Benefit and mischief from commensal bacteria¹

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A normal man probably provides residence for some 10^{14} living bacterial cells: some 10^{12} on the skin, 10^{10} in the mouth, and 10^{14} in the gut. Included within this vast population there are, in some individuals some of the time, bacteria belonging to varieties that can be unequivocally classed as 'pathogens'; indeed virtually all pathogenic bacteria are recognized from time to time in healthy carriers. For some of the pathogens, the relatively low carrier frequencies presumably depend on the fact that when present the pathogens tend to provoke an immunological reaction, which helps to eliminate them; for other pathogens, sources for carriage are now rare in Britain. Symptomless carriage of the classical pathogens that induce a protective immunological response is beneficial to the host, but the benefit is purchased at the price of risking disease.

With the decline in frequency of the 'classical' bacterial diseases, there has been increasing study of the effects of the bacteria that live in or on most normal people, and it is with these that this review deals. I shall take examples from the bacterial inhabitants of the nose and skin, the mouth, and the intestinal tract, and discuss the evidence that among them are some that yield a benefit, some that cause a mischief, and that in many cases the beneficial bacteria can themselves also prove mischievous.

Nose and Skin

A total bacterial count for the skin surface of 10^{12} , which is equivalent to about 10^4 per sq cm, appears considerable but it does not actually imply the close packing of bacteria that is found in other carrier sites: even 10^6 per sq cm if evenly distributed would provide only one bacterium per 100 sq microns. In fact, the bacteria are not distributed evenly but almost certainly exist in the form of microcolonies. Holt (1971) suggested that comparison of the bacterial counts obtained by an

impression method with that obtained by scrubbing offered an indication of the microcolony size, which he and Somerville and Noble (1973) found often to be of the order of several thousand colony-forming units. Lacey's (1971) demonstration of transfer of neomycin resistance between staphylococci on healthy skin is another indication that bacteria must commonly lie close together.

STAPHYLOCOCCUS AUREUS

Staphylococcus aureus, although manifestly an active pathogen, commonly behaves as a true member of our commensal bacterial flora. At any moment something between 25 and 70% of normal adults harbour *S. aureus* in the nose or on the skin and there must be very few individuals on whom pathogenic staphylococci do not at some time multiply. However, this frequent and often prolonged symptomless carriage in the nose or on the skin does not appear to generate protective immunity. This may be because the cocci are resident on the surface of the skin or skin-like epithelium of the anterior nares and antigens may not be absorbed from these sites, although there is, in fact, little evidence for a protective immunity generated even by repeated tissue infections. In fact, in the balance sheet for *S. aureus* the only benefit from healthy carriage that I can detect, and that rather tenuous, is the interference effect by which a resident domestic strain of *S. aureus* carried in the nose of patients admitted to hospital protects somewhat against colonization by hospital strains (Noble, Williams, Jevons, and Shooter, 1964). This interference phenomenon has been put to use for controlling epidemics of staphylococcal infection among newborn infants (Shinefield, Wilsey, Ribble, Boris, Eichenwald, and Dittmar, 1966) and, with less consistent success, for controlling recurrent sepsis in adults (eg, Boris, Shinefield, Romano, McCarthy, and Florman, 1968). The mechanism of the interference is not understood and although some strains of *S. aureus* inhibit the growth, *in vitro*, of *Corynebacterium diphtheriae* and other corynebacteria (Parker and Simmons, 1959) it is not known whether this phenomenon operates *in vivo*, nor whether this or any similar activity may be

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concerned in the 'interference' between strains of staphylococci on carrier sites.

The mischief attributable to *Staphylococcus aureus* is well known: wound infection, septicaemia, and minor skin sepsis, and these occur when the staphylococci are transferred by accidental or surgical trauma from carrier sites on the patient (or from elsewhere) to a site in which they do not normally occur and in circumstances that allow them to overcome normal tissue defences. The 'spontaneous' staphylococcal infections that occur in patients with defects of the polymorph leucocyte system suggest that the localization of the staphylococci to their normal carrier sites is in part achieved by the activities of the phagocytes.

COAGULASE-NEGATIVE STAPHYLOCOCCI AND CORYNEBACTERIA

Coagulase-negative staphylococci and micrococci are certainly part of the resident bacterial flora of the skin of all normal individuals, and are very commonly harboured in the anterior nares also. Corynebacteria, including both aerobic and anaerobic varieties (sometimes referred to as propionibacteria), constitute another major element of the skin flora.

These bacteria may well be beneficial, for there is good evidence that they are responsible for the liberation of free fatty acids from the glycerides present in the sebum (Reisner and Puhvel, 1969), and these acids certainly have an antibacterial action against *Staphylococcus aureus* and some streptococci (Ricketts, Squire, and Topley, 1951). Removal of fats and fatty acids from the skin by acetone decreases the antibacterial activity of the skin (Lacey, 1968). The use of antibacterial drugs and disinfectants that reduce the numbers of staphylococci and diphtheroids on the skin or in the nose is commonly followed by proliferation of a Gram-negative flora (Shehadeh and Kligman, 1963) and it is tempting to attribute this change to a decrease in the amount of bactericidal fatty acids produced by the Gram-positive bacteria but direct evidence is lacking.

Coagulase-negative staphylococci and micrococci have been shown to produce, *in vitro*, substances, probably polypeptides, that inhibit the growth of corynebacteria, some micrococci and some *S. aureus* (Selwyn and Ellis, 1972). As with analogous observations for *S. aureus*, we do not know whether these agents play a part in maintaining the balance of the bacteria on the skin, or whether they are simply laboratory artefacts.

Marples and Williamson (1969) showed that, in subjects with a predominance of corynebacteria on the skin of the axilla, tetracycline treatment

resulted in a reduction in the proportion of corynebacteria and their replacement by resistant micrococci; after administration of the drug had ceased the corynebacteria re-established themselves at the expense of the micrococci. These results suggest that there is some interaction between the two bacterial forms on the skin, though whether it is an 'antibiotic' effect or competition for site or nutriment is not known.

This is probably only one of the relevant interactions of skin microbes and there must be numerous factors apart from antibiotics that affect their distribution and numbers; it would surely be rewarding to study the effect of hormonal, dietary, and other environmental influences on the balance and activity of skin bacteria.

Acne appears to be a mischief attributable to the action of the skin commensals; the lesion probably results from the blockage of the mouth of a sebaceous gland and the accumulation of sebum, which is attacked by the bacteria to yield fatty acids that produce a local inflammatory reaction (Freinkel, 1969). Both *Corynebacterium acnes* and *Staphylococcus epidermidis* are lipolytic but there is controversy as to whether *C. acnes* alone, or both together, are responsible for the acne.

The commensal bacteria of the skin, therefore, appear to be beneficial when they hydrolyse the sebum on the surface but mischievous when they perform the same reaction in a blocked sebaceous gland.

The coagulase-negative staphylococci have changed status recently from that of the textbook 'non-pathogen' to that of 'opportunistic pathogen'; outstanding in leading to this change has been the repeated observation of *S. epidermidis* as the cause of intractable endocarditis complicating operations for the insertion of prostheses into the heart or brain stem. We do not know what it is about these situations that enables *S. epidermidis* to flourish (and kill the patient) when they are so rarely able to produce progressive disease elsewhere, nor why staphylococci should be relatively so common in endocarditis following surgery in contrast to the dominance of streptococci in endocarditis complicating rheumatic or congenital lesions. Perhaps staphylococci rarely enter the blood stream spontaneously, in the way that streptococci are known to do, and have to rely on entry during the surgical operation. Since the interval between operation and the appearance of infection may be many months, this implies a remarkable latent period. However, similar extended latent periods are seen with infections of the Spitz-Holter valves inserted for the relief of hydrocephalus (Holt, 1969) and perhaps in infections with coagulase-negative staphylococci

following operations for replacement of the head of the femur so the ability to remain latent in the tissues for long periods may be a characteristic of the bacterial species.

Mouth and Throat

Bacteria are present in the normal mouth and throat in enormous numbers and great variety: saliva commonly yields 10^8 or 10^9 per ml, and both the debris in the gingival margin and dental plaque, which is adherent to the teeth and consists very largely of close-packed microorganisms, have total cell counts of about 10^{11} per g wet weight (Socransky, Gibbons, Dale, Bortink, Rosenthal, and MacDonald, 1963; Poole and Gilmour, 1971).

The idea that the normal bacterial flora of the mouth has a protective effect against exogenous bacteria has a venerable history, though many of the earlier assertions are based on observations of doubtful relevance. The idea has, however, gained great support from observations that patients who are treated with antibiotics that reduce the normal streptococcal flora not uncommonly show overgrowth of *Candida* or Gram-negative bacilli (eg, Sprunt and Redman, 1968). *In vitro*, many of the mouth streptococci can inhibit the growth of the invading species, and peroxide, thiocyanate, and lysozyme have all been suggested as being involved in the inhibitory system (Hoffmann, 1966; Hamon and Klebanoff, 1973); there is, however, no evidence for the activity of these agents in the mouth.

During the last few years some progress has been made in distinguishing species of streptococci within the mouth flora (Carlsson, 1967; Colman and Williams, 1972) and this reveals striking differences in pathogenic activity. Five relevant taxa can be recognized, which we have suggested should be called *salivarius*, *sanguis*, *milleri*, *mutans*, and *mitior*; we use the epithet '*mitior*' in place of '*mitis*' or '*viridans*' to indicate a species with a more restricted definition.

Streptococcus salivarius seems to be the least harmful of the five species and is virtually never implicated in systemic disease. It can cause dental caries in the hamster but, in man, *S. salivarius* appears preferentially to colonize epithelial surfaces such as the tongue rather than the dental plaque (Krasse, 1954) and there is no good evidence that it plays any important role in human dental caries.

Streptococcus sanguis is the name now given to the species described by White and Niven (1946) as the streptococcus characteristically isolated from endocarditis complicating rheumatic heart disease. *S. sanguis* seems to be particularly apt to

attach to teeth and to epithelial surfaces; it is not found in the mouth before tooth eruption (Carlsson, Grahnen, Jonsson, and Wikner, 1970; Gibbons and van Houte, 1971) and it is said to disappear from the mouth of edentulous adults when dentures are not worn (Carlsson, Söderholm, and Almfeldt, 1969). This distribution in the mouth may give special opportunities for entry to the bloodstream and so for settling on diseased heart valves, but the excess of *S. sanguis* in endocarditis may be due to some inherent pathogenic characteristic. Elliott (personal communication, 1973), who noted that *S. sanguis* seems to be much less common than other mouth streptococci (probably mostly *S. mitior*) in the bacteraemia accompanying the extraction of teeth, has suggested that the dextran layer that can be formed on the cell surface of these bacteria may provide a mechanism for attachment to the damaged endocardium. *S. mutans* and *S. bovis*, both of which also form dextrans, are also found in subacute bacterial endocarditis (Parker, personal communication 1973). However *S. mitior* (*mitis*), which does not form dextran, was also recognized from a number of cases of 'significant bacteraemia' by the Streptococcus Reference Laboratory (personal communication, 1973).

Streptococcus mutans is a species that was described as a putative cause of human dental caries by Clarke (1924) and recently, some 40 years after its first discovery, returned to the limelight when it was demonstrated to be cariogenic in animals (Fitzgerald and Keyes, 1960; Keyes, 1968). Strains of this species are particularly apt to adhere to teeth and, with *S. sanguis*, constitute most of the streptococcal component of dental plaque (Carlsson, 1967).

Streptococcus mutans can clearly be shown to be cariogenic in animals and, in man, these streptococci are found in greater numbers in carious lesions than on healthy tooth surfaces (Littleton, Kakehashi, and Fitzgerald, 1970; Shklair, Keene, and Simonion, 1972) so there is a presumption that they play a part in human caries. *S. mutans* produces a dextran from sucrose and this dextran constitutes a part of the matrix of the dental plaque (Gibbons, 1968), within which, it is suggested, the streptococci and doubtless other bacteria can liberate acid from sugars, and thus attack the dental enamel; bacterial degradation of salivary glycoproteins has also been implicated (Pinter, Hazashi, and Bohn, 1969).

A diet containing a large amount of sucrose leads to an increase in the weight of dental plaque and in the proportion in it of *S. mutans*, with a decrease in the relative numbers of *S. sanguis*, while a diet low in sucrose has the opposite effect (de Stoppelaar, van Houte, and Backer, 1970). A

high-sucrose diet is, of course, known to predispose to caries. There is also a great increase in the numbers of *S. mutans* (and some actinomyces also implicated in caries) in dental plaque in patients treated by irradiation for cancer involving the salivary glands (Llory, Dammion, Gioanni, and Frank, 1972), and this treatment is commonly complicated by rampant caries (Frank, Hendley, and Philippe, 1965).

With *Streptococcus mutans* we appear to have, therefore, a commensal microbe that can produce disease at its normal carrier site, especially perhaps when the microbial balance of this site is upset, in this case by the provision in the diet of an excess of the sucrose substrate or by some metabolic defect resulting from irradiation.

In complex ecological systems, such as the bovine rumen, metabolites produced by one species of bacteria can serve as energy sources for other bacteria. Virtually nothing is known about the sequential use of substrates by bacteria in the mouth but recently Mikx, van der Hoeven, König, Plasschaent, and Guggenheim (1972) showed that germ-free rats contaminated with veillonella and a streptococcus developed fewer carious lesions than rats contaminated with the streptococcus alone. A possible explanation of this finding is that the lactate produced by the streptococci was metabolized by the veillonellae to propionic and acetic acids, which are weaker acids than lactic acid and so less liable to produce caries.

Streptococcus milleri has not been shown to have any beneficial effects in the mouth, but has not been studied specifically from this point of view; it produces suppurative lesions around the mouth and elsewhere.

Gastrointestinal Tract

The gastrointestinal tract of normal adults must contain upwards of 10^{14} living bacteria, the vast majority of them in the colon. In healthy people the stomach is an effective self-sterilizing organ and, though bacteria may be numerous in its contents immediately after a meal, they are reduced to very small numbers by the gastric acid. In the proximal small intestine the bacterial count of the fluid contents is generally in the region of 10^2 to 10^3 per ml and even in the terminal ileum the count does not ordinarily exceed about 10^7 per ml. In faeces counts of 10^{10} to 10^{11} viable bacteria per gram are normal; these numbers imply that about 20% of the wet weight of faeces consists of viable bacteria. The dominant bacteria in the colonic contents and in faeces are the non-sporing anaerobes: *Bacteroides*, *Bifidobacterium* and *Eubacterium*. Gram-negative aerobes, principally *Escherichia coli*

and *Streptococcus faecalis*, and the anaerobic *Veillonella* and *Peptostreptococcus* together with *Clostridium* species, other streptococci and staphylococci are also normally present.

There are certainly interactions between the bacteria in the gut and it seems very likely that the strict anaerobes can flourish only because the facultative aerobic bacteria reduce the Eh to a low level. Many of the anaerobes produce fatty acids that inhibit the growth of other bacteria (Meynell, 1963) and bile acids, after deconjugation by bacteria, may also have an antibacterial effect (Percy-Robb and Collee, 1972). Diet almost certainly affects the relative proportions of various species in the gut but clear evidence on this is not yet available.

Studies of germ-free animals indicate some of the benefits that are derived from the possession of a healthy bacterial population in the gut. In germ-free rats and guinea pigs, and in small animals in which the gut flora is largely eliminated by antibiotics, the caecum and colon are much enlarged and contain a great excess of water and mucin (Khoury, Floch, and Hersh, 1969). It is suggested that in the normal animal bacteria hydrolyse the mucins, which indeed may form one of their main energy sources (Hoskins and Zamchek, 1968), and that when there is no bacterial degradation the mucin increases the colloid osmotic pressure within the caecum and so inhibits water absorption (Gordon, 1969).

The digestion by the colon bacteria of other secretions and of epithelial cells shed from the ileum is doubtless of value in allowing recycling of much of their constituents.

Despite the larger total weight of the caecum and colon in germ-free animals, the total surface area of the intestine seems to be reduced (Gordon and Bruckner-Kardoss, 1961), a fact that may be attributable to a reduction in epithelial cell proliferation (Khoury *et al*, 1969). Intestinal motility seems also to be reduced in germ-free animals (Abrams and Bishop, 1966) and it has been suggested that bacteria in some way promote muscular contraction in the caecum (Savage and McAllister, 1971). In animals and humans on a normal mixed diet, bacterial degradation of various carbohydrate residues included under the general term of 'fibre' may liberate substances that have a cathartic effect.

Herbivorous animals are well known to rely on their commensal microbes – in rumen or caecum – for help in obtaining nutriment, and McBee (1970) showed that the rabbit may derive as much as 20% of its daily energy requirements from volatile fatty acids produced by bacterial action in the caecum. Indeed it has been suggested (Krebs and Perkins, 1970) that, in man, the presence of an alcohol dehydrogenase in the liver is explicable by

the production of ethanol in the gut – a benefit that many would consider to transcend all the others put together. It is, of course, well recognized that rats become deficient in B vitamins if denied the opportunity for coprophagy; the vitamins are certainly produced by the gut bacteria in man, but, with the possible exception of vitamin K, there seems no indication that we can make use of them.

Many of the normal bacteria of the gut produce a urease and hydrolyse the urea that diffuses into the gut, with production of ammonia, which is re-absorbed. This may have a beneficial effect in recycling nitrogen in some circumstances (Brown, Hill, and Richards, 1971).

Gut bacteria are also implicated in the enterohepatic circulation of bile salts. Many strains of the non-spore-forming anaerobic bacteria are able to remove the taurine or glycine with which the bile salts are conjugated when secreted by the liver. Dietschy, Salomon, and Siperstein (1966) suggested that the conjugation may serve to protect the bile salts against absorption too high up the small intestine and that the bacterial deconjugation may allow absorption of the free acids in the terminal ileum.

It seems, therefore, that the normal structure and activity of the intestine are dependent on the presence within it of a normal complement of bacteria. There is clearly great scope for studies designed to elucidate the way in which the bacteria perform this function, but the work of Freter and Abrams (1972) suggests that a considerable variety of strains is needed to bring a germ-free animal to a state corresponding to a normal animal.

The gut bacteria certainly play a part in the defences against exogenous infection. Germ-free mice are far more susceptible to oral challenge with salmonellae and shigellae than conventional animals (Bohnhoff, Drake, and Miller, 1954; Maier and Hentges, 1972). This increased susceptibility has been attributed partly to a decrease in gut motility which allows greater growth of the salmonellae in the ileum (Abrams and Bishop, 1966), but more attention has been given to another mechanism.

Streptomycin reduces the number of *Escherichia coli* in the colon with a consequential rise in Eh and a decrease in the numbers of strict anaerobes. The anaerobes of the gut produce volatile fatty acids – including acetic and butyric – which are apparently responsible for inhibiting the growth of the exogenous pathogens (Bohnhoff *et al.*, 1954; Bohnhoff, Miller, and Martin, 1964; Meynell, 1963); both anaerobes and aerobic *E. coli* are necessary for maximal protection (Freter and Abrams, 1972; Maier and Hentges, 1972). There are suggestions of a similar phenomenon in man: intestinal carriers of salmonellae treated with neomycin have been shown

to continue as carriers longer than those not so treated (Association for the Study of Infectious Disease Report, 1970).

The large intestine of breast-fed infants harbours fewer *Escherichia coli* and more bifidobacteria than that of bottle-fed infants and the bifidobacteria of breast-fed infants have been implicated in the protection against enteric pathogens. Bullen and Willis (1971) have suggested that it is the high lactose and low protein content, and the low buffering power of breast milk that promotes the effective bifidobacterium flora.

As mischief makers, the gut bacteria are versatile. Many of them escape from the gut at times and invade other, normally sterile, parts of the body. *Escherichia coli* is the commonest species isolated from urinary tract infections and, outside hospital at least, appears generally to be derived from the patient's own gut (Grüneberg, 1969); presumably enterococcal urinary tract infections have the same source. There is now evidence that the *Clostridium welchii* in cases of postoperative gas gangrene are derived from the patient's gut (Parker, 1969) and the same must be true of many cases of wound infection with *E. coli*. In patients whose defences are seriously impaired by immunosuppressive drugs or by whole-body irradiation there may be direct systemic invasion from the gut (eg, Kent, Cardelli, and Stander, 1969).

Without leaving the gut the bacteria may do harm. The ammonia normally produced by the colonic bacteria can be metabolized by the liver in normal persons and causes no trouble; if the liver is seriously diseased or bypassed following surgery, the ammonia content of the blood may be elevated and lead to an encephalopathy (Fisher and Faloon, 1957).

Alterations in the distribution of the normal bacteria within the gut can also lead to disease, as in the 'stagnant loop syndrome'. When there is a heavy growth of bacteria – coliforms, bacteroides, and others – in the ileum or jejunum there may be so much deconjugation of the bile salts that fat absorption is impeded and the patient suffers a steatorrhoea that can be alleviated by antibiotics. The situation is clearly complex, for some patients have heavy colonization of the small intestine with bacteria but no malabsorption; Tabaqchali, Hatzioannou, and Booth (1968) suggested that the steatorrhoea occurs when there is bile-salt deconjugation throughout the small intestine.

The bacteria most active in bile-salt deconjugation are the non-spore-forming anaerobes, bacteroides, and bifidobacteria (Drasar, Hill, and Shiner, 1966; Shimada, Bricknell, and Finegold, 1969). The deconjugated bile acids are less effective in forming

micelles with the products of lipolysis than the conjugated bile acids and may even interfere with micelle formation (Tabaqchali, 1970); they can, however, be reabsorbed from the intestine and so are not lost from the bile-salt pool. The deconjugated bile steroids are, however, susceptible to dehydroxylation, which can be effected by *Escherichia coli* as well as by the anaerobes, and these further degraded bile steroids are not reabsorbed but pass on to the colon and are eventually lost in the faeces, so reducing the total bile salt pool in the body.

Bacterial growth in the small intestine may lead to malabsorption of vitamin B₁₂ as well as fat. Many species of bacteria bind vitamin B₁₂ *in vitro* but this binding is generally inhibited when the B₁₂ is combined with intrinsic factor; there is, however, an indication that some strains of bacteroides can bind the B₁₂ intrinsic factor complex (Schjónsby, Drasar, Tabaqchali, and Booth, 1973).

We have been particularly interested in the possible production of carcinogenic substances by bacteria in the gut. Carcinoma of the colon is more frequent in countries where the diet typically contains large quantities of meat and fat than in those where the diet has a low meat content (Drasar and Irving, 1973). We have suggested that the fat and meat in the diet have the effect of stimulating the secretion of bile and also of favouring the growth in the lower intestine of bacteria that are able to degrade biliary and other steroids, and that some product of this degradation process may be carcinogenic. There is in fact a rather striking correlation between the recorded colon cancer rates in several countries and the faecal concentration of dihydrocholic acids, which are products of the bacterial metabolism of biliary cholic acid (Hill, Crowther, Drasar, Hawksworth, Aries, and Williams, 1971). Possibly these acids are carcinogens and there is some direct evidence for this (Salaman and Roe, 1956). We have, however, also explored the possibility that colonic bacteria can desaturate the steroid nucleus to convert it into a carcinogen of the polycyclic aromatic type. Aries, Goddard, and Hill (1971) and Goddard and Hill (1972) have worked with strains of *Clostridium paraputrificum* isolated from human faeces, and have shown that many of these clostridia can desaturate at least the A and B rings of the steroid nucleus. These clostridia appear to be much more numerous in the faeces of persons living on a mixed western diet than those living on a largely vegetarian diet in Africa, India, or Hong Kong. Moreover, in a preliminary study, faeces from patients with newly diagnosed carcinoma of the colon were found to have the combination of a high concentration of

dihydrocholic acid and large numbers of *C. paraputrificum* much more frequently than controls (Hill *et al.*, in preparation).

Much more work is needed before it can be concluded that gut bacteria are concerned in the causation of colon cancer, but there is enough hard evidence to make a very plausible theory. One might speculate that although a western-type diet favours the growth of non-sporing anaerobes, which may well have a beneficial effect in defending us against exogenous pathogens, the protection is purchased at the price of an increased risk of colon cancer.

We are only at the beginning of studies on the metabolic potential, for good and ill, of the gut bacteria. Another pathway in steroid metabolism leads to the production of oestrogens (Hill, Goddard, and Williams, 1971), and the incidence of breast cancer, like that of colon cancer, is correlated with the fat content of the diet (Drasar and Irving, 1973); perhaps bacterial production of oestrogens may be concerned.

There is also a great amount of work in animals on the effect of gut bacteria on drugs and food additives (Williams, 1972; Drasar, Hill, and Williams, 1970). Although much of this work cannot be extrapolated directly to man because of the much more extensive bacterial colonization of the gut in rodents than in man, there is evidence that the conversion of cyclamate to cyclo-hexylamine, which occurs in the gut of some people, is effected by bacteria (Drasar, Renwick, and Williams, 1972).

Conclusions

Medical bacteriologists have been slow to appreciate and study the beneficial effects of human commensal bacteria or to study the factors that determine their relative abundance in carrier sites. This brief survey surely makes it clear that if we are to understand the factors that allow the commensals to cause disease, we need a better understanding of the factors that govern their normal behaviour and, in particular, methods are urgently needed for studying the interactions of bacteria in situations more realistic than a test tube of diluted meat extract.

Some commensal bacteria are only harmless when contained in their normal carrier site; they possess a complement of aggressins and impedins that turn them into undoubted pathogens when they escape into less well defended tissues. Such escape may occur in surgery, or may result from a breakdown in the defences that normally retain bacteria in carrier sites, as when irradiation changes the intestinal epithelium.

But most of our commensals require assistance, as well as dispersal from their carrier site, if they are to cause disease. The commensal streptococci of the mouth frequently escape from their carrier sites into the blood stream and are ordinarily destroyed; they cause disease only if they can find some protected resting place on a damaged heart valve.

It is only recently that we have come to recognize that the metabolic activities of normal commensal bacteria at their normal carrier sites may lead to disease. Hepatic coma may result if the liver is unable to deal with ammonia normally absorbed from the colon. Dental caries seems to result when, among other factors, the diet promotes the growth and activity of cariogenic streptococci in the mouth. Perhaps colon cancer results if the diet promotes the growth of particular bacteria in the colon and if sufficient steroid substrates reach them and are converted to carcinogens. The malabsorption of the stagnant loop syndrome is due to normal bacteria that have extended their habitat. Among the aetiological factors in acne appears to be the normal lipolytic activity of the skin bacteria operating in a confined situation and perhaps in individuals in which excess substrate is available as a consequence of some endocrinological defect.

In a short review such as this one cannot offer more than a few examples of the good and bad effects of commensal bacteria. I feel quite certain that there is a very large field that is ripe for exploration, and that the results of the exploration may provide important contributions to preventive medicine. The exploration is going to require the development of new bacteriological techniques—for the quantitative isolation of fastidious microbes and for the investigation of their mode of growth in the body. It will also demand the collaboration of chemists in the study of the metabolic activities and requirements of the bacteria—not only in pure cultures, but in mixed culture, and with substrates, and in conditions, approximating to those that obtain in the body. But all our sophisticated bacteriology and chemistry will be a purely academic exercise if it is not applied to the real-life problems facing the clinician and the epidemiologist. The 10^{14} bacteria that we all harbour have an immense metabolic potential and their numbers, their nature, and their activity can be influenced by the food we eat, the drugs we take, the environment we inhabit, and doubtless by the metabolic activities of our own tissues. We need to define and understand these influences if we are to get from our bacteria the most benefit and the least mischief.

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References

- Abrams, G. D., and Bishop, J. E. (1966). Effect of the normal microbial flora on the resistance of the small intestine to infection. *J. Bact.*, **92**, 1604-1608.
- Aries, V. C., Goddard, P., and Hill, M. J. (1971). Degradation of steroids by intestinal bacteria. III. 3-Oxo-5 β -steroid Δ^1 -dehydrogenase and 3-Oxo-5 β -steroid Δ^4 -dehydrogenase. *Biochim. biophys. Acta (Amst.)*, **248**, 482-488.
- Association for the Study of Infectious Disease Report (1970). Effect of neomycin in non-invasive salmonella infections of the gastrointestinal tract. *Lancet*, **2**, 1159-1161.
- Bohnhoff, M., Drake, L., and Miller, C. P. (1954). Effect of streptomycin on susceptibility of intestinal tract to experimental *Salmonella* infection. *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 132-137.
- Bohnhoff, M., Miller, C. P., and Martin, W. R. (1964). Resistance of the mouse's intestinal tract to experimental *Salmonella* infection. *J. exp. Med.*, **120**, 805-816 and 817-828.
- Boris, M., Shinefield, H. R., Romano, P., McCarthy, D. P., and Florman, A. L. (1968). Bacterial interference; protection against recurrent intrafamilial staphylococcal disease. *Amer. J. Dis. Child.*, **115**, 521-529.
- Brown, C. L., Hill, M. J., and Richards, P. (1971). Bacterial ureases in uraemic men. *Lancet*, **2**, 406-408.
- Bullen, C. L., and Willis, A. T. (1971). Resistance of the breast-fed infant to gastroenteritis. *Brit. med. J.*, **3**, 338-343.
- Carlsson, J. (1967). Presence of various types of non-haemolytic streptococci in dental plaque and in other sites of the oral cavity in man. *Odont. Revy.*, **18**, 55-74.
- Carlsson, J., Grahnen, H., Jonsson, G., and Wikner, S. (1970). Establishment of *Streptococcus sanguis* in the mouth of infants. *Arch. oral Biol.*, **15**, 1143-1148.
- Carlsson, J., Söderholm, G., and Almfeldt, I. (1969). Prevalence of *Streptococcus sanguis* and *Streptococcus mutans* in the mouth of persons wearing full dentures. *Arch. oral Biol.*, **14**, 243-249.
- Clarke, J. K. (1924). On the bacterial factor in the aetiology of dental caries. *Brit. J. exp. Path.*, **5**, 141-147.
- Colman, G., and Williams, R. E. O. (1972). Taxonomy of some human viridans streptococci. In *Streptococci and Streptococcal Diseases*, edited by L. W. Wannamaker and J. M. Matsen, p. 281-299. Academic Press, New York and London.
- Dietschy, J. M., Salomon, H. S., and Siperstein, M. D. (1966). Bile acid metabolism. I. Studies on the mechanisms of intestinal transport. *J. clin. Invest.*, **45**, 832-846.
- Drasar, B. S., Hill, M. J., and Shiner, M. (1966). The deconjugation of bile salts by human intestinal bacteria. *Lancet*, **1**, 1237-1238.
- Drasar, B. S., Hill, M. J., and Williams, R. E. O. (1970). The significance of the gut flora in safety testing of food additives. In *Metabolic Aspects of Food Safety*, edited by F. J. C. Roe, p. 245-260. Blackwell, Oxford.
- Drasar, B. S., and Irving, D. (1973). Environmental factors and cancer of the colon and breast. *Brit. J. Cancer*, **27**, 167-172.
- Drasar, B. S., Renwick, A. G., and Williams, R. T. (1972). The role of the gut flora in the metabolism of cyclamate. *Biochem. J.*, **129**, 881-890.
- Fisher, C. J., and Faloon, W. W. (1957). Blood ammonia levels in hepatic cirrhosis. *New Engl. J. Med.*, **256**, 1030-1035.
- Fitzgerald, R. J., and Keyes, P. H. (1960). Demonstration of the etiologic role of streptococci in experimental caries in the hamster. *J. Amer. dent. Ass.*, **61**, 9-19.
- Frank, R. M., Herdly, J., and Philippe, E. (1965). Acquired dental defects and salivary gland lesions after irradiation for carcinomas. *J. Amer. dent. Ass.*, **70**, 868-883.
- Freinkel, R. K. (1969). Pathogenesis of acne vulgaris. *New Engl. J. Med.*, **280**, 1161-1163.
- Freter, R., and Abrams, G. D. (1972). Function of various intestinal bacteria in converting germfree mice to the normal state. *Infect. and Immunity*, **6**, 119-126.
- Gibbons, R. J. (1968). Formation and significance of bacterial polysaccharides in caries etiology. *Caries Res.*, **2**, 164-171.
- Gibbons, R. J., and van Houte, J. (1971). Selective bacterial adherence to oral epithelial surfaces and its role as an ecological determinant. *Infect. and Immunity*, **3**, 567-573.
- Goddard, P., and Hill, M. J. (1972). Degradation of steroids by

- intestinal bacteria. IV. The aromatisation of ring A. *Biochim. biophys. Acta (Amst.)*, **280**, 336-342.
- Gordon, H. A. (1969). Anomalous bowel function in germ-free animals and regulatory effects of intestinal microbes. *J. Lab. clin. Med.*, **74**, 877-878.
- Gordon, H. A., and Bruckner-Kardoss, E. (1961). Effect of normal microbial flora on intestinal surface area. *Amer. J. Physiol.*, **201**, 175-178.
- Grüneberg, R. N. (1969). Relationship of infecting urinary organism to the faecal flora in patients with symptomatic urinary infections. *Lancet*, **2**, 766-768.
- Hamon, C. B., and Klebanoff, S. J. (1973). A peroxidase-mediated, *Streptococcus mitis*-dependent antimicrobial system in saliva. *J. exp. Med.*, **137**, 438-450.
- Hill, M. J., Crowther, J. S., Drasar, B. S., Hawksworth, G., Aries, V., and Williams, R. E. O. (1971). Bacteria and aetiology of cancer of large bowel. *Lancet*, **1**, 95-100.
- Hill, M. J., Goddard, P., and Williams, R. E. O. (1971). Gut bacteria and aetiology of cancer of the breast. *Lancet*, **2**, 472-473.
- Hoffman, H. (1966). Oral microbiology. *Advanc. appl. Microbiol.*, **8**, 195-251.
- Holt, R. (1969). The classification of staphylococci from colonized ventriculo-atrial shunts. *J. clin. Path.*, **22**, 475-482.
- Holt, R. J. (1971). Aerobic bacterial counts on human skin after bathing. *J. med. Microbiol.*, **4**, 319-327.
- Hoskins, L. C., and Zamcheck, N. (1968). Bacterial degradation of gastrointestinal mucins. I. Comparison of mucus constituents in the stools of germ-free and conventional rats. *Gastroenterology*, **54**, 210-217.
- Kent, T. H., Cardelli, R. M., and Stamler, F. W. (1959). Small intestinal ulcers and intestinal flora in rats given indomethacin. *Amer. J. Path.*, **54**, 237-249.
- Keyes, P. H. (1968). Research in dental caries. *J. Amer. dent. Ass.*, **76**, 1357-1373.
- Khoury, K. A., Floch, M. H., and Hersh, T. (1969). Small intestinal mucosal cell proliferation and bacterial flora in the conventionalization of the germ-free mouse. *J. exp. Med.*, **130**, 659-670.
- Krasse, B. (1954). The proportional distribution of *Streptococcus salivarius* and other streptococci in various parts of the mouth. *Odont. Revy*, **5**, 203-211.
- Krebs, H. A., and Perkins, J. R. (1970). The physiological role of liver alcohol dehydrogenase. *Biochem. J.*, **118**, 635-644.
- Lacey, R. W. (1968). Antibacterial action of human skin. *In vivo* effect of acetone, alcohol and soap on behaviour of *Staphylococcus aureus*. *Brit. J. exp. Path.*, **49**, 209-215.
- Lacey, R. W. (1971). High-frequency transfer of neomycin resistance between naturally occurring strains of *Staphylococcus aureus*. *J. med. Microbiol.*, **4**, 73-84.
- Littleton, N. W., Kakehashi, S., and Fitzgerald, R. J. (1970). Recovery of specific 'caries-inducing' streptococci from carious lesions in the teeth of children. *Arch. oral Biol.*, **15**, 461-463.
- Llory, H., Dammron, A., Gioanni, M., and Frank, R. M. (1972). Some population changes in oral anaerobic microorganisms, *Streptococcus mutans* and yeasts following irradiation of the salivary glands. *Caries Res.*, **6**, 298-311.
- Maier, B. R., and Hentges, D. J. (1972). Experimental *Shigella* infections in laboratory animals. I. Antagonism by human normal flora components in gnotobiotic mice. *Infect. and Immun.*, **6**, 168-173.
- Marples, R. R., and Williamson, P. (1969). Effects of systematic demethylchlorotetracycline on human cutaneous microflora. *Appl. Microbiol.*, **18**, 228-234.
- McBee, R. H. (1970). Metabolic contributions of the cecal flora. *Amer. J. clin. Nutr.*, **23**, 1514-1518.
- Meynell, G. G. (1963). Antibacterial mechanisms of the mouse gut. II. The role of Eh and volatile fatty acids in the normal gut. *Brit. J. exp. Path.*, **44**, 209-219.
- Mikx, F. H. M., van der Hoeven, J. S., König, K. G., Plasschaert, A. J. M., and Guggenheim, B. (1972). Establishment of defined microbial ecosystems in germ-free rats. I. The effect of the interaction of *Streptococcus mutans* or *Streptococcus sanguis* with *Veillonella alcalescens* on plaque formation and caries activity. *Caries Res.*, **6**, 211-223.
- Noble, W. C., Williams, R. E. O., Jevons, M., and Shooter, R. A. (1964). Some aspects of nasal carriage of staphylococci. *J. clin. Path.*, **17**, 79-83.
- Parker, M. T. (1969). Post operative clostridial infections in Britain. *Brit. med. J.*, **3**, 671-676.
- Parker, M. T., and Simmons, L. E. (1959). The inhibition of *Corynebacterium diphtheriae* and other Gram-positive organisms by *Staphylococcus aureus*. *J. gen. Microbiol.*, **21**, 457-476.
- Percy-Robb, I. W., and Collee, J. G. (1972). Bile acids: a pH dependent antibacterial system in the gut? *Brit. med. J.*, **3**, 813-815.
- Pinter, J. K., Hayashi, J. A., and Bahn, A. N. (1969). Carbohydrate hydrolases of oral streptococci. *Arch. oral Biol.*, **14**, 735-744.
- Poole, A. E., and Gilmour, M. N. (1971). The variability of unstandardized plaques obtained from single or multiple subjects. *Arch. oral Biol.*, **16**, 681-687.
- Reisner, R. M., and Puhvel, M. (1969). Lipolytic activity of *Staphylococcus albus*. *J. Invest. Derm.*, **53**, 1-7.
- Ricketts, C. R., Squire, J. R., and Topley, E. E. (1951). Human skin lipids with particular reference to the self-sterilising power of the skin. *Clin. Sci.*, **10**, 89-111.
- Salaman, M. H., and Roe, F. J. C. (1956). Further tests for tumour-initiating activity: N,N-DI-(2-chloroethyl)-P-aminophenylbutyric acid (CB1348) as an initiator of skin tumour formation in the mouse. *Brit. J. Cancer*, **10**, 363-378.
- Savage, D. C., and McAllister, J. S. (1971). Cecal enlargement and microbial flora in suckling mice given antibacterial drugs. *Infect. and Immun.*, **3**, 342-349.
- Schjónsbj, H., Drasar, B. S., Tabaqchali, S., and Booth, C. C. (1973). Uptake of vitamin B₁₂ by intestinal bacteria in the stagnant loop syndrome. *Scand. J. Gastroent.*, **8**, 41-47.
- Selwyn, S., and Ellis, H. (1972). Skin bacteria and skin disinfection reconsidered. *Brit. med. J.*, **1**, 136-140.
- Shehadeh, N. H., and Kligman, A. M. (1963). The effect of topical antibacterial agents on the bacterial flora of the axilla. *J. invest. Derm.*, **40**, 61-71.
- Shimada, K., Bricknell, K. S., and Finegold, S. M. (1969). Deconjugation of bile acids by intestinal bacteria: review of literature and additional studies. *J. infect. Dis.*, **119**, 273-281.
- Shinefield, H. R., Wilsey, J. D., Ribble, J. C., Boris, M., Eichenwald, H. F., and Dittmar, C. I. (1966). Interactions of staphylococcal colonization. *Amer. J. Dis. Child.*, **111**, 11-21.
- Shklair, I. L., Keene, H. J., and Simonson, L. G. (1972). Distribution and frequency of *Streptococcus mutans* in caries-active individuals. *J. dent. Res.*, **51**, 882.
- Socransky, S. S., Gibbons, R. J., Dale, A. C., Bortnick, L., Rosenthal E., and MacDonald, J. B. (1963). The microbiota of the gingival crevice area of man. I. Total microscopic and viable counts, and counts of specific organisms. *Arch. oral Biol.*, **8**, 275-280.
- Somerville, D. A., and Noble, W. C. (1973). Microcolony size of microbes on human skin. *J. med. Microbiol.*, **6**, 323-328.
- Sprunt, K., and Redman, W. (1968). Evidence suggesting importance of role of interbacterial inhibition in maintaining balance of normal flora. *Ann. intern. Med.*, **68**, 579-590.
- de Stoppelaar, J. D., van Houte, J., and Backer Dirks, O. (1970). The effect of carbohydrate restriction on the presence of *Streptococcus mutans*, *Streptococcus sanguis* and iodophilic polysaccharide-producing bacteria in human dental plaque. *Caries Res.*, **4**, 114-123.
- Tabaqchali, S. (1970). The pathophysiological role of small intestinal bacterial flora. *Scand. J. Gastroent.*, Suppl., **6**, 139-163.
- Tabaqchali, S., Hatzioannou, J., and Booth, C. C. (1968). Bile-salt deconjugation and steatorrhea in patients with the stagnant-loop syndrome. *Lancet*, **2**, 12-16.
- White, J. C., and Niven, C. F., Jr. (1946). *Streptococcus S.B.E.*: a streptococcus associated with subacute bacterial endocarditis. *J. Bact.*, **51**, 717-722.
- Williams, R. T. (1972). Toxicologic implications of biotransformation by intestinal microflora. *Toxicol. appl. Pharmacol.*, **23**, 769-781.