tact. Three compounds prevented the satisfactory redissolution of the freeze-dried haemoglobin.

Four compounds with more alcohol functions than Tris were also more active while the simple replacement of one -OH in Tris with an -H, making AMPD, increased the amount of methaemoglobin formed. This result was confirmed with the ethyl and demethyl homologues (3 and 4). One alcohol function is even less effective, as 2-amino-2-methyl propanol (5) and alaninol (6) show. It seems that the simplest effective structure is that of 2-amino-2-methylpropane-1,3-diol (2), which may have a dose-effect relationship different from that of Tris, while the protective effect may be a function of the physical properties of aqueous solutions of the active compounds.

If the protection given is of chemical origin, and the result of one or more well-defined haemoglobin-amine interactions, the compounds allow an evaluation of the importance of several structural elements.

The presence of at least 2 primary alcohol functions is necessary. If 2-amino-2-methylpropane-1,3-diol (2) is considered the simplest active molecule, all the compounds richer in alcohol functions are more active, even if the functions are differently distributed, as in bis-AMP. Addition of more alcohol functions leads to the most effective compounds, mono-Tris, bis-Tris, and bis-Tris-propane. This observation is true for trialcohols containing nitrogen (triethanolamine) or phosphorus (trishydroxymethyl phosphine oxide), which are not totally devoid of protective effect.

The presence of a quaternary carbon atom with several alcohol functions and one amine function seems to be necessary. This function directly bound to the carbon atom bearing the alcohol functions, constitutes the third necessary condition. The need for this function is demonstrated by the ineffectiveness of pentaerythritol (14) and of dimethylpropanediol (19). Its position is, however, critical, as the bad results with the diamines and Bicine show. The amine nitrogen atom may carry one or two hydroxyethyl ($-CH_2CH_2OH$) substituents, or may even join two Tris moieties, which increase the protective effect, but it must not carry a carboxymethyl ($-CH_2$ COOH) substituent, as with Tricine. Certain compounds of theoretical and no doubt practical interest, in which this amine function is replaced by $-CH_3$ $-CH_2OH$, or is separated from the carbon at the core of Tris or AMPD by $-CH_2-$, are not yet commercially available and could not be studied. The same is true for 2,2-diaminopropane and for 2,2-diaminopropane-1,3-diol.

Why such structures prevent the oxidation of haemoglobin remains unexplained. Several explanations of the denaturation (the presence of free radicals, the protection of the iron, the blockage of the heme pocket, etc.), have been put forward. The protection of haemoglobin did not seem to depend on the pH of the medium being freeze-dried. The solutions had pH values, ranging from about 5·5 to 10·5, while the pK values for some of the amine buffers are also very widely separated.

October 29, 1979

REFERENCES

Evelyn, K. A., Malloy, H. I. (1938) J. Biol. Chem. 126: 655–662

Labrude, P., Loppinet, V., Vigneron, C. (1976) Ann. Pharm. Fr. 34: 143–149

Labrude, P., Vigneron, C., Streiff, F. (1976) J. Pharm. Belg. 31: 191–198

LETTERS TO THE EDITOR

Gastrointestinal erosions and the lack of inflammatory response

P. G. Robins, *Lilly Research Centre Ltd, Erl Wood Manor, Windlesham, Surrey, U.K.*

As part of an investigation into the pathogenesis of drug induced gastric erosions (Robins 1978) it was noted that when aspirin and indomethacin cause erosions in the mucosa of the rat stomach, remarkably they fail to provoke an inflammatory cell response.

This observation confirms that of Muir & Cossar (1961) who gave soluble aspirin to patients about to undergo gastrectomy and of Brodie et al (1970) who saw a similar lack of cellular response to aspirin in the rat intestine. Smith & Butler (1974) also noted that mechanical trauma to the full thickness of the mucosa of the mouse colon elicited no inflammatory cell response. In each case this lack of response was recorded while describing the lesion and its significance was not discussed. My own findings in rats indicated that, in the stomach, inflammation proceeds normally if the submucosa is damaged, but if it is not and damage is confined to cytolysis of the mucosa and its microvasculature, resolution occurs after 4–12 h without the appearance of the polymorphonuclear and mononuclear cells usually associated with an episode of necrosis.

There is no easily apparent reason why the inflammatory process is not provoked in the gastrointestinal tract. The mucosa is mainly epithelial but also contains a reticulin network, a vascular system and it is innervated. It contains therefore the features essential to the recognition of a necrotic episode. The products of necrosis are not immediately diluted into the lumen of

the stomach or intestine. Demonstrable necrosis was apparent 30 min after administration of the drug and persisted for a few hours. Smith & Butler (1974) used no drug treatment so the presence of aspirin or indomethacin does not account for this phenomenon. Tolerance akin to immune tolerance does not explain the lack of an inflammatory response in these circumstances. Tolerance in this sense is an acquired characteristic but the inflammatory response is not evoked by aspirin or indomethacin at the first or indeed after several doses. One must consider either that a chemotactic influence is absent or that there is a factor present inhibiting the inflammatory response in the gastrointestinal mucosa. In view of the large number of chemotactic factors which have been identified it is highly unlikely that all will be absent from gastrointestinal mucosa.

The most likely of the possible reasons for this phenomenon is that an inhibitor of cellular chemotaxis exists in the gastrointestinal mucosa. This proposal is not as unlikely as it might seem. Cells of the gastrointestinal mucosa are constantly exposed to foreign proteins, amino-acid residues etc. which in other sites would elicit an inflammatory response. Wilkinson (1974) has shown that most chemotaxins are polypeptides or proteins and it might be supposed that unless an inhibitor exists absorption of these materials in the gastrointestinal system should provoke an inflammatory reaction.

January 14, 1980

REFERENCES

Brodie, D. A., Tate, C. L., Hooke, K. F. (1970) Science 170: 183–185

Muir, A., Cossar, I. A. (1961) Am. J. Dig. Dis. 6: 1115–1125

Robins, P. G. (1978) Some studies on the pathogenesis of drug induced gastric erosions. Ph.D. Thesis, University of London

Smith, B., Butler, M. (1974) Br. J. Exp. Pathol. 55: 615–621

Wilkinson, P. C. (1974) Chemotaxis and Inflammation. Churchill Livingston, Edinburgh & London p 54

Scirpus kysoor Roxb. a new plant source of progesterone

A. M. MUJUMDAR, R. D. PATASKAR, A. H. KAPADI, G. S. PENDSE*, *Indian Drugs Research Laboratory, 561-B, Shivajinagar, Pune- 411 005. India*

The tubers of the plant *Scirpus kysoor* Roxb. Cyperaceae or 'Kaseru' are mentioned in the Indian system of medicine for the prevention of abortions. We have made chemical and pharmacological investigations to find the responsible compounds for uterine sedative activity.

Roxburgh (1874) equated the plant Kaseru with *Scirpus kysoor*. The tubers, collected by us, in winter from Western coastal areas of India, were authenticated; dried and coarsely powdered. Phytochemical tests showed the presence of steroids, sugars, tannins, starches and saponins.

The acetone extract had no effect on the rat uterus in vitro (Turner 1965). It blocked oxytocin but not acetylcholine-, 5-hydroxytryptamine- and $BaCl_2$-induced contractions. After adsorption of the acetone extract on Supercel the activity was eluated with light petroleum (b.p. 40°–60 °C), and the eluant chromatographed on neutral grade alumina using light petroleum (b.p. 40°–60 °C). The extract, on drying under vacuum yielded a residue, which was crystallized to constant m.p. 128 °C. The structure of the compound was determined by micro-analysis, mass, i.r., u.v., n.m.r. and was suspected to be progesterone. It was confirmed by mixed m.p., superimposition of i.r. and preparation of the dioxime derivative.

* Correspondence

Small amounts of progesterone appear to occur in yeast, wheat, rice, cabbage and potato (Ramstad 1959). Progesterone-like activity is reported from white beans (Sütö-Nagy 1940). Gawienowski & Gibbs (1968) detected the presence of cholesterol and progesterone in apple seeds. The occurrence of progesterone with alkaloids is reported from *Holarrhena floribunda* (Michel et al 1969).

We thank Organon (India) Limited, Calcutta, for the supply of progesterone as a reference standard.

May 10, 1979

REFERENCES

Gawienowski, A. M., Gibbs, C. C. (1968) Steroids 12 (4): 545–50

Michel, L., Andre, C., Robert, G. (1969) Ann. Pharm. Fr. 27 (3): 217–28

Ramstad, E. (1959) Modern Pharmacognosy, McGraw Hill Book Co. London, New York, Toronto, p. 122

Roxburgh, W. (1874) Flora Indica or Description of Indian plants, Thacker Spink & Co. Calcutta, p 77

Sütö-Nagy, G. de. (1940) Proc. Soc. Exp. Biol. Med. 43: 674–75

Turner, R. A. (1965) Screening methods in pharmacology, Academic Press, New York and London, p 119