Clinical Trial

INITIAL EVALUATION OF A NEW BISMUTH COMPOUND IN THE THERAPY OF PEPTIC ULCER WITH *IN VIVO* GASTRIC ANALYSIS

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THE MEDICAL therapy of peptic ulceration is at present most unsatisfactory. Some people draw a distinction between the medical treatment of gastric ulcer and that of duodenal ulcer, but we believe that this distinction is unimportant as the same general principles apply to both, apart from a few specific forms of treatment that we shall mention later. For practical clinical purposes therapy can be considered as applying to both types of ulcer and this view is shared by other authorities (Avery Jones, 1964; *Lancet*, 1962).

A probable reason for the difficulty in applying specific therapy to peptic ulcer is the obscurity and controversy surrounding the underlying aetiology. The roles of stress, hormonal dysfunction, acid hypersecretion, excessive pepsin production, lowered tissue resistance and bile regurgitation have all been considered and explored and these factors as aetiological agents all have their supporters (*Lancet*, 1962; Spira, 1956, 1964). The most widely accepted direct causal agent is hydrochloric acid in excess and much of present day therapy is aimed at "neutralising" this by means of antacids. In Great Britain alone there are over 100 antacid preparations or mixtures in common use.

It is easy in the laboratory to demonstrate convincingly the acid neutralising effect of the antacids in common therapeutic use, and this has been done many times. Under these artificial conditions gastric emptying is not adequately allowed for, nor is the normal physiological production of more acid by the stomach. This further acid secretion may also be excessive in some cases due to over-reaction to the exciting influence of food on the stomach, or a temporary change in the gastric pH producing over compensation ('acid rebound'). In spite of this, there is little doubt that antacids do produce definite symptomatic relief particularly of pain, and this may be of sustained therapeutic benefit.

The therapeutic virtues of antacids have mainly been demonstrated by clinical trials without conclusive *in vivo* evidence of sustained gastric neutralisation of hydrochloric acid, and it is clear from studies of gastric emptying that even if antacids were given in such quantities to have a significant effect on the acid in the stomach, it could only be transient due to the rate at which the antacid would be passed on into the

duodenum. Thus there is some doubt as to how they produce the sustained pain relief that occurs in many patients. Further it has been shown that acid neutralisation does not accelerate healing in gastric ulcer even if the gastric pH is maintained above 4.0 throughout the 24 hours by means of a continuous milk drip (Doll, Friedlander and Pygott, 1956). Further it is known that in order to obtain a significant effect on gastric pH with alkalies, continuous tablet sucking is necessary and this cannot be done by the patient at night.

If acid neutralisation is not then practicable *in vivo*, could pepsin neutralisation be an acceptable alternative therapeutic measure? Various workers have demonstrated that bismuth salts have the power of inhibiting the enzyme action of pepsin (Stephens, 1953; Bateson, 1958), and are not powerful antacids, thus avoiding possible acid rebound. For many years and especially in the 1930's, bismuth salts enjoyed great popularity as therapeutic agents in peptic ulceration, and some authorities have attributed the gradual rise in the incidence of peptic ulceration of recent years to the reduction in their use (Leak, 1963).

In order to determine the validity of these postulates a preliminary survey has been carried out both clinically and biochemically. The purpose of this is to test firstly if bismuth salts have any therapeutic value, and secondly if they have any *in vivo* effect on the gastric contents.

Method:

Fifty patients were admitted to the trial. They were all treated similarly for a period of one calendar month, the first two weeks at complete rest, the remainder at diminished activity. Bismuth aluminate (Bislumina M.C.P. Pure Drugs), a new stable bismuth salt, was chosen as the therapeutic agent, and was given in a dose of 1.6 g. before each meal for one month. Results were assessed before and after therapy. Supplementary advice was given to take small frequent meals and to avoid any foods known by the patients to upset them, but no other therapy was given.

The patients selected for therapy were all suffering from either gastric or duodenal ulcers, confirmed radiologically or gastroscopically, or both. They were graded at the end of therapy as either the same, worse or improved and this result was only based

TABLE I
RESULTS OF GASTRIC ANALYSIS IN 11 CASES

	Case No. 3		Case No. 11		Case No. 14		Case No. 21		Case No. 24		Case No. 29		Case No. 33	
	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.
Resting juice	2.04	1070	6.50	208	2.10	636	5.40	162	6.40	214	3.42	780	6.65	208
$\frac{1}{2}$ hour	2.68	570	2.40	1390	2.42	580	6.00	292	3.45	310	4.20	870	6.25	278
1 hour	1.88	1050	3.00	1240	2.29	813	1.55	760	1.70	422	5.24	640	2.65	1010
$1\frac{1}{2}$ hours	1.64	1600	6.40	61	2.41	640	1.80	930	1.63	215	5.60	240	6.00	490

	Case No. 38		Case No. 40		Case No. 44		Case No. 49	
	pH	*U.P.A.	pH	U.P.A.	pH	U.P.A.	pH	U.P.A.
Resting juice	2.35	610	1.58	520	1.84	590	1.55	1700
$\frac{1}{2}$ hour	2.40	612	1.52	1770	1.62	950	1.60	1060
1 hour	1.65	745	1.70	1210	1.62	1370	1.40	655
$1\frac{1}{2}$ hours	1.67	592	1.56	3360	1.68	1020	1.50	1040

*U.P.A.=Units of Proteolytic Activity at pH of 2.1 (estimated by a modification of Hunt's method).

on measuring the radiological or gastroscopic appearance of the ulcer, symptoms being ignored in order to get unequivocal and objective evidence of change in the actual ulcer.

One patient in five was taken by a method of random selection and had gastric analysis performed as follows:—

A fine-bore rubber tube was passed into the stomach and all the resting juice aspirated. Then 6 g. of strained porridge and 1.6 g. of bismuth aluminate were given to simulate the therapeutic conditions of the tablets being taken directly before a meal. Complete gastric aspiration was then performed at half-hourly intervals for one and a half hours and the contents analysed for pH and pepsin activity, using a modification of Hunt's method.

Results:

Forty out of the 50 patients showed improvement (80%), as evinced by partial or complete healing of their ulcer, radiologically or gastroscopically. Four patients were worse and six the same.

The *in vivo* gastric analyses showed that there was little detectable effect on the gastric pH or pepsin activity of the bismuth aluminate in the dose given (see Table I).

Discussion

The whole matter of therapy of peptic ulceration is fraught with unanswered questions. Antacid treatment, although the widest used, cannot be convincingly shown to change the gastric pH and

total acidity for any significant length of time due to rapid gastric emptying and further acid secretion. However, antacid therapy does appear to produce symptomatic relief and this is supported by the experience of many practising clinicians, and the popularity of antacids as therapeutic agents can be explained on these grounds.

Pepsin neutralisation is an alternative method of treatment to be considered. As pepsin activity is reduced when the pH rises, it has been thought that antacids would have a combined effect on the acid and pepsin, and some authorities have disregarded the action of pepsin from the therapeutic angle because it depends on an acid medium and therefore control of acidity will obviously abolish it (Douthwaite, 1958). However, as control of acidity cannot be shown to occur *in vivo* with normal dosage of antacids it should perhaps be considered separately.

Bismuth aluminate is a powerful antipepsin agent but a weak antacid and is therefore suitable to test this hypothesis. The results of the trial described in this paper do not support the supposition that the significant neutralisation of pepsin does occur in the gastric contents in the lumen of the stomach, *in vivo*, with normal therapeutic dosage of bismuth aluminate. Neither is there much demonstrable effect on the gastric pH. In the light of these facts one could not

expect much therapeutic benefit from treatment. However, the enigma is presented of considerable objective evidence of improvement in the treated patients, amounting to an improvement rate of 80% in the series.

We are now faced with many apparent contradictions in the therapy of peptic ulceration. Antacids, found by experience to be of symptomatic and possible therapeutic benefit, do not really significantly affect the gastric acidity *in vivo* in the normally used doses. Antipepsin agents effective *in vitro*, show little influence on gastric pepsin *in vivo*, although a striking improvement in patients with peptic ulceration follows their employment. An antisecretory agent (Nacton) is recommended in therapy and shown to be of value (Douthwaite, 1958), although later work shows it to have no effect in reducing the gastric acidity in duodenal ulcer patients taking a bland diet (Lennard-Jones, 1961).

Other interesting therapeutic agents are biogastrone and stilboestrol. Both have been subjected to carefully controlled clinical trials in peptic ulceration and have been clearly shown to be valuable (Doll, Hill, Hulton and Underwood, 1962; Truelove, 1960), but the mode of action of either is not clear.

We would like to suggest that existing information on the underlying aetiology of peptic ulcer is inadequate to support any of the current views of the roles of acid, pepsin, stress, hormonal dysfunction and lowered tissue resistance. However therapeutic benefit has been demonstrated in many agents used in the treatment of peptic ulcer, but how this benefit occurs is obscure. We propose that by continuing investigations into therapeutically effective agents, some light may be thrown onto the way in which they work, and may ultimately help in understanding the aetiology of peptic ulceration.

Further studies on bismuth aluminate are at present in progress and we hope that these will yield additional information.

Summary

A trial of the objective therapeutic effect of bismuth aluminate was carried out in the 50 patients with peptic ulcer. The results were assessed by evaluating only the radiological or gastroscopic appearances of the ulcer. After one month's treatment, 80% of patients showed objective improvement. Studies of gastric contents in 10 patients selected randomly, showed little influence of therapy on either pH or pepsin activity. The relevance of these findings to the aetiology of peptic ulcer is discussed, and the importance of further work suggested.

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