracycline	10	2	112±2, 0	8

Average starting weight of animals in all groups was 49 grams.

pothesis that necrosis develops after the experimental animals have become depleted of protective food constituents. Antibiotics appear to prolong this period of depletion. In groups C and D (Table I) the depletion probably has already progressed too far; consecutive administration of antibiotics may not have much effect in staving off the early development of massive hepatic necrosis. The experiments with alternating administration of chlortetracycline and Bicillin furnished results no better than those with continuous use of one given antibiotic (group E and F or G and H, respectively). These results[25] not only do not favor the toxic etiology as the only cause of experimental hepatic necrosis, but at the same time leave the mode of action of the antibiotics, and in particular their role in delaying the state of "depletion," unexplained.

An impressive illustration for the sparing of a nutrient through the action of antibiotics in man is furnished by the effect of antibiotics on the metabolism of choline. When a relatively large amount of choline is ingested by normal persons about 60 per cent appears in the urine as total trimethylamine, mostly within 24 hours.[26] Oral administration of chlortetracycline, oxytetracycline and penicillin or sulfaphthalidine, but not intravenous chlortetracycline, causes a considerable reduction in the urinary excretion of trimethylamine after simultaneous ingestion of a test dose of choline, as the result of a diminished intestinal degradation of choline to trimethylamine by intestinal bacteria. With continuous administration of antibiotics, such as penicillin, the antimicrobial effect disappears within one or two weeks indicating refractiveness of the bacteria.[27] Thus, in this particular case, antibiotics, may help temporarily at least to increase the available amount of ingested vitamin by protecting it from bacterial degradation in the intestine. Such sparing of a vitamin could easily be mistaken for its intestinal synthesis under the influence of the antimicrobial agent in question.

Sparing or intestinal synthesis of vitamins must be the explanation for the beneficial effect of some antibiotics in rats fed rations deficient in B vitamins, such as pyridoxine or riboflavin or pantothenic acid. This positive effect of antibiotics observed by Daft and his associates[28,29] is not seen in all the animals treated, but on the other hand, if present, it may last for many months.

Metabolic Effects

Antibiotics may also produce secondary metabolic effects, which are not of strictly nutritional nature. In our laboratory it has been found that rats fed a diet producing necrosis of the liver, or the same ration supplemented with cystine or vitamin E excreted large amounts of ether-soluble acids, especially methylmalonic acid in their urine. Rats on the same diet supplemented with chlortetracycline and penicillin excreted only small amounts of these acids. This effect persisted as long as the antibiotics were given and is the first long-term persistent *in vivo* effect noted of chlortetracycline and penicillin.[30] The urinary excretion of methylmalonic acid was increased in rats fed the necrogenic basal ration after supplementation with valine. This increase after administration of valine was not observed in rats which were kept on the necrogenic diet and received supplements of chlortetracycline. In contrast, in liver perfusion experiments the production of methylmalonic acid from valine (or from propionate) took place regardless whether chlortetracycline was added to the perfusion mixture or not. These experiments seem to indicate that chlortetracycline acts through the bacterial flora of the intestine, and not primarily through the metabolism of the liver.[31]

Use in Posthemorrhagic Shock

Recently it has been claimed, especially by Fine and his group,[32,33] that irreversible posthemorrhagic shock, as produced experimentally on animals, may be beneficially influenced by preventive medication with antibiotics. The further assumption has been made that antibiotics may eliminate intestinal bacteria which produce endotoxins of primary etiologic importance in the chain of events leading to irreversible shock. If this were the case, animals raised under germ-free conditions should be resistant to the same posthemorrhagic insult, which in conventional animals end in fatal shock. In unpublished experiments, carried

out independently in two laboratories, at Notre Dame University and at the Walter Reed Army Institute of Research, no distinct difference was observed in the behavior of conventional and germ-free rats when they were exposed to the conditions of irreversible posthemorrhagic shock. Germ-free rats have developed shock of apparently the same intensity and in about the same time, as the conventional controls. Whether the unavoidable possible admixture of traces of endotoxin and bacterial bodies in the sterilized semisynthetic ration fed to both groups may play a role in the production of shock under germ-free conditions, only further special studies will be able to decide. In this connection it would be important to know whether the beneficial effect of some antibiotics on the prevention of irreversible posthemorrhagic shock may be duplicated in germfree animals. If this were the case, a direct metabolic effect of the antibiotics in question would have to be postulated.

It appears to be obvious that antibiotics may interfere in both a beneficial or harmful manner with the nutritional state and with several metabolic reactions of the host organism. The observations illustrate clearly the interdependence of nutrition, metabolism, and infection.

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