INNOVATION IN GASTROENTEROLOGICAL MANAGEMENT: THE CASE OF CIMETIDINE*

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Gastroenterological medicine has, in recent decades, experienced two major innovations, viz. *fibre optic endoscopy (a diagnostic technology) and cimetidine, an innovation in ulcer therapy. This paper is concerned with determining the efficacy of cimetidine in reducing the number of surgical procedures for gastric and duodenal ulcer. It is found that, since the introduction of cimetidine, a statistically significant decline in gastric ulcer operations has occurred. A similar result was not obtained for persons with a diagnosis of duodenal ulcer. The picture of substitution of therapies given by this study is in sharp contrast to that depicted in clinical drug trials. This has significance for technology assessment.*

Keywords: gastric and duodenal ulcer, cimetidine, medical innovation, substitution, technology assessment

INNOVATIONS IN GASTROENTEROLOGY

The medical management of disorders of the upper gastrointestinal tract has been significantly affected by two major technological innovations. In the order of their development these innovations are the diagnostic technique of fibre optic endoscopy and the pharmacological agent cimetidine.

The fibre optic age of endoscopy began in 1954 when it was argued that flexible endoscopes could be developed using fibre optic principles.[1] Hopkins and Kapany wrote:

> . . . an optical unit has been devised which will convey images along a flexible axis. The unit comprises a bundle of fibres of glass, or other transparent material, and it therefore appears appropriate to introduce the term 'fibrescope' to denote it. An obvious use of the unit is to replace the train of lenses employed in conventional endoscopes.[2]

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By 1958 a fully flexible fibre optic gastroscope had been demonstrated.[3] The dominant use of fibre optic endoscopes is for diagnosis. However, modern instruments also enable the removal of foreign bodies, sphincterotomy for duct stones, dilation of oesophageal strictures and the treatment of bleeding lesions by diathermy or laser photocoagulation.[4] Prior to the fibre optic age, barium meal radiological diagnosis of the oesophagus, stomach and duodenum was unchallenged by any alternative technology. Since the advent of fibre optic instruments such radiological diagnoses have been shown to be relatively inaccurate.[5]

The second innovation in the medical management of gastrointestinal disorders was the development of a new pharmacological agent which has added to the range of therapeutic alternatives. The development of cimetidine, the third drug in the class of histamine H_2-receptor antagonists, is regarded as a major breakthrough in chemical therapy. Although the first antihistamine was synthesised in 1937, and many variants have been developed since, it was found that the antihistamines blocked only some of the actions of histamine, such as the control of allergic conditions, for example, hay fever. They had no effect on other histamine-mediated processes, including gastric acid secretion. Ash and Schild argued that there may be two types of receptor sites in the gastric mucosa.[6] This argument involved a reclassification of 'classical' antihistamines as histamine H_1-receptor antagonists. Histamine receptors at which the 'classical' antihistamines are ineffective could be defined as histamine H_2-receptors.

In 1964 Black began a search for compounds which would block those receptors which were insensitive to the H_1-receptor antagonists. This work culminated in the synthesis of burimamide, the first histamine H_2-receptor antagonist.[7] This compound had little clinical potential as a result of its low potency when administered orally. The second H_2-receptor antagonist, metiamide, inhibited gastric secretion markedly but was withdrawn from further clinical trials when bone-marrow depression, which was subsequently reversed, developed in some patients.[8] Cimetidine trials were then undertaken.[9]

In early studies with quite small numbers of patients ulcer symptoms improved and ulcers healed, as determined by endoscopic examination.[10] Subsequent double-blind trials with larger numbers of participants indicated rapid symptomatic relief and a high healing rate.[11] Cimetidine has not yet shown any major side effects.[12] Since these early studies, other issues, such as the efficacy of cimetidine as a maintenance therapy,[13] and comparisons with other therapies,[14] have been investigated. It is clear that the literature associated with the cimetidine 'industry' is voluminous and we make no attempt to provide a comprehensive survey.

More recently another histamine H_2-receptor antagonist, ranitidine, has become available. It is suggested by experimental evidence that ranitidine is approximately five times as effective as cimetidine as an inhibitor of gastric acid secretion.[15] Clinical trials have shown ranitidine to be more effective than placebo[16] and as effective as cimetidine, although ranitidine was administered at a fraction of the daily dose of cimetidine.[17] Two other H_2-receptor antagonists, SK&F92994 and tiotidine, have also been reported.[18] The medical profession thus has available a choice of histamine H_2-receptor antagonists.

Cimetidine was marketed in the United Kingdom in November 1976 and in August 1977 in the United States. Following the deliberations of the Commonwealth Drug Evaluation Committee in early 1977, cimetidine became available on prescription in Australia on 27 May 1977. It was first approved as a short term therapy for proven duodenal and gastric ulcer as well as the Zollinger-Ellison syndrome. Subsequently approval was extended to its use as a maintenance therapy. In August 1978, cimetidine became available as a pharmaceutical benefit, subject to restriction, under the Pharmaceutical Benefits Scheme, as authorised by the National Health Act, 1953.

Ranitidine was introduced to the Australian market on 29 April 1982, following its release in the United Kingdom in October 1981. The therapeutic indications for ranitidine in Australia are exactly the same as those for cimetidine. At the time of writing (December 1983), ranitidine had not yet been approved for government subsidy under the Pharmaceutical Benefits Scheme. As ranitidine was not available in the period being considered in this study it is not necessary to document its sales.

Figure 1 shows the temporal diffusion of cimetidine in the State of Queensland in the six years since it became available. Queensland is unique in Australia in that since 1942 the Queensland Department of Health has administered a state-wide network of public hospitals in which both in- and out-patient services have been provided free to all persons unless they prefer to be treated on a fee-for-service basis by a private medical practitioner of their own choice. The lower graph in Figure 1 indicates the volumes of cimetidine prescribed in this system of public medical provision, and the intermediate graph shows the volumes prescribed through private medical provision. The diffusion of this new drug in Australia, in comparison with other innovations, has been very rapid.[19]

The numerous clinical studies evaluating the histamine H_2-receptor antagonists have shown their effectiveness in the carefully defined circumstances of those clinical trials. However, such studies cannot be used to indicate the effectiveness of the drugs when freely prescribed

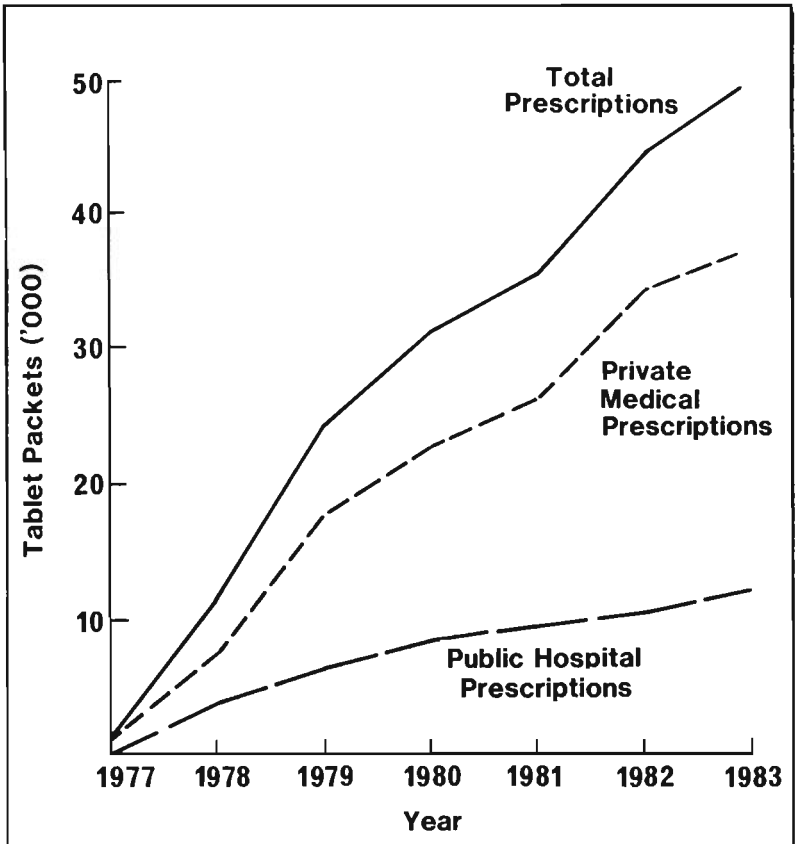

Fig. 1 - Temporal diffusion of cimetidine in Queensland, 1977 to 1983

Source: Information supplied by Smith Kline and French Laboratories (Aust.) Ltd. and Central Drug Store of the North Brisbane Hospital Board, 1983.

in the real world of gastroenterological practice. To shed light on this matter the controlled clinical trial is not appropriate.

The purpose of this paper is to determine if the prescription of histamine H_2-receptor antagonists has had an effect on a major therapeutic alternative for peptic ulcer, that is, surgery. In other words, to what extent has this new drug therapy become a substitute for surgical therapy? Our analysis will be conducted on separate data

for gastric ulcer and duodenal ulcer. This will enable us to determine if cimetidine is having a differential impact on stomach and duodenal ulcers.

DATA AND METHODS

The first studies to address this question appeared in 1981. Fineberg and Pearlman, using sample data on United States short-term hospitals, found that the annual numbers of surgical procedures (partial gastrectomy and vagotomy) for peptic ulcer were significantly fewer after cimetidine was introduced.[20] A British study, using aggregated data from six hospitals, reached a similar conclusion for duodenal ulcer.[21] Subsequently a number of other studies have been published, though some are merely anecdotal in nature and others undertake no statistical tests on the data.[22]

It is clear from the above that all studies mentioned are subject to qualification as a result of data sources and/or method. It is evidently necessary to analyse not the *absolute* number of surgical procedures, as has been done by all authors, but rather a surgical *rate*. The data set that we will use to shed light on this matter is the Queensland Hospital Morbidity Collection. This collection is a total enumeration of all patient separations (male and female discharges) from all hospitals (public and private) for all patient classes (public and private, where the latter term includes intermediate ward accommodation) in Queensland. The Queensland Department of Health and the Australian Bureau of Statistics co-operate in the collection and compilation of the data. The data include, *inter alia,* standard demographic details, primary diagnosis and principal medical procedure for all separations.[23] Primary diagnosis is coded by reference to the various revisions of the International Classification of Diseases (ICD),[24] and medical procedures by use of the English *Code of Surgical Operations* and, since 1979, by the WHO system.[25] There is no way by which the comparability of the morbidity data, coded by these four documents, can be determined. However, in coding cause of death by the eighth and ninth revisions, the Australian Bureau of Statistics found that, in 1979, there was a perfect correspondence between the two revisions with respect to the diagnostic codes relevant to peptic ulcer.[26] Thus there is indirect evidence to indicate that we may have confidence in regarding the data from 1969 to 1981 as consistent.[27]

We comment on one more preparatory point. In recognition of the problem of non-correspondence in the coding of surgical procedures, a wide definition of ulcer surgery has been adopted. In other words, we have included more codes than unqualified 'partial gastrectomy' and 'vagotomy'. The guiding principle of choice was to construct a

time series of data that is as consistent as possible. This objective is achieved by using a wide rather than a narrow definition. The effect of this specification is to make our conclusions conservative. By this we mean that if cimetidine has been able to substitute for surgery, the base from which our comparisons will be made, by including some procedures which cimetidine is not likely to affect, will be such as to underestimate the substitution.

Our method of analysis is to calculate a surgical rate (number of partial gastrectomies and vagotomies per 10,000 population) for persons with ICD diagnostic codes 531 (gastric ulcer) and 532 (duodenal ulcer). The numerator was obtained by extracting from the Hospital Morbidity computer tapes all records with these two diagnostic codes. These records were then examined to determine the numbers of surgical procedures performed on the persons with these diagnostic codes. The data thus obtained were then divided by the population of Queensland. These procedures were adopted for all years from 1969 to 1981, the latest year for which hospital morbidity data are available.

Linear regression equations were then fitted to the surgical rate data for the years 1969 to 1977. In other words, we have regarded 1977 as a pre-cimetidine year. Thus our equations are based on nine (annual) observations. Using these estimated equations, we have predicted the values for the four years from 1978 to 1981 and calculated the relevant

TABLE 1. Estimated Regression Equations for Numbers of Surgical Procedures per 10,000 Population for Gastric Ulcer, Duodenal Ulcer and Both Categories of Ulcer, Queensland, 1969-1977.

Ulcer Category	Estimated Equations
Gastric Ulcer	rate = 0.9533** + 0.03984t*
	(0.1113) (0.01978)
Duodenal Ulcer	rate = 1.3510** − 0.02387t
	(0.08138) (0.01446)
Gastric and Duodenal Ulcer	rate = 2.2670** + 0.01859t
	(0.11240) (0.01997)

Source: Queensland Hospital Morbidity Collection, Australian Bureau of Statistics, *Australian Demographic Statistics June Quarter 1983,* ABS, Canberra, 1983, Table 3; Australian Bureau of Statistics, *Queensland Demography,* ABS, Brisbane, 1974, Table 1.

Notes: Standard errors of the estimates are indicated by the data in brackets.
* Significant at the 5 per cent level.
** Significant at the 1 per cent level.

95 per cent confidence intervals associated with the equations in the four years to 1981. This enables us to compare the actual observations with the values predicted by the estimated equations based on the surgical rates in the pre-cimetidine period.

RESULTS

Linear regression equations provided reasonable fits to the annual data.[28] The results are reported in Table 1 for gastric and duodenal ulcer and both ulcer categories combined.

We obtained one negative and two positive slope coefficients for our three equations. The positive slope coefficient for gastric ulcer is significant at the five per cent level, indicating that the increase in gastric ulcer operations per 10,000 population in the period 1969 to

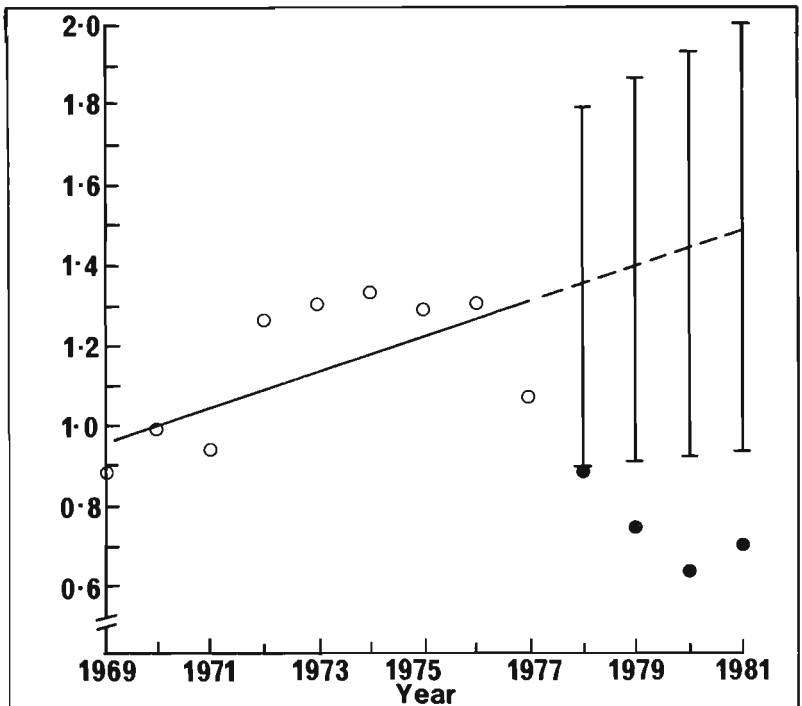

Fig 2- Surgical Procedures / 10,000 Population for Gastric Ulcer, Queensland, 1969 to 1981

Source: Queensland Hospital Morbidity Collection, Australian Bureau of Statistics, *Australian Demographic Statistics June Quarter 1983,* ABS, Canberra, 1983, Table 3; Australian Bureau of Statistics, *Queensland Demography,* ABS, Brisbane, 1974, Table 1.

1977 is meaningful. However, the negative slope coefficient for duodenal ulcer and the positive slope coefficient for both categories of ulcer are not significantly different from zero. Using these three regression equations we have calculated the predicted values for the four years to 1981. Figures 2, 3 and 4 indicate our results for gastric ulcer, duodenal ulcer and both categories of ulcer together. The 95 per cent confidence intervals for the years 1978 to 1981 are indicated by the vertical lines in each figure.

Figure 2 indicates that all four post-cimetidine observations are less than the predicted values and furthermore that all four observed values in the post-cimetidine period lie outside the lower end of the relevant 95 per cent confidence intervals. These results indicate that there is a phenomenon (a decline in the surgical rate for gastric ulcer) that requires explanation. This decline has occurred shortly after the introduction of cimetidine, which suggests that cimetidine may be the causal factor.

It is noteworthy that the 1977 observation in Figure 2, which we have interpreted to be a pre-cimetidine value, lies well below the

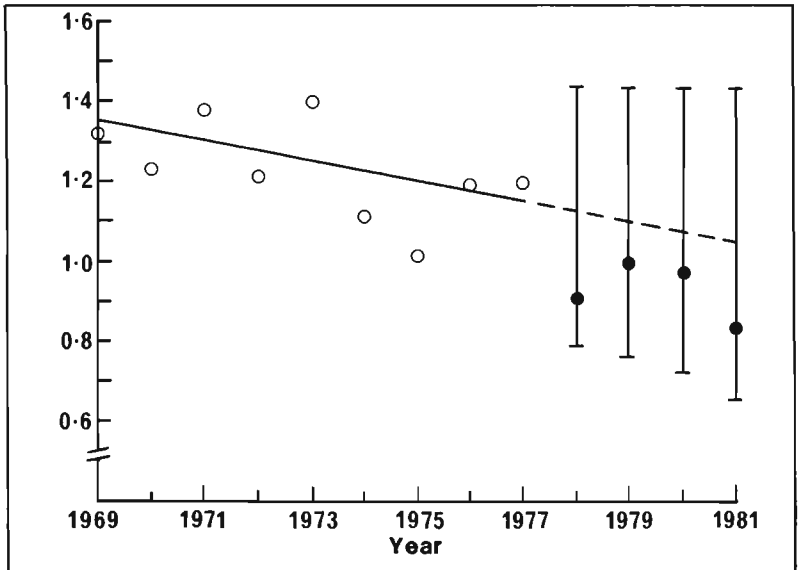

Fig 3– Surgical Procedures/10,000 population for duodenal ulcer, Queensland, 1969 to 1981

Source: Queensland Hospital Morbidity Collection, Australian Bureau of Statistics, *Australian Demographic Statistics June Quarter 1983,* ABS, Canberra, 1983, Table 3; Australian Bureau of Statistics, *Queensland Demography,* ABS, Brisbane, 1974, Table 1.

estimated regression line. Given that cimetidine was marketed in late May 1977, it is conceivable that this low 1977 observation may be explained by the decline in surgery for gastric ulcer which occurred in the second half of 1977. Another factor which could explain this low surgical rate might be people's decisions to postpone surgery in the expectation that cimetidine would be efficacious for them. Our analysis of the data by six-month time periods indicates that this did in fact occur.

The results for duodenal ulcer, depicted in Figure 3, are somewhat different from those for gastric ulcer. As with gastric ulcer, all four

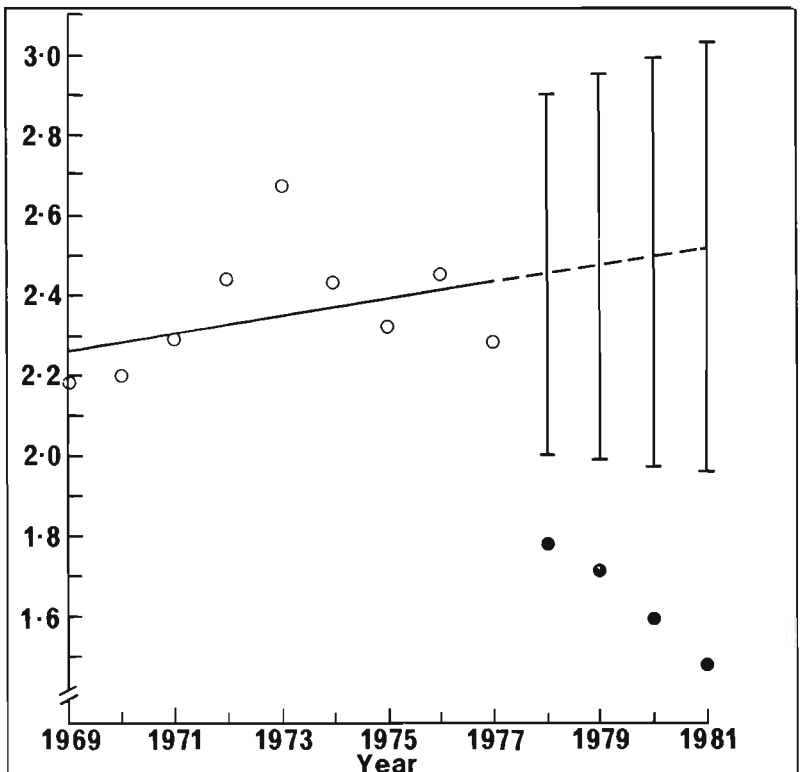

Fig 4- Surgical Procedures/10.000 population for gastric and duodenal ulcer, Queensland, 1969 to 1981

Source: Queensland Hospital Morbidity Collection, Australian Bureau of Statistics, *Australian Demographic Statistics June Quarter 1983,* ABS, Canberra, 1983, Table 3; Australian Bureau of Statistics, *Queensland Demography,* ABS, Brisbane, 1974, Table 1.

post-cimetidine observations are less than the predicted values. However, in marked contrast to the gastric ulcer results, all four observations lie well within the relevant 95 per cent confidence intervals. In other words, these lower than predicted observations could have occurred by chance. These results can be interpreted as indicating that cimetidine has not had a significant effect on the surgical rate for persons with diagnoses of duodenal ulcer.

The 1977 observed value, which has been interpreted as being in the pre-cimetidine period, lies above the estimated regression line. This is in contrast to the 1977 observation for gastric ulcer, which was well below the estimated equation. In fact, the surgical rate for duodenal ulcer in 1977 was the highest since 1973. The number of operations in the second half of 1977 in fact *rose* in comparison with comparable time periods for all years from 1973. Thus the 1977 observation also indicates that there is a difference between gastric and duodenal ulcer since the introduction of cimetidine.

In Figure 4 the effect of cimetidine on both categories of ulcer is indicated. As with gastric ulcer, all four post-cimetidine observations are less than the predicted values and all lie well outside the 95 per cent confidence intervals. In other words, the relatively large decline in the gastric ulcer surgical rate has been such as to outweigh the relatively small decline in the duodenal surgical rate. It is noteworthy that this study has indicated that an aggregate analysis (as indicated in Figure 4) conceals an important difference in the efficacy of cimetidine on stomach and duodenal ulcer. This is a result that has not been found in clinical trials of cimetidine.

DISCUSSION

Our analysis of surgical rates for gastric and duodenal ulcer in Queensland indicates that there have been temporal declines since 1977 which require explanation. These declines have coincided with the introduction of a pharmacological agent (cimetidine) which suppresses gastric acid secretion which in turn facilitates natural healing of mucosal lesions in the upper gastrointestinal tract. However, we have found that there is a statistically significant difference between the reductions in surgery for stomach and duodenal ulcers. The decline in the gastric ulcer surgical rate is considerably larger than that for duodenal ulcer, and all post-cimetidine observations lie outside 95 per cent confidence intervals, whereas all post-cimetidine observations for duodenal ulcer are within these confidence intervals. This could be interpreted as evidence which indicates that the efficacy of cimetidine is not uniform between the stomach and duodenum, a point which has not been reported in any clinical trial of the efficacy of cimetidine.

The randomised clinical trial is the most appropriate research strategy for determining the effectiveness of medical therapies.[29] However, the studies using this experimental design cannot indicate the efficacy of cimetidine when prescribed in the real world of clinical medicine. If interest is focussed on this question of efficacy in a non-controlled environment, then the nature of the study being undertaken can be described as a 'general association' one.[30] By this is meant that neither exposed nor non-exposed, diseased nor non-diseased cases are examined; rather the work involves a 'passive' mathematical exercise undertaken on sets of general data not generated for the specific problem under investigation. This is an appropriate description of studies such as we have undertaken here. We have examined and analysed statistics from various sources and attempted to draw conclusions based on statistical inference.

However, a study such as this cannot provide conclusive evidence. The results suggest that there has been an effect on stomach and duodenal surgical rates. This effect has been shown to be non-uniform. Clearly cimetidine has not replaced (or displaced) surgery in a complete way. If cimetidine were a perfect substitute for surgery then the surgical rates for ulcers would approach zero through time. Our data do not show such a trend. Put otherwise, these results indicate that cimetidine, rather than being a perfect substitute for surgery, is an imperfect substitute.

This conclusion is, in a sense, the most notable result of this study. In terms of forming judgements about innovations in medicine, reliance is placed on the results of the randomised clinical trial. The clinical trials of cimetidine, typically, are of a short duration, usually three months. The common procedure is to establish the existence of an ulcer, prescribe cimetidine to one group of patients and a placebo to another group of patients, both patients and doctors being in a state of ignorance (until the trial is completed) as to which patients are on cimetidine or placebo. After three months each patient is once more examined by radiology or endoscopy to determine the extent of ulcer healing. Such experiments have shown that cimetidine is a powerful healing agent.

The results of randomised clinical trials present a 'rosy' picture of the drug's efficacy. The following is a typical conclusion:

> After 28 days, 85 per cent of patients receiving cimetidine showed ulcer healing, compared with 25 per cent receiving placebo ($P < 0.0005$). Patients receiving cimetidine had significantly more pain-free days and pain-free nights than those receiving placebo. There was good correlation between ulcer healing and symptomatic relief ($P < 0.0005$).[31]

The results we have reported here (for four post-cimetidine years in the real world of clinical medicine), in terms of declines in surgical

rates, are in marked contrast to results expressed in terms of endoscopically-verified ulcer-healing and patient-reported symptomatic relief after relatively short periods in a controlled clinical trial. Explanations for this difference need to be sought.

First, it is possible that the persons in the clinical trials may be subject to a 'Hawthorne effect' as a result of their knowing that they were part of an experiment. For example, they may be more careful to take tablets at the stipulated time than the non-observed general population. Second, the differences may be explained by the interaction of a number of inter-related matters. Ulcer diseases are, by their nature, recurrent. Hence it is important to consider the efficacy of a therapy over a number of illness episodes, and to avoid basing judgements on only one episode. The randomised clinical trials of cimetidine have been predominantly concerned with short run efficacy and it has been only more recently that sufficient time has elapsed for the results of long term maintenance therapy trials to be reported. This temporal factor ties in with a related matter, *viz.* that health (and illness) is a multidimensional phenomenon. The clinical trials have relied mainly on two measures: endoscopically-indicated ulcer-healing, and patient-reported symptomatic relief. (Not all trials have reported a correlation between these two measures.) By implication, a study such as that reported here relies on a general measure which can be described as 'indications for surgery'. It is not possible to measure this: what can be observed is the effect — ulcer surgery. If the general measure could be observed it would be ulcer morbidity which was unresponsive to alternative therapies, with the patients subject to acute pain and/or haemorrhage.

The explanation for this difference between the results of clinical trials and the results reported here is more likely to be the second factor. If this is the case then there is an important point to be noted. With respect to forming judgements about new technologies in the health sector, reliance on the results of short term clinical trials may be somewhat misleading. Technology assessment, if one aspires to accuracy, may have to wait some time, in fact, years, before verdicts can be brought down on innovations in medicine.

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