Leading Article

Prospects for peptic ulcer prevention

Sir Francis Avery Jones

Mill House, Nutbourne, Pulborough, West Sussex RH20 2HE, UK.

Present-day research is rapidly providing evidence to suggest that therapeutic and dietetic advances may enable peptic ulcer to become preventable within the next decade. This could be achieved by being able to strengthen the defence mechanisms of the gastric and duodenal mucosa rather than by limiting the forces of aggression causing ulceration. It is an exciting prospect.

The defences of the gastric and duodenal mucosa are incredibly efficient. The normal mechanical, thermal or chemical insults from food are well within its powers to deal with. Trauma such as a biopsy wound is healed remarkably quickly even within hours. The mechanisms for protection and for repair are intimately inter-related and operate as a team of at least three providing mutual support. The three vital mechanisms are the mucus layer, prostaglandins and the urogastrone/epidermal healing factor (URO/EHF). These powerful defences have been evolved over aeons of years by the evolutionary process but for optimum efficiency they need the necessary nutritional support to which evolution has adapted them. These mechanisms can protect the stomach against hydrochloric acid up to twice the maximum concentration which the stomach is capable of secreting; yet drops of water continuing on one spot have been shown experimentally to cause an ulcer. This it does by washing away the important first line of defence—mucus. Mucus is a viscous gel ideally suited for its function of protection from chemical and physical hazards, of waterproofing and lubrication. It lines the digestive tract serving as the skin of the gut. It is selectively permeable and, for instance, in the stomach allows the acid and pepsinogen to be activated only when they reach the lumen.

Mucus is one of Nature's perfections in protection, but unhappily even Nature has not anticipated all the noxious influences of Western civilization which can reduce its protective powers.¹ Mucus goes far back into evolutionary history and its function clearly has

not been only lubrication but also waterproofing and indeed protecting the organism from sudden changes in osmotic pressure, which it may find difficult or impossible to withstand. For example, mucus provided a permeable skin for the earthworm, allowing the passage of oxygen and carbon dioxide, the single layer of goblet cells producing mucus which provides a waterproof protective coat. Claude Bernard in 1856 commented that the mucus encloses the gastric juice as in a vase as impermeably as though it were made of porcelain. It does indeed form a coherent protective layer covering the living lining of the gastrointestinal tract, and its integrity in health prevents both bacterial infection and biochemical damage.

The second line of defence, the prostaglandins, are derivatives of a 20-carbon chain unsaturated fatty acid widely distributed in the body and serving vital protective functions as they do in the gut; they were first isolated in the seminal fluid and hence their name.² They are released locally in the mucosa and submucosa in response to any irritant stimulus, instantly accelerating cell replacement, opening up the microcirculation to bring cell nutrients and to remove toxic metabolites. It is a mechanism which enables the gastric mucosa to withstand even absolute alcohol and boiling water and to counter a wide variety of chemical hazards even without any help from simultaneous reduction of gastric acid secretion. Its action can be blocked for example by the non-steroidal anti-inflammatory drugs which prevent the enzyme cyclo-oxygenase from producing prostaglandins from its precursor arachidonic acid and hence their liability to promote peptic ulceration. Its efficiency depends on an adequate dietary supply of essential fatty acids needed for their formation and which can be deficient in the present day food in Western Countries.

The third line of defence is urogastrone – epidermal healing factor, first known over fifty years ago but now back on the frontiers of research.³ Indeed it seems to be Nature's special contribution to healing ulcers. It has been shown to promote wound healing, accelerate peptic ulcer healing and increase crypt cell production rate along the gastrointestinal tract. It stimulates

Correspondence: Sir Francis Avery Jones, Mill House, Nutbourne, Pulborough, West Sussex RH20 2HE
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DNA synthesis and the uptake of amino acids by cultured skin fibroblasts. Immunofluorescent studies have shown its localization in the human mandibular gland and also in the Brunner's glands in the duodenum. It is present in saliva, plasma and milk. It is not destroyed by tryptic activity. It has been shown to be a polypeptide and its sequence of amino acids includes three internal disulphide bonds. In the digestive tract it has been shown to be a potent inhibitor of gastric acid secretion. It is more effective than cimetidine in promoting the healing of experimental gastric ulcer and increases the resistance of the gastric mucosal barrier to the damaging effects of ethanol. In man it could clearly play an important role by inhibiting gastric acid secretion on the one hand, and by stimulation of cell proliferation and regeneration on the other it could make a significant contribution to the healing of peptic ulcers.

URO/EHF has had a long and frustrating history. It seems to be the same substance extracted from urine by Sandweiss over 50 years ago. This was shown to reduce acid secretion in the stomach and also to stimulate healing in the Mann-Williamson experimental ulcer in the dog. It was designated 'anthelone' (Greek: *anti*-against, *helcos*-ulcer) It was studied in London at the same time by Wilfred Card but sadly he failed to get continued research support from the Medical Research Council. It was finally isolated from urine by Harold Gregory in 1975. A parallel line of research had begun in 1962 when Stanley Cohen first isolated epidermal growth factor from the submaxillary glands of mice and established its structure ten years later. It stimulates epithelial proliferation in tissue culture and healing in a number of experimental situations. Now it seems that these two factors are essentially the same and are now designated URO/EHF. These findings link up with the well known observation that animals lick their wounds with remarkable success in healing. Furthermore if the salivary glands are extirpated or irradiated this healing effect is lost.

These three mechanisms provide the protection for the gastric and duodenal mucosa against the hazards which have been met in our long evolutionary history, but not against all the new chemicals liable to be consumed today.

These three defence mechanisms are the subjects of intense research activity not just because of their particular importance in the alimentary tract but they also relate to other diseases. Mucus is equally important, for example, in the respiratory and genito-urinary tracts.

Prostaglandins play a ubiquitous role in the body being especially concerned with response to cell injury. Their importance in the alimentary tract was realized by the discovery that aspirin damaged the gastric mucosa by inhibiting prostaglandin synthesis and that

the cholera toxin caused diarrhoea by stimulating it. In the gut prostaglandin and related compounds are particularly involved with mucosal protection, ulcer healing, gastrointestinal inflammation and diarrhoea. For its optimum contribution it needs constant stimulation from minor degrees of stress. The gut does not need to be specially protected from the normal daily stresses. The urogastrone/epidermal healing factor is attracting intense biochemical interest because of the possible links with the oncological field, and there is great interest in its potential for ulcer-healing.

In the animal world these defences are extraordinarily effective and efficient. Peptic ulcers in animals in the wild are very rare because of their full adaptation to their environment including their food. One exception is the Californian seal which swallows irregular black laval stones and which develop gastric ulcers. However, it has been shown that these are not just due to mechanical trauma which would normally heal but the ulcers become chronic because of the presence of a fish nematode *Eustomatum rotandum*. This is also known to happen in man in the Scandinavian countries. It is when animals bred in captivity are given food which they are not normally adapted to in nature that hazards including peptic ulcer arise. Veterinary surgeons are very familiar with this problem which has been seen in pigs, foals, dolphins and even tigers. Endoscopy has been used for diagnosis and ulcers treated successfully with H₂ receptor antagonists (Taylor, personal communication).

Impaired defence mechanisms and peptic ulcer

In man there are four ways in which the normal defence mechanisms could have become impaired causing the epidemic of peptic ulcer which has involved the Western World during this century.

Once recognized all could be brought under control and then peptic ulcer would no longer remain an important clinical problem. The first group, and the least important, are the apparently rare novel causes of peptic ulcer possibly *Campylobacter pyloridis*, herpes simplex, nematode infestation and autoimmunity reaction. The second group are anti-healing factors in present-day living. They do not initiate ulcers but could enable small acute lesions to become chronic. These include smoking, strong alcohol, caffeine and sustained nervous stress particularly frustration and resentment. All of these could lead to an increase of gastric secretions which particularly at night time could lead to an increase of the damaging proteolytic activity delaying or preventing healing. The third group relate to the many new chemicals in present-day living and some of which can cause serious damage to the gastric mucosa. The best examples are the non-steroidal anti-inflammatory drugs including aspirin

which inhibit the enzyme cyclo-oxygenase essential for converting arachidonic acid into the protective prostaglandins. There is a prospect that synthetic prostaglandin analogues may enable this problem to be overcome. The fourth and potentially the most important group is the possibility that changes in the national diet in this century have led to a fall in intake of the essential fatty acids needed for the production of the protective prostaglandins. Such a lipid factor could act directly on cell membranes enabling cell repair to overtake cell destruction in the dynamic mucosal environment. It is known that such healing factors exist and furthermore they act evenly at the edge of the ulcer; this is why ulcers are always round.

Dietary factors

It was Cleave who first pointed out that man, like the whole animal world, has built up his natural defence by the long evolutionary adaptation.⁴ It is when the accustomed environment, particularly food, is changed that disease may become a problem. He believed that introduction of refined cereals was the prime factor in causing the great increase in duodenal ulcer. He did not advocate the addition of bran except for constipation but the taking of unrefined wheat or other cereals. He produced much epidemiological support for this concept but there were some exceptions. These difficulties have been largely resolved by the interesting and important studies by Tovey in collaboration with A.P. Jayaraj and Professor C.G. Clark working at University College Hospital, London.⁵ Their epidemiological evidence had suggested that there might be some other protective foods besides whole cereals, particularly in locally grown pulses and millets in areas where peptic ulcer incidence was unexpectedly low. Using an experimental animal model, a protective factor has been found in various items of food including unrefined wheat and unrefined rice; certain pulses, on the other hand, refined wheat and refined white polished rice, gave no protection. One of the pulses, horse gram (*Dolichus biflorus*), is a particularly potent source of this protective factor. It has been shown that the active principle from the horse gram is a lipid fraction which awaits full identification. In wheat and rice it is concentrated in the bran fraction. In ricebran it is particularly liable to undergo oxidation but this can be prevented by pasteurization. The rancid fraction is then no longer protective but becomes highly ulcerogenic. This may well account for some previous unexpected epidemiological findings. Their evidence of the protective lipid fraction present in unrefined wheat and rice and associated with the bran fraction, confirms the point long made by Cleave of the importance of not stripping the bran away and using the milled residue as the staple cereal. It also

provides confirmation and extension of the earlier animal modes. The work of Cheney⁶ in 1952 and Singh⁷ ten years later indicates that there was a protective factor in fresh cabbage juice and also in dairy fats and eggs. Since then much information has been found particularly on the international scene all pointing to the possibility of a vital food factor which might be needed to maintain the optimum defences of the stomach and duodenum. Much evidence has come from the East and also from South Africa. In his Cantor Lectures in 1936 Sir Robert McCarrison commented on the better health in the Punjab where wheat was the staple cereal compared with South India where milled rice is eaten and how he had confirmed his clinical impressions by studies on laboratory animals fed on different diets. He noted the extreme rarity of peptic ulcer in the north compared with how common duodenal was in the south, particularly in Travencore, and demonstrated the same trend on ulcer incidence in the rats fed on the different regional diets. Sommerville, working as a surgeon in South India, confirmed the prevalence of duodenal ulcer and noted the rarity of gastric ulcer. On a visit to India in 1952 I met Sommerville and on this visit I noted the rarity of duodenal ulcer among the fisherfolk living on the coast of Travencore, suggesting a possible dietary link. Surgeon Captain T.L. Cleave collected much evidence from the prisoner of war camps on peptic ulcer in relation to polished rice.¹⁸ Peptic ulcer was a problem when polished rice was the staple diet but not when brown unmilled rice was used. Furthermore the use of fresh rice bran seemed to provide protection when it was given. Since then information has come from India and Africa showing that in those areas where milled rice, tapioca or sorghum formed the staple diet duodenal ulcer tended to be a major problem. In contrast it was a minor consideration in areas where unrefined wheat was the main cereal and also in localized areas where certain millets or pulses were eaten, particularly horse gram. Frank Tovey who has been responsible for much new epidemiological evidence has recently reviewed our present knowledge.¹⁹

The concept of a dietary protective factor associated with unrefined cereals received confirmation from Malhotra¹⁰ who followed up 42 patients with healed duodenal ulcers for 5 years and found a significantly lower recurrence rate in patients who changed to a diet containing unrefined wheat than in patients who continued their traditional rice diet. In Norway, Rydning & Berstad¹¹ confirmed this in a shorter 6-months trial, again finding the recurrence rate significantly higher in the low-fibre than in the high-fibre group. Their recent review on dietary fibre and peptic ulcer brings together all the information on this subject. They note that it can be argued that it is the low-fibre diet that is harmful and not the high fibre

diet which is beneficial. They found no ill-effects from a high-fibre regime. They conclude that there is no reason for ulcer patients whether they have active ulceration or are in remission to stick to a bland diet but rather eat a 'normal' or high-fibre diet. Previously Doll¹² in his studies on ulcer healing in the fifties had not found any benefit from a bland gastric regime and recommended normal food.

There is clearly increasing evidence that there is dietary protective factor for peptic ulcer and that this is present in unrefined cereal and may be a lipid associated with the cereal fibre. The same factor may be present in a number of green vegetables and pulses; there may well be other sources. The present decline in

peptic ulcer prevalence preceded the introduction of the H₂ receptor antagonist drugs and could be linked with the change in the national diet in recent years with the greater interest in 'healthy' eating, with the increased consumption of unrefined cereals and greens, and unsaturated fats. If Tovey's work is confirmed, if the new prostaglandin analogues give protection against the non-steroidal anti-inflammatory drugs, with the present trend in the national diet continuing with more unrefined cereals, more polyunsaturated fats, more fish, then it is indeed possible that even by the turn of the century peptic ulcer will have been brought under control as a major clinical problem.

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