



CIMETIDINE AND THE TREATMENT OF DUODENAL ULCER

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Abstract.Cimetidine and the treatment of duodenal ulcer.

This thesis examines the clinical development of the H₂-receptor antagonist cimetidine as a treatment for duodenal ulcer disease.

The work was carried out at the Royal Adelaide Hospital between 1976 and 1980, and partly in collaboration with Prince Henry's Hospital, Melbourne.

In Chapters one and two the historical evolution, aetiology and pathogenesis of duodenal ulcer disease are reviewed. The importance of acid-pepsin secretion by the stomach is emphasized. Chapter 3 describes the development and pharmacology of the histamine H₂-receptor antagonists, with particular emphasis on cimetidine.

A clear picture of the course and prognosis of duodenal ulcer is essential to allow logical design of treatment trials and to provide a yardstick against which the results of a new treatment can be judged. Chapter four provides a critical review of published studies on the natural history of duodenal ulcer and indicates the problems of interpreting existing data. The choice of different ways of expressing the course and outcome of this chronic, relapsing (but rarely fatal) disease is identified as an important factor contributing to controversy over the prognosis of duodenal ulcer.

In Chapter five the design of clinical trials in general and the particular methods that were chosen for the Adelaide studies are discussed. The importance of ethical safeguards, control groups, random allocation and choice of clear criteria

of response is emphasized.

The results of treatment of 85 duodenal ulcer patients with cimetidine for six weeks are presented in chapter six. Eighty four percent of cimetidine treated patients and thirty eight per cent of patients receiving placebo had healed ulcers, judged by endoscopy. Assessment of pain and antacid use confirmed the advantage of cimetidine over placebo in producing rapid relief of symptoms.

Longer term trials of cimetidine treatment were then undertaken. Following initial ulcer healing with a short course of cimetidine fifty six patients were randomly allocated to treatment with cimetidine or placebo for one year. The results demonstrated that ulcer relapse which occurred in most patients receiving placebo could be prevented in the majority of patients by cimetidine. (Chapter seven).

To try and assess whether prolonged cimetidine treatment conferred any lasting benefit, treatment was changed to placebo at the end of one year in a further double blind study (chapter eight). Ulcers recurred at a similar rate to that found in patients who had received only six weeks cimetidine to heal their ulcer. It was concluded that prolonged cimetidine treatment was unlikely to alter the natural history of duodenal ulcer disease, once the drug was stopped.

This observation raised the question of how cimetidine should best be used for the longer term management of duodenal ulcer. In order to attempt to answer this a further one year study was devised. Patients were randomly allocated to continuous maintenance treatment with cimetidine or intermittent

short courses of the drug for each recurrence (chapter nine).

Throughout all these studies no serious side effects attributable to cimetidine occurred. Small elevations in plasma creatinine were found (usually within the normal range) without significant impairment of renal function. One interesting observation was the interaction of cimetidine with warfarin and phenytoin (chapter ten). Further investigation supported the concept that cimetidine inhibits hepatic microsomal oxidation of drugs metabolised by this route.

The number of patients required to confirm the safety of the drug is much greater than the relatively small number of patients studied during these trials. Chapter ten therefore examines the safety and side effects of cimetidine by reviewing all available sources of information from clinical studies to spontaneous reports of adverse events. Minor unwanted effects are uncommon and serious side effects are extremely rare. In only a handful of the twenty million or more patients treated worldwide has cimetidine been thought to be a factor that may have contributed to their death. The safety of cimetidine as a life long treatment for peptic ulcer remains to be demonstrated.

STATEMENT

This thesis contains no material which has been accepted for the award of any other degree or diploma in any other university. To the best of my knowledge the thesis contains no material previously published or written by another person, except when due reference is made in the text of the thesis.

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Professor David Shearman initiated the work and has continued to guide and support each study to completion.

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DAVID HETZEL

CHAPTER I

DUODENAL ULCER - A DISEASE OF THE TWENTIETH CENTURY



Duodenal ulcer before 1900.

Duodenal ulcer is now such a commonplace disease that it is hard to believe that it was a rarity a hundred years ago. Gastric ulcers, as a pathological entity had been documented since the sixteenth century. Morgagni mentioned ulcers of the stomach in relation to arsenic poisoning and Albertus in 1725 refers to the perforation of a gastric ulcer as a rare cause of sudden death (Jennings 1940). However it was not until the nineteenth century that Rokitanski and Cruveilhier clearly traced the connection of the typical symptom pattern of peptic ulcer with the anatomical alterations of the disease. At that time it was gastric ulcer that predominated. For example Willigk in mid nineteenth century Prague found at post mortem 225 cases of gastric ulcer but only 6 cases in which the duodenum was affected. At Guys Hospital in London, of 1765 autopsies performed between 1826 and 1892 duodenal ulcer or scarring was mentioned in only 0.4% (Perry and Shaw, 1893).

The dearth of reports of duodenal ulcer may partly be ascribed to underrecognition: it was impossible to make a certain diagnosis while the patient remained alive. Perforation or severe haemorrhage from a duodenal ulcer could hardly have been completely overlooked but were infrequently described even in the mid nineteenth century. When Charles Reeves wrote his textbook "Diseases of the stomach and duodenum" in 1856 his review of the literature found descriptions of only 31 patients who had died from duodenal ulcer, 17 of whom died from perforation (Reeves 1856). Brinton in 1867, in a comprehensive discussion of gastric ulcer, does not mention duodenal ulcer except in association with burns (Brinton 1867).

Jennings has reviewed the dramatic changes in the age incidence and sex distribution of patients with perforated peptic ulcer, which have occurred in the last 150 years (Jennings 1940). It seems that between 1850 and 1900 most perforations were of gastric ulcers. Of every 6 patients with perforations three were young women, one was an elderly woman, one an elderly man and only one a young man. Jennings concluded that perforations of the body of the stomach mainly in young women, formed a sharply defined group which started at the beginning of the nineteenth century and faded out by 1920.

Duodenal ulcer after 1900

The earliest account of the modern pattern of occurrence of perforated duodenal ulcer was from Sweden. Bager tabled all cases of perforation at 50 Swedish Hospitals from 1911 to 1925 (Bager 1929). The incidence in women remained at 12-25 cases per annum but that in men increased from 25 cases in 1911 to over 50 by 1914, and after a stable period during World War 1 there was a steep increase to over 125 cases per annum by 1925. This remarkable increase occurred in "pyloric perforations in young men".

These changes were reflected worldwide. In 1904 Will and Charles Mayo had operated on 58 chronic or perforated duodenal ulcers (Mayo 1913) and in England in the first decade of the twentieth century Lord Moynihan was demonstrating this "new disease" to Arthur Hurst (Moynihan 1912). Thus duodenal ulcer was coming to be recognised as an important and frequent disorder. It became a major cause of morbidity as well as mortality especially in males of

working age and in the armed forces in the 1920's and 1930's (Ivy 1946). The changing pattern was mirrored by an increase in the ratio of duodenal ulcer to gastric ulcer of 3 or 4 to 1 during the mid twentieth century.

Another source of information, mortality rates, confirmed the increasing frequency of duodenal ulcer as a cause of death in the first half of the twentieth century (Langman 1979). Mortality rates are of course a crude reflection of the incidence of a disease like peptic ulcer which is rarely fatal. High death rates may be associated with high overall incidence rates, but may also reflect inadequate health care, an elderly or low socio-economic status of the affected population in that area, differences in frequency or carefulness of post mortem examinations or merely a variation in coding practices on death certificates (Langman 1979).

Despite these limitations, changes in mortality rates have revealed some remarkable patterns. Susser and Stein considered the annual death rate in Great Britain from gastric and duodenal ulcer between 1825 and 1935 in relation to age, sex and the year of birth, (Susser, Stein 1962). Examination of cohorts of different age groups showed a progressive rise in death rates in all cohorts born in the years up to about 1885-1900, with a decline in death rates, particularly for the 15-24 years old, 25-34 years old and 35-44 years old cohorts born in subsequent years. They came to the startling conclusion that the generation born in the last quarter of the nineteenth century was exposed to the greatest risk of death from the disease and that this risk was carried onward throughout their life. The maximum risk of

dying from duodenal ulcer existed for those born around 1890. Susser and Stein suggested that this may represent either a disease of the early phase of urbanization or it may be a result of conditions in World War 1, since this was the generation most affected by the war. This hypothesis of an environmental influence acting maximally in the late nineteenth century is certainly compatible with a rise in mean patient age in the twentieth century and a decreasing frequency of new cases but leaves a more precise cause and mechanism unexplained.

Autopsy studies have been used as a source of information on ulcer frequency, but are also beset with problems of interpretation. The findings at postmortem will obviously depend on the care with which the stomach and duodenum were examined for scarring as well as ulcer, while the selected nature of the necropsy population and special interests of the hospitals which are served may make evaluation of results impossible. Even when these problems are borne in mind it is clear that ulcer in the western world can be very common. Watkinson has emphasised the value of meticulous post mortem examination in prospective surveys of all hospital deaths, or of sudden deaths unrelated to ulcer (Watkinson 1960). He found that in Leeds, England after exclusion of ulcer deaths, approximately 20% of men and 10% of women had evidence of past or present peptic ulcer. In approximately 15% of men and 6% of women the ulcer disease was duodenal. Similar high frequencies have been found in Sweden (Lindstrom 1978) and Holland (Levij, De le Fuente 1963). Watkinson also coordinated a similar national U.K. survey which found ulcer with approximately half this frequency - the difference being accounted for almost entirely by a

lower reported incidence of ulcer scars (Watkinson 1960).

The best method of determining ulcer frequency is by surveying a random population sample or whole population of known age and sex structure in a defined area. By this method disease incidence (the number of new cases in a known time interval for a set population) or prevalence (the total number of patients having the disease, irrespective of date of diagnosis, in a set population) can be measured. A pre-requisite is of course that some simple means of making the diagnosis is readily available.

With the development of radiological techniques in the 1920's and 1930's, studies on the incidence of uncomplicated duodenal ulcer in living populations were first made possible. Criteria were agreed for the diagnosis of the disorder in patients who had not suffered complications or died. By the 1940's a number of centres world wide had the techniques available to appraise the incidence or prevalence of duodenal ulcer in a defined population. The results of a number of population surveys from various parts of the world where ulcer is common are shown in table 1.1, with an indication of the different survey methods.

The apparent uniformity of these figures conceals a much wider variation in the world wide distribution of ulcer and also local regional variation. The clinical presentation, complications and sex ratio also show considerable differences. Sophisticated (and demanding) population surveys have not been widely applied and simpler clinical statistics such as hospital admission and complication rates have to be used. Table 1.2 (adapted from Langman, 1979) illustrates some of these differences when evidence from various sources is combined.

Table 1.1

Percentage frequency of all peptic ulcer in some population surveys.

Author (country)	Diagnosed Ulcer	Likely Ulcer	All dyspepsia and ulcer.
Doll et al 1946 ¹ (London U.K.)	5.2	1.3	31.0
Weir and Backett 1968 ² (Aberdeen,UK)	9.9	5.2	35.2
Malhotra 1964 (Assam, India)	8.4	15.1	28.4
Mendeloff and Dunn 1971 ³ (USA)	2.5	-	-
Gillies & Skyring 1969(Sydney,Aust) [*]	7.2	-	-
Medalie et al 1974 ⁴ (Israel)	8.9	-	-

* Males and females. The other studies refer to men only.

1. Questionnaire, and clinical and radiological examination if appropriate..
2. Questionnaire, hospital record check and 3 year follow up.
3. Questionnaire alone, to detect recent symptomatic disease.
4. Questionnaire, clinical examination and five year follow up.

Table 1.2

Ulcer frequency in some different parts of the world during the mid twentieth century.

<u>Country</u>	<u>Clinical Characteristics</u>	<u>Regional Characteristics</u>
Africa	Almost entirely duodenal. Stenosis and obstruction frequent. Almost entirely men.	Common near the equator. West Coast, Nile/Congo watershed. Rare in north savannah of West Coast, N.Nigeria, Zaire, Zambia.
Australia	Duodenal and gastric ulcer common. DU two to five times as frequent as GU. Relatively high frequency of gastric ulcer in younger women.	Gastric ulcer (and analgesic abuse) may be especially common in New South Wales, Queensland.
Europe	Duodenal and gastric both common (DU two to four times as frequent as GU)	No recognised areas of rarity. Some regional variation e.g. DU three times as frequent in Scotland as in S.England.
India	Almost entirely duodenal. Stenosis and obstruction frequent. Haemorrhage relatively infrequent. Almost entirely men (18:1)	Common in South and in Assam. (staple rice diet) Infrequent in North (unrefined wheat diet).
North America	Duodenal ulcer common. Gastric ulcer probably less frequent than in Europe.	Probably fairly even.

This information should help to dispel the myth that duodenal ulcer is solely a disease of "western civilisation" (Malhotra 1964, Malhotra 1967, Tovey, Tunstall 1975).

Duodenal ulcer after 1950

The frequency of duodenal ulcer in westernized countries continues to change. Just as Susser and Stein showed a peak incidence of duodenal ulcer in the generation of men born in the 1890's, so it follows that cohorts of Englishmen born since 1900 exhibit a gradual decline in incidence of duodenal ulcer. There is considerable evidence that the disease reached a peak prevalence in the mid 1950's and is now slowly declining. The decline in mortality rate from duodenal ulcer after 1950 is supported by a decline in the incidence of newly diagnosed duodenal ulcer. Pulvertaft's population survey in York, England found an annual incidence of active duodenal ulcer of 0.3% in 1952-54 and only 0.15% in 1961-63 in urban living men (Pulvertaft 1968). Other surveys of more restricted populations confirm a decline in incidence of duodenal ulcer in insured doctors in the U.K. (Meade et al 1968) and in physicians in Massachusetts, U.S.A. (Monson, McMahon 1969) in the 1960's.

Further data indicating a decreasing incidence of duodenal ulcer are found by considering the incidence of hospital admissions - both elective and for perforated duodenal ulcer. The U.K. hospital inpatient enquiry (H.I.P.E.) samples 10% of all discharges and deaths annually. From 1958 to 1972 gastric ulcer admission (and perforations) declined by 37% (perforations 42%) and duodenal ulcer admissions by 12.5% (perforations by 11%) (Brown, Langman, Lambert 1975).

Similar trends have been found in Oxford U.K. (Sanders 1967), in the west and north-east of Scotland (Weir 1960, MacKay 1966) and in non Federal, short term hospitals in the USA (Elashoff, Grossman 1980).

Recent analysis of the HIPE data up to 1977 confirms the continuing reduction in total admissions and perforations (Coggon, Lambert, Langman 1981). Within this overall pattern there was a wide variation between subgroups. For example, admissions for perforated duodenal ulcer in men aged less than 45 years declined by 40-50%, with less decline in older men and a 40-50% increase in admissions in women aged over 65.

The ebbing of the flood of duodenal ulcer particularly in younger men has been at least partially responsible for a recent reduction in male domination of the sex-ratio (e.g. in perforated duodenal ulcer male: female ratio was 19:1 in 1930 but 6:1 in 1958) (MacKay 1966) and rise in mean patient age and incidence in the elderly (Bonnievie 1975a).

The reasons for the continuing chronological changes in the incidence of peptic ulcer are unknown. The dramatic alterations in incidence, easily detected during a few decades, attest to the importance of some environmental factor or factors in the aetiology of peptic ulcer.

The variations found in the British H.I.P.E. data between subgroups of different age and sex do not support Susser and Stein's concept of a simple cohort phenomenon, but suggest that one or more factors are having different effects at different ages. Changes in some of the putative risk factors for ulcer, such as diet, alcohol, smoking and drugs do not provide an adequate explanation for many of the changing trends and other environmental factors must await identification (Coggon et al 1981).

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The weight of evidence suggests that the decline in incidence of ulcer in the 1960's is real but the reasons for this change are uncertain. It cannot be ascribed to new potent methods of treatment, as the decline started before the free availability of these agents in the late 1960's. The fact that perforations have also decreased, even though they are often the presenting feature of an ulcer, also makes it unlikely that improved treatment is responsible for reduced ulcer prevalence. It seems ironic that just as we are embarking on a new era of highly effective medical and surgical treatments for peptic ulcer, the disease is spontaneously becoming a decreasing problem.

CHAPTER II

THE PATHOGENESIS OF DUODENAL ULCER

Introduction

In most patients the cause - or causes - of duodenal ulcer is unknown. A number of aetiological "risk factors", the possession of which increase the chance of a subject developing duodenal ulcer, have been identified (Table 2.1) but the pathophysiological mechanism with which they are linked or through which they might act are largely unidentified.

When duodenal ulcer has become established it is possible to compare ulcer patients with groups of normal subjects with respect to a host of anatomical and physiological functions. In this way a number of abnormalities have been identified (Table 2.2). Most of these abnormalities involve acid-pepsin and its regulation. This bias is partly inevitable, as these secretions are accessible and hence have been intensively investigated and is partly deliberate in the context of this thesis.

It must be emphasized that it is not known whether these physiological alterations precede the ulceration or whether they are a consequence of it. They cannot automatically be assumed to be a cause of the ulcers. Theoretically they could be coincidentally linked with an aetiological process, aggravate unrecognised aetiological disturbances or even represent a 'protective' reaction against the aetiological factors or the mucosal damage.

It is also important to recognise that even the strongest risk factors or most striking physiological abnormalities yet identified are only present in a minority of patients.

TABLE 2.1

Risk factors which may predict an increased risk of developing DU

Male sex

First degree relative with D.U.

Blood group O

Nonsecretion of ABO blood group antigens in saliva HEREDITARY

Inherited elevated serum pepsinogen I.

? HLA Antigen B5

Birth in years 1875 - 1925

Cigarette smoking

? coffee/cola consumption during college years

? social/geographical factors

ENVIRONMENTAL

Chronic renal failure

Chronic obstructive pulmonary disease

Alcoholic cirrhosis

Zollinger Ellison syndrome/G cell hyperplasia

Retained antrum after Bilroth II-jejunal ulcer

Extensive small intestinal resection

MEA type I.

? psychological factors

ASSOCIATED
DISEASES

Table 2.2

Abnormalities of gastric function found with increased frequency in patients with duodenal ulcer.

Increased numbers of parietal cells.

Increased peak acid output (PAO) in response to pentagastrin/histamine.

Increased fasting (BAO) and nocturnal acid and pepsin secretion.

Increased parietal sensitivity to secretagogues.

Decreased acid induced inhibition of meal stimulated acid secretion.

Increased meal stimulated gastrin release.

Impaired acid induced inhibition of gastrin release.

Increased acid-pepsin load to duodenum.

Increased gastric emptying.

Increased serum Pepsinogen I.

In all parameters of physiological or pathophysiological function a range of responses can be identified and there is extensive overlap between those found in duodenal ulcer and normal subjects. Ulcers presumably develop for different reasons in different patients. Many of the alterations of gastrointestinal function listed in table 2.2 have been assessed in only a very small number of patients and controls. How far the results obtained in a selected few patients can be extrapolated to the entire population of duodenal ulcer is unknown.

One other basic problem that sometimes causes confusion in both epidemiological and experimental studies is the varying definition of "duodenal ulcer" patients and normal controls. Endoscopy is now accepted to be the most accurate technique for determining presence or absence of ulcer, but much of the published data relies on radiological, surgical or autopsy confirmation of the diagnosis. Sometime symptoms pattern alone is thought to justify the diagnosis- and absence of symptoms universally accepted to identify 'normal' controls.

Acid-pepsin versus mucosal resistance.

Two fundamental observations indicate that gastric secretion of acid and pepsin plays at the least a permissive role in the causation of duodenal ulcer.

1. *Ulcer site.* Chronic peptic ulcers occur only in those parts of the gut that are exposed to acid and pepsin. This includes the oesophagus, stomach, first part of duodenum, those Meckel's diverticula which contain acid-pepsin secretory mucosa and (following surgery) other parts of the gastrointestinal tract which have become exposed to gastric

acid and pepsin. Conversely if acid and pepsin are diverted away from an established ulcer, this will heal and not recur. Simple excision of an ulcer does not cure the disease: recurrence is the rule. Thus an ulcer is only a symptom of ulcer disease.

2. *No acid, no ulcer.* Schwarz first enunciated this rule in 1910 and it still holds true. (Schwarz 1910, 1925).

Duodenal ulcer has never been reported in a patient who does not secrete readily detectable amounts of acid. It is extremely rare to find patients with duodenal ulcer who do not secrete at least 10mmol/hour in response to conventional histamine or pentagastrin stimulation (Baron 1963a, Wormsley & Grossman 1965, Kronberg & Christiansen 1977). In contrast gastric ulcer may occur in patients in whom acid secretion is barely detectable with conventional tests despite so called "maximal stimuli". In a few case reports no gastric acid secretion was detectable (Isenberg et al 1971, Duberstein and Efrusy 1977). Although it is conceivable that more sophisticated techniques might demonstrate small quantities of acid, this observation makes it clear that factors other than acid play an important role in the development of gastric ulcer.

The fact that acid-pepsin is an indispensable factor in the formation of duodenal ulcers should not be construed as meaning that an increase in acid-pepsin secretion is necessary to produce ulcer. That duodenal ulcers are also caused by factors other than excess secretion of acid and pepsin is suggested by the results of secretory testing in normal controls and duodenal ulcer patients (Wormsley and Grossman

1965, Baron 1963a, Marks et al 1963). The average rate of acid-pepsin secretion is higher in duodenal ulcer patients than control subjects, but comparison of the results for each patient show that the groups overlap: only about 30% of patients with duodenal ulcer (and 10% with gastric ulcer) are "hypersecretors". Acid-pepsin levels are in the normal range in 70% of patients. Conversely even in patients with gross hypersecretion due to Zollinger Ellison syndrome a small proportion do not develop gastroduodenal ulcers (Ellison and Wilson 1964).

Schwarz postulated that ulcers arose from an imbalance between the autodigestive power of gastric juice and the resistance of the mucosa to digestion. It is this concept of "mucosal resistance" (or lack of it) that is usually invoked to explain ulcer in patients with normal levels of gastric secretion and the fact that ulcers are usually focal even in patients with gross hypersecretion. Current theories of the pathogenesis of gastric and duodenal ulcer still favour the concept (Isenberg et al 1978) and suggest that the relative importance of acid peptic "aggressive" factors and mucosal "defence" will vary from patient to patient even within the subgroups of duodenal or gastric ulcers.

Acid or pepsin: Which is more important?

Separation of the roles of acid and pepsin in the genesis of ulcer is difficult. Pepsin activity cannot be disassociated from that of acid because pepsin is only active in the presence of acid and becomes denatured if the pH rises above 4. Prolonged perfusion (5 hours) of the feline duodenum with acid alone in concentrations present in gastric juice overwhelms mucosal acid removing mechanisms and results

in mucosal damage. (Chung et al 1976). Oesophagitis, in a cat experimental model was produced by concentrated acid solutions (pH 1.0, 127mEq/l) alone and the addition of pepsin did not increase the severity of the oesophagitis probably caused by protein denaturation (Goldberg et al 1969). However between pH 1.6 and 2 (31 and 12mEq/l respectively) oesophagitis was only produced when pepsin was added. Other animal evidence suggests that much of the ulcerogenic potency of gastric juice depends on its content of active pepsin (Alphin et al 1977, Kamegashira et al 1977, Safaie-Shirazi 1977). An inhibitor of pepsin introduced into the stomach reduced the development of pentagastrin induced ulcers in cats (Lee et al 1976) and supports the pathogenetic role of pepsin.

What evidence is there to indicate that pepsin plays a role in peptic ulcer in man? The secretion of acid and pepsin into the gastric lumen tend to run in parallel despite their origin from different cells. (Hunt 1950, Janowitz, Hollander 1952, Venables 1969). Patients with duodenal ulcer secrete more pepsin than control subjects (Walker, Taylor 1976) and one group found that maximal pepsin secretion in response to pentagastrin was proportionately greater than acid secretion (compared with normal values) and hence provided better discrimination between duodenal ulcer patients and non duodenal ulcer subjects (Petersen, Myren 1975). Studies of serum pepsinogen I (the precursor of pepsin, see below) also show that this may discriminate better between duodenal ulcer and non duodenal ulcer subjects (Samloff, Liebman, Panitch 1975)

than direct tests of gastric secretion, although there is a close correlation (coefficient =0.74) between serum group I pepsinogens and peak acid output. (Samloff, Secrist, Passaro 1975).

One of the few observations that directly implicate pepsin in the pathogenesis of ulcer recurrence was the report of Elder and Smith that patients with active symptoms from their duodenal ulcer have hypersecretion of pepsin compared with patients who were in remission. (Elder, Smith 1975). This interesting study clearly needs to be confirmed.

Inhibitors of pepsin have been used in man as a treatment for peptic ulcers but conflicting results have been obtained. The agent that has been tried most extensively is sodium amylosulfate, (amylopectin sulfate, depepsen) a synthetic mucopolysaccharide that inhibits peptic activity, not by acting on pepsin but by combining with tissue proteins and rendering them less digestible by pepsin (Berstad 1974). A more effective long acting inhibitor of peptic activity is necessary to define the relative roles of acid and pepsin in the pathogenesis of duodenal ulcer. From a therapeutic viewpoint methods of treatment which elevate intragastric pH above 4 have the dual advantage of inactivating the potentially corrosive effects of pepsin as well as acid.

Abnormalities of acid-pepsin secretion

That gastric acid-pepsin is a sine qua non for the development of duodenal ulcer has been noted above. William Prout in 1823 when writing "on the nature of the acid and saline matters usually existing in the stomachs of animals" also examined human gastric secretion (courtesy of Sir Astley

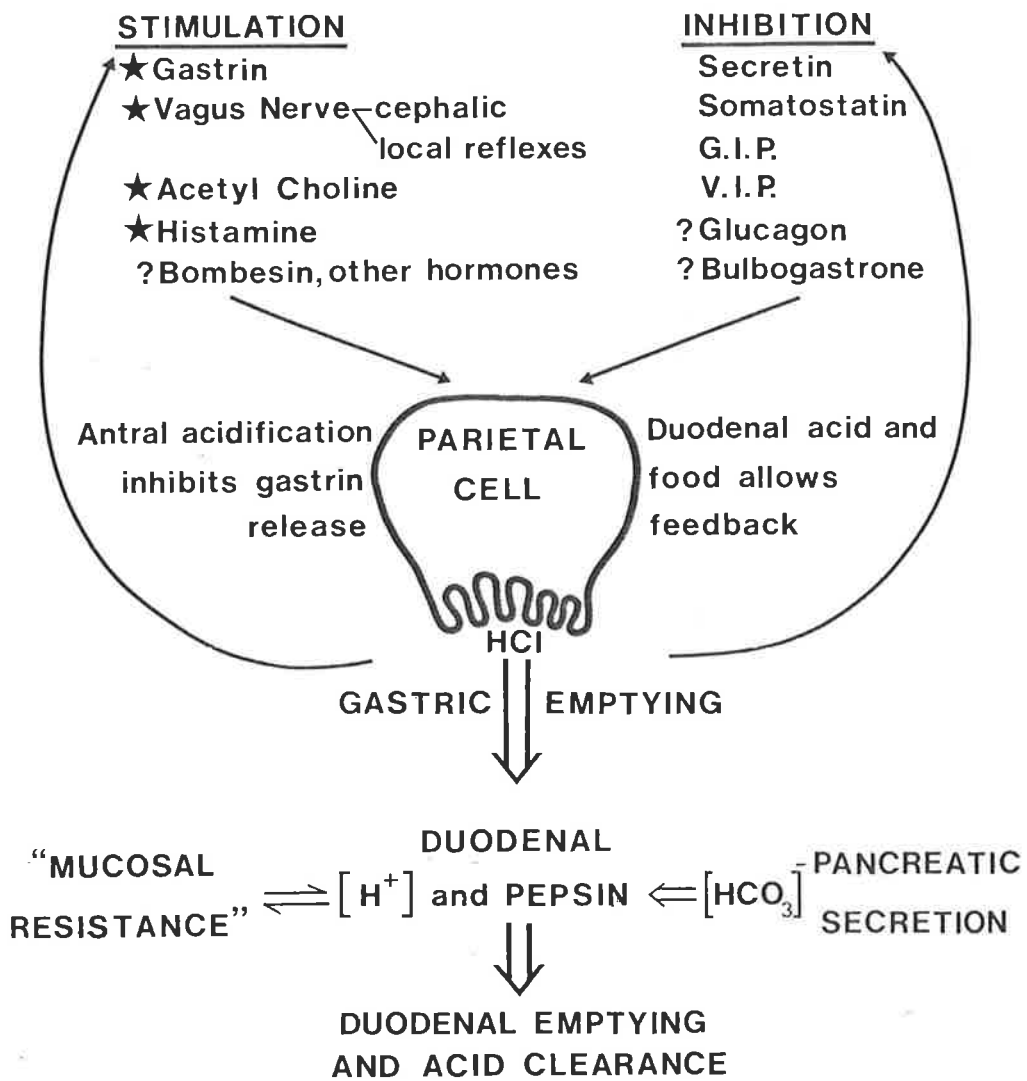
Cooper) and noted "I have also uniformly found free muriatic acid in great abundance in the acid fluid ejected from the human stomach in severe cases of dyspepsia". (Prout,1823). This pioneering observation has been confirmed by numerous authors who have shown that as a group, patients with duodenal ulcer secrete more acid than normal subjects. This difference might arise by alterations in one or more parts of the complex mechanisms that regulate gastric acid secretion (Soll,Walsh 1979). A schematic illustration of the interwoven network of neurohumoral modulators of secretion is shown in Figure 2.1. Also shown in the figure are other factors that might influence the balance of acid pepsin and mucosal resistance within the duodenum. If one accepts that in the 30% of patients who produce excessive gastric secretion ulceration in the duodenum is caused by excess duodenal acid-pepsin then these other possible mechanisms have to be explored to try and account for ulceration in the 70% of patients with a 'normal' level of gastric secretion.

A number of direct and indirect methods for assessing acid-pepsin and its secretion have been studied and will be considered separately:

1. *Duodenal pH*. In the 1950-1960's attempts were made to assess acid base parameters in the site where the ulcers occurred, the duodenum. Technical problems with probes or periodic sampling by tube gave conflicting results (Benn, Rovelstad et al 1952,Cooke 1971). Exact position of tubes were found to be crucial, as dramatic gradients of pH occur both along the 1st and 2nd parts of duodenum and radially from mid lumen to mucosa - the latter usually registering as neutral whatever the intraluminal pH (Bircher et al 1965,

Fig 2.1 REGULATION OF GASTRIC ACID SECRETION AND DUODENAL pH

(★ = Probably has a physiological role)



Rhodes and Prestwich 1966). The pH of descending duodenum is near neutral- due to intraluminal bicarbonate (Andersson, Grossman 1965, Wormsley, Brewis 1968). Since the original observation by Morton in 1929 most other studies confirm more prolonged or more profound lowering of proximal duodenal pH than normal in patients with duodenal ulcer both fasting (Archambault et al 1967, Comfort 1945, Kearney et al 1941) and after meals (Comfort 1945, Rhodes, Prestwich 1966, Rune 1972). This finding is hardly unexpected given that many of the duodenal ulcer patients studied had abnormally high levels of gastric acid secretion.

Perhaps a more important observation was that in a group of duodenal ulcer patients, selected specifically because of their normal gastric acid secretory capacities, pH of the proximal duodenum was not found to be significantly different from normal (Rune, Viskum 1969). If this result were applicable to most "normosecreting" patients with duodenal ulcer it would negate the idea that ulcer in these patients could be caused by excess duodenal acid-pepsin secondary to other abnormalities such as rapid gastric emptying, inadequate pancreatic neutralization or delayed emptying of acid from the duodenum. We would be forced back to the hypothesis of impaired mucosal resistance in this major sub group!

Thus the causation of duodenal ulcer is no better explained by studies of duodenal pH than by gastric secretory testing. Some patients have greater than normal amounts of acid in the bulb, others have quite normal pH values - at least under the conditions of the experiment. Some disease conditions that are associated with an increased incidence of duodenal ulcer also

predispose to low duodenal pH (e.g. Zollinger Ellison Syndrome, chronic renal failure) but most patients with, for example, chronic pancreatitis do not have duodenal ulcers despite prolonged periods of low intraduodenal pH (Wormsley 1978).

2. *Parietal cell mass and peak acid output.* Cox, in an often quoted paper (never directly confirmed) found at necropsy that many patients with duodenal ulcer had large stomachs, with thick walls and, on average, more parietal cells than normal (Cox 1952). As found with tests of gastric secretion, there was extensive (and almost complete) overlap with the range found in the control group without duodenal ulcers. This greater "parietal cell mass" might obviously explain the higher rates of gastric secretion than normal seen in duodenal ulcer patients, when the stomach is stimulated to its maximum degree by histamine or pentagastrin. (Wormsley, Grossman 1965). It could also explain in part the higher rates of 'basal' fasting acid secretion.

Attempts have been made in vivo in man to correlate peak levels of gastric secretion with other indices of parietal cell number. Unfortunately most methods are of dubious validity. For example, Card & Marks found a close correlation between preoperative acid output and number of parietal cells resected at gastrectomy (Card, Marks, 1960). Unfortunately antrectomy alone reduces PAO by reducing the responsiveness of parietal cells - without actually removing any of them (Broome, Olbe, 1969). No correlation between acid output and parietal cell mass was found in the specialised case of 4 patients with Zollinger-Ellison Syndrome in whom total gastrectomy was performed (Neuberger et al 1972). Other authors have measured mucosal thickness or parietal cell

density and related this to acid output (Stave et al 1978, Tongen 1950). Positive correlations have not always been found within groups of duodenal ulcer patients, although parietal cell density does show an increase from low levels in patients with gastric cancer and gastric ulcer to higher levels in patients with duodenal ulcer (Stave et al 1978). It seems reasonable to assume that the tendency of duodenal ulcer patients to hypersecrete is correlated with their tendency to have more acid producing cells. At present we have no validated way of estimating the number of parietal cells in the stomachs of living subjects and so this attractive hypothesis remains untested.

A variety of possible causes of the higher peak acid output in duodenal ulcer have been suggested ranging from a primary genetic disorder causing parietal hyperplasia to suggestions that hypersecretion is a secondary consequence of duodenal ulcer. The latter was suggested after early observations (Hunt, Kay 1954, Sircus 1960) that MAO showed a positive correlation with reported duration of preceding symptoms. Alternatively one might conclude from this observation that high MAO predisposes to prolonged clinical course. However the authors have also suggested that MAO does not differ from normal in duodenal ulcer patients within the first few years of dyspepsia (Fiddian-Green et al 1976, Hobsley et al 1976). The conclusions of the former were based on only 8 patients with a history of less than 4 years compared to 21 with a longer history and the study of Fiddian Green et al has been severely criticized statistically, and on the data presented as well as their interpretation of it.

(Prescott 1977, Sircus 1977). Because MAO varies with age in normal subjects and duodenal ulcer, age matched controls should be studied as well as ulcer patients. This has been done in a good retrospective study of a large group of patients about to undergo operation (but not selected on the basis of acid studies!) and clearly demonstrated that gastric hypersecretion is present in individuals with a short clinical history (less than 1, and less than 3 years) and that there is no obvious correlation of acid output and length of history (Kronberg, Christiansen 1977). The latter confirms the results of some other large series (Baron 1963(c), Wormsley, Grossman 1965) and should lay matter to rest for a while. This sterile controversy illustrates the difficulty of interpreting much of the published literature on gastric acid secretion in duodenal ulcer. Different authors have drawn contradictory conclusions, which are often based on uncontrolled or inadequately analysed data from too few subjects. Much of the data mentioned above relied entirely on the patient's own assessment of the duration of their previous symptoms. It would be desirable (but difficult) to screen a defined population for ulcer, measure acid secretion in all subjects and follow the group to determine which ones later developed ulcer. Limited studies on medical students previously tested with a sub-maximal histamine stimulus have been inconclusive (Baron 1962). Unless non invasive methods of measuring acid secretions are developed studies of normal populations seem unlikely to be realised. However it would also be instructive to determine acid secretion sequentially during long term follow up of medically managed patients. Few such studies exist!

As well as genetic factors other hypothetical causes of "parietal cell hyperplasia" such as "excessive vagal tone" or increased trophic stimulation due to excessive gastrin release have been postulated. In animals pentagastrin can induce parietal cell hyperplasia (Crean et al 1969) and the high circulating gastrin level in Zollinger Ellison syndrome results in gastric mucosal hypertrophy (Polacek, Ellison 1963). Evidence to implicate these factors in simple duodenal ulcer is difficult to obtain and not available.

3. *Group 1 pepsinogens in serum.* Serum possesses weak peptic properties when activated by acid. "Blood pepsin" levels were initially determined by proteolytic assay and found to be correlated with levels of gastric acid secretion. (Mirsky et al 1952). Electrophoresis demonstrated two immunochemically distinct groups of the pepsin precursor in serum, urine and gastric mucosa - pepsinogens I and II (Samloff, Townes 1970). Immunofluorescent studies showed that Group I pepsinogens were found only in the peptic cells in oxyntic gland mucosa while Group II pepsinogens were present in chief and mucus gland neck cells in oxyntic mucosa but also in pyloric glands in the gastric antrum and in Brunners glands in the duodenum (Samloff 1971, Samloff, Liebman 1973).

The development of a sensitive radioimmunoassay for pepsinogen I (PG-I) allowed the demonstration of a close correlation between serum PG-I and peak acid output (Samloff, Secrist, Passaro 1975). Serum PG-I provided slightly better discrimination between normal and duodenal ulcer subjects than stimulated gastric acid output (Samloff, Liebman, Panitch 1975). An elevated level of serum PG-I was found in about two thirds of unrelated patients with

duodenal ulcer, and the highest levels were found in patients with Zollinger-Ellison syndrome. Abnormally low levels were found in patients with pernicious anaemia and 10% of patients with gastric ulcer but none of the duodenal ulcer subjects had low levels. In all age groups duodenal ulcer patients had higher PG-I levels than controls and no correlation with duration of disease was found. This provides indirect confirmation of the conclusions of Kronberg and Christiansen that peak acid output does not increase with duration of disease (see above).

Although serum PG-I might thus seem a useful indirect measure of acid secretion it has proved to have even greater importance: elevated PG-I levels are a strong genetic marker for duodenal ulcer disease, presumably because of their relationship to acid pepsin secretory capacity. The early studies of Mirsky had suggested pepsinogen levels might be genetically determined, and that high levels could identify those who had an increased risk of developing duodenal ulcer. (Mirsky 1958). Recently Rotter and his co-workers have found that elevated serum PG-I is inherited as an autosomal dominant trait, and is associated with duodenal ulcer (Rotter, Sones et al 1979). In two large families with duodenal ulcer the trait occurred in half the offspring of persons with the trait and in none of those without it. Duodenal ulcer occurred in about 40 per cent of those with the trait and none of those without it. Why only 40 per cent of those with hyperpepsinogenaemia developed duodenal ulcer is unknown. Presumably other environmental or genetic factors interact with the hyperpepsinogenaemia to determine the outcome.

Not all patients or families with duodenal ulcer have elevated serum PG-I. In a study of 123 patients with duodenal ulcer and their sibs about half the patients had familial hyperpepsinogenaemia. It is noteworthy that familial aggregation was just as great among duodenal ulcer patients with normal serum PG-I levels (Rotter, Peterson et al 1979). This suggests that other genetic markers are yet to be discovered.

4. *Basal and nocturnal acid pepsin secretion.* Under the rather artificial circumstances of fasting with a tube in the stomach to allow aspiration of secretions, a measure of "basal" acid secretion may be made - for an hour (BAO) or overnight. Both are elevated in groups of patients with duodenal ulcer (Baron 1963b, Grossman et al 1963, Winkelstein 1935). Not all patients have elevated levels of basal or nocturnal secretion. BAO does not discriminate duodenal ulcer from normal any better than PAO, and is subject to even greater variability on repeated testing.

In basal hypersecretion (as in excessive secretory response to food or other stimulants) the volumes of gastric juice are abnormally large with normal concentrations of acid (Wormsley, Grossman 1965).

The elevation in basal secretion may be explained in some patients by the correspondingly high peak acid output - and presumably their higher parietal cell mass. However some subjects show a high ratio of basal/peak acid output suggesting a high basal "drive" to parietal secretion, less inhibition - or greater sensitivity of the parietal cells to an endogenous stimulant. In two different large studies of gastric secretion the ratio of BAO/PAO was elevated in

patients with duodenal ulcer compared with normal controls in one, and normal in the other. (Baron 1963a, Wormsley, Grossman 1965).

Investigation of the cause of high basal secretion is difficult, as of all the secretagogues, only immunoreactive gastrin is measurable. Several controlled studies have found that fasting levels of total serum gastrin are low or normal in simple duodenal ulcer (and increased in Zollinger Ellison syndrome) (Korman, Soveny, Hansky 1971, Trudeau, McGuigan 1970, Walsh, Grossman 1975).

This has been suggested to be an "inappropriately normal" level of gastrin as the high antral acidity in duodenal ulcer patients might be expected to inhibit gastrin release more fully (Berson, Yalow 1971). Unfortunately the measurement of total serum immunoreactive gastrin is only a crude index of the biological activity of the hormone. The radioimmunoassay measures a mixture of the three major circulating molecular forms of gastrin: "Big big Gastrin" (BBG) which may have little or no biological activity as well as "Big gastrin" (G34, containing 34 amino acids) and "little gastrin" (G17 containing 17 amino acids). BBG may be a major part of normal fasting gastrin levels while G17 is the most potent form and predominates in the antral mucosa. G34, present in only small amounts in antral mucosa, has a longer half life than G17 and although less potent on a molar basis predominates in the circulation (Walsh, Grossman 1975). Until the individual molecular forms of circulating gastrin can be measured in low concentrations the role of gastrin in basal hypersecretion cannot be finally dismissed.

One of the few inhibitory hormones ("enterogastrones") that might play a role in regulating gastric acid secretion

and is measurable is secretin. Fasting plasma concentrations were the same or higher in duodenal ulcer than in normal controls (Chey, Hendriks, Tai 1977, Isenberg, Cano, Bloom 1975) and the pH threshold for secretin release (between 2 and 3) when induced by duodenal perfusion of isotonic citrate buffers of varying pH was not different from normal in duodenal ulcer (Fahrenkrug, Schaffalitzky de Muckadell, Rune 1978).

The question of an increased sensitivity of the parietal cell to gastrin in patients with duodenal ulcer has been raised. Earlier studies had found that normal doses of stimulants were required to elicit half maximal or maximal secretory responses in duodenal ulcer (Hunt, Kay 1954, Wormsley, Mahoney 1967). Using graded doses of pentagastrin or G17 Isenberg and other authors have been able to calculate the dose of either stimulus required to produce one half maximal response in a series of duodenal ulcer patients and normal controls. The average dose was lower in duodenal ulcer patients, with the 'dose-response' curve shifted to the left. As with most phenomena relating to acid secretion there was considerable overlap with the control group (Isenberg et al 1975, Petersen, Myren 1975) and another study failed to confirm the finding (Koffman, Elder 1977)! Despite the increased reactivity to gastrin the patients did not secrete acid more readily than normal in response to a peptone meal (a good stimulant of gastrin release) (Lane et al 1977).

The mechanism underlying the possible parietal super sensitivity in duodenal ulcer has not been elucidated. Several hypotheses include "increased vagal tone" or diminished levels of gastric inhibitors like secretin or other enterogastrones.

5. *Food stimulated gastric secretion.* Food is a strong stimulus to gastric secretion and groups of patients with duodenal ulcer secrete more acid in response to food than do groups of normal subjects. This is the conclusion of a small number of studies which have used recently developed techniques to measure acid secretion in response to normal meals. Using intragastric titration with bicarbonate infusion to fix pH at 5.5 Fordtran and Walsh found that the mean peak rate of acid secretion in 7 duodenal ulcer patients was 64mEq/hour in response to food, exceeding their mean peak histamine response (58mEq/hr) and was twice the peak meal induced response of 6 controls (30 mEq/hr) (Fordtran, Walsh 1973). Meal stimulated secretion in the control subjects was a little less than their mean peak histamine response (34mEq/hr). It should be noted that the duodenal ulcer patients in this study were 'hypersecretors' of acid in that their peak histamine response was significantly greater than the controls.

Using the same technique of intragastric titration to pH 5.5 after a normally eaten beefsteak meal other authors have found almost identical results (Bodemar, Walan, Lundquist 1978). Duodenal ulcer patients produced higher rates of gastric acid secretion which persisted longer than the controls. Peak acid secretion measured at this fixed "unphysiological" pH was 34-46% greater in response to food than to pentagastrin - but did not discriminate ulcer from controls any better.

Malagelada and his colleagues have used a more refined technique with both gastric and duodenal markers to measure gastric secretory responses without artificially maintaining

intra-gastric pH at 5.5 (Malagelada et al 1976). They found that the peak rate of acid secretion in response to a normally eaten meat meal was not greater in duodenal ulcer patients than healthy control subjects (even though peak response to betazole was much greater in the duodenal ulcer patients) but that the secretory response was considerably prolonged in duodenal ulcer patients (Malagelada et al 1977). Unfortunately the complexity of this method - requiring duodenal intubation and perfusion with a non absorbable marker to measure volume shifts across the pylorus, as well as simultaneous gastric intubation with another marker in the meal, limits its wider usage.

Other authors have used intra-gastric titration techniques similar to the methods of Fordtran and Walsh, but feeding simpler peptone or "Oxo" liquid meals, instilled not swallowed (Halter, Keller 1978, Taylor et al 1978). Not surprisingly rather varied results have been obtained. Halter and Keller measured the response to pentagastrin by conventional aspiration as well as by intra-gastric titration in the same subjects on a separate occasion. The latter technique gave a 35% greater response: the difference may have a number of explanations - for example the different pH conditions intra-gastrically. Different degrees of gastric distension and intestinal stimulation (after gastric emptying) may also contribute.

What are the mechanisms underlying the food stimulated hypersecretion in duodenal patients? The increased capacity to secrete acid and increased sensitivity of the parietal cell have already been discussed. Other possibilities include an excessive drive to secretion - in the form of gastrin or vagal 'tone', or defective inhibition of secretion.

6. *Food stimulated gastrin release.* The majority of studies of gastrin release after stimulation with a protein meal have found higher or more sustained responses in patients with duodenal ulcer than controls. (Korman et al 1971, McGuigan, Trudeau 1973, Walsh, Grossman 1975). The studies in which acid response to the meal was measured as well as serum gastrin do not show the clear correlation between the two that might be expected if excessive gastrin release were the cause of food stimulated hypersecretion (Bodemar et al 1978, Fordtran, Walsh 1975). However the difficulty of drawing conclusions about the biological activity of gastrin from measurements of total serum immunoreactive gastrin, a mixture of molecular forms of different potency, has already been discussed. Recent studies suggest that the increase in gastrin levels with food is not in the G17 fraction and is therefore presumably in the G34 fraction which is the main non-G17 component (Dockray, Taylor 1978). The intragastric titration method (which fixes intragastric pH, itself an important determinant of gastrin release) may not be suitable for exploring the normal physiological inter-relation of gastrin release and acid secretion and there is only meagre data available from studies using dye dilution techniques (Gross et al 1978, Malagelada et al 1977).

It seems reasonable to conclude that gastrin release after meals is enhanced in at least a proportion of patients with duodenal ulcer and that some of the contradictory results are partly attributable to the heterogeneity of the pathophysiological reactions of patients with duodenal ulcer. (For example, it has been suggested that the acid and gastrin responses to "Oxo" stimulation separates patients into "antral responders" and

"antral non responders" (Perrault et al 1977). To try and explain enhanced gastrin release considerable effort has been applied to the difficult techniques for estimating the number of antral G cells or antral gastrin concentrations in duodenal ulcer and control subjects. No consistent differences have been demonstrated (Creutzfeldt et al 1976, Malmström, Stadil 1976).

An alternative explanation for enhanced postprandial gastrin release is that "autoregulation" of gastrin secretion is defective in duodenal ulcer - i.e. that the inhibition of gastrin release by low antral luminal pH, clearly demonstrated in animal experiments (Andersson, Elwin 1971) is less in duodenal ulcer than normal. That this mechanism to inhibit gastrin release functioned (to some degree) in duodenal ulcer patients was shown by Gillespie: perfusion of the gastric antrum with sulphuric acid in patients undergoing gastrectomy inhibited basal and histamine induced gastric acid secretion when the pH was lowered to 1.5 (Gillespie 1959). Konturek et al demonstrated that intragastric pH could regulate gastrin release by food in duodenal ulcer patients" a peptone meal maintained in the stomach at pH 5.5 produced a marked increase in serum gastrin level and gastric acid secretion equivalent to the maximal response to pentagastrin. With decreasing intragastric pH both were suppressed (Konturek et al 1974). Using the intragastric titration technique with the fixed end point at pH 5.5 or pH 2.5 Walsh et al compared gastrin release and acid secretion in duodenal ulcer patients with normal subjects. At pH 5.5 duodenal ulcer patients released only slightly more gastrin than normals. However at low pH levels the duodenal ulcer patients showed less suppression of acid and gastrin - the latter decreasing by about 50% compared with

an average reduction of 75% in the normal controls. The alterations in acid secretion became statistically significant in the second hour after the meal when duodenal ulcer patients at pH 2.5 were still secreting 70% of the amounts produced at pH 5.5 while normal individuals secreted only 30% at the lower pH.

There is thus some evidence that low intragastric pH does reduce food stimulated gastric acid secretion and reduces it more in normal subjects than duodenal ulcer patients. However another study failed to confirm this (Thompson, Swierczek 1977). Failure of exogenous acid to reduce the peak acid response to insulin has also been noted in duodenal ulcer patients (Stenquist et al 1977). Peak response was reduced by 45% in normal individuals, but only by 16% in patients with duodenal ulcer. However the overall (2½hour) gastric secretory response was reduced in both groups - by 56% in normal individuals and 35% in duodenal ulcer patients. It was concluded that patients with duodenal ulcer were less sensitive than normal to the inhibitory effects of the exogenous acid.

To draw conclusions from all this data on gastrin release and its suppression by acid is not easy. The different molecular forms of gastrin constituting the "serum gastrin level" in these experiments are unknown. The origin of the gastrin may not always be the gastric antrum and the mechanisms of the inhibition of acid and gastrin secretion by acidification of the contents of the stomach may be attributed to mechanisms other than suppression of antral hormone. A direct local inhibiting effect of low luminal pH in the oxyntic gland area on the parietal cell has been found in animals

(Konturek 1976). This is independent of gastrin release. Furthermore the acidified meal is emptied into the duodenum and may release secretin, bulbogastrone, cholecystokinin or other "enterogastrones" which in turn may suppress gastrin release but also directly inhibit gastric acid secretion. Antral acid also releases immunoreactive somatostatin and deficient release in duodenal ulcer patients has been proposed (Konturek 1977).

Gastric emptying

Abnormally rapid emptying of gastric acid might theoretically give rise to abnormally low duodenal pH if acid disposal mechanisms in the duodenum were unable to increase in parallel with the influx of acid. This concept has given rise to a large body of work in which different techniques have been used to measure gastric emptying in duodenal ulcer patients and controls. Whether any of the abnormalities that have been claimed to be found precede the development of ulcer or a consequence of other pathophysiological changes is unknown. Clearly the rate of emptying of gastric acid (and semi-solid food buffer) is only one of a number of variables influencing duodenal pH and information on gastric emptying alone has to be interpreted with caution.

In view of the fact that the rate of gastric emptying may be increased by gastric distension and inhibited (usually) by fat, high acid concentration or high osmolarity within the duodenum the technique used to assess emptying (aspiration/ marker infusion/scintiscanning etc). may influence the results obtained.

In the 1950's Hunt using saline and glucose test meals found that duodenal ulcer patients tended to empty both kinds of meal more rapidly than healthy controls (but the difference was not statistically significant). (Hunt 1957a,b). Despite some contradictory results since then the majority of studies suggest that most patients with duodenal ulcer empty both fluid (Faxen 1978, Lagerlöf et al 1960; Moberg 1974) and solid (Benmair et al 1977; Dubois et al 1976, Griffith et al 1968, Fordtran, Walsh 1973) abnormally rapidly. Other recent evidence obtained using liquid and solid phase markers (Heading et al 1976) or solid meals (Howlett et al 1976) have not always shown abnormally rapid emptying and indicates that abnormalities of gastric emptying are complex and probably not homogeneous.

Malagelada and his colleagues at the Mayo clinic using proximal duodenal infusion of a marker and sampling in the distal duodenum have confirmed the increased duodenal acid load in patients with duodenal ulcer compared to healthy controls, but gastric acid output was also abnormally increased in the patients and the extent to which rapid emptying contributed to the excess duodenal load is uncertain. (Malagelada et al 1977). This study also showed that although peak levels of acid secretion (and duodenal acid load) around 1 hour after a bread, butter and steak meal were little different from normal in the duodenal ulcer patients, abnormally increased rates of acid secretion persisted for the second third and fourth post cibal hours. Because food buffer had emptied rapidly, the duodenum was

exposed to unbuffered gastric juice and duodenal acid load remained abnormally high during this time.

The cause of abnormally rapid gastric emptying in some patients with duodenal ulcer is unknown. Receptive relaxation (judged by the lack of intragastric pressure rise in response to rapid infusions of 200-600ml of air) was no less effective in duodenal ulcer patients than controls (Jahnberg 1977). The 'braking' effect of fat on gastric emptying in patients with duodenal ulcer is not abnormal and fatty meals inhibit gastric secretion and duodenal acid load to the same extent as in normal controls. (Gross et al 1976). Using catheters to measure duodenal motility and simultaneous recording of the gastro-duodenal movements of a barium test meal Borgstrom and Arborelius confirmed that duodenal infusion of sodium myristate (a fatty acid) inhibited gastric emptying and antegrade duodenal motility, thus reducing abnormal acid content of the duodenal bulb after food. (Borgstrom, Arborelius 1975a,b, 1978). These authors hypothesised that duodenal ulcer may arise through failure of retrograde peristalsis of pancreatic bicarbonate into the duodenal cap. This is difficult to reconcile with findings of enhanced duodeno-gastric reflux in patients with duodenal ulcer. (Fiddian-Green 1974, Kallner 1975, Wormsley 1972). The study of duodenal motility mixing and emptying into the jejunum is in its infancy and conclusions cannot yet be drawn on any role abnormalities may play in the pathogenesis of duodenal ulcer. (Monte et al 1976).

Duodenal acid and buffering by bicarbonate.

Two mechanisms have been proposed to explain the disappearance of acid from the duodenum: buffering by secreted bicarbonate (from pancreas, hepatic-biliary system or duodenal mucosa) and diffusion into the mucosa. The rapid production of CO_2 when acid is introduced into the duodenum confirms that buffering occurs but "back diffusion" has proved impossible to measure directly. Unfortunately as Wormsley points out, many authors under experimental conditions have failed to measure the production of CO_2 or water loss in their system and make invalid assumptions about "bicarbonate secretion" by measuring only changes in volume and osmolarity of fluid aspirated from the duodenal lumen after addition of acid (Chung et al 1975, Dorricott et al 1975, Sethbhakdi, Roth 1977, Wormsley 1979). Whatever the merits of the idea of "back diffusion" the secretion of bicarbonate by rabbit duodenal mucosa has clearly been shown to be an important factor in neutralising duodenal contents even when influx of pancreatic and biliary bicarbonate is prevented (Fiddian Green, Silen 1975).

Disappearance of acid from the duodenum has been shown in man (Wilhelm et al 1950, Wormsley 1969) and the neutral pH in descending duodenum indicates the presence of intraluminal bicarbonate (Wormsley, Brewis 1968). (The pH of water at 37°C is 6.8 and when equilibrated with a PCO_2 of 40mm Hg is 4.5).

Is there evidence that bicarbonate secretion is inadequate in duodenal ulcer? There seems little doubt that patients with duodenal ulcer are capable of producing as much bicarbonate in response to exogenous secretin as normal controls

(Banks et al 1967, Gutierrez, Baron 1976, Peterson 1970, Wormsley, Mahoney 1967b). However there is fundamental disagreement between authors on whether "basal" pancreatic secretion is abnormally low (Gutierrez, Baron 1976) or even greater than normal (Isenberg et al 1977). Similarly there is controversy over the bicarbonate secretory response to submaximal or more physiological stimuli such as intraluminal acid in the duodenum. Some workers have found a diminished response to intraluminal acid in at least some patients with duodenal ulcer (Butt et al 1977, Fiddian Green, Hobsley 1976). Other workers have reported a normal rate of disappearance of infused acid from the duodenum (Fahrenkrug et al 1976) while different authors have found an increased bicarbonate secretory response to graded amounts of intraduodenal acid (Isenberg et al 1977).

Even if impaired bicarbonate secretion in response to duodenal acid is a feature of established duodenal ulcer this does not prove it causes duodenal ulcer - but might be a consequence of, for example impaired secretin release due to acid induced mucosal damage or fatigue of secretin response (Chung, Johnson 1977, Henriksen et al 1976).

Defensive mechanisms of the duodenal mucosa.

In contrast to the wealth of information about acid secretion, the factors that prevent ulceration in normal mucosa, or promote healing and reconstitution of damaged mucosa, have been relatively little studied. None of the factors involved in 'mucosal resistance' have been identified with certainty but possible candidates include mucus, cellular regeneration of mucosa, blood flow and chemical factors such as prostaglandins and epidermal

growth factor. Unfortunately much of the work on these relates to gastric rather than duodenal mucosa.

1. *Mucus*. The idea that the layer of mucus lining the stomach provides a physical or chemical barrier against injury is hallowed with age. Claude Bernard in 1856 wrote that "the mucus lining the stomach encloses the gastric juice in a vase as impermeable as though it were porcelain" (Bernard 1856). More recently Hollander has promoted discussion of the "mucous barrier in the stomach" (Hollander 1951, 1954).

Gastric mucus is a polymer of 4 glycoprotein subunits (Cramp et al 1978) secreted by gastric mucosal cells under the influence of a variety of stimuli (vagal activity secretin gastrin parathyroid hormone, topical stimulants etc). It forms a hydrated viscous gel adherent to the mucosa but depolymerization by peptic digestion or breaking of sulphhydryl bonds destroys the gel like properties. The composition of the soluble glycoproteins present in gastric juice can be measured, and assuming that these reflect the composition of the mucus adhering to the mucosa, normal amounts of gastric glycoproteins of normal composition have been found in patients with duodenal ulcer (Glass, Boyd 1950, Roberts-Thomson et al 1975, Schräger 1968). Chemical analysis of the carbohydrate and ester sulphate content of duodenal mucosa biopsies showed that the amount and composition of the sulphated glycoproteins was not different from normal in patients with duodenal ulcer (Andre et al 1974). In patients with active duodenal ulcer

the activity of glucosamine synthetase in the duodenal mucosa is increased but is normal in patients with healed duodenal ulcers (Goodman et al 1975). This finding has been interpreted as indicating mucosal regeneration since the formation of glucosamine 6 phosphate is the first step in the biosynthesis of acetylhexosamines and sialic acid.

A more recent interpretation of the role of mucus is related to its maintenance of an "unstirred layer" immediately adjacent to the mucosa which may help explain how the stomach is able to maintain such a high concentration of hydrogen ions within its lumen. Hydrogen ion concentration in secreted gastric acid may be 10^{-1} mmol/l (N/10HCl) compared with concentrations in blood of 10^{-7} . The presence of this steep electrochemical gradient has been assumed to indicate the presence of a functional barrier to diffusion of hydrogen ions from the gastric lumen into the mucosa and sodium down their reverse concentration gradient from mucosa to lumen. This "gastric mucosal barrier" is probably sited at the luminal surface of the gastric mucosal cells which are joined laterally to each other by tight junctions at their apices.

Mucus itself was thought to contribute little to the "gastric mucosal barrier" because it does little to prevent permeation and diffusion of water and electrolytes (Heatley 1959). However recent studies have shown that the surface cells of the stomach secrete small amounts of bicarbonate (Garner and Flemstrom 1978). The constant entry of bicarbonate into the unstirred layer of gel mucus increases its ability to maintain a high gradient of hydrogen ion concentration between luminal fluid and apical surfaces of the cells. (Allen, Garner 1980, Turnburg et al 1981).

2. *Mucosal cells.* The mucosal cells lining stomach and duodenum have a rapid rate of turnover (in common with the rest of the gastrointestinal mucosa). In the stomach the mucous gland neck cells is the major cell type undergoing mitosis with cells migrating upward to replace those lost by desquamation. Complete renewal of the surface columnar mucus cells occurs every 1-3 days although oxyntic and chief cells turn over more slowly. (Lipkin et al 1963, McDonald et al 1964). Small defects in mucosa such as loss of a few cells are rapidly repaired - in as little as 30 minutes - by the flow of surrounding cells into the gap with reformation of tight junctions (Hudspeth 1975). A defect in these regenerative processes could theoretically contribute to ulcer formation but no evidence exists to indicate that such a factor operates.

The histopathological changes found in the duodenal mucosa in patients with established ulceration are those of ulceration with surrounding "chronic duodenitis". These changes do not of course provide information about the state of the mucosa before ulcer develops and we do not know whether histologically apparent abnormalities predispose to ulceration. Chronic duodenitis is a much abused term used to describe clinical symptoms (otherwise unexplained dyspepsia) radiological findings (coarse duodenal mucosal folds) and endoscopic appearances (reddening and oedema) as well as histopathologically apparent chronic inflammation! It has been suggested that endoscopic duodenitis (without ulcer) is merely part of the spectrum of ulcer disease with similar symptomatology and that many patients if

followed for long enough subsequently develop duodenal ulcer (assuming it was not overlooked initially!) Greenlaw et al 1976, Thomson et al 1977, Whitehead et al 1975).

In summary the relationship between duodenal ulcer and duodenitis is not an exclusive one. Through the endoscope reddening and oedema is often seen at the edges of duodenal ulcers, sometimes may extend to the whole bulb, and on biopsy often shows histological duodenitis. In patients with duodenal ulcer no correlation between peak acid output and gastritis or duodenitis was found (Meikle et al 1976). Vagotomy may heal ulcers and lessen the severity of duodenitis (Marks 1977) but whether duodenitis precedes ulceration, is a consequence of it, or whether both are produced by a common pathophysiological disturbance is uncertain.

3. *Mucosal circulation.* Recent experimental work has shown that a decrease in mucosal blood flow in the face of a constant level of diffusion of acid into the mucosa can lead to mucosal injury (Moody et al 1978). Whether this is a clinically important mechanism is unknown. Studies on the gastric microcirculation (using the clearance of a weak base ¹⁴C aminopyrine, into gastric juice as an index of blood flow) have yielded conflicting results. In patients with duodenal ulcer one group (Guth et al 1978) found a normal relationship of acid secretion to blood flow while another found a decreased blood flow (Knight et al 1977). There is inadequate evidence to draw any conclusions about circulatory changes as a possible cause for ulcer.

4. *Prostaglandins*. Exogenous prostaglandins inhibit gastric secretion and also protect gastric mucosa against the injurious effects of a wide variety of damaging agents (Robert et al 1976). This protection may be seen even when the hydrogen ion concentration of the luminal contents is kept constant and thus "cytoprotection" seems independent of effects on acid secretion. (Robert et al 1979).

Recently the possibility has been raised that endogenous prostaglandin production by gastric mucosa may provide protection against injury (Robert, 1979). That gastric mucosa can produce prostacyclin has recently been demonstrated (Moncada et al 1978). Aspirin and related drugs applied topically to gastric mucosa lead to gastric damage and also suppress prostaglandin formation. Further elucidation of the cytoprotective mechanisms of action of prostaglandins is clearly of great importance.

5. *Urogastrone*. Urogastrone is a peptide isolated from human urine which had been found to inhibit gastric acid secretion (Gregory, Willshire 1975). Its structure was determined and after synthesis the gastric inhibitory properties were confirmed (Elder, Ganguli, Gillespie, Gerring, Gregory 1975). Its structure was then noted to be similar to a peptide isolated from the salivary glands of mice which had the property of promoting epidermal growth (Cohen, Elliott 1963, Savage et al 1972). Each peptide was then found to possess the biological properties of the other: urogastrone promoted epidermal growth and epidermal growth factor inhibited gastric secretion. Urogastrone may be human epidermal growth factor (Gregory 1975). It inhibits acid and intrinsic factor secretion powerfully but has little effect on pepsin secretion (Elder et al 1975).

Acid secretion is also inhibited in patients with duodenal ulcer (Koffman et al 1977) and Zollinger Ellison syndrome (Elder, Ganguli, Gillespie, Delamore, Gregory 1975). There are exciting theoretical possibilities about the role of endogenous human urogastrone in preventing duodenal ulcer - or lack of it predisposing to ulcer, but information is not yet available to confirm or refute these hypotheses.

Conclusions.

Acid-pepsin secretion is an indispensable ingredient in the formation of duodenal ulcers. Some, but not all duodenal ulcer patients secrete excessive quantities of acid-pepsin under a variety of basal and stimulated conditions. A number of abnormalities of gastric function have been identified which in part may account for the hypersecretion or increased acid-pepsin load to the duodenum. Duodenal structure and function have been less amenable to investigation and no abnormalities of duodenal defence leading to duodenal ulcer in man have been conclusively identified.

The greatest heritable risk factor yet identified for duodenal ulcer is the inheritance of high levels of serum pepsinogen I, which also shows a strong correlation with acid pepsin secretion. Environmental risk factors for developing a duodenal ulcer may be important but few have been identified with certainty and the mechanisms through which they might act are speculative. A number of the other diseases associated with duodenal ulcer also cause gastric hypersecretion. The Zollinger Ellison syndrome is the most dramatic and the pathophysiology of

duodenal ulcer here is clearly related to hypergastrinaemia and hypersecretion.

Thus the central aetiology role of acid and pepsin inevitably makes them a target for the physician or surgeon intent on treating duodenal ulcer.

CHAPTER III

THE HISTAMINE H₂-RECEPTOR ANTAGONISTS

"Everyone looks forward to the day when mutilating operations will be unnecessary. Present knowledge provides the basis for the hope that future research will reveal an orally active innocuous substance for specifically preventing the formation of acid by the parietal cell, and/or rendering the gastric and duodenal mucosa less susceptible to injury".

Ivy, Grossman, Bachrach. Peptic Ulcer, 1951.

Development and characterization of histamine H₂-receptor antagonists.

Histamine is widely distributed throughout the body in animals and humans. First isolated in 1910, its simple chemical structure gives little indication of its complex biochemical actions.

The physiological role of histamine is controversial but it has a pharmacological effect on a number of different organs. These effects include vasodilation of arterioles and capillaries leading to headache and fall in blood pressure, contraction of smooth muscle in gut and bronchi, increased capillary permeability, chronotropic *and* inotropic effects on the heart, and stimulation of gastric acid secretion.

Although its pharmacological action in stimulating gastric secretions was discovered in 1920 (Popielski 1921) it was not until 1938 that it was realized that histamine might play a physiological role in the process. McIntosh found

that histamine could be isolated from the gastric secretions of animals undergoing vagal stimulation (McIntosh 1938). In 1956 Code proposed that histamine acted as the "final common mediator" of gastric secretion, and that other potent stimulants such as gastrin and acetylcholine acted via histamine (Code 1956). This simple and attractive hypothesis has been the subject of controversy, experiment and modification ever since (Baron 1978b, Gardner et al 1978, Lorenz et al 1978, Soll 1978).

In the 1940's a number of 'antihistamines' were synthesized. Mepyramine for example was found to be a potent and selective competitive antagonist of the action of histamine on smooth muscle from various organs such as guinea pig ileum, bronchus and uterus. However, not all of the pharmacological actions of histamine were blocked. The vasodilator effects of large doses of histamine were only partially blocked and the antihistamines completely failed to inhibit histamine stimulated gastric acid secretion. Hence in the augmented histamine test of gastric secretion an injection of mepyramine was always given before histamine (Kay 1953) to minimise unwanted effects while provoking gastric acid secretion.

These facts suggested the existence of more than one type of histamine receptor and prompted Dr. James W. Black to initiate in 1964 a research programme to discover an antagonist of the histamine receptors which were not blocked by conventional antihistamines. In 1966 Ash and Schild defined the H_1 -receptor as that which mediates those responses to histamine which can be antagonized by conventional

antihistamines (Ash, Schild 1956). The receptor mediating gastric acid stimulation was left unclassified. The search for the antagonist to this receptor was carried out by a research team at Smith, Kline French Laboratories, Welwyn Garden City in England. In seeking a compound that would bind with the receptor but not trigger the usual response, they started from the structure of histamine and modified it chemically in various ways. Compounds were screened for their ability to inhibit histamine stimulated gastric secretion in anaesthetized rats. Because other types of inhibitor of gastric secretion could be picked up by this test, specific antagonism of histamine was assessed by two other in vitro actions of histamine not mediated by the the H_1 -receptor. These were stimulation of the rate of spontaneous beating of the guinea pig isolated right atrium and inhibition of evoked contractions of the isolated rat uterus.

In 1972, after the synthesis of over 700 compounds, the research programme culminated in the publication in Nature of a paper describing the properties of burimamide (Black et al 1972). It was a highly specific competitive antagonist of histamine on non- H_1 tissue systems, thus defining the histamine H_2 -receptor antagonist (Figure 3.1).

Burimamide was active in rat, dog and man (Wyllie et al 1972) but only when given parenterally. Further research gave rise to the more potent compound, metiamide, the first orally active H_2 -receptor antagonist (Black et al 1973, Grossman, Konturek 1974). However, reversible agranulocytosis

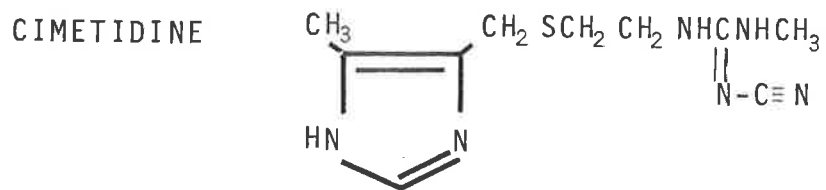
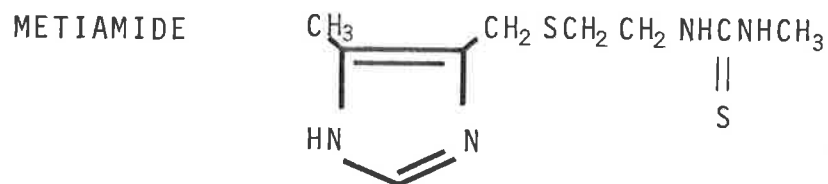
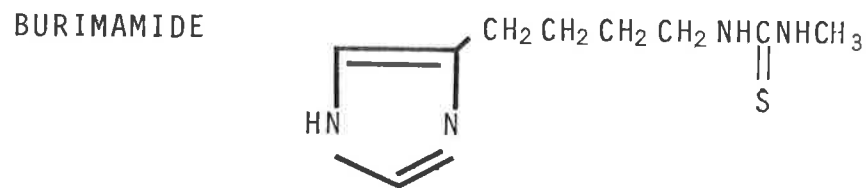
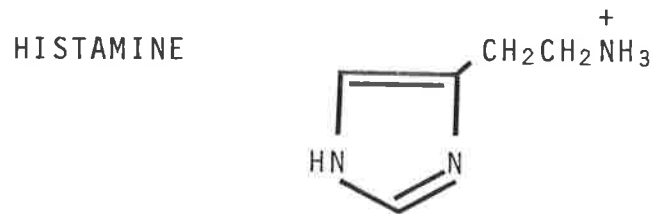


Figure 3.1: Structural formula of histamine and the histamine H₂-receptor antagonists burimamide, metiamide and cimetidine.

was seen in two dogs during high dose toxicological studies (Brimblecombe et al 1973) and in clinical trials agranulocytosis occurred in a number of patients, one of whom died (Feldman, Isenberg 1976, Forrest et al 1975). The thiourea group in the side chain was thought to be responsible for this effect and further work led to the synthesis of cimetidine in which the thiourea moiety was replaced by a cyanoguanidine group (Figure 3.1) (Brimblecombe et al 1975). This was at least as potent as metiamide in blocking H_2 receptors (Burland, Duncan et al 1975) but did not possess the toxicological side effects of metiamide. More importantly patients who had developed agranulocytosis during metiamide treatment were given cimetidine without ill effect (Burland, Sharpe et al 1975).

The chemical structures of histamine and some H_2 -receptor antagonists are shown in Figure 3.1. The chemical differences between H_1 -receptor and H_2 -receptor antagonists are outlined in table 3.1. The conventional antihistamines (H_1 -receptor antagonists) do not have a close structural resemblance to histamine, the only common feature being a basic amine group in the side chain. They possess aryl or heteroaryl rings which do not necessarily have any structural relationship to the imidazole ring of histamine. The aryl groups confer considerable lipophilicity and account for entry into the central nervous system - often clinically evident as the unwanted effect of drowsiness.

In contrast the H_2 -receptor antagonists are hydrophilic compounds (octanol-water partition coefficient, $P=2.5$ for

Table 3.1

Chemical differences between histamine and its antagonists

	Histamine (agonist)	H ₁ -receptor antagonist	H ₂ -receptor antagonist
Ring structure	Imidazole	Aryl	Imidazole*
Fat/water soluble	Hydrophilic	Lipophilic	Hydrophilic
Side chain	Ammonium (charged)	Ammonium (charged)	Thiourea cyanoguanidine (uncharged)

* see text

cimetidine at 37°C and pH 9.2 while P for H₁-receptor antagonists is often greater than 1000). They have a similar ring structure to histamine. Burimamide, metiamide and cimetidine all have the same imidazole ring although recent work has shown that this may be replaced by other suitable structures, such as the furan ring in ranitidine, an even more potent H₂-receptor antagonist developed by Glaxo Laboratories (Domschke et al 1979, Peden, Saunders Wormsley 1979). They differ from histamine and H₁-receptor antagonists in having a polar but uncharged side chain. This presumably accounts for their inability to mimic the stimulant actions of histamine: they are not agonists.

Pharmacology of cimetidine - effects on gastric secretion.

Animal Physiology. In isolated gastric mucosa and intact animal preparations cimetidine administered orally, intravenously or rectally inhibits basal and pentagastrin stimulated secretion (Brimblecome et al 1975, Khamis et al 1977, Kuhn et al 1977, Sjostrand et al 1977). It is generally less effective in inhibiting carbachol stimulated secretion in animals (Brimblecombe et al 1975). This lower potency against cholinergically mediated stimuli does not seem to obtain in man (see below).

The in vitro dose response curve of acid secretion evoked by histamine in guinea pig isolated mucosa was displaced to the right without change in slope or maximum response, suggesting competitive inhibition (Sjostrand et al 1977) and confirming in vitro data from other tissue systems

(Brimblecombe et al 1975). In vivo preparations from rat, cat and dog confirmed the rapid dose-related inhibition. ID₅₀ values of 1.4-2.0 $\mu\text{mol/kg}$ against both stimuli lend some support to the hypothesis of gastrin acting via a final histamine link, while the lesser inhibition of cholinergic stimuli might be explained by cholinergic receptors without a final histamine link. Vagally stimulated secretion might be inhibited if a substantial part of the response were mediated via release of antral gastrin. That the inhibitory effect of H₂-receptor antagonists is not produced via a primary reduction of mucosal blood flow was confirmed by the evidence of activity in the isolated in vitro gastric mucosal preparations (Bunce, Parsons, Rollings 1976).

Studies on isolated parietal cells are at odds with the in vivo observations that cimetidine blocks the action of all manner of secretagogues in addition to histamine. Using indirect indices of parietal cell activity (as acid secretion cannot be measured directly) Soll found that the response to histamine, but not acetylcholine or gastrin was inhibited, although atropine produced inhibition of the action of acetylcholine (but not gastrin or histamine). This apparent contradiction may be explained by interaction of secretagogues in vivo, in which a small 'background' of histamine greatly enhances the effect of gastrin or acetylcholine. H₂-receptor antagonists might then inhibit the 'histamine interaction' component and give rise to the apparent lack of specificity in vivo (Soll 1978).

In animals theophylline acts to stimulate gastric secretion by inhibiting the breakdown of cyclic adenosine monophosphate (cyclic AMP) by phosphodiesterase. Cyclic AMP is involved as an intracellular mediator of gastric secretion in several species (Harris et al 1969). Histamine activates the enzyme adenylate cyclase that forms cyclic AMP and this effect is blocked by H₂-receptor antagonists (Dousa, Code 1974). However in animals acid secretion stimulated by theophylline or cyclic AMP in its dibutyryl form was not inhibited by H₂-receptor antagonists (Fromm et al 1975) presumably because the H₂-receptor antagonists' action in preventing formation of cyclic AMP is bypassed. Contrary to the animal findings, in man cimetidine completely inhibited the moderate increase in acid secretion produced by the methyl xanthine caffeine (Cano et al 1976). The mechanism of this action is unknown and if this work is confirmed raises the question of the specificity of the concept of H₂-receptor blockade.

Human pharmacology. The problem of variation between different species in the physiology and pharmacology of mechanisms involved in gastric acid secretion has the important implication that results in animals cannot always be extrapolated to human beings. However the ability of cimetidine to inhibit all modalities of stimulated acid secretion has been amply demonstrated in man. In healthy volunteers as well as in patients with duodenal ulcer, oral or intravenous cimetidine significantly reduces gastric acid secretion stimulated by solid, liquid or peptone meals as well as that stimulated by sham feeding, fundic distension or by intravenous infusion of histamine, caffeine or pentagastrin (normal subjects: Aadland et al 1976, Burland, Duncan et al

1975, Cano et al 1976, Carter et al 1976, Pounder, Williams, Russell et al 1976; duodenal ulcer patients: Bodemar et al 1977, Henn et al 1975, Longstreth et al 1977, Pounder et al 1977, Richardson, Fordtran 1975).

The extent of inhibition is dose-related and a 50% reduction of stimulated gastric acid secretion is obtained by doses of cimetidine giving a blood concentration of 1-2 μ mol/L (0.25 to 0.5 μ g/ml) (Burland, Duncan et al 1975, Henn et al 1975, Longstreth et al 1976, 1977, Pounder, Williams, Milton-Thompson et al 1976, Pounder, Williams, Russell et al 1976). Not only the volume but the hydrogen ion concentration of gastric secretion is reduced. A single 300mg or 400mg dose maintains reduced acid secretion throughout the night (Hollander et al 1976, Longstreth et al 1976, Pounder et al 1977). In a study of 24 hour intragastric acidity in patients receiving standard meals a dose of 200mg four times a day reduced mean hourly intragastric acidity by 55% and double this dose produced a 67% mean reduction. The additional effect of the larger dose was largely accounted for by the decrease in acidity between 2.a.m. and 8.a.m. (Pounder et al 1975b). It should be noted that even with the larger dose of cimetidine intragastric pH fell below 2 for much of the day time part of the 24 hours. Although individual responses show some variation between patients, 400mg of cimetidine at night caused prolonged anacidity in all duodenal ulcer patients, lasting for 8 hours in about half of the group studied (Longstreth et al 1976).

The increase in intragastric pH profile produced by cimetidine was similar to that found in 4 patients who had undergone clinically successful truncal vagotomy and pyloroplasty for duodenal ulcer, suggesting that such intragastric pH levels are compatible with successful therapy for duodenal ulcer. (Pounder et al 1975b).

The timing of cimetidine dosage in relationship to meals is probably not critical although earlier and higher concentrations occurred in patients taking the dose before meals compared with delayed peak concentrations in those who took it postprandially (Pounder et al 1976a, Spence et al 1976). The mean 24 hour intragastric pH pattern was similar in pre and post prandially treated groups. However, dosage with or immediately after meals should provide maximum blood levels at a time when gastric emptying has minimised the amount of food buffer within the stomach, and provides therapeutic blood levels of the drug for a longer period if the next dose should be delayed.

Inhibition of gastric secretion-comparison with other drugs.

Comparison of the effects of cimetidine on gastric acid secretion with other agents designed to lower gastric acidity is important. Cimetidine 300mg was more effective in inhibiting peptone meal stimulated acid secretion than an "optimally effective dose" of propantheline bromide (Henn et al 1975) and cimetidine 400mg at 10 p.m. produced 93% inhibition of secretion from 12.30-6.30 a.m. while a large (8mg) dose of poldine produced only 61% inhibition.

(Blackwood, Northfield 1977). In a study of 24 hour intragastric pH, atropine 2.4mg/day, had no effect on mean hourly intragastric hydrogen ion concentration, nor on the total amount of acid produced overnight, while cimetidine 1.0g/day decreased the former by 41%, inhibited nocturnal secretion by 83% and resulted in half the nocturnal samples being anacidic with a pH.>7 (Pounder et al 1977). The combination of drugs offered no added advantage and did not change cimetidine's absorption or urinary excretion. This latter study shows a total lack of effect of atropine that appears remarkable - although it confirms older studies using similar doses (Kirsner, Palmer 1940, Nicol 1939). The dose of atropine was adequate to produce mild side effects in two of the four subjects. The measurement of hydrogen ion concentration (rather than acid output) is not the best index of anticholinergic action as these drugs are well recognised to reduce volume rather than pH of gastric secretion - but the lack of effect on nocturnal acid output is a little surprising.

Thus cimetidine in a 300mg or 400mg dose is clearly more potent than tolerable doses of anticholinergic drugs. The latter also have the disadvantage of producing a number of unwanted effects due to parasympathetic blockade, such as dry mouth and blurred vision.

Can the addition of anticholinergic drugs to cimetidine increase the degree of inhibition of gastric secretion obtained with cimetidine alone? Clearly the circumstances of test will have a major impact on the results obtained.

For example, large doses of cimetidine alone have a potent effect on nocturnal secretion: 400mg at bedtime produced 93% inhibition of the secretion from 12.30 - 6.30 a.m. (Blackwood, Northfield 1977). The addition of an anticholinergic drug obviously has little chance of producing a significantly greater degree of inhibition. The results obtained by adding a large dose of poldine confirmed this, but poldine did augment the effect of a submaximal 200mg bedtime dose of cimetidine. Saunders measured 12 hour secretion from 8.p.m. to 8.a.m. and found that a 6.30p.m. dose of cimetidine 400mg following the evening meal decreased acid output by 66%. The addition of poldine 4mg increased this to 77% inhibition (Saunders et al 1977). Another quaternary compound, propantheline bromide 15mg, also augmented the inhibition produced by cimetidine 300mg of acid secretion stimulated by a steak meal and measured by intragastric titration in 9 patients (Feldman et al 1977). Cimetidine alone reduced acid output from 77mMol/3 hours (control) to 39mMol/3 hours; Probanthine alone reduced the output to 51.5mMol/3 hours, but the two drugs combined reduced acid output to 27mMol/3 hours - a significant improvement.

The studies of Pounder and colleagues are the only ones which demonstrate a total failure of additional atropine 2.4mg/day to increase the inhibitory effect of cimetidine 1.0g/day (Pounder et al 1977). Some of the possible explanations have already been discussed, and others such as decrease in cimetidine bioavailability were excluded by

measurements of drug absorption and excretion. Atropine is a tertiary compound rather than a quaternary one but whether this is relevant is uncertain. It is certainly well absorbed from the gut and has been recommended for clinical use for this reason (Ivey 1975).

Comparison of cimetidine with antacids has also been made. The total load of unbuffered acid delivered to the duodenal bulb during four hours after an eaten steak meal in duodenal patients was decreased by 86% after a 400mg dose of cimetidine. Antacid give 1 and 3 hours after the meal in a dose capable of buffering 114mEq of acid produced more variable results, with a mean reduction in duodenal unbuffered acid load of 75% - not significantly different from the result found after cimetidine (Deering et al 1977). Comparisons of the effects of cimetidine or antacids on nocturnal acid secretion have not been made. Liquid antacids are rapidly emptied from the stomach and this is a major limitation to their usefulness. Patients are unlikely to choose to disturb their sleep to take 2 hourly doses through the night!

Pharmacology of cimetidine - effects other than acid inhibition.

Pepsin output by the stomach is decreased by cimetidine but to a lesser and more variable degree than acid secretion (Aadland, Berstad 1976, Burland, Duncan et al 1975). The reduction is largely due to a reduced volume of secretion.

Conflicting results have been reported on the effects of cimetidine on secretion of intrinsic factor by the

parietal cell. (Burland et al 1976a, 1977, Fielding et al 1976). Infusion of cimetidine acutely probably reduces intrinsic factor secretion in most subjects (Binder, Donaldson 1978, Fielding, Chalmers et al 1978). Twelve hours after a 12 week course of cimetidine intrinsic factor output has returned to normal levels (Epstein et al 1978) and absorption of Vitamin B₁₂ measured by a Schilling Test was normal in three patients after a six week course (Pounder 1977). Further studies of patients receiving long term cimetidine treatment are necessary but it seems unlikely that cyclic inhibition of intrinsic factor release would be enough to cause Vitamin B₁₂ deficiency, especially if only a single bedtime dose is used.

Acute administration of an oral dose of cimetidine does not influence fasting serum levels of gastrin. When intragastric pH is kept constant there is no change in gastrin response to a meal (Henn et al 1975, Pounder, Williams, Russell et al 1976) but when intragastric pH is allowed to seek its own level addition of cimetidine to the meal enhances gastrin release, presumably because of the increase in antral pH (Richardson 1978). The question of longer term effects on gastrin release and acid secretion will be discussed in Chapter 10.

Studies on gastric emptying of liquid or solid meals (Heading et al 1977, Longstreth et al 1977, Pounder, Williams, Russell et al 1976) and lower oesophageal

sphincter pressure (Carter et al 1977) have shown no consistent effect of cimetidine. The fractional rate of gastric emptying (percentage volume of gastric contents emptied per unit of time) was unchanged by oral or intravenous cimetidine in normal subjects and duodenal ulcer patients.

In normal volunteers oral cimetidine increased gastric transmucosal potential difference (P.D.) (Ivey et al 1975) and prevented the fall in PD resulting from ingestion of aspirin (MacKercher et al 1976). Biopsy of the mucosa in this study confirmed that fewer epithelial cells were damaged after prior administration of cimetidine. The mechanism of this protective effect seems likely to be due to suppression of acid secretion. There is some evidence that cimetidine may exert a cytoprotective effect independent of its effects on acid secretion, but the discussion of experimentally induced ulceration is beyond the scope of this thesis.

Biliary and pancreatic secretion is not influenced by cimetidine. Postprandial output of lipase, trypsin and bile acids was unchanged by pretreatment with cimetidine 200mg or 300mg (Longstreth et al 1977) and pancreatic bicarbonate and enzyme secretion was not changed by a 4 week course of cimetidine (Domschke et al 1977). Amylase and lipase output in response to maximal stimulation with secretin and cholecystokinin was unchanged by cimetidine 400mg orally. (Galmiche et al 1977). It should be noted that histamine H₂-receptors have been demonstrated in a wide variety of tissues (Chand, Eyre 1975). They must of course be defined not only by demonstrating an action of histamine that can be blocked by cimetidine, but also by

the selective H₂-receptor agonists producing stimulation at these sites. The relation between the stimulatory and the inhibitory effects must be the same as in the original experimental models in which histamine H₂-receptors and their antagonists were defined (Black 1975). Using these criteria H₂-receptors are present on mast cells, T lymphocytes, in blood vessels, reproductive organs and in the brain as well as the heart, smooth muscle and stomach. Whether histamine receptors at all these sites have a physiological (rather than pharmacological) role is uncertain. At the dose required to produce 50% inhibition of gastric secretion (ID₅₀), approximately 2 μmol/litre, there appears to be no immediate effect on other physiological systems (Brimblecombe et al 1978). A variety of animal test systems found that large doses of cimetidine, 100-150 times the ID₅₀, were necessary before transient bradycardia was seen - and this occurred only in the conscious untrained dog.

Animal Toxicology

This field has been summarised (Leslie, Walker 1977). The only important effect noted was a weak antiandrogenic effect of high dose cimetidine (Brimblecombe et al 1978). The growth of prostate and seminal vesicles was retarded by doses of 100-950mg/kg in rat and dogs but the effect was reversible on stopping treatment. There was no effect on mating performance or fertility, and progeny were normal. None of the foetuses of female rats treated before and throughout pregnancy and lactation showed evidence of feminisation thus confirming the weakness of the antiandrogenic effect.

Pharmacokinetics of cimetidine in man.

Kinetic studies were initially performed using carbon 14 radioactive labelling of the imidazole ring. Subsequently a high performance chromatographic method was developed for measuring unchanged cimetidine in blood or urine (Randolph et al 1978). Alternative extraction methods have also been described (Larsen et al 1979). Earlier studies measured cimetidine concentrations in whole blood, but plasma may be used. If comparisons of studies using whole blood are made with others using plasma it should be noted that if whole blood stands at room temperature for some hours free cimetidine may be converted to its sulphoxide metabolite (Larsen et al 1979).

Absorption. Cimetidine is readily absorbed, probably from the small bowel, after oral administration (Griffiths et al 1977). Peak blood concentrations in fasted subjects generally occur 60-90 minutes after ingestion (Henn et al 1975, Pounder et al 1976, Spence et al 1976) with mean values of 3-6 μ mol/l, 6-9 μ mol/l and 9-12 μ mol/l after single doses of 200mg, 300mg, and 400mg respectively. Blood concentrations are disproportionately high after 800mg orally - Mean 28.8 μ mol/l (Griffiths et al 1977).

Peak concentrations are lower and delayed when cimetidine is given with or after meals (Pounder et al 1976, Spence et al 1976) with mean peak blood concentrations of 2-3 μ mol/l 80-120 min. after a 200mg dose, but the area under the plasma level curve, the time that levels are

above the I.C.₅₀ and the mean intragastric hydrogen ion concentrations, are not significantly different (Pounder et al 1976, Spence et al 1976). Fasting subjects often show a second peak within the first three hours (Bodemar et al 1979).

Comparison of the area under the concentration-time curve after oral dosing with the area following intravenous administration shows that bioavailability of an oral dose is 62-75% and that there is probably a small "first-pass" effect (Griffiths et al 1977, Walkenstein et al 1978).

Concomitant administration of antacids in one study of 6 subjects produced no significant reduction in bioavailability (Burland et al 1976), while a second study in 9 subjects showed a mean 22% reduction in the area under the time-concentration curve (Bodemar et al 1979).

Distribution. Following intravenous (i.v.) injection of 100mg the concentration first falls rapidly ($t_{1/2}$ =6.8 mins) then at a rate comparable to that seen 3-6 hours after oral dosage ($t_{1/2}$ = 110 mins). The apparent volume of distribution in 4 subjects was large, 52.3 ± 10 l. (Griffiths et al 1977). There are few data on distribution pattern in man. Concentrations of 47.5 to $157 \mu\text{mol/l}$ have been recorded in bile 1 to 2 hours after an oral 800mg dose. Corresponding portal and peripheral venous blood concentrations were 14 to $48 \mu\text{mol/l}$ and 8 to $30 \mu\text{mol/l}$ respectively. Despite the higher bile concentrations only 1.2mg of cimetidine was excreted in 6 hours of continuously collected bile (Spence et al 1977b).

Autoradiographic studies in animals have shown that radiolabelled cimetidine does not appear to enter the central nervous system (Cross 1977). However a report on severely ill patients in an intensive care unit found cimetidine in the C.S.F. in all five patients who underwent lumbar puncture for other clinical indications (Schentag et al 1979). Whether cimetidine crosses the normal human blood barrier is unknown.

Metabolism and excretion. After i.v. administration of 50-120mg of labelled cimetidine 80-96% of the administered dose was recovered in the urine within 24 hours (Burland, Duncan et al 1975), Of this approximately 70% was unchanged cimetidine (Griffiths et al 1977). After 200-300mg oral doses 40-60% was recovered unchanged in urine within 24 hours (Walkenstein et al 1978). A smaller proportion of 400-800mg oral doses was present in the urine as unchanged drug. After i.v. doses about 10% of the radioactivity in the urine was present as the sulphoxide of cimetidine and 5% as the hydroxymethyl derivative independent of dose or route of administration. An unidentified polar material, possibly hepatic conjugates, constituted 7-20% of the urinary radioactivity.

A small proportion of the drug is excreted in the faeces. In 2 subjects 8% and 12% of oral radiolabelled 400-800mg doses was found in the stool, but only 1.6 - 2% of 60mg administered intravenously (Griffiths et al 1977).

Cimetidine pharmacokinetics in renal failure. The slow phase elimination half life of cimetidine after intravenous injection or oral dosing is 1.6 - 2.2 hours in healthy subjects. (Burland, Duncan et al 1975, Walkenstein et al 1978).

In patients with minimal renal function requiring haemodialysis (urine volume < 1ml/min to > 1 litre/24 hours; creatinine clearance < 1ml/min to 2 ml/min) the half life in 6 subjects was prolonged to 3½ to 8 hours with a mean of about 5 hours (Canavan, Briggs 1977). In these patients peak blood levels after 100mg orally were 5-10µmol/L (comparable to those levels attained after 300mg orally in patients with normal renal function). Blood levels above 2µmol/L were maintained for 7-8 hours after this single oral 100mg dose. However haemodialysis rapidly and completely removed cimetidine. The authors recommended that cimetidine 200mg twice daily would produce blood levels equivalent to those achieved by 1g/day given to patients with normal renal function. This dose has been shown to be safe and clinically effective in patients with gastrointestinal disease who were undergoing haemodialysis (Jones et al 1979). Prolongation of half life of cimetidine in patients with renal failure has been confirmed. (Ma et al 1978). An inverse correlation of half life with creatinine clearance was found, the former being increased to 3-5 hours when creatinine clearance was less than 20ml/min.

Cimetidine pharmacokinetics in hepatic failure. Although cimetidine is partially metabolised by the liver there is little information on the pharmacokinetics in patients with impaired liver function. Cimetidine has been used in a considerable number of patients with severe hepatic failure at full recommended doses without apparent adverse effect (MacDougall et al 1977). However Schentag et al found 1 patient, out of a group of 6 with serum bilirubin

> 4mg/dl and elevated transaminases, who developed a raised 'trough' concentration of cimetidine and some change in mental state while receiving 300mg i.v. every 6 hours; this compared with 2 patients out of 22 with normal biochemistry who developed elevated trough concentrations (Schentag et al 1979).

Cimetidine pharmacokinetics in the elderly. It is worth noting that much of the information on the pharmacokinetics and bioavailability of cimetidine has been obtained on volunteers rather than ulcer patients. Few elderly volunteers were included in the studies (Grahnen et al 1979) or age was not stated (Walkenstein et al 1978). Recent work suggests that the bioavailability of cimetidine increases with age in both normal subjects (Redolfi et al 1979) and patients with gastric or duodenal ulcers (Somogyi et al 1980). Thus therapeutic plasma concentrations are maintained for longer in the elderly, than in younger patients following a fixed dose. This increased bioavailability may partly explain why some side effects (e.g. confusion, gynaecomastia) seem to occur mainly in the elderly. The increased area under the time-concentration curve in older patients is partly due to reduction in renal clearance, the main excretory route for cimetidine, and also due to a reduced volume of distribution (Somogyi et al 1980).

CHAPTER IV

THE COURSE AND PROGNOSIS OF DUODENAL ULCER

"There is no disease of which a fuller or additional description does not remain to be written."

John Ryle, 1931.

Introduction.

How should we judge the success or failure of any new drug or regime used to treat peptic ulcer? To answer this we must have a clear idea of the way the disease can be expected to behave without treatment or with the treatments that have been available to date.

The clinical hallmark of duodenal ulcer is the periodic recurrence of bouts of abdominal pain. In a minority of patients active ulceration may cause complications. Occasionally, these may be the presenting problem, without prior symptoms, but for most patients symptom recurrence is the main problem. What does the literature tell us about the frequency, severity and duration of recurrences, and what is the chance of prolonged remission occurring?

Interpretation of papers published before 1940

In 1950 Bralow et al, after reviewing the literature on recurrence rates from 1890 to 1948, noted that "It is obvious that comparison between any 2 investigations is almost impossible as each author has his different criteria of recurrence as well as follow up at various time intervals.

In fact, several authors do not even mention how long the patient has been studied. No truly objective method has yet been determined for the evaluation of ulcer activity following medical treatment." (Bralow et al 1950a, 1950b).

The study of Emery and Monro (Emery, Monro 1935) illustrates some of the problems of interpretation of earlier data. At first sight this is an impressive collection of all the 1435 cases of peptic ulcer diagnosed at the Peter Brent Brigham Hospital (Mass. USA) up to January 1st 1932. They emphasize the important of "prolonged and careful observation" but in the absence of a section outlining their methods it is only gradually that some confused facts emerge:

- (1) The 1435 cases include 1167 duodenal, 215 gastric ulcer and 53 with both. Unfortunately these are not separated in subsequent tables.
- (2) Some cases presented with the clinical problems of ulcer but others were diagnosed incidentally during the course of another disease, or only at autopsy but are nonetheless included as cases "requiring no treatment".
- (3) The basis for the initial diagnosis is not clearly stated although radiology was used in a small proportion of patients.
- (4) The time elapsed from diagnosis varies from 0-25 years with a mean of 3.9 years. The lack of a minimum period of follow up causes considerable confusion. 30% of the patients have been followed for 1 year or less

and these short or medium term results are mixed with those of longer term treatment. Because of this and the inclusion of 300 patients under both medical and surgical treatment, the general "summary of results" is meaningless.

- (5) The tendency of ulcer to recur is illustrated by their table which shows a decreasing percentage of patients "cured" with increasing periods of observation. Unfortunately there is no definition of what "cured" means, nor the total number of patients observed for each time interval.

Problems of data interpretation.

Problems in the interpretation of data in studies of the course of duodenal ulcer have diminished as authors have presented their methods in greater detail, but some of the difficult areas which still confound assessment of the outcome of duodenal ulcer disease must be outlined.

1. *The diagnosis.* In many published series the criteria for establishing both the initial diagnosis and the cause of recurrent symptoms are absent, not clearly stated or inadequate. It was only with the development of radiological techniques in the 1930's that criteria could be agreed upon for the diagnosis of the disorder in patients who had not suffered complications. For this reason and the fact that most papers published before 1940 fail to detail their methods, I have not attempted to assess the earlier literature, much of which was reviewed by Bralow et al in 1948. In more recent studies radiology is often used to make the initial diagnosis with subsequent reliance on clinical features to diagnose recurrence. Conversely a few series have repeated

barium studies without reference to symptoms, while other authors have selected subgroups of patients (usually those with symptoms) for further radiological examination. Longer term studies utilizing endoscopic examination are largely clinical trials of drug treatment performed since 1974. In most studies cimetidine treated patients or placebo control groups have been followed for relatively short periods (up to one or two years).

2. *Selection of patients.* Most studies assess patients who have been referred to hospital. A high proportion of these patients are specifically referred because of intractable symptoms or the presence of complications. This clearly introduces bias and ignores the fate of the high proportion of patients who are satisfactorily treated by their family doctors. There are few studies of the entire spectrum of patients who are diagnosed by their family doctor. Even reports from general practice take no account of the undiagnosed dyspeptics with duodenal ulcer in the community who treat themselves and avoid the medical profession. Community surveys of dyspepsia provide a broader picture of disease in a chosen population but they suffer from the drawback of self assessment and unconfirmed diagnosis. Thus no single methodology is entirely satisfactory and a compromise has to be struck between diagnostic accuracy and selection bias.

Figure 4.1 illustrates the "ulcer iceberg". The manifestations of ulcer disease in any population may range from none (in the unknown proportion of patients without symptoms), through transient undiagnosed indigestion, medical attendance, diagnosis and treatment, to the complications and morbidity of ulcer disease. Mortality

<u>Manifestations of ulcer.</u>	<u>Study, author.</u>	<u>Source of Data.</u>
Ulcer Deaths	Watkinson 1960 Emery, Moore 1935.	Post mortem survey (ulcer incidence in cases of sudden death). Hospital records including autopsy.
Perforation Haemorrhage	Natvig, Romcke 1943 Flood 1948, 1955.	All hospital admissions with peptic ulcer.
Elective Surgery Hospital Inpatients	Malmros, Hierton 1948 Martin, Lewis 1948.	
Hospital Outpatients Barium Meal, Endoscopy	Griebe et al 1977.	GP and hospital patients with duodenal ulcer diagnosed radiologically.
G.P. Attendance Sickness Absence	Fry 1964.	General practice patients with ulcer.
Ulcer Dyspepsia in a defined community	Pulvertaft 1959, 1968.	York population survey: all residents with newly diagnosed ulcer.
All Indigestion	Weir, Backett 1968.	Aberdeen community survey of ulcer and dyspepsia in a random population sample.
The General Population (no indigestion, some asymptomatic ulcers)		

FIGURE 4.1 The Ulcer "Iceberg". The varied manifestations of peptic ulcer, with examples of studies on its natural history or prevalence which have used different levels of resource data.

forms the tip of the iceberg. Death because of ulcer is uncommon despite the common occurrence of the disease.

"Underlying any description of the natural history of peptic ulcer is the problem of definition . The classification of patients (and often their treatment) depends on not only the severity and persistence of symptoms but individual tolerance, the experience, work load and interests of the doctor, and the availability and extent of local facilities for diagnosis" (Weir and Backett 1968). These sources of variation make comparisons of data obtained from different 'levels' in the iceberg well nigh possible. Therefore later in this chapter groups of publications that have obtained their information in comparable ways will be discussed in separate sections.

3. *Retrospective data.* Very few authors have carried out prospective follow up of patients. The majority of studies are either totally retrospective reviews of case records, or involve a single recall or questionnaire interrogation of patients diagnosed some years before; these then rely on the patients retrospective recall of recent symptoms. Studies which use the latter method will be called "semi-retrospective" and are discussed later in this chapter. The few prospective studies often fail to detail their methods and frequency of patient review, or rely on patients' memories of the previous year at an annual follow up appointment.

4. *Criteria for relapse.* A return of symptoms is the prime indicator of relapse but trivial dyspepsia or other causes of abdominal pain can cause confusion. Even early studies which had no way of objectively confirming the diagnosis did not attempt to define relapse. Recent longer term drug trials have often failed to define the level at which symptoms are said to constitute relapse although most demand endoscopic confirmation of recurrence. Other studies have used repeat endoscopic examination in asymptomatic patients without distinguishing the proportion of patients in whom recurrence was found by this means from those who have suffered symptomatic relapse.

5. *Single recurrence of "intractable ulcer"?* In treatment trials a single relapse during a follow up period may be taken as evidence of treatment failure and is a convenient end point. However, it is clinically more important to know whether the patient suffers repeated recurrences during continued treatment. It seems unlikely that any treatment will totally eliminate recurrence but a useful reduction in frequency of relapse might be overlooked if a single exacerbation of symptoms was used as the sole criterion of success. While a single recurrence may indicate therapeutic failure in a trial it is not equivalent to "intractability" as an indication for surgical intervention, which can only be judged after prolonged follow up.

6. *Case selection by surgical intervention.* In order to assess the natural history of duodenal ulcer it would be

desirable for no patient to undergo surgical treatment during the period of observation. This is clearly not possible. Patients selected for operation are those with complications or the most severe or prolonged symptoms. As most operations are performed electively (Fry 1964, Griebe et al 1977) it would aid interpretation of results if the indications were clearly delineated and the proportion of patients undergoing surgery identified. These cases ought not be excluded from any analysis even though they may be viewed as a separate category. A failure to take into account the proportion of patients requiring operation would tend to underestimate the severity of the disease. These patients cannot be lumped together with those treated conservatively as surgery clearly does change the course of the disease. However, it would seem impossible for a surgical unit to provide useful data on the "natural history" of the disease as patients who require operation are likely to be selectively referred to them. For this reason I feel that, for example, the data provided by Krause (1965) are of dubious value. He reviewed 349 cases of duodenal ulcer a minimum of 25 years after diagnosis and concluded 81% had pursued a "serious course". However a total of 56% of all patients had been operated and were included by him in the "serious course" group.

7. Expression of results. Even when the questions of patient selection, diagnosis and mode of follow up have been answered, the problem of how to express the results remains. In a rapidly fatal disease the end point is clear, even though it may be expressed in different ways. For example, survival may be calculated as a mean number

of months or years after diagnosis with a given range, or alternatively a life table may be used to show the numbers of patients who survive for successive periods of time.

For a non fatal, chronic disease with a relapsing and remitting course there is much less agreement on how to express the outcome. Two approaches which have been used may be called the "cross sectional" and the "cumulative". Each has its merits but gives a widely different perspective. A "cross sectional" view indicates the proportion of patients who are suffering symptoms at a given time, or who have suffered symptoms within a given short time span. During prolonged observation an individual patient may move in or out of the symptomatic group.

In contrast the "cumulative" view indicates the proportion of patients who have suffered symptoms at any stage up to the point of review and paints a "gloomier" picture. Here a single recurrence years before may put the patient into the "failure" group despite recent well being. On reviewing the literature it is clear that these extremely different modes of expression of results have contributed to argument on whether the long term course of duodenal ulcer is benign or malevolent.

The rather different impressions of the prognosis of duodenal ulcer produced by different modes of expression of the results are illustrated later in this chapter in the discussion of the work of Flood (St. John and Flood 1939, Flood 1948, 1955) Pulvertaft (Pulvertaft 1968) and Viskum (Viskum 1976).

Semi- retrospective reviews of hospital patients.

A series of publications from the decade 1940-1950 in which the diagnosis of duodenal ulcer was securely based provided some of the first interpretable data on the course of duodenal ulcer (Table 4.1). In all the diagnosis was based on radiology, sometimes with supporting operative or autopsy evidence. The patients studied were hospital admissions, most with symptoms of duodenal ulcer and some with complications such as haemorrhage or perforation. Duodenal ulcer was clearly distinguished from gastric ulcer. The studies were semi-retrospective in that the patients who could be recontacted after a period of years were asked about their current or recent symptoms, dietary habits and other treatment. Unfortunately some authors did not explain how recently symptoms had to have occurred for them to be considered current and all relied on the patients memory. Most patients received dietary treatment, some antacids and a minority operative intervention - although oversew of perforation, gastrojejunostomy or gastrectomy are not usually distinguished.

Despite differences in the length and completeness of follow up, and variation in definitions of outcome, there is a surprising degree of agreement and a number of common conclusions. After 3-10 years interval, 25-35% of patients were asymptomatic, or suffering only minor symptoms, while 20-35% continued to get moderate symptoms on occasions and 35-45% showed no improvement or had required operation. Operation had been performed in 7-25%. Four of the five series found that the prognosis was improved if the history of ulcer symptoms was short -

Table 4.1 Outcome of duodenal ulcer in patients initially admitted to hospital, diagnosed radiologically and subsequently reviewed on a single occasion some years later.

Author, country.	Years since admission	Patients	Dropouts	Categories of outcome	Other conclusions
Krarup 1945 (Denmark)	Min. 5 Max. 10	All admissions 1931-1938 (inc. haemorrhage), 246 D.U. alive	6% untraced 11% dead	1. Asymptomatic Asymptomatic after 1 relapse 20% 2. Improved (some symptoms) 34% 3. Poor result (no change or worse) 43%	i. 90% of all D.U. relapsed, most within 2 years ii. 6.7% operated iii. Prognosis better if history short, or presentation with bleeding.
Natvig, Romcke 1943 (Norway) and Quigstad, Romcke 1946 (Norway)	Min. 3 Min. 6	All admissions 79 D.U.*	< 2%	1. Asymptomatic 34%	i. Prognosis better if history short.
Kahr.s, Schrupf 1947 (Norway)	Min. 3½ Max. 8½	Admissions 1938-1942 144 D.U. (Haemorrhage reviewed separately)	Not stated	1. Asymptomatic (or a single relapse) 25% 2. Improved (some symptoms) 38% 3. Not healed (includes operated patients) 37%	i. Prognosis better in patients with bleeding ii. 16% operated
Malmros, Hiertonn 1948 (Sweden)	Min. 7 Max 10½	Medical admissions 1936- 1939 (inc. haemorrhage)	< 1%	1. Favourable course (slight symptoms 16.3%) 29% 2. Less favourable 22% 3. Serious course (ulcer related deaths 3.4%) 41% 4. Unrelated death 8%	i. Prognosis better if history < 5 yrs. ii. 104 (21%) operated.
Martin, Lewis 1949 (England)	Min. 10 Max. 15	All admissions 1934-1938 62 D.U. alive	7% untraced 33% dead	1. Inactive (no symptoms within 5 yrs) 39% 2. Active 61%	i. Prognosis better if history < 2 yrs. ii. 19 (30%) operated.

TABLE 4.2

RELATIONSHIP OF LENGTH OF PREVIOUS HISTORY OF PEPTIC
ULCER SYMPTOMS TO SUBSEQUENT INCIDENCE OF REMISSION.

AUTHOR	YEARS SINCE ADMISSION	PROGNOSIS WITH SHORTER HISTORY	PROGNOSIS WITH LONGER HISTORY
KRARUP 1945	5-11 years	< 6/12, 48% recovered 6/12-1yr., 28% recovered	> 1yr., 17% recovered
QUIGSTAD, ROMKE 1946	3-5 years	< 5yrs., 40% symptom free	> 5 yrs., 25% symptom free
KAHRS, SCHRUMPF 1947	3-8 years	< 5yrs., 21% recovered	> 5yrs., 25% recovered
MALMROS, HIERTONN 1948	7-10 years	< 5yrs., 37% favourable course	> 5 yrs., 12.5% favourable course
MARTIN, LEWIS 1949	10-15 years	< 2yrs., 41% inactive	> 2yrs., 27% inactive.

Table 4.3 Relationship of presenting symptoms to subsequent haematemesis or melaena during the following 7-10 years (Malmros, Hiertonn 1948).

Presentation at first admission	Patients (G.U.+D.U.)	Previous History G.I.Bleeding	Subsequent G.I. Bleeding
G.I. Haemorrhage	125	17.6%	34.4%
No Haemorrhage	562	8.7%	3.9%

although definition of short varied from less than 6 months to less than 5 years (Table 4.2).

Presentation with acute haemorrhage also was associated with a better prognosis in some series. However accurate (endoscopic) diagnosis of the source of bleeding was not possible at that time and cases of haemorrhage from sites other than chronic ulcer may have been included. This conclusion therefore must be considered of doubtful validity. What is shown by Malmros and Hiertonn is that the chance of gastrointestinal haemorrhage occurring during the period following the first admission is much greater in patients who initially presented with bleeding rather than with pain (Table 4.3). Other factors such as the age or sex of the patient generally had little effect on prognosis.

Despite a variety of punitive diets and antacids most authors concluded that treatment was ineffective. "To be quite honest the investigation presented here is proof that medicinal ulcer therapy in the accepted form has resulted in almost complete failure. We have certainly succeeded in healing the ulcer (or perhaps the ulcer has healed without our help) but we have not succeeded in preventing relapse". (Malmros, Hiertonn 1949). Martin and Lewis found that 65.5% of 'active' duodenal ulcers had adhered to their treatment compared with 43% of 'inactive' duodenal ulcers. Subsequent haemorrhage during follow up had occurred in 1 patient who abandoned treatment and in 10 patients who had persisted with diet and powder.

"The facts suggest that the natural course of the disease was not influenced by medical treatment. Those cases which were active persevered with their regimen and also suffered complications while those who were inactive abandoned treatment and had no trouble". (Martin and Lewis 1949).

Prospective studies of the course and prognosis of duodenal ulcer.

The data collected in a semi-retrospective fashion suggest that a substantial minority of even those patients requiring hospital admission will have a relatively benign long term course. Does evidence collected in a prospective fashion support this concept?

Duodenal ulcer in hospital patients. One of the earliest prospective studies is that of Flood (St. John, Flood 1939, Flood 1948, Flood 1955). He studied 233 duodenal ulcer patients who had initially required hospital admission and were followed every 3-6 months, All had been seen for 1 year, most at least 3 years and half for 7 years. The mean duration of observation was 6.9 years. He notes that the fluctuating course of the disease makes analysis difficult and accordingly expressed his results "both in terms of the proportion of permanently satisfactory cases and in terms of the proportion of satisfactory years of observation".

Most patients suffered a recurrence with only 21%(48) remaining symptom free throughout. This proportion progressively fell from 51% of those followed for 1 year to 22% of those followed 5 years and 15% of those patients followed for 10 years. However Flood noted "this fails to take account that most patients are symptom free most of

the time even if they have occasional recurrences".

For the entire group of patients there were 756 recurrences during 1603 follow up years, an average of one recurrence every 2.1 years. Of all the 1603 years of observation 63% of years were free of symptoms.

The remaining years were marked by one or more recurrences which in 24% of years were of moderate severity and in 13% were incapacitating. The only adverse prognostic feature was a greater frequency of recurrence in 62 patients whose symptoms persisted for longer than 2 weeks during hospital treatment. Strict adherence to an ulcer diet was again found to be of no prophylactic benefit.

Thus Flood and his coworkers were the first authors to emphasize that the "cumulative" approach was an inadequate way of expressing the long-term course of duodenal ulcer. Even in a highly selected hospital population a high proportion of patients were free of symptoms for much of the time.

Peptic ulcer in general practice. Another landmark in prospective studies was that of John Fry in 1964. He set out to record the course of peptic ulcer in unselected patients in his suburban general practice in Beckenham, England. 212 patients with duodenal ulcer were followed over 5-15 years with functional assessment annually. Considering symptoms from their date of onset he found the disease caused increasing disability for 5 to 8 years and then tended to "burn itself out". (Table 4.4).

Thus the "mean annual grading" showed a rise in the first 5 years with a peak after 8.1 years for males and 7.1 years in females and a decline thereafter with only about 5% suffering moderate or severe symptoms after 10

Table 4.4

Duodenal ulcer patients in general practice (Fry 1964).Functional gradings at 5 year intervals of follow up.

		* <u>Grade 1</u>	<u>Grade 2</u>	<u>Grade 3</u>	<u>Grade 4</u>	<u>Mean Annual Grade</u>
At Onset	Males	5 (3%)	100 (58%)	61 (33%)	10 (6%)	2.4
	Females	1 (3%)	21 (58%)	12 (33%)	2 (6%)	2.4
5 Years	Males	3 (2%)	36 (22%)	55 (33%)	70 (43%)	3.2
	Females	-	4 (12%)	16 (47%)	14 (41%)	3.3
10 years	Males	70 (60%)	40 (35%)	4 (3%)	2 (2%)	1.5
	Females	10 (50%)	9 (45%)	1 (5%)	-	1.9
15 years	Males	35 (76%)	10 (22%)	1 (2%)	-	1.3
	Females	4 (80%)	1 (20%)	-	-	1.3

* Grade 1 - No symptoms

Grade 2 - Some medication required

Grade 3 - Attended doctor

Grade 4 - Severe symptoms - absence from work.

years. The results were remarkably similar for patients who had undergone medical therapy (84%) or elective surgery (16%) although the criteria for choosing the latter are unstated.

Fry's work was valuable in providing an impression of duodenal ulcer disease in a population less highly selected than previous hospital series. However his conclusion - that duodenal ulcer has a benign long term course - is a consequence of the "cross-sectional" mode of assessment as well as the view of a broader spectrum of disease. What other data are available to support Fry's conclusions?

The York population survey. This ambitious project is one of the few attempts to document prospectively the incidence and natural history of newly diagnosed gastric and duodenal ulcer in a well defined community centred around the city of York, in England. (Pulvertaft 1959,1968).

All 900 new cases of duodenal ulcer, in whom the diagnosis had never previously been established, diagnosed in the York area in 1952-57 were seen annually at a gastric clinic up to 1963. Criteria for diagnosis were strict and the minimum period of observation was six years for all but the 6% who failed to return. A complete cross section of the ulcer population was thus obtained including patients presenting with ulcer symptoms, or complications and irrespective of whether they attended a physician, surgeon or their family doctor. No attempt was made to influence treatment and indications for surgery, for example, were not standardized. The patient's condition for the preceding year was given a Visick grading at each clinic attendance irrespective of mode of treatment:

- Grade 1 or 2, Good result: No symptoms or slight symptoms.
- Grade 3, Moderate result: Symptoms not controlled but not severe.
- Grade 4 or 5, Bad result: Severe symptoms, 2 weeks or more off work, haemorrhage, perforation or elective surgery.

The percentage of patients falling into each category each year was fairly similar, with 45-55% reporting a good year, 15-25% a moderate year and 15-35% a bad year. This "cross-sectional" view is slightly distorted by the automatic cumulative inclusion of all patients who have had elective surgery in the "bad result" grade. Nonetheless, the impression gained from this "cross-sectional" view seems that the majority of duodenal ulcer patients are moderately or fully well for most of the time.

The causes of bad results, each year, were similar for men and women. On average, 7.2% of men and 9.3% of women experienced severe symptoms, 2.7% of men and 2.5% of women had a haemorrhage, 0.8% of men and 0.3% of women had acute perforations and 4.5% of men and 3.2% of women proceeded to elective surgery.

Thus by the sixth year of observation of the male duodenal ulcer patients (694 entered initially) the grades were: good 49%, moderate 15%, bad 36%. Female patients with duodenal ulcer (205 initially entered) were recorded as good 46%, moderate 25% and bad 29%. Again it is apparent how cumulative aggregation of all patients undergoing elective surgery in the 'bad' group gives a rather different impression, as during the 6 years, 27% of the men and 19% of the women were operated upon. If the cumulative approach to symptoms is adopted then it may

be calculated that the proportion of male patients remaining well (Grade 1 or 2) throughout the 6 years was just under 20%. It is interesting to note how the initial presentation influenced the outcome: of those men who presented with clinical symptoms only 16% remained grade 1 or 2 throughout, compared with 24% of those who presented with haemorrhage and 37% of those with acute perforation.

Two recent semi-retrospective surveys of duodenal ulcer.

Two recent publications from Denmark are of interest although they both use "semi-retrospective" review of patients.

Viskum in 1971 reviewed the records of 1415 duodenal ulcer patients who had been admitted to Medical Department of the Bispebjerg Hospital between 1938 and 1952 inclusive. (Viskum 1976). All were diagnosed radiologically. Approximately 43% had died in the interviewing period and 5% could not be traced. Thus 728 patients were available for interview, an average of 18.3 years after the index admission. Hospital records were used, as well as relying on the patient's memory. Patients were asked about "immediate" recent dyspepsia as well as the overall course of symptoms during the years since admission.

Of the original 1415 patients a high proportion (43%) had been operated (mainly Billroth II partial gastrectomy), 7% had died because of ulcer, 16% had required further admissions and in only 20% were no further symptoms evident, with mild symptoms in a further 12%. This rather depressing picture is a product of the selected nature of the series, local management policies and the "cumulative"

perspective. However, it is interesting to contrast this with the opinions of the interviewed patients about their recent symptoms. Of 346 unoperated patients 58% reported no recent dyspepsia and 40% some mild dyspepsia with only 2% suffering from severe symptoms. As might be expected results in operated patients were a little better with 77% reporting no dyspepsia, 15% mild dyspepsia and 8% severe symptoms. Again it is evident that a "true" picture of the prognosis can only be gained by combining both perspectives.

The other Danish study in 1976 reviewed patients diagnosed for the first time 13 years before, randomly selected from the radiological files in the county of Copenhagen (Griebe et al 1977). It supports the concept that duodenal ulcer tends to have a benign long term course. The design of the study was semi-retrospective but utilised a broad cross section of patients referred for barium meal. Two thirds of patients had been referred for barium meal in 1963 as outpatients by general practitioners and the remainder were hospital inpatients. Of this cohort of 227 patients during the 13 year interval 50 had died and 23 were lost to follow up. Of the remaining 154 patients 120 had been treated medically. Almost half of the latter (57) reported they had suffered no symptoms within the preceding 12 months. Of these approximately 75% said they had been symptom free for more than five years and about 50% for more than 11 years. Another 44 patients (approximately one third of the medically managed group) reported only mild symptoms during the preceding year, while 19 still had moderate or severe symptoms.

Of the 34 surgically treated patients eight had undergone

emergency operation because of acute complications. As might be expected elective operation had been performed in a greater proportion of hospitalized than general practice referred patients.

Dyspepsia and peptic ulcer in a rural community.

A rather different perspective on peptic ulcer disease has been provided by Weir and Backett (Weir, Backett 1968). in a study of the prevalence of dyspepsia and ulcer in a stable rural community near Aberdeen in north east Scotland. 1500 men over the age of 15 years were sent a questionnaire on current (within the previous 3 months), recent (within 5 years) and past dyspepsia. After 3 years a second questionnaire was sent to the same men, while computer linkage allowed review of their hospital and general practice records. Personal interview of a sample of patients confirmed the reliability of the postal survey.

A high prevalence of severe dyspepsia (154 per 1000) and demonstrable peptic ulcer (102 per 1000) was found. Comparison of the results at the beginning and end of the survey period suggested a substantial recovery rate (17 per 1000) from dyspepsia to no dyspepsia, but this was balanced by 16 per 1000 new dyspeptics. Thus of 295 men who admitted to "current dyspepsia" at the first survey, three years later at the second survey 65% reported current symptoms, 21% had had no further symptoms while 7% were doubtful and 5% denied ever having dyspepsia! The totally different methodology employed prevents direct comparison with the other studies but it does confirm the high recovery rate in a broadly based population of subjects with dyspepsia.

Conclusions.

In summary it may be concluded that duodenal ulcer is a chronic and recurrent disease that is rarely fatal. A small proportion of patients will suffer complications but in a larger proportion the disease will run a benign course with spontaneous resolution of symptoms. Many patients will continue to be troubled by symptoms of varying severity for many years. The proportion of patients falling into each category will vary depending on the population chosen, their presenting complaint and in particular on the methodology used in the study. Studies performed in general practice using retrospective and cross-sectional methods or infrequent prospective review, and the inclusion of more patients with a short history will all tend to produce results which indicate a more benign long term course. Hospital based studies, often selecting patients with more prolonged or severe symptoms, employing frequent and prospective patient review and sensitive techniques such as endoscopy for diagnosing ulcer recurrence will paint a gloomier picture of the long term outlook. Expression of results showing the cumulative incidence of relapse will tend to emphasize this view.

CHAPTER V

THE DESIGN OF CLINICAL TRIALS

Ethical safeguards

Before embarking on any clinical trial, all doctors must be aware of the need to protect the best interests of the patients involved. It is also crucial that these interests should be seen to be safeguarded. Towards these ends both national and local regulatory and advisory committees have been involved in the assessment and approval of these studies.

1. Drug Evaluation Committee, Australian Federal Department of Health, Canberra. This body approved these studies with cimetidine, until cimetidine was released for short term use in 1977. Joint submissions by Smith Kline and French Australia Limited and the Department of Medicine, Royal Adelaide Hospital, detailed the trial designs and also the necessary animal, pharmacological and toxicological data on cimetidine.

2. The Research Review Committee of the Royal Adelaide Hospital approved the design of the studies and reaffirmed the need to carry them out in accordance with the declaration of Helsinki, as revised in Tokyo in 1975, and the National Health and Medical Research Council statement On human experimentation, 1976. The provisions of this declaration include the important necessity for fully informed consent by the patient. In these trials all patients were given a simple explanation of the reason for the study, the methods used and the tests involved. It was carefully explained that they might or might not receive an effective drug, and that they were free to withdraw from the study at any stage. A sample consent form, which all signed is shown in Figure 5.1.

The design of treatment trials

It is now 30 years since Sir Austin Bradford Hill and his colleagues published the first clinical trials in which patients

Figure 5.1 A sample consent form

I voluntarily agree to participate in the clinical investigation of cimetidine.

I understand that cimetidine is a drug that may be of value in the treatment of peptic ulcer. I realize the drug I am taking may or may not be effective and that the aim of the study is to determine whether cimetidine is effective.

The nature of the investigation and specific procedures involved in the study have been explained to my satisfaction, and I understand that blood and urine tests, and endoscopy tests will be necessary during the period I am on treatment.

I understand that any enquiries I have during the course of this study will be answered, and that I may terminate my participation in this study at any time.

.....
Patient's signature

.....
Doctor's signature

.....
Date

were "randomly allocated to one of the treatment groups". Since then the randomized controlled trial has gradually become accepted as the most effective way of determining the relative efficacy and toxicity of a new drug therapy. A number of texts have outlined the principles of trial design, methodology and analysis of results (Hill 1971, Langman 1978, National Conference 1979, Peto et al 1976, 1977, Witts 1964).

In a disease such as peptic ulcer which is subject to unpredictable remission and relapse, the necessity for a control group is clear. The incidence of ulcer healing during placebo treatment has varied from 20-60% throughout the world and emphasizes the need for a local yardstick against which new treatments can be measured. There are so many potential sources of bias in selection, exclusion and assessment (especially in view of the subjective nature of some therapeutic responses such as pain) that "blindness" of investigators and patients to the nature of the treatment is crucial, and a placebo control particularly desirable.

Before conducting trials of new drug treatment (or in examining results obtained by others) a number of fundamental questions need to be answered:

1. What end point is to be used to define response to treatment and how accurately can it be measured?
2. What are the likely chances of influencing this measurement?
3. What other criteria for admitting patients to the trial need to be considered?
4. How many patients will be necessary to obtain a result (and can this number be achieved in a reasonable time span in one centre, or will multicentre collaboration be necessary?).

5. Can existing treatments ethically be withheld?
6. Can two (or more) treatments be allocated at random and can blindness to the nature of each treatment be maintained by doctor and/or patient?
7. Which patients should be excluded from entering the trial, and under what circumstances should patients who have entered be withdrawn?
8. How should dosage of a novel treatment be decided?
9. How should protocols and record forms be designed?
10. How should results be analysed and the trial stopped?
11. Are the results clinically as well as statistically significant?

1. Criteria of treatment response

These studies, in common with most recent treatment trials in peptic ulcer, use endoscopy as being the most accurate way of confirming the diagnosis of duodenal ulcer.

Barium meal assessment of ulceration may be difficult particularly in a shrunken or deformed duodenal cap. Thus the criterion for success has been complete ulcer healing at a further endoscopic examination. Other authors (and ourselves) have attempted to measure changes in ulcer size but this is fraught with difficulty. A measuring stick cannot always be manipulated alongside the ulcer and as the apparent size of an image varies with object distance from the lens, errors are frequent (Sonnenberg et al 1979). The end point of complete ulcer healing is also clinically more desirable than partial healing (Piper et al 1978). Endoscopic assessment of "duodenitis" is highly subjective and also dependent on object distance and duodenal motility. It was not used as an end point.

The appearance of the duodenum at endoscopy was graded:

- I Completely normal
- II Hyperaemia (or deformity) without mucosal break
- III Shallow erosion(s) without crater formation
- IV Chronic ulcer crater \pm erosions, inflammation, scarring

In order to enter the trials, the ulcer found at initial endoscopy had to be grade IV. At subsequent endoscopy ulcers were recorded as healed or unhealed, and grades III and IV constituted unhealed ulceration. Studies of observer variation have not been performed to assess the reproducibility of these grades. The process of training in endoscopy relies upon learning from more experienced colleagues and thus within one institution uniform standards are likely to be the rule. It would obviously be valuable to compare observers from different institutions but this has not been done. The absolute accuracy of endoscopy is more difficult to determine. Comparisons of the results of endoscopy (and barium meal) with laparotomy within the next 48 hours have been performed in ulcer disease(?). They confirm the superiority of endoscopy over barium meal but it is arguable whether the naked eye, necessarily some distance from the duodenum, gives more accurate results than the fibre-optic eye placed within it. The modern fibre-optic endoscopes used in the present studies (mainly the Olympus GIFK and GIFP₂) have a wide angle of view and remarkable flexibility of the tip making "blind spots" much less likely to occur than with early fiberoptic instruments.

Initially efforts were made to keep a photographic record of the duodenal appearances. It rapidly became obvious that the technical difficulty of obtaining a complete view at the correct

exposure without change in object to lens distance was too great and photography was abandoned. Confirmation of endoscopic appearances by a second observer (who was not aware of the patient's clinical course) was carried out whenever possible and rarely produced discordant opinions.

The timing of the second endoscopy must take into account the natural healing of duodenal ulcer. Experience of other investigators had shown that successive endoscopic examinations might be necessary. Early differences between placebo and treatment groups may be obscured if endoscopic assessment is made only at the end of a trial because ulcers tend to heal naturally regardless of treatment (Brown, Salmon et al 1972). For this reason endoscopy was performed after 2 weeks and 6 weeks treatment in the first trial.

The use of changes in patients' symptoms as a criterion of response to treatment seems logical but may be misleading. Many studies have shown relief of symptoms despite persistence of the ulcer at endoscopy, and sometimes vice versa (Misiewicz 1978). However symptom relief is obviously important to the patient and if within a well conducted double blind study a major advantage in extent or speed of symptom relief is found for one of the treatments, then this cannot be ignored. Because of the difficulty of grading the severity of pain the simple criterion of the number of days (and nights) of pain each week was chosen.

2. The chances of influencing the chosen end point

Some theoretical assessment of the outcome, assuming the treatment is effective, must be made initially to try and assess whether the trial is capable of completion, given the time and appropriate number of patients available. An improvement of 25% or 50% is often assumed as the reasonable minimum of improvement

in therapeutic response necessary to make a study feasible, and this allows some prediction of the number of patients required.

If for example 80% of ulcers heal whatever is done, then it would be difficult to show a statistically significant improvement (to say 90%) without a huge number of patients - and clinically much less important than if only say 20% of ulcers healed spontaneously. This question of the "natural history" of the disease and the ability of a study to detect a therapeutic effect, if it exists, is inseparable from the points discussed below in sections 3 and 4.

3. Other criteria for admission to the trial

To ensure that any therapeutic effect is detected, the physician may decide to increase either the number of patients studied by widening admission criteria, or may try to select a subgroup of ulcers with the lowest spontaneous healing rate. In the former case subjects with milder disease who might be more liable to heal spontaneously might be included, and in the latter case patients with only particularly chronic or severe disease might be included. However any selection process like this tends to make the trial group less representative of the patients usually presenting for treatment and may make the conclusions less applicable to the ordinary ulcer patient.

Another example of problems of case selection is when limitations are put on the age of subjects, the presence of other disease and the use of other drugs. There are advantages in imposing some limitations. For example, interpretation of results is clearer if no other disease is present, while older patients may be more difficult to supervise and prone

to develop unrelated problems. It is not surprising that few elderly or frail patients enter clinical trials, but it is this group, in the case of ulcer disease, who most require conservative management. Unwanted effects occur more frequently in the elderly and may not be identified in trials that exclude them. In the case of cimetidine, the occurrence of mental confusion and gynaecomastia has been rare outside the older age group. Similarly drug interactions cannot always be predicted from animal work or in vitro pharmacology, and may go undetected in clinical trials where "other therapy" is a criterion for exclusion.

In general it seems desirable that the conditions under which a drug is used in clinical trials should mimic as far as possible the conditions of everyday medical practice under which it is likely to be used later.

4. Number of patients

The size of a trial is one factor that determines whether a therapeutic effect is detectable, if it exists. If a negative result is obtained size will also determine whether or not we can be reasonably sure that a clinically meaningful therapeutic effect has not been missed. The choice of size involves the statistical concepts of Type I (false positive) and Type II (false negative) errors, the probability of these errors occurring, (often referred to as alpha (α) and beta (β) respectively) and (Δ) the size of a clinically important therapeutic effect (the difference in effect (Δ) between two treatments).

Thus in these trials the response rate P_t for the treatment has been compared with the response rate P_c for control therapy (here placebo). The observed difference, $\Delta = P_c - P_t$ and is an estimate of the effectiveness of the treatment. Even if the true response rates P_c and P_t are equal, the workings of chance in

different samples of patients will produce non zero observed differences. Various sizes of observed differences will occur with various probabilities. When the observed difference is large, the probability of this occurring by chance is small and the null hypothesis that $P_c - P_t = 0$ can be rejected. The conventional level of "smallness" of this probability, α , has been used in these studies viz. $\alpha = 0.05$. That is, we accept that the probability P of such a result occurring by chance is 0.05, 5%, or 1 in 20. If $P > \alpha$, i.e. the observed result is "not statistically significant" there is a probability β of missing a true difference of between the treatments. This false negative error is called a type II error. There is no single value for β (unlike α) in that it is based on the premise that there is a difference Δ between the treatments. There is an infinity of values for Δ , each with a different value of β , which make a curve of β as a function of Δ (Frieman et al 1978). The larger Δ is, the smaller β becomes. The probability of avoiding type II error, that is the probability of detecting the difference Δ , is called the power of the test and defined as $1 - \beta$. Assuming various values of α, β and Δ a minimum sample size table will give the number of patients required in each group. Alternatively, the investigator can decide on α (0.05 usually), Δ (the difference between treatments accepted as clinically significant) and the number of patients expected to enter the trial. From these facts can be determined the probability that such a difference is likely to be found if it exists, and the chance that real differences of other magnitudes will be missed.

Frieman et al have argued for meticulous planning of clinical trials including evaluation of β by making the appropriate

assumptions. However this is only ultimately of importance if a study yields negative results (test treatment not significantly different from standard or control treatment) and unless there is some indication from past experience of the size of Δ it is impossible to assess the size of β . In common with most clinical trials no attempt was made to evaluate β at the initial planning stage of these trials.

The advantages of increasing the number of patients in the studies (for example, in shortening the time required to reach a significant result and increasing the certainty of the outcome) led to collaboration with Dr. Jack Hansky and Dr. Mel Korman of Monash University and Prince Henry's Hospital, Melbourne. This was a valuable exercise in interstate cooperation despite the logistic problems involved, and has led to a number of joint publications. It should be noted that problems of organisation and interpretation increase greatly if more than two centres are involved. Multicentre studies need massive organisational expertise to minimise non-uniformity and hence variation of results.

5. The ethics of withholding existing treatments

It is clinically important to compare new treatments with the best available existing therapy to assess whether the novel treatment really is an improvement in terms of efficacy or side effects. If an active treatment, in this case for healing ulcers, with few side effects already existed, then trials of new agents would be difficult to justify. Under these circumstances, the use of a placebo is probably unethical, even though it may offer a yardstick to judge whether the new agent has any activity at all.

Although this approach may seem straightforward it is often difficult to obtain a consensus among doctors about whether or not existing treatments have been clearly shown to work and which ones are accepted as standard. Disagreement about the treatment of peptic ulcers is particularly common. The merits and demerits of diets, antacids, anticholinergics and other drugs have been the subject of contention for decades. This controversy and wide international variation in therapy supported the belief in 1976 that none of the available treatments for duodenal ulcer was of certain value and all had significant disadvantages. Thus it seemed ethical to make the control therapy a visually identical placebo. The use of a placebo control has the dual advantage of discounting bias (in patient or doctor) and allowing assessment of the "spontaneous" process of ulcer healing.

The question of allowing additional symptomatic treatment was carefully considered. The possibility of antacids exerting complicating effects (e.g. by drug interaction, or changing bio-availability) makes them undesirable, and clearly they might potentiate the effects of an antisecretory drug. However, Australian and European patients and doctors have been conditioned for years into using antacids for pain relief. Therefore a solid antacid tablet (Mylanta) was provided in addition to the coded medication, with written instructions to use it only for pain relief. Tablet preparations of antacids are less effective than liquid forms and have not been shown to heal ulcers, but in view of a possible effect it was obviously important to record consumption of antacids and allow the two treatment groups to be compared.

6. Random allocation and 'blindness'

The H₂-receptor antagonists offered the prospect of improving on existing remedies for duodenal ulcer, while concern about possible side effects made it doubly important that results were unequivocal and not open to methodological criticism. Therefore acceptance of random allocation of patients to placebo or cimetidine seemed completely logical. This ensures that a balanced mixture of patients has entered each of the treatment groups, provided reasonable numbers have been included, and also allows 'blindness' of doctor and patient to the allocation of treatments. This does not ensure that 'double blindness' is maintained as the effects or side effects of some treatments may become obvious, e.g. fluid retention with carbenoxolone or dry mouth with anticholinergics. During these studies one patient commented that the medication had a metallic taste, and another that the tablets had an unusual smell, but to most patients cimetidine and placebo tablets looked and tasted identical.

The need for stratification (e.g. into large or small ulcers, smokers or non-smokers), was considered and rejected. None of these parameters had previously been shown to have a dramatic bearing on the outcome in duodenal ulcers. Duodenal and gastric ulcers were of course separated as different disease entities, with pyloric channel ulcers being included with duodenal ulcers in view of their identical epidemiology, acid secretory status, etc. It was of course accepted that the two treatment groups should be examined for comparability of age, sex and other factors at the end of the trial, relying on randomization to produce a reasonable balance.

7. Withdrawals and exclusions

Patients included in a clinical trial are rarely a random selection of the disease population. For example, most trials are carried out in hospitals and patients referred to hospital may well represent the more severe or recurrent end of the spectrum of disease (see chapter 4). Just as criteria for inclusion in the study must be carefully scrutinized, so should the exclusion clauses be critically assessed to see how the clinical case mix has been altered. Exclusion before randomization does not bias the trial result towards one or other treatment but it obviously limits the applicability of the results to the entire disease population.

The reasons for exclusion used in these studies were generally similar for all the trials. They included

- (a) patients with ulcer due to other diseases, e.g. Zollinger-Ellison syndrome or "ulcerogenic" drugs (corticosteroids and phenylbutazone, indomethacin) or who continued with other ulcer-healing drugs;
- (b) patients with combined duodenal and gastric ulcers;
- (c) patients who had had previous vagotomy or gastric surgery (except simple oversewing of a perforation);
- (d) patients with other diseases which rendered them unsuitable for trial of an investigational drug (e.g. severe hepatic, renal, cardiac or respiratory disease);
- (e) premenopausal women who had not had a hysterectomy.

The last clause was lifted after teratogenicity studies had been satisfactorily completed.

The withdrawal of patients after they have entered trials may well be a source of bias. Patients who default are rarely a representative sample of the treatment group. They may do so because symptoms remit or more commonly because they are dissatisfied with treatment or are suffering complications. Every effort must be made to continue follow up, and treatment if possible.

Patients who suffer adverse effects which necessitate withdrawal are treatment failures and should be analysed as such to avoid painting an unduly rosy picture of the results.

8. Dosage of new treatments

The human volunteer studies carried out on cimetidine give some guidance on dosage. Patients may show important differences from normal volunteers because of physiological abnormalities related to the disease (e.g. higher levels of gastric acid secretion in duodenal ulcer, or changes in drug disposition or bio-availability). Hence pharmacological or kinetic studies in at least a small number of patients are essential and allow a preliminary estimate of dose. American investigators opted for cimetidine 300mg qid (1.2 g/day) while their European counterparts used 200mg tds and 400mg at bedtime (1.0 g/day) as the standard dose. Various trials using 800mg-2.0 g/day showed similar results in short term healing of duodenal ulcer and encouraged us to reduce the dose from 1.2g in our first trial to 1.0g/day subsequently.

Pharmacokinetics are usually different in the elderly (in whom volume of distribution and renal excretion may be reduced) and of course in patients with other diseases which interfere with the main excretory routes - the kidney in the case of cimetidine. Dosage may need to be changed in these groups.

It should also be noted that some unwanted effects or adverse reactions may be dose related. Early studies may not identify these and further reappraisal of dosing may be necessary.

9. Design of protocols and record forms

Protocols should be logical and simple. Over complicated designs that aim to fulfill several objectives simultaneously are likely to remain uncompleted. Patients and doctors may shrink from even approaching a study with a demanding battery of tests and procedures.

Patient records must also be simple and easily understood - even by someone ill acquainted with the study. Thus a single page resume of the protocol is useful. Doctor compliance is increased by minimising the amount of writing by providing check lists of questions which only need marking with a tick. This also avoids "open ended" questions which may be interpreted or answered in varying ways. Space must be provided to record clinical responses, compliance with instructions and to note unwanted effects. Biochemical and haematological results are best recorded on a separate single page to emphasize any consecutive changes. In general only spontaneous complaints about side effects should be noted - or answers to a general enquiry about unwanted effects. Specific questioning is best reserved for rare or serious possibilities as the occurrence of common minor complaints will be unduly overemphasized.

10. Stopping the trial and the analysis of results

The choice of a particular statistical test is less important than ensuring the basic experimental design is sensible. However it is important that some aspects of the statistical analysis are determined beforehand.

Some statistical techniques - the methods of sequential analysis - allow a continuous appraisal of progress so that it is possible to stop a trial as soon as a statistically significant result has been obtained. However these techniques are most useful in closely paired comparisons where most variables can be identified (e.g. in the comparison of two analgesics in the same patient at different times) and were not used in these studies.

The factors affecting the outcome in trials of ulcer treatment are obscure and as duodenal ulcer is common enough to allow us to obtain large groups of patients we have used more conventional designs. Two moderately large groups were treated with placebo or cimetidine and the outcome analysed after a fixed minimum number of patients had entered. A chi square test was then used to compare the incidence of healed ulcers in cimetidine and placebo groups. This test was not designed for repetitive use in the same trial as the probability of a chance finding reaching the conventional level of statistical significance ($p=0.05$) is increased by making repeated comparisons. This did not prevent of course, repeated observation of the patients for side effects or other disasters which might necessitate stopping the trial. Fortunately no problems were encountered.

Other variables in treatment and control groups were examined using the appropriate t test.

In the longer term maintenance trials a life table technique was used (Merrell and Shulman 1955, Peto et al 1976, 1977). This has the advantage of using all available data even though the duration of follow-up of patients may vary widely. This occurs because patients enter the trial consecutively. If an interim

analysis is made some will not have completed the full study period. A few patients may need to be withdrawn and thus never complete the study but the life table techniques allow use of all data up to the point that the patient has reached.

11. Clinical and statistical significance.

The conventional level of statistical significance with a probability value of $p = 0.05$ merely implies that a result such as the one found would have been found by chance once in twenty times. Thus even the finding of a statistically significant outcome does not prove that a difference between two treatment groups is real. Chance is still a possible but unlikely explanation.

The reasons for a statistically significant finding may be that there is a genuine difference between treatments (in the case of treatment trials) but other possibilities must be considered: the treatment groups may be different in some important characteristics, bias may have crept into the assessment of outcome or this might be the one trial, of several other negative and unreported studies, which by chance gave a positive result.

As discussed above (section 4) the failure to find a significant difference between treatments does not mean that no difference exists, merely that chance might also explain the difference. In this way a trial with limited numbers of patients can give a statistically insignificant result even though trends in the few patients were quite substantial.

Even though a result may achieve statistical significance it does not imply that the result is of any material importance. For example, a large number of observations all showing the same trend may show a statistically significant change - in say

antacid consumption from 70 to 65 tablets per week, or frequency of healing from 80 to 85%, a change of little clinical importance. Consideration of the results themselves not the size of the p value determines clinical importance.

CHAPTER VI

CIMETIDINE IN THE SHORT TERM TREATMENT OF DUODENAL ULCER

Introduction

Following the demonstration of the potent inhibitory effects of the histamine H₂-receptor antagonists on gastric acid secretion the next stage of development was to explore their potential in acid peptic disease. Duodenal ulcer is the disease in which excess secretion of gastric acid has been most clearly documented and hence was the first to be studied.

In controlled trials metiamide was shown to relieve symptoms (Pounder et al 1975) and promote healing, assessed endoscopically (Multicentre Trial 1975) in patients with duodenal ulcer. The development of agranulocytosis in a small number of patients receiving metiamide led to withdrawal of the drug (Forrest et al 1975).

The development of cimetidine (Brimblecombe et al 1975) allowed us to start work in February 1976 to assess whether this drug could safely fulfill the promise shown by metiamide. This study examined the effects of six weeks cimetidine treatment on ulcer healing, symptoms and acid secretion in Australian patients with duodenal ulcer.

Patients and Methods

The trial was conducted at two centres, Royal Adelaide Hospital and Prince Henry's Hospital Melbourne, using the same protocol. Patients entering the trial had symptoms from endoscopically proven duodenal (76 patients) or pyloric canal ulcer (9 patients). None had undergone previous gastric surgery or suffered recent bleeding from the ulcer. They had no other serious illness and showed no clinical or laboratory evidence of renal hepatic or haematological abnormalities.

Fertile females were excluded from this trial because teratogenicity studies on the drug had not been completed at the beginning of the trial. Endoscopy using the Olympus GIFK or occasionally the JF type B2 instrument, was carried out in the 3 days before the beginning of treatment and was repeated by the same endoscopist in the first three days after the six weeks of treatment. The endoscopist was not made aware of the clinical response of the patient. Ulcers were recorded as healed or unhealed, and unhealed ulcers included craters and erosions.

Acid secretion: A standard pentagastrin test of gastric acid output was carried out in the 3 days before treatment and was repeated one week after the end of treatment. In this the patient attended hospital following an overnight fast. Nasogastric intubation was performed and the tip of the radio-opaque 12F Ryles tube was positioned fluoroscopically at the most dependent point about two thirds along ^{the} greater curve. The patient was positioned lying down on a bed and inclined towards the left side with a good supply of paper tissues to allow saliva to be expectorated. Fasting gastric aspirate was discarded. Basal acid output (B.A.O.) was collected for 4 periods of 15 minutes. A subcutaneous injection of pentagastrin, 6 μ g/kg body weight, was given and Maximal acid output collected for a further 4 periods of 15 minutes. Samples were titrated to a pH of 7 and acid output calculated.

Basal acid output (mmol/hour) = sum of first 4 x 15 min periods.

Maximal acid output (mmol/hour) = sum of second 4 x 15 min periods.

Peak acid output (mmol/hour) = 2 x sum of the highest two consecutive 15 min periods during the second hour.

The PAO thus calculated makes an allowance for the slightly variable delay in onset of action of the pentagastrin and its subsequent decline in activity. It is less subject to 'carryover' of secretion from one period to the next than calculations based on 4 x the single highest, 15 minute stimulated output. Pentagastrin was used as the gastric stimulant in preference to histamine because of its safety and freedom from unwanted effects. (Baron 1979).

During an interview before treatment an assessment was made of the patient's smoking and alcohol consumption. They were not specifically advised to curtail these habits but all were asked to refrain from taking salicylates. All patients remained outpatients and continued their normal daily activities during the trial. They were randomly allocated in a double blind fashion to cimetidine (300mg three times a day immediately before meals and 300mg at bedtime) or placebo. Each received a supply of antacid tablets (Mylanta) for pain or indigestion as required and the consumption of trial tablets and antacids was checked at each visit. Patients and their diary cards, used to record episodes of pain, were reviewed weekly and symptoms recorded. Routine tests of blood (blood picture and biochemical screen) and urine (microscopy and dip tests) were performed before the trial and at each visit. These included estimations of haemoglobin level, platelet and white cell and differential count plasma bilirubin level, plasma urea and creatinine levels plasma alkaline phosphatase level and plasma aspartate amino transferase (AST, SGOT) level.

Results were analysed by the χ^2 test to assess healing. Other results were analysed by the appropriate t test or analysis of variance.

Results

Eighty eight patients entered the trial. One receiving placebo was withdrawn after 36 hours when amended pretrial laboratory values were shown to be abnormal. One cimetidine treated patient failed to return after the second week and a third patient receiving placebo suffered a myocardial infarction and was withdrawn after five weeks. Details of the remaining eighty five patients are shown in table 6.1

There were no significant differences between the groups in age, sex, duration of peptic ulcer disease or duration of the current relapse. The high male to female ratio results from the exclusion of fertile women. In the week before the trial both groups showed a similar frequency of occurrence of daytime and night-time pain and a similar consumption of antacids.

Ulcer healing: At six weeks the ulcers of 36 (84%) cimetidine treated patients were healed at endoscopy while the ulcers of 16 (38%) of those receiving placebo had healed. (Table 6.2). The difference is highly significant.

In Melbourne all patients were also endoscoped after only 2 weeks treatment. At that stage the ulcers of 5 out of 14 on cimetidine therapy and 4 out of 14 receiving placebo had healed, an insignificant difference.

Pain relief: The number of days and nights each week that the patient was free of pain was recorded. Patients taking cimetidine showed a rapid increase in the mean number of pain free days and this number was significantly different from that in the placebo group in all treatment weeks (Table 6.3). A similar but less dramatic trend was seen with respect to pain free nights. By week 6 most patients receiving cimetidine were symptom free, but the placebo group had also shown improvement.

Table 6.1 Patients completing the 6 week study

Treatment	No. of patients		Mean age (years)	Mean duration of disease (years)	Mean duration of current relapse (months)
	M	F			
Cimetidine	39	4	44.1	7.4	4.1
Placebo	37	5	44.1	8.4	4.7

Table 6.2 Endoscopic findings at 6 weeks

Treatment	Number of patients	
	Ulcer healed	Ulcer not healed
Cimetidine	36 (84%)	7
Placebo	16 (38%)	26

$\chi^2 = 11.27$ $p < .001$

Table 6.3 Pain relief in each treatment group

Mean number of painfree days or nights per patient

<u>Days:</u>	Preceding week	Week 1	Week 2	Week 4	Week 6
Cimetidine	1.6	4.9	6.3	6.6	6.7
Placebo	1.5	2.8	3.1	4.6	5.5
P	NS	<0.001	<0.001	<0.01	<0.01

<u>Nights:</u>	Preceding week	Week 1	Week 2	Week 4	Week 6
Cimetidine	3.9	6.6	6.9	7.0	6.9
Placebo	3.1	5.6	5.0	6.3	6.5
P	NS	NS	<0.001	<0.02	NS



Thus in addition to any effect on ulcer healing cimetidine also produces a much more rapid relief of symptoms than placebo. This effect is apparent often within 24 hours in some patients and as shown above is clearly evident by the end of the first week of treatment, long before complete ulcer healing can be demonstrated.

The subjective nature of pain and the ease with which its appreciation can be influenced makes it an unreliable end point in open studies. However, the double blind design of this trial should ensure that any bias operates in both treatment groups and permits valid comparison of one with the other.

What is more contentious is the correlation (or lack of it) of ulcer healing with relief of symptoms. (Table 6.4). Inspection of results for placebo treated patients shows a positive but weak correlation between healing (judged endoscopically) and relief of patients' symptoms: 10/16 (62%) of patients with healed ulcers are asymptomatic while 14/26 (54%) of those with persistent ulcer still have symptoms. The cimetidine treated patients with healed ulcers have almost uniformly lost their symptoms (34/36, 94%). In contrast to the placebo group the trend towards symptom relief is seen in the cimetidine treated patients in whom the ulcer has not fully healed: 5/7 (71%) are asymptomatic.

Antacid consumption: Significantly fewer cimetidine treated patients required antacid compared with patients receiving placebo, in all treatment weeks (Table 6.4).

The fact that not all patients were taking antacid in the week preceding the trial does not imply that they had no pain. Some of the patients used other remedies - in particular milk or food - to relieve their symptoms. In the week before treatment a similar number of patients in each group were taking antacids

Table 6.4 Correlation of ulcer healing with symptom relief at the end of 6 weeks treatment

<u>Treatment</u>	<u>Ulcer healed</u>		<u>Ulcer unhealed</u>	
	Asymptomatic	Symptoms persist	Asymptomatic	Symptoms persist
Cimetidine	34/36 (94%)	2/36 (6%)	5/7 (71%)	2/7 (29%)
Placebo	10/16 (62.5%)	6/16 (37.5%)	12/26 (46%)	14/26 (54%)

Table 6.5 Antacid consumption

<u>Treatment</u>	<u>Number of patients taking antacid</u>				
	Preceding week	Week 1	Week 2	Week 4	Week 6
Cimetidine	35/43	24/43	15/43	8/43	8/43
Placebo	35/42	34/42	30/42	28/42	21/42
P	NS	< .01	< 0.001	< 0.001	< 0.01

which suggests that the randomisation had produced satisfactorily balanced groups.

The mean number of antacid tablets consumed each week is shown in table 6.6. It should be noted that these mean values include all patients, not just those who continued to take antacid. In view of the wide interindividual variation in antacid consumption the table also indicates the range of number of tablets used. No meaningful figure could be produced for the week before the trial as a wide variety of different liquid and solid preparations of varying and often unknown neutralizing capacity had been used.

Whichever way antacid consumption is viewed it is clear that far fewer cimetidine treated patients had to take antacids than placebo treated patients, and that the cimetidine group consumed far fewer antacid tablets than the placebo group.

Acid secretion studies: The results of the pentagastrin tests performed on 74 patients before treatment show that acid output in the two groups was comparable (Table 6.7).

Sixty six of these patients agreed to a second acid secretion study one week after completion of therapy. There was no significant change in acid secretion in either cimetidine or placebo groups (Table 6.8).

An analysis of acid secretion before treatment in relation to subsequent ulcer healing is shown in Figure 6.1. The mean pretrial basal acid output (BAO) in 6 patients who failed to heal during cimetidine treatment was significantly greater than the mean BAO of those 31 patients who healed. ($t=3.95$, $df=35$, $p < 0.001$). The mean maximal acid output in those 6 patients who did not heal was higher than in those who healed but this did not reach conventional levels of statistical significance ($t=1.85$, $df=34$, $p = 0.07$).

Table 6.6 Antacid consumption per patient

Number of antacid tablets used per patient per week					
Treatment		Week 1	Week 2	Week 4	Week 6
Cimetidine	Mean \pm SE.	4.3 \pm 1.1	1.7 \pm 0.5	1.0 \pm 0.5	0.6 \pm 0.3
	Range	0 - 30	0 - 12	0 - 20	0 - 10
Placebo	Mean \pm SE.	13.6 \pm 2.4	14.3 \pm 2.9	13.2 \pm 2.9	9.8 \pm 2.8
	Range	0 - 50	0 - 71	0 - 68	0 - 72

Table 6.7 Gastric acid secretion before treatment (mmol/hr).

Treatment	Number studied	BAO (Mean \pm SE)	MAO (Mean \pm SE)
Cimetidine	37/43	4.7 \pm 0.7	25.1 \pm 1.4
Placebo	37/42	5.0 \pm 0.6	25.7 \pm 1.3

Table 6.8 Gastric acid secretion (mmol/hr) in those patients studied both before and after treatment

	Number studied	BAO (Mean \pm SE)	MAO (Mean \pm SE)
<u>Before treatment</u>			
Cimetidine	32/43	4.9 \pm 0.7*	24.7 \pm 1.6 †
Placebo	34/42	5.0 \pm 0.7	25.3 \pm 1.4
<u>After treatment</u>			
Cimetidine	32/43	4.2 \pm 0.5*	25.0 \pm 1.6 †
Placebo	34/42	5.6 \pm 0.6	28.0 \pm 1.8

* Paired t statistic, BAO before/after. $t=1.15$ $df=31$ $0.2 > p > 0.1$

† Paired t statistic, MAO before/after. $t=0.27$ $df=31$ $0.8 > p > 0.7$

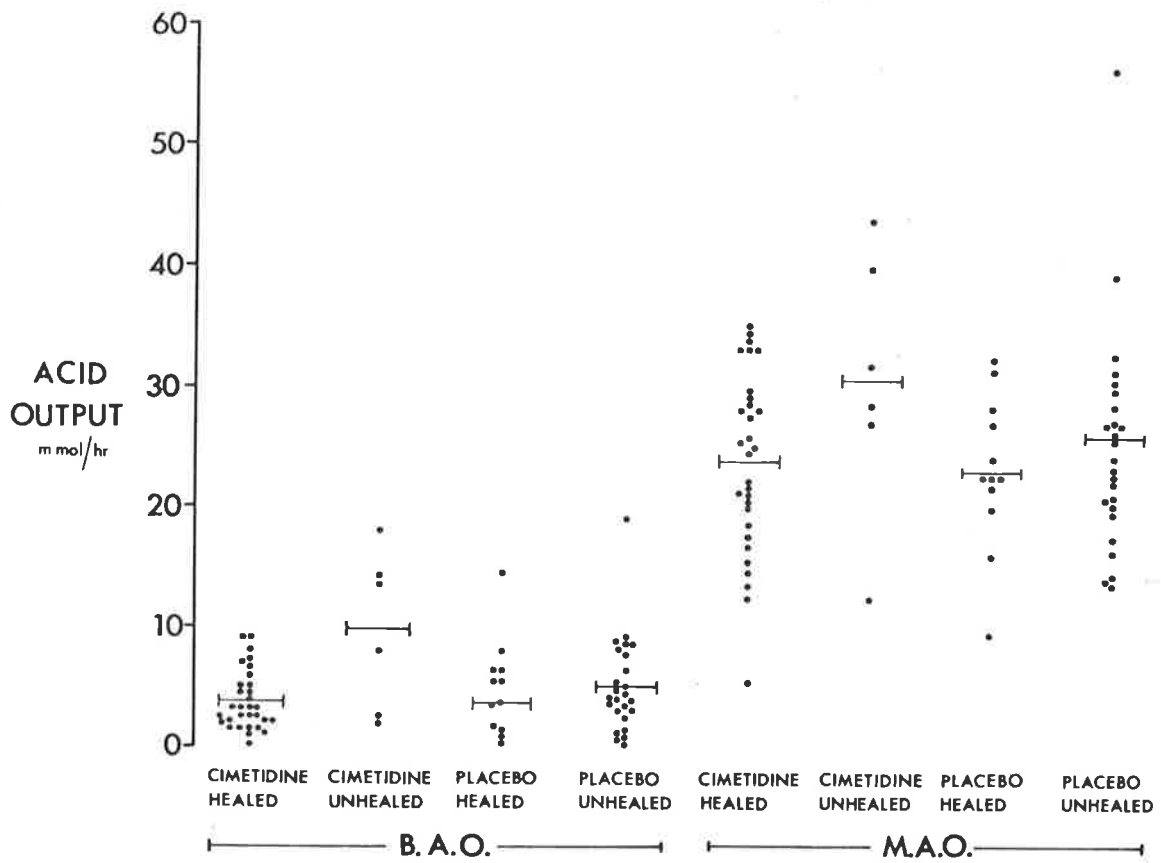


FIGURE 6.1 Pretreatment basal acid output (BAO) and maximal acid output (MAO) in relation to ulcer healing.

● Individual values.

— The bar represents the mean value of that group.

Side effects: There were no subjective side effects in patients taking cimetidine and none developed abnormal physical signs. No patient in the trial developed any important abnormalities in haematological indices. In 33 patients receiving cimetidine (and 27 receiving placebo) there was a slight rise in serum creatinine within the normal range at some stage during treatment. This tended to occur within the first two weeks of cimetidine treatment and fell towards pre-treatment values from week 4 to 6 (Table 6.9). The same trend was evident in both Melbourne and Adelaide. Analysis of variance confirms that these small changes seen during cimetidine treatment are statistically significant ($p < 0.01$). However they do not seem clinically important. In only 7 patients receiving cimetidine (and 3 receiving placebo) was the creatinine level outside the upper limit of the normal range, the highest value being 0.18 mmol/l. In the week following treatment all except one patient from the cimetidine group and two from the placebo group had normal plasma concentrations of creatinine, the highest level remaining at 0.14 mmol/l in each group. There were no corresponding changes in plasma urea levels.

Plasma alkaline phosphatase and bilirubin levels showed no significant change during treatment. Six patients taking cimetidine and three taking placebo developed isolated abnormal levels of plasma aspartate transaminase during treatment, the highest values being 65 and 41 u/l respectively (normal range 5 to 40 u/l).

Smoking and alcohol: An analysis of smoking (85 patients) and alcohol consumption (81 patients) shows that smokers and drinkers

Table 6.9 Plasma creatinine levels

	<u>Plasma, creatinine level, mmol/l (mean ± SE)</u>			
	<u>Pretrial week</u>	<u>Week 1</u>	<u>Week 6</u>	<u>Following week</u>
Melbourne patients*				
Cimetidine	0.086±0.005	0.106±0.005	0.097±0.008	0.090±0.006
Placebo	0.091±0.007	0.087±0.006	0.085±0.006	0.081±0.008
Adelaide patients ⁺				
Cimetidine	0.094±0.002	0.103±0.003	0.099±0.003	0.085±0.002
Placebo	0.094±0.003	0.099±0.004	0.095±0.003	0.097±0.004

* Normal range, Melbourne 0.03 to 0.12 mmol/l

+ Normal range, Adelaide 0.05 to 0.12 mmol/l

Table 6.10 Smoking habits and ulcer healing

	<u>Smokers</u>		<u>Non-smokers</u>	
	<u>Number</u>	<u>% healed</u>	<u>Number</u>	<u>% healed</u>
Cimetidine	28/43	86%	15/43	80%
Placebo	30/42	37%	12/42	42%

Table 6.11 Alcohol and ulcer healing

	<u>Alcohol</u>		<u>No alcohol</u>	
	<u>Number</u>	<u>% healed</u>	<u>Number</u>	<u>% healed</u>
Cimetidine	28/39*	89%	11/39*	82%
Placebo	26/42	38%	16/43	38%

* No information available on 4 patients

had a similar percentage frequency of ulcer healing during cimetidine or placebo treatment, to non-smokers and non-drinkers. (Table 6.10 and 6.11).

Relapse after the six week study: Of the 36 patients healed with cimetidine treatment 6 entered the maintenance study directly. The remaining 30 patients and the 16 patients who had healed with placebo treatment were followed in the outpatient clinic without further therapy. The first appointment was 1 month after the trial and thereafter as symptoms dictated. All patients were asked to recontact the clinic in the event of recurrent symptoms, but no rigid protocol was followed at this stage. Thirteen (43%) of the 30 patients who had received cimetidine relapsed (with endoscopic confirmation) at periods between 14 and 360 days later, while 6 (37%) of the 16 who had received placebo relapsed between 56 and 242 days later.

Discussion

This study demonstrates that ulcers of patients treated with cimetidine 1200mg daily have a significantly higher healing rate than those of patients receiving placebo. The results of this study and seven other double blind placebo controlled trials, one antacid controlled trial and four uncontrolled studies have recently been reviewed (Winship 1978). Overall the results have shown a remarkable degree of uniformity. In the placebo controlled studies despite varying dose and trial duration all cimetidine regimens, with one exception, were associated with a statistically significant increase in the frequency of ulcer healing. In 4 or 6 weeks 71% of 348 cimetidine treated patients and 37% of 300 placebo treated patients had healed.

The evidence from trials conducted in the USA (Binder et al 1978, Ippoliti et al 1978) is not so convincing partly because of fairly low healing rates in cimetidine treated patients

(57-76%) and also because of a high healing rate in placebo treated patients. (48-63%). Patients in the American studies consumed larger amounts of more potent liquid antacids for symptom relief than patients elsewhere in the world (Bardhan 1978) - but nowhere near the 1000mEq daily necessary to produce an ulcer healing effect comparable with cimetidine (Ippoliti et al 1978, Petersen et al 1977). The possibility remains that duodenal ulcer is somewhat different disease in different countries (Fordtran 1978).

In separate studies doses of cimetidine varying from 800mg-2000mg daily produced similar healing rates. In those trials in which a direct comparison of 2 dose regimens of cimetidine was made, small trends in favour of the higher dose were found but the differences were both statistically and clinically insignificant. (Bardhan et al 1979, Gillies et al 1978, Ippoliti et al 1978). In unselected cases of duodenal ulcer there seems no advantage in using a higher dose than 1g. daily.

There is no clear explanation why some patients heal and others do not during a 4 to 6 week course. It is possible that the aetiology of the diseases varies between individuals and that ulceration in the 'non-responders' is related to factors other than acid secretion. The analysis of smoking and drinking habits would seem to suggest that these factors do not influence ulcer healing. However these groups are self selected and the conclusion is therefore not valid. The data presented can only be used to demonstrate that there was a comparable number of healed smokers and drinkers in each treatment group.

An alternative explanation of why some patients have not healed in 4 to 6 weeks, is that these patients have higher rates of acid secretion than those who have healed. This study suggests that a high BAO and MAO impairs healing. This seems logical in that inhibition of meal stimulated acid secretion by a fixed dose of metiamide has been shown to be less profound in duodenal ulcer patients with marked acid hypersecretion (Richardson et al 1975). Thus it is possible that those patients with marked hypsecretion may require a higher concentration of drug to reduce acid secretion below the threshold for healing. Similar findings have been reported by Binder et al (1978) but others have found no significant difference in acid secretion between patients whose ulcers did or did not heal. (Venables et al 1978).

Although the ulcers of the majority of patients have healed after six weeks cimetidine treatment, some take longer to heal. Sequential endoscopic examination has shown that the proportion of patients with completely healed ulcers increased from 60-80% at 6 weeks to 88-96% at 10 or 12 weeks. (Berstad et al 1979, Northfield, Blackwood 1977). This is typical of our clinical experience at the Royal Adelaide Hospital where it is extremely rare to find a patient who is completely resistant to cimetidine in short term treatment. Provided that the diagnosis of duodenal ulcer is firmly based the possibility of patient non compliance, analgesic abuse or Zollinger-Ellison syndrome may need to be examined. Hyperparathyroidism may also cause cimetidine resistant gastric hypersecretion (McCarthy et al 1979). However it is notable that most patients referred to us because of "failure to respond to cimetidine" have been incorrectly diagnosed

radiologically. Functional abdominal pain, carcinoma of the stomach, carcinoma of the gall bladder invading the duodenum and even angina pectoris have presented in this way!

Cimetidine also relieves the symptoms of duodenal ulcer. The present findings of a striking early reduction of ulcer symptoms have been confirmed by all of the recently reviewed short term controlled trials. In each one cimetidine was significantly better than placebo in influencing one or more of the parameters of pain (Winship 1978). Severity and frequency of pain during day or night were less in cimetidine treated patients.

Antacid consumption is another measure of the symptom relief provided by the trial treatment. International comparisons of antacid consumption are impossible because of worldwide variation in medical and cultural habits of drug use. However within a single double blind trial comparisons between the treatments are valid. Most studies have found (as did this one) that the groups of patients treated with cimetidine consumed significantly less antacid than did the placebo treated groups. Thus any bias that may have been introduced by unequal antacid consumption between the groups is likely to favour healing in placebo treated patients rather than those receiving cimetidine. However in this study the low neutralizing capacity of Mylanta tablets and the small numbers consumed makes it unlikely that antacids influenced ulcer healing in either treatment group.

It is interesting that symptoms are relieved by cimetidine before an effect on ulcer healing can be demonstrated (Blackwood et al 1976, Hetzel et al 1977). This reinforces the concept that it is not just the presence of an ulcer which causes pain but the exposure of ulcer (or inflamed duodenal

mucosa) to acid-pepsin that is the cause of the pain. This may in part account for the lack of correlation between ulcer healing, judged visually via the endoscope, and symptom relief. In one study relief of symptoms correlated best not with ulcer healing but the degree of duodenitis visible endoscopically (Misiewicz 1978).

Comparison of the acid secretion studies performed before and one week after the trial showed no evidence of "rebound hypersecretion" of acid at this time. Concern had been expressed that prolonged suppression of acid secretion by cimetidine could, perhaps by facilitating gastrin release, lead to increased acid secretion upon discontinuing treatment. Review of 5 studies (including this one) which made controlled observations on this point showed no significant change in acid secretion after cimetidine treatment in 3, an increase in BAO after 2 weeks (but not 4 or 6 weeks) in one and a significant decrease in pentagastrin stimulated (but not meal stimulated) secretion in the other (Winship 1978).

An alternative approach designed to detect changes in parietal cell activity after cimetidine treatment also yielded negative results. The dose response curve relating gastric acid output to increasing submaximal doses of pentagastrin showed no changes after courses of cimetidine lasting up to 16 weeks (Aadland, Berstad 1979, Holden et al 1978). To date evidence of increased parietal cell sensitivity leading to 'acid rebound' is lacking.

No patient suffered from side effects in this study. The slight increase in plasma creatinine confirms the findings of Haggie et al (1976) and Blackwood et al (1976). The level

usually remained within the normal range, did not continue to rise and returned to pretreatment levels during treatment or immediately after the drug was stopped. The mechanism is unclear but cannot be explained by drug interference with laboratory estimations of creatinine, by changes in glomerular filtration or increased production of creatinine. There is no evidence of serious nephrotoxicity (Dubb et al 1978).

Abnormal liver function tests have been found in similar numbers of placebo and cimetidine treated patients during short term treatment (Kruss, Littman 1978). Clinical evidence of liver damage has been rare and in the few documented cases it has been ascribed to individual hypersensitivity (Villeneuve, Warner 1979).

These results suggest that cimetidine is a safe and effective drug, compared with placebo, in promoting healing of duodenal ulcer on a short term basis. The preliminary observations of patients after the short course of treatment confirmed that despite complete healing ulcer recurrence was commonplace and often rapid. Early reports of perforation or bleeding soon after stopping treatment had raised the spectre that H₂-receptor antagonists might cause a subsequent increase in duodenal ulcer (Saunders, Wormsley 1977). So far the evidence suggests that this is not the case. Recurrence was found in 37% of patients whose ulcers had healed with placebo and 43% of patients with ulcers healed by cimetidine. However these observations were made retrospectively and more carefully controlled, prospective studies were clearly necessary.

CHAPTER VII

PREVENTION OF DUODENAL ULCER RELAPSE BY
CIMETIDINE: A ONE YEAR DOUBLE BLIND TRIAL

Introduction

In the preceding chapter it was shown that a six week course of cimetidine relieves symptoms and promotes healing of duodenal ulcers when compared with placebo. However our initial unblinded observations suggested that a high proportion of patients suffered ulcer recurrence during the subsequent months. We therefore carried out a double blind study to compare the frequency of ulcer relapse in patients treated with cimetidine 400mg b.d. or a matched placebo for one year, following initial ulcer healing with a short course of cimetidine.

Patients and methods

The trial was carried out at the Royal Adelaide Hospital during 1977 and 1978. Patients who had undergone previous gastric surgery (except simple oversewing of perforation) or who had other acute illness or recent bleeding from the ulcer were excluded. Fertile females were also excluded because teratogenicity studies had not been completed at the beginning of the trial.

A standard pentagastrin test of gastric acid secretion (subcutaneous pentagastrin 6ug/kg body weight) was carried out as described in the preceding chapter on 36 patients and basal acid output BAO and maximal acid output was measured.

Patients who were initially symptomatic with endoscopically proven duodenal ulcers were treated with cimetidine 1.0g or 1.2g daily for 6 weeks. After this time endoscopy was repeated and 56 patients who were healed were randomly allocated in a double blind fashion to cimetidine therapy (400mg immediately before breakfast and 400mg at bedtime) or to placebo. There was

no break in therapy. All were treated as outpatients and provided with Mylanta tablets to take as required. Smoking and alcohol consumption were recorded but no advice was given to change these or diet. Every month, or immediately on relapse, patients were clinically assessed and blood tests performed. Clinical relapse was defined as 3 or more days symptoms, similar to those previously experienced, in any 7 consecutive days. When two observers agreed that symptomatic ulcer relapse had occurred, a further endoscopy was carried out. Endoscopy was also carried out as a routine after six month's treatment and at the end of one year's treatment on all patients remaining in the trial. The endoscopist was not responsible for clinical follow up of the patient and was not aware whether the patient was suffering symptoms. Instruments used were the Olympus GIFK, JFB2 and GIFP2. Ulcers were recorded as healed or unhealed. Endoscopic healing was defined as a duodenal cap free from crater or erosion.

Results were analysed by χ^2 to assess healing and Students t test for independent variables. A life table method was used to produce the figure (Merrell and Shulman 1955).

Results.

Fifty six patients entered the study, and 51 completed 1 year of study. Three patients (2 receiving cimetidine, 1 receiving placebo) were withdrawn after 6 months because they were going overseas. All were in clinical remission with no ulcer present at endoscopy. One patient receiving cimetidine was withdrawn after 97 days because of muscle pain. After 11 months of successful treatment, one cimetidine treated patient stopped taking his tablets. Data obtained from these

5 patients have been included in the analysis up to the point at which they were withdrawn from the trial.

Details of patients entering the trial are shown in Table 7.1. The two groups are comparable in regard to age, sex, duration of ulcer disease. Cimetidine and placebo groups contained similar numbers of non smokers (11 and 9 respectively), teetotallers (5 and 7 respectively) and patients with previous gastrointestinal bleeding (4 and 3 respectively) or perforation (2 and 1 respectively). The numbers of patients in each group who stated that a first degree relative had suffered from duodenal ulcer were also comparable (6 cimetidine, 9 placebo). The mean levels of acid secretion in each group were not statistically significantly different (Mean \pm SE. Cimetidine group - 17 out of 28 patients studied: BA0 5.0 ± 0.81 mmol/h; PA0 41.8 ± 3.47 mmol/h. Placebo group - 19 of 28 patients studied: BA0 6.9 ± 1.24 mmol/h; PA0 38.1 ± 2.38 mmol/h.)

Endoscopy

The total numbers of patients found to have relapsed during the year are shown in Table 7.2. The numbers are subdivided to distinguish those patients who developed clinical symptoms of relapse, confirmed by endoscopy, from patients without symptoms who were found to have ulceration in the duodenal cap at routine endoscopic examination at 6 months or 1 year. The results of this routine endoscopic examination are shown more fully in Table 7.3.

A more complete picture of the pattern of relapses is shown by actuarial analysis (Figure 7.1). This shows the cumulative remission rate in each group at 10 day intervals throughout the year. It demonstrates clearly that most relapses occur early in the follow up year. At 3 months 46% of placebo treated patients have relapsed compared with 7% of those patients receiving cimetidine.

Table 7.1 Patients entering the trial

Treatment	Number of patients		Mean age (years)	Mean duration of ulcer disease (years)
	Male	Female		
Cimetidine	23	5	44.8	8.4
Placebo	24	4	45.2	10.3
			NS*	NS*

* NS = Not significant

Table 7.2 Recurrence of ulceration, determined by endoscopy
Relationship to presence or absence of symptoms.

Treatment	Number of patients completing 1 year in study	Symptomatic relapse confirmed endoscopically	Asymptomatic ulcer found at endoscopy	Total relapsed
Cimetidine	24	3 (12.5%)	3 (12.5%)	6 (25.0%)
Placebo	27	17 (63.0%)	8 (29.6%)	25 (92.6%)

CIMETIDINE	28	27	26	26	25	25	24	21	21	21	21	21	20	18
PLACEBO	28	21	19	15	15	14	5	4	4	4	4	4	4	2

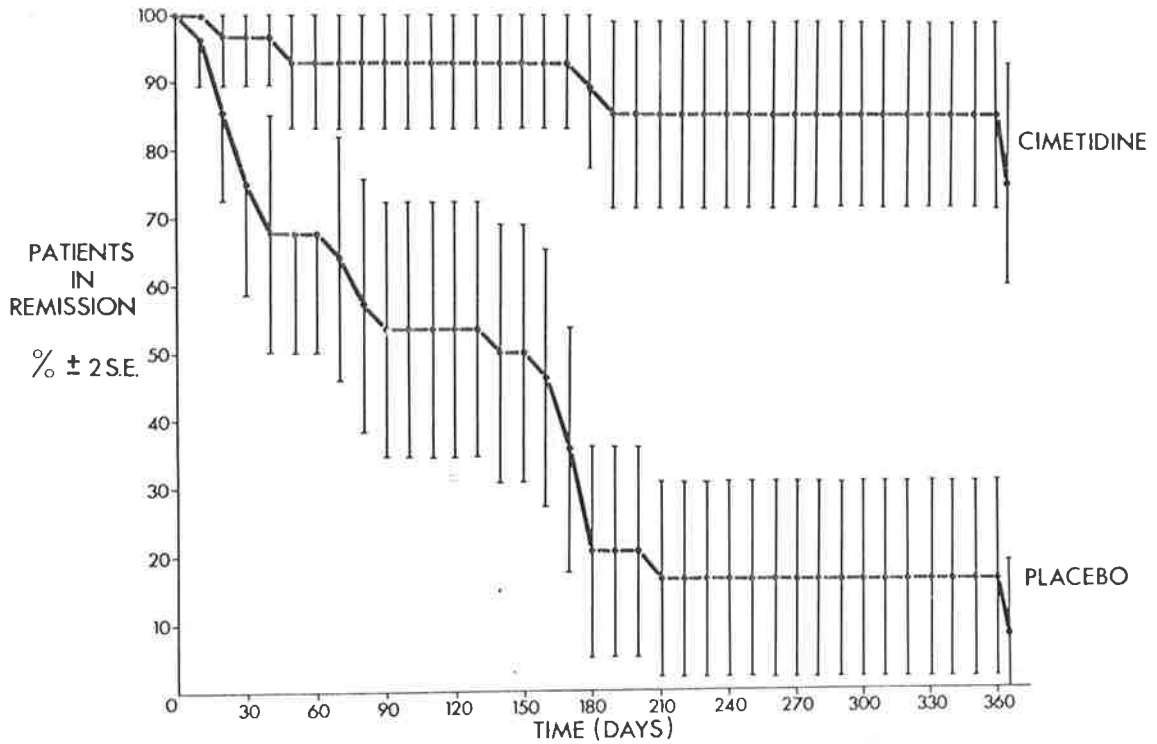


FIGURE 7.1 Life table analysis showing the cumulative percentage of patients who remained in remission at successive 10 day intervals. The p values at 40,60,90 and 120 days are <0.02 , <0.05 , <0.01 and <0.01 respectively and <0.001 for all intervals thereafter. The absolute numbers of patients in each group who remained in remission at successive 30 day intervals are shown above the figure.

By 6 months, this proportion has increased to 79% and 10% respectively. The sudden fall in the proportion of patients in remission at 6 months and 1 year represents those patients in whom recurrent asymptomatic ulceration was found at routine endoscopic examination.

It was noted that in the 3 cimetidine treated patients with asymptomatic recurrence, the duodenum contained shallow multiple erosions which were unlike the discreet chronic craters present before treatment. The routine endoscopic findings in asymptomatic placebo-treated patients were different: all 8 patients with recurrence had deep chronic ulcers (more than 1 ulcer was present in 5 patients) which were similar in appearance to those present before treatment.

Symptoms

All patients were symptom free at the time maintenance therapy was commenced and clinical relapse was unequivocal in most patients. Only one patient, with acute marital problems, developed symptoms thought to represent ulcer recurrence, but endoscopy showed no evidence of ulcer. In all of the other 20 patients who developed symptoms of ulcer, recurrent ulceration was present in the duodenum. Thus reliance on clinical symptoms gives a low number of "false positive" diagnoses compared with endoscopy. However, as shown in Table 7.2, 3 patients receiving cimetidine and 8 receiving placebo developed recurrent ulceration (as judged by the independent endoscopist) without accompanying symptoms of relapse. Thus, compared with endoscopy, reliance on symptoms gives a high proportion of "false negative" diagnoses: over 29% of the whole placebo group.

Table 7.3 The outcome of routine endoscopy, performed on all patients remaining clinically in remission at 6 months and 1 year

Treatment	6 months		1 year	
	Number examined	Ulcer present	Number examined	Ulcer present
Cimetidine	24	1	21	2
Placebo	12	6	4	2

Table 7.4 Gastric acid secretion*in patients receiving cimetidine

	Number studied	Basal acid output (mmol/h)	Peak acid output (mmol/h)
Patients who had a relapse despite cimetidine treatment	5/6	7.2 ± 1.9	48.4 ± 7.6
Patients who remained in remission during cimetidine treatment	12/22	4.1 ± 0.8	39.1 ± 3.7
P		0.1 > P > 0.05	0.5 > P > 0.1

* Mean ± SE

Antacid consumption

The group of patients receiving cimetidine consumed fewer antacid tablets than the group receiving placebo treatment. A much smaller proportion of the cimetidine treated patients required any antacids at all: 14/28 took no antacid at any stage compared with 4/28 placebo treated patients. Individual consumption varied widely, ranging from 0-100 tablets in a month in the placebo treated patients and 0-90 tablets in cimetidine treated patients. In total throughout the study the group receiving cimetidine consumed 350 antacid tablets and the group receiving placebo consumed 1408 antacid tablets. This gives an average total consumption of 12 tablets per cimetidine treated patient and 50 tablets per placebo treated patient. The disparity between the groups is even greater when the fact is taken into account that the cimetidine group was observed for far more months of treatment (because far more cimetidine treated patients remained in remission). Thus the mean consumption of antacid tablets was 1.1 tablets per patient per month of cimetidine treatment compared with 10.3 tablets per patient per month of placebo therapy. This difference is highly significant statistically.

Relapse despite cimetidine therapy

The 6 patients who had a relapse despite treatment with cimetidine did not differ from the remainder of the group in duration of the disease, in presence of previous complications or family history of ulcer, and in cigarette or alcohol consumption. However the patients who had a relapse despite cimetidine treatment tended to be younger than the remainder (mean age 33.3 years and 48.0 years respectively, $p < 0.02$). These patients also tended

to be hypersecretors of acid, although in this small group of patients mean levels of acid secretion were not significantly different statistically from the patients who remained healed while taking cimetidine (Table 7.4). Serum gastrin was within the normal range in the 3 patients in whom it was measured.

Of the patients who had a relapse, as judged endoscopically, despite treatment with cimetidine, two remained asymptomatic taking cimetidine 400mg twice daily, 1 requires 400mg of cimetidine three times a day to remain symptom free and 3 are asymptomatic after highly selective vagotomy.

Side effects

There were no serious side effects attributable to cimetidine. One patient receiving cimetidine was withdrawn after 3 months because of gradual onset of myalgia. This consisted of pain mainly in the shoulder girdle and upper arms on using these muscles. No weakness, tenderness or abnormal joint signs could be found. Laboratory values including ESR, serum creatinine kinase, serum aldolase and full biochemical screen were normal, and rheumatoid factor, antinuclear factor and LE cells were absent. His symptoms resolved in the 2 weeks after drug withdrawal and recurred on open challenge with cimetidine. Another patient was receiving treatment for long standing hypertension in addition to cimetidine. He developed atrial fibrillation with left ventricular failure after 5 months in the study. However he already had electrocardiographic evidence of hypertensive heart disease and cimetidine was not thought to have been an aggravating factor. He responded to diuretics and digoxin and remained well taking these and his coded ulcer medication until the end of the trial. One patient receiving placebo developed transient giddiness.

No haematological or biochemical abnormalities occurred which could be attributed to cimetidine.

Discussion

This study demonstrates that continuation of cimetidine 400mg twice daily will keep the majority of patients in remission during a year of careful observation following a successful short course of cimetidine treatment. The extremely high recurrence rate in placebo treated patients amply confirms our previous uncontrolled observation of early and frequent ulcer recurrence after successful short term therapy had been discontinued.

The results of this study and eight other placebo controlled trials are shown in Table 7.5. There is a remarkable degree of international agreement that patients maintained on cimetidine treatment after their ulcers have healed have fewer relapses than placebo treated patients. In all these studies (except Gudmand-Hoyer et al) ulcers were diagnosed first by endoscopy, healing confirmed after a short course of treatment and then endoscopy repeated in the event of symptoms suggesting relapse. In addition as shown in the final column of Table 7.5 endoscopy was repeated after a fixed time interval even if the patients were asymptomatic. In this way most studies found a number of "asymptomatic ulcers" in cimetidine treated patients, although in the majority of patients endoscopy confirmed that the drug was preventing ulceration and not merely suppressing symptoms.

The clinical value of routinely looking for ulcers in the absence of symptoms is arguable. Marks has suggested this may amount to "treating the hole in the patient instead of the patient as a whole" (Marks 1979). Limitations of resources and patient

Table 7.5 Cimetidine maintenance therapy for duodenal ulcer: placebo controlled studies.

Percentage of patients in remission during six or twelve month's treatment.

Author (country)	Treatment groups	Dose	Patient numbers	Per cent in remission			Endoscopy of asymptomatic patients
				3/12	6/12	1yr	
Blackwood et al (U.K.) 1978	Cimetidine Placebo	800 mg bedtime	21 24	81.0% 12.5%	76.0% 12.5%	- -	All patients 1½, 3, 6 months
Bodemar & Walan (Sweden) 1978	Cimetidine Placebo	400mg bid	19 ^a 23 ^a	- -	- -	84.0% 22.0%	All patients 7, 12 months
Gudmand-Hoyer et al (Denmark) 1978	Cimetidine Placebo	400mg bid	29 28	100.0% ^b 46.0%	96.0% ^b 24.0%	88.0% 20.0%	Not performed
Gray et al (U.K.) 1978	Cimetidine Placebo	400mg bedtime	26 30	85.0% 45.0%	73.0% 20.0%	- -	All patients 6 months
Hetzel et al (Australia) 1979	Cimetidine Placebo	400mg bid	24 27	93.0% 54.0%	90.0% 21.0%	75.0% 7.4%	All patients 6, 12 months
Hansky et al (Australia) 1979	Cimetidine Placebo	400mg bid	20 20	- -	95.0% 40.0%	95.0% 10.0%	All patients 1 year
Bardhan et al (U.K.) 1979	Cimetidine Placebo	400mg bid	29 31	- -	79.0% 32.0%	- -	28/38 patients 6 months
Dronfield et al (U.K.) 1979	Cimetidine Placebo	400mg bid	20 22	85.0% 45.0%	75.0% 30.0%	- -	6/23 patients 6 months
Berstad et al (Norway) 1979	Cimetidine Placebo	400mg bedtime	20 23	100.0% ^b 88.0% ^b	95.0% ^b 52.0% ^b	90.0% 30.0%	18/27 patients 1 year

^aDuodenal ulcer patients only ^bDerived from figure

tolerance clearly dictate that everyday clinical management must rely on subjective assessment. However even asymptomatic ulcers may bleed or perforate. If potent drugs are to be used for prolonged periods it is important for the clinician to have research data available indicating how accurately clinical history reflects the state of the patient's stomach or duodenum. Six of the "maintenance" studies shown in table 7.5 examined all asymptomatic patients after fixed time intervals, as well as confirming the clinical diagnosis of ulcer recurrence by endoscopy. (Bardhan et al 1979, Blackwood et al 1978, Bodemar, Walan 1978, Gray et al 1978, Hansky et al 1979, Hetzel et al 1979). Asymptomatic ulcer recurrence constituted 0-50% (mean 21%) of relapses which occurred during cimetidine treatment and 0-42% (mean 31%) of those relapses which occurred during placebo treatment.

Endoscopy at 6 months was a theoretical disadvantage for the second 6 months of the study. Even though double blind conditions were maintained the clinical observer might have been influenced to disregard complaints of symptoms during the 7th month of the trial in the knowledge that recent endoscopy had been carried out and no ulcer found. However any possible bias was minimised by using two observers to assess each possible symptomatic relapse, and the second observer was unaware of the duration of cimetidine therapy. In fact, 1 patient was judged clinically to have relapsed in the 7th month and this was confirmed by the independent endoscopist. The withdrawal of patients found to have asymptomatic ulcer at endoscopy at 6 months and 1 year increases the disparity between placebo treated and cimetidine treated patients. However, a statistically highly significant difference between the two groups is apparent from 40 days onwards (see figure 7.1).

The optimal dose of longer term cimetidine treatment may vary from patient to patient. However the two studies shown in Table 7.5 which used a single 400mg dose at bedtime achieved results comparable to the trials in which cimetidine 400mg twice daily (or 800mg at bedtime) was used.

Pooled data from 696 patients studied in an international collaborative double blind trial (Britain, France, Germany, Holland, Ireland, Italy, Norway, South Africa and Sweden) also suggest that a bedtime 400mg dose produces results that are similar to a twice daily dose. (Burland, Hawkins, Beresford 1979). Symptomatic recurrence of duodenal ulceration during treatment occurred in 31/179 (17.3%) of patients who received cimetidine 400mg at bedtime and in 28/184 (15.2%) of those who received cimetidine 400mg twice daily - an insignificant difference. However 178/333 patients receiving placebo had a symptomatic recurrence.

As a general rule cimetidine 400mg at bedtime is the initial dose which should be used for patients in whom maintenance treatment is thought necessary. The larger doses of cimetidine, 400mg twice daily, may be justified on theoretical grounds for patients known to hypersecrete acid or to be liable to severe and frequent recurrences of duodenal ulcer. However, as this study demonstrates, some patients will still have a relapse despite the larger dose - and these patients have higher levels of acid secretion than those who remain in remission.

The international collaborative study also addressed the question of asymptomatic ulcers. Two hundred and seventy seven symptom free patients were examined by endoscopy: 8/83 patients receiving cimetidine 400mg at bedtime, (9.6% of those examined from that group) 17/104 patients receiving 400mg twice daily

(16.3%), and 24/90 patients receiving placebo (26.7%) were found to have a duodenal ulcer. The difference between cimetidine treated patients and placebo treated patients is significant ($p < 0.01$) and confirms our own observations that although asymptomatic ulcers occur in cimetidine treated patients they occur even more frequently in placebo treated patients. The endoscopic appearance of the asymptomatic ulcers found in 8 placebo treated patients in the present study was categorized as grade IV - deep chronic craters. The asymptomatic ulcers in 3 cimetidine treated patients were all grade III shallow erosions. It seems possible that the latter are less likely to give rise to complications, although this point remains unproven as none occurred in either group.

The data on recurrence rate in placebo treated patients in these maintenance trials suggest that relapse occurs more frequently and more rapidly than clinical assessment or radiological studies had previously estimated. Recurrence in 60-85% of patients within 6 months and 70-90% within 1 year contrasts with, for example, an average of 58% recurrence within 2 years noted by Bralow et al in a review of 60 years of the literature on duodenal ulcer (Bralow et al 1950).

Is this apparent change in the behaviour of duodenal ulcer an artefact related to differences in methodology, or has there been a fundamental change for the worse in the nature of the disease?

In Chapter IV a number of factors were identified which might tend to emphasize or increase relapse rates in a group of patients with duodenal ulcer. For example the study of hospital patients (rather than patients from general practice) with frequent review (monthly rather than annual), prospective rather than retrospective follow up, and the use of a sensitive technique to detect ulcer

(endoscopy instead of clinical assessment or radiology) are all factors which tend to paint a gloomier picture of the long term prognosis. It is just these methods which have been employed in the present study. In addition the results have been expressed in a cumulative actuarial fashion which emphasizes a single recurrence as a final end point, rather than viewing it as a transient problem in the course of a chronic disorder. Thus it seems likely that the combination of the methods used and the mode of expression of results accounts for the apparently aggressive nature of duodenal ulcer disease in these studies.

The question of side effects of long term treatment is clearly of great importance. No serious adverse reactions were found in this study but the number of patients treated was small. If an important toxic effect occurred in only one patient out of 1,000 then it might not have been encountered in this study, although an incidence such as that (1 in 1000) might be enough to make the drug unusable clinically. Efficacy of a drug may be established by its use in a few hundred patients but far greater numbers of patients must be studied to establish safety. A review of the safety and side effects of cimetidine is presented in Chapter X.

Long term treatment with cimetidine cannot be recommended for every patient with duodenal ulcer until a number of questions have been answered. Even if it is assumed that it is effective and probably safe to treat patients with cimetidine for a year it does not follow that all patients should be treated in this way. A careful assessment must be made of the costs and benefits of treatment not just for the selected minority who enter clinical trials, but for the whole spectrum of ulcer patients. Comparisons

with alternative forms of treatment are essential and other factors such as patient compliance require review. One area which clearly needs to be reconsidered is that of the "natural history" of ulcer disease both with and without treatment. If subgroups of patients with a high or low incidence of ulcer recurrence could be identified (other than by trial and error) then treatment could be designed appropriately.

However, the present study indicates that 3 out of 4 patients can safely be retained in remission over a period of one year. There are patient groups for whom this therapy may be particularly appropriate: for example those at a high risk from surgery, the aged and those with other serious intercurrent disease. As a post script to this chapter it should be noted that the Australian Federal Government on 1st December 1980 increased the national health benefit to allow 900 tablets of cimetidine to be prescribed in the year after recurrence of duodenal ulcer has been shown. This allows the doctor the alternative of maintenance treatment with cimetidine 400mg daily for one year, at minimal cost to the patient.

CHAPTER VIII

THE RELAPSE RATE OF DUODENAL ULCER AFTER
STOPPING LONG TERM TREATMENT : A DOUBLE
BLIND CONTROLLED STUDY.

Introduction

The demonstration (Chapter VII) that longer term 'maintenance' therapy with cimetidine 400 - 800mg daily reduced the otherwise high rate of recurrence of duodenal ulcer immediately raised a number of questions. One of these was "what happens when long term treatment is stopped?"

Reports of ulcer perforation or bleeding soon after stopping short courses of metiamide or cimetidine had raised the possibility that H₂ receptor antagonists might cause a subsequent increase in duodenal ulcer (Saunders, Wormsley 1977, Wallace et al 1977). However, in double blind trials, complications were uncommon in patients allocated to placebo maintenance therapy after short courses of cimetidine (studies in table 7.5, Chapter VII). The incidence of ulcer recurrence after stopping longer term treatment was clearly a matter of some interest. One report on relapse rates, which relied on symptoms alone, had been provided by open and uncontrolled follow-up of patients who had taken part in a one year maintenance study (Gudman Hoyer et al 1978).

In collaboration with Dr. Jack Hansky and Melvyn Korman of Prince Henry's Hospital Melbourne in 1978 we therefore designed a double blind and controlled follow up study to establish relapse rates of duodenal ulcer following 1 year of continuous cimetidine therapy. By comparison with the "historical controls" of our earlier studies of ulcer recurrence after 6 weeks cimetidine treatment, we planned to assess whether prolonged therapy had beneficial or adverse effects on the prognosis of duodenal ulcer disease and its complications.

In Adelaide the 18 patients who had completed one year of cimetidine 400mg b.d. treatment, without relapse of ulcer, as part of our "maintenance trial" were eligible for inclusion. The smallness of this number underlines the need for collaboration, particularly when trials demanding long term patient observation are planned. Medical enthusiasm tends to diminish with time, and recruitment of adequate numbers of patients as rapidly as possible is important. We were thus enabled jointly to enter 41 patients who had already received 12 months treatment with cimetidine 400mg b.d. (as well as the preceding 6 week healing course) at a time (early in 1978) when the drug had only been available for clinical use for about six months.

Materials and methods

Studies were performed at Prince Henry's Hospital, Melbourne and the Royal Adelaide Hospital, Adelaide and were approved by the Research Advisory Committee of Prince Henry's Hospital and by the Research Review Committee of the Royal Adelaide Hospital. Advised consent was obtained from all patients. At both hospitals, a large number of patients with proven symptomatic duodenal ulcer had been managed on long term maintenance cimetidine. All these patients had originally presented with chronic ulcer-type pain and were treated with cimetidine 200mg t.d.s. and 400mg nocte. After 6 weeks, the patients eligible for this study were asymptomatic and endoscopy demonstrated complete healing of their ulcer. They were then maintained on cimetidine 400mg orally twice daily. Forty-one consecutive patients with proven duodenal ulcer who had remained symptom free and were found to be endoscopically healed

following 12 months of cimetidine 400mg b.d., formed the group selected for this study.

Our initial aim was to cease active therapy and assess the relapse rate. However, it was decided to have a small group on active treatment to ensure that both patient and investigator were "blind". Thus, the patients were randomised double blind into 2 unequal groups; 15 patients to active cimetidine 400mgs orally twice daily and 26 patients to identical placebo tablets.

Patients were seen as outpatients at monthly intervals for 6 months or immediately on relapse and symptoms assessed. Antacid tablets (Mylanta) were allowed for pain and indigestion. Patients were asked to refrain from taking salicylates but no advice was given regarding smoking or alcohol consumption. Relapse was defined as a return of symptoms similar to those previously experienced for more than 3 days in seven. At relapse patients were endoscoped by 2 endoscopists, one not involved in the clinical follow-up. The ulcer was recorded as healed or unhealed. Endoscopic healing was defined as a duodenal cap free from crater or erosion. Duodenitis was not considered a relapse. Instruments used were Olympus GIF Type K, and GIF Type P2.

Results

Table 8.1 shows that the cimetidine and placebo groups are comparable with respect to age, sex, duration of disease and previous complications. The mean number of antacid tablets consumed per patient per month of treatment was 6 for the placebo and 1 for patients receiving cimetidine.

Table 8.1 Age, sex, duration of disease and previous complications in patients treated with cimetidine or placebo.

	Age mean \pm S.E. (range)	Sex		Duration disease (years)	Previous Complic- ations*
		M	F		
Cimetidine	45.5 \pm 4.8 (18-77)	13	2	7.1 \pm 1.5	26%
Placebo	48.5 \pm 2.6 (27-65)	23	3	8.4 \pm 1.7	34%

* Previous perforation or haemorrhage.

Table 8.2 illustrates the cumulative number of patients in relapse after 1, 2, 3, and 6 months. Thus, only 1 of 15 patients relapsed in the cimetidine treated group whilst 20 of 26 patients have relapsed in the placebo group. So far, in all patients who have developed recurrence of ulcer-type symptoms, a duodenal ulcer has been confirmed at endoscopy. No false positive symptomatic relapses have been found in this study, that is, in all patients with recurrent symptoms, ulceration was diagnosed by the endoscopist who was unaware of the patient's clinical state.

Figure 8.1 compares the relapse rate after 12 months continuous cimetidine with that found from our previous studies following 6 weeks cimetidine (Hansky, Korman 1979, Hetzel et al 1979); The slopes of the curve are identical thus suggesting that the relapse rates after either 6 weeks or 12 months cimetidine therapy are similar.

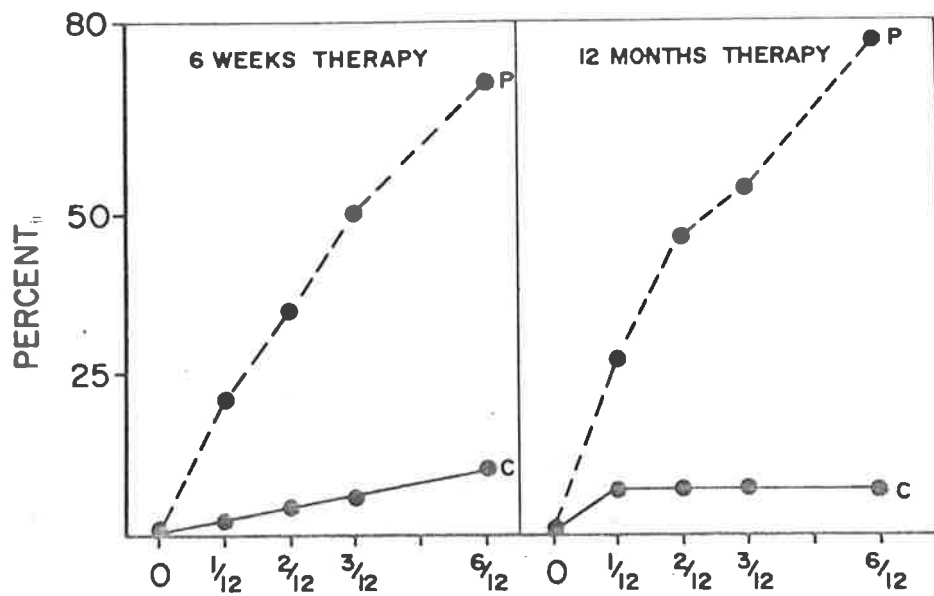
Discussion

This study has shown that although 12 months of maintenance cimetidine therapy was able to keep patients symptom free and without ulcer, it was followed by a high rate of recurrence on substituting placebo treatment. Indeed it is disappointing that the relapse rate after this prolonged therapy is precisely the same as that previously found after a 6 week course (Hansky, Korman 1979, Hetzel et al 1978, 1979) In the current study, all patients who developed ulcer symptoms during follow-up had a duodenal ulcer demonstrated at endoscopy. Periodic endoscopy in all patients was not performed. Thus, detection of asymptomatic ulcer recurrence has not been studied.

Table 8.2 Cumulative numbers of patients who have relapsed 1,2,3 and 6 months after commencing maintenance cimetidine or placebo.

PRECEDING MEDICATION FOR BOTH GROUPS.	CURRENT STUDY MEDICATION	NUMBER ENTERED	TOTAL NUMBER RELAPSED at (MONTHS)			
			1	2	3	6
Continuous cimetidine:						
6 weeks at 1 gram daily then 1 year at 400mgs b.d.	Cimetidine 400mg b.d.	15	1	1	1	1
	Placebo b.d.	26	7	12	14	20

FIGURE 8.1 Cumulative relapse rates of cimetidine (C) and placebo (P) treated groups in two patient groups: one treated with cimetidine for 6 weeks beforehand, and the other treated continuously with cimetidine for the preceding 12 months.



Our previous experience with long term cimetidine (Hansky, Korman 1979, Hetzel et al 1979) has shown that asymptomatic relapse occurs in placebo patients but has been less frequent in the cimetidine treated group. If this is the case, asymptomatic relapse in the placebo group would only serve to increase the already high recurrence rate.

Although our previous studies form only an "historical" control group for comparison, many of the problems associated with the use of these controls have been avoided. All studies were performed at the same centres by the same investigators, and the patient's mean age, sex and duration of ulcer disease were similar in both studies. However, it was of course a pre-requisite for the present study that patients should have remained asymptomatic and ulcer free during one year of cimetidine maintenance therapy. It could be argued that this excludes the small number of patients who have already relapsed during the year despite cimetidine treatment and this may have introduced a bias in favour of milder disease. However, the rapid relapse after cessation of therapy suggests that the group studied did indeed have significant disease.

Is there any other evidence that treatment with cimetidine could cause a subsequent increase in duodenal ulcer? The data that is available in humans does not support the concept that hyperplasia of parietal cells or an increase in parietal cell sensitivity is a consequence of cimetidine therapy. Prolonged cimetidine therapy does enhance the integrated gastrin response to food and this effect may persist for a short time after the drug is stopped (Forrest et al 1979). However, this is not matched by any consistent rise in acid secretion. Most investigators have found no change, some a decrease and some a

small increase in acid secretion (Forrest et al 1978, Hetzel et al 1979, Winship 1978) The response of acid secretion to graded doses of pentagastrin before and after courses of cimetidine has also been studied (Aadland, Berstad 1979, Holden et al 1978). No change in the sensitivity of the parietal cell to this stimulus, as judged by an unchanged slope of the dose-response curve, was found during or after the study periods which extended up to 16 weeks of therapy.

Having concluded that the rate of relapse after one year of maintenance cimetidine therapy is no different from that after a 6 week course, it is important to know whether ulcer relapse after even 6 weeks cimetidine treatment is any different from that occurring after other active treatments or even placebo treatment. Unfortunately there is only a little amount of data available.

Following short term trials comparing cimetidine with other healing agents, prospective follow up has suggested that duodenal ulcer recurrence is just as frequent after 6 weeks high dose treatment with Mylanta II (Hansky et al, 1980, C.U.R.E. 1980) or carbénoxolone (Schenk et al 1980) as cimetidine. One interesting study has found that in the year following 8 weeks treatment with tri-potassium dicitrate bismuthate (De-Nol) ulcers recurred in only 39% of 28 patients, compared with 85% recurrence in 27 patients who had been treated with 8 weeks cimetidine (Martin et al 1981). This challenging report clearly needs confirmation.

Comparison of relapse after cimetidine therapy with that after a successful healing course of placebo may not be valid as placebo treatment heals fewer patients with duodenal ulcer than cimetidine therapy. Nevertheless, comparisons of relapse

after short term placebo or short term cimetidine induced healing have been made during prospective maintenance studies (Bardhan et al 1977, Burland et al 1978) and there is no consistent difference between the two groups.

In conclusion, 6 months further cimetidine therapy continues to keep in remission the majority of patients who have already been maintained well for one year. Withdrawal of therapy leads to high relapse rate but there is no evidence that relapse rates are higher or lower after long term than short term therapy. It may be that a longer period of treatment with H₂-receptor antagonists will alter the natural history, but it seems unlikely from these and other results (Cargill et al 1979). To maintain healing it seems that therapy may have to be continued indefinitely in which case other factors such as patient compliance, side effects and comparison with alternative treatments become increasingly important. The advent of cimetidine has provided us with a valuable ulcer healer - unfortunately it seems to have no influence on the course of the disease itself.

CHAPTER IX

LONG TERM TREATMENT OF DUODENAL ULCER WITH CIMETIDINE:
INTERMITTENT OR CONTINUOUS THERAPY?

Introduction

The success of cimetidine and other drugs in relieving pain and healing ulcers in the short term has allowed attention to be turned to the long term management of duodenal ulcer. The demonstration of very high rates of ulcer recurrence after short term healing has emphasized that prevention of ulcer recurrence must be the next goal of future research.

"Maintenance treatment" with continuous cimetidine treatment 400-800mg daily for one year will prevent relapse in the majority of patients during that time, but only limited data are available on results beyond one year. Before cimetidine can be recommended for use indefinitely several questions about long term treatment need to be answered: Is such treatment effective over longer periods? Approximately 20% of patients relapse in the first year despite treatment. Will a similar proportion relapse in each subsequent year? Will patients' compliance be satisfactory while they remain free of symptoms? Will treatment remain safe? How long should treatment be continued and is the expense justified? Do all patients require continuous treatment and if not, how should such patients be selected?

Because of these uncertainties, it seemed important to explore alternative ways of using the drug in the longer term management of duodenal ulcer. In 1979, when this study was carried out, cimetidine was available (outside public hospitals) as a subsidized Commonwealth Government pharmaceutical benefit for only two four-week courses per year, on the basis of radiologically or endoscopically proven active ulceration.

This limitation further stimulated us to assess patients managed over a prolonged period of time, by intermittent treatment with short courses of cimetidine to control symptoms and heal ulcers. It seemed important to determine in what proportion of patients this could offer an adequate alternative to continuous treatment and whether clinically useful prognostic factors could be identified.

There were many studies which reported the incidence of ulcer healing after 4-6 weeks of drug treatment, but few had followed up patients to determine how frequently short term treatment might be needed. Clinical experience shows that many patients have only occasional attacks; such patients may not require prolonged treatment. We therefore compared two groups of patients with duodenal ulcer, allocated at random to receive either intermittent treatment or continuous maintenance therapy with cimetidine during one year of follow up.

Methods

All patients were referred to the Royal Adelaide Hospital with symptomatic duodenal ulceration. No patient with recent complications or other serious illness was included. The ulcer was confirmed by endoscopy and patients were treated with cimetidine, 200mg t.d.s. with meals and 400mg at bedtime, for six weeks. Endoscopy was then repeated and those patients with healed ulceration were randomly allocated to one of two groups (using a table of random numbers) for a further year of outpatient follow up.

Group A, continuous treatment. These patients received cimetidine 400mg with breakfast and at bedtime. Endoscopy by means of the Olympus GIFP2 paediatric size instrument was

repeated at 6 and 12 months after beginning of study or if the patient relapsed symptomatically whilst receiving this treatment.

Group B, intermittent treatment. These patients received no further therapy until they had symptomatic relapse, at which point endoscopy was repeated and a further 6 week course of cimetidine given. Endoscopy was repeated at the end of each course and treatment was again stopped if the ulcer had healed (but continued for a further 6 weeks if the ulcer had not healed). Routine endoscopy at 6 and 12 months after beginning the study was also carried out. Patients who were found to have asymptomatic ulceration at 6 months received a further course of therapy.

Patients in groups A and B were seen monthly and immediately on recurrence of symptoms. Symptomatic relapse, defined as symptoms similar to those previously experienced occurring on at least 3 days out of 7 consecutive days, was agreed by two observers before endoscopy was requested. Antacid tablets (Mylanta) were allowed for pain or indigestion and tablet counts were checked each month. Advice to curtail alcohol or cigarette consumption was given to each patient initially but not reinforced. All patients were asked to avoid taking salicylates. At endoscopy ulcers were classified as healed or unhealed. Unhealed ulcers comprised ulcer craters and erosions. A standard pentagastrin test (6 µg per kg subcutaneously) was performed in 22 of 24 patients in group A and 23 of 24 patients in group B.

Results

Forty eight patients, 24 in each group, entered the study. The groups were similar in terms of age, sex, previous

TABLE 9.1: DETAILS OF PATIENTS WHO ENTERED THE STUDY

		Group A	Group B
		Continuous treatment	Intermittent treatment
Number of patients	Men	20	21
	Women	4	3
Mean age (years)		46.8	47.6
Previous complications [†]		2	3
Mean BAO mmol/hr		5.7*	6.2 [†]
Mean PAO mmol/hr		43.2*	43.3 [†]

*22 patients

[†]23 patients

[‡]All complications had occurred more than 2 years previously

complications and acid secretion (Table 9.1).

Group A. Of the 24 patients, one died from myocardial infarction 5 months after beginning of study, at which point his ulcer was in remission. One patient developed multiple myeloma 6 months after beginning of study and was withdrawn; and two further patients decided not to continue after the 6 month endoscopy. All three patients were in clinical and endoscopic remission when they were withdrawn from study.

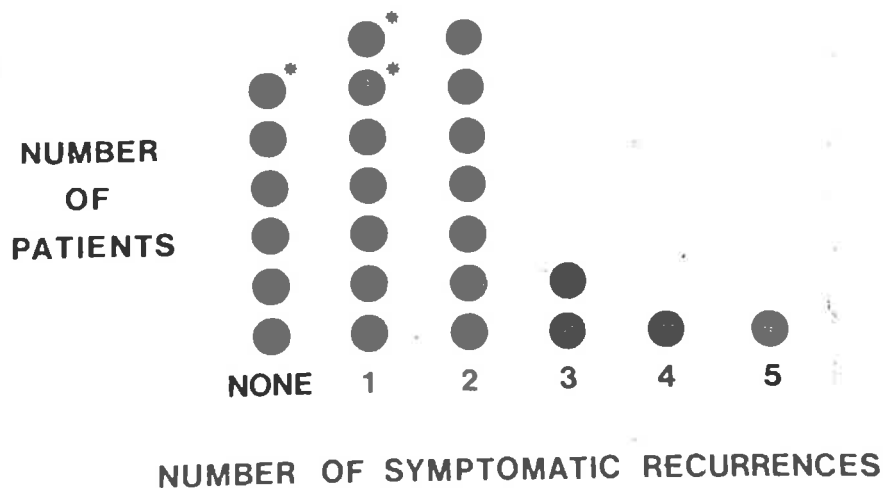
Of the 20 remaining patients, clinical relapse, confirmed by endoscopy, occurred in one patient who was then treated by highly selective vagotomy. Routine endoscopy at 6 months in the remaining 19 patients showed that one had an ulcer and three other had duodenitis with "salt-and-pepper" shallow ulceration. All four patients continued therapy and remained asymptomatic; endoscopy at 1 year showed that the patient with ulcer at 6 months had duodenitis but no ulcer, and that one of three patients with duodenitis had now healed. Thus 15 out of 20 patients remained in clinical and endoscopic remission over 1 year.

Group B. Of the 24 patients, three withdrew from study during the year. One (female) withdrew at two months for social reasons, one (male) was lost to follow up after 7 months, and one (female) withdrew 8 months after beginning of study.

The number of symptomatic relapses suffered by 24 patients and necessitating 36 endoscopies is shown in Figure 9.1. An ulcer was found on 30 occasions and duodenitis with erosions on 6 occasions. All these exacerbations were treated with a further course of cimetidine.

FIGURE 9.1 Intermittent treatment group. Number of recurrent exacerbations of symptoms in 24 patients during the year immediately following healing of their duodenal ulcer.

* Three patients withdrawn during the year (see text).



Routine endoscopy was carried out at 6 and 12 months after the beginning of the study in patients who were asymptomatic and were not receiving treatment at that time; of 12 patients examined at 6 months, six had a chronic duodenal ulcer and one had duodenitis. Patients with an asymptomatic chronic ulcer crater were treated with a further 6 week course of cimetidine whilst treatment was withheld in the patient with duodenitis.

Figure 9.2 shows the number of patients who received from none to seven courses of cimetidine during the year of study. It includes three patients who required more prolonged courses of cimetidine to allow complete ulcer healing. The prolonged course of 12 or 18 weeks is counted as two to three six week courses. In all, 18 courses of therapy were given, including six courses of cimetidine given for asymptomatic ulcer crater discovered at the six month endoscopy. At 12 months, 21 patients remained in the study; of these, six were already receiving cimetidine because of recent relapse and two did not attend for routine endoscopy. Of 13 patients who underwent routine endoscopy, three had just developed a symptomatic relapse at the time of the prearranged endoscopy and all three had duodenal ulcer. Of the 10 asymptomatic patients, one had duodenal ulcer and four had duodenitis with erosions.

In the Group B patients, the number of symptomatic relapses was unrelated to pre-trial basal or stimulated acid output, as illustrated in Figure 9.3. Neither did the age of onset or duration of disease, alcohol consumption or smoking habits show any correlation with the clinical course

FIGURE 9.2. Intermittent treatment group. Number of 6 week courses of cimetidine prescribed during the follow up year for the 24 patients (including 6 courses given for asymptomatic ulcers).

*More prolonged therapy than 6 weeks necessary to produce healing.

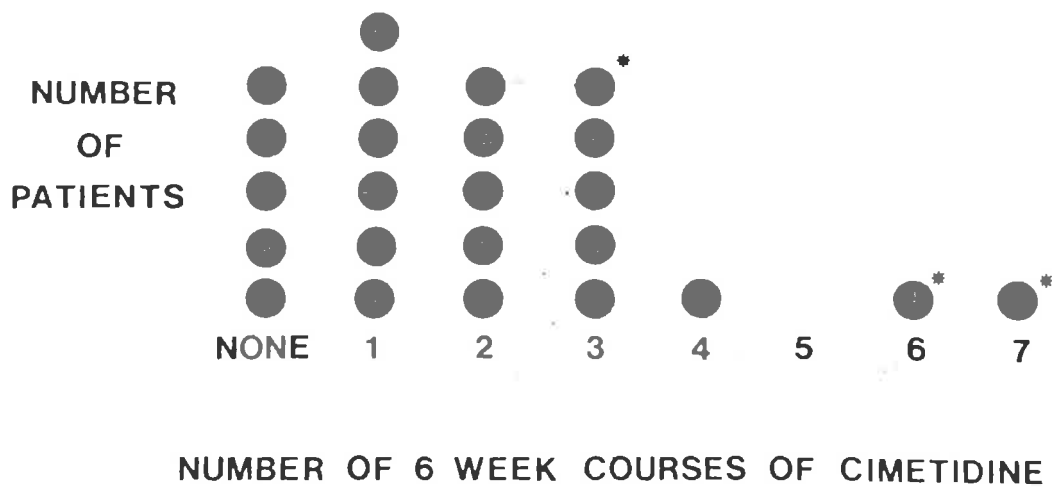
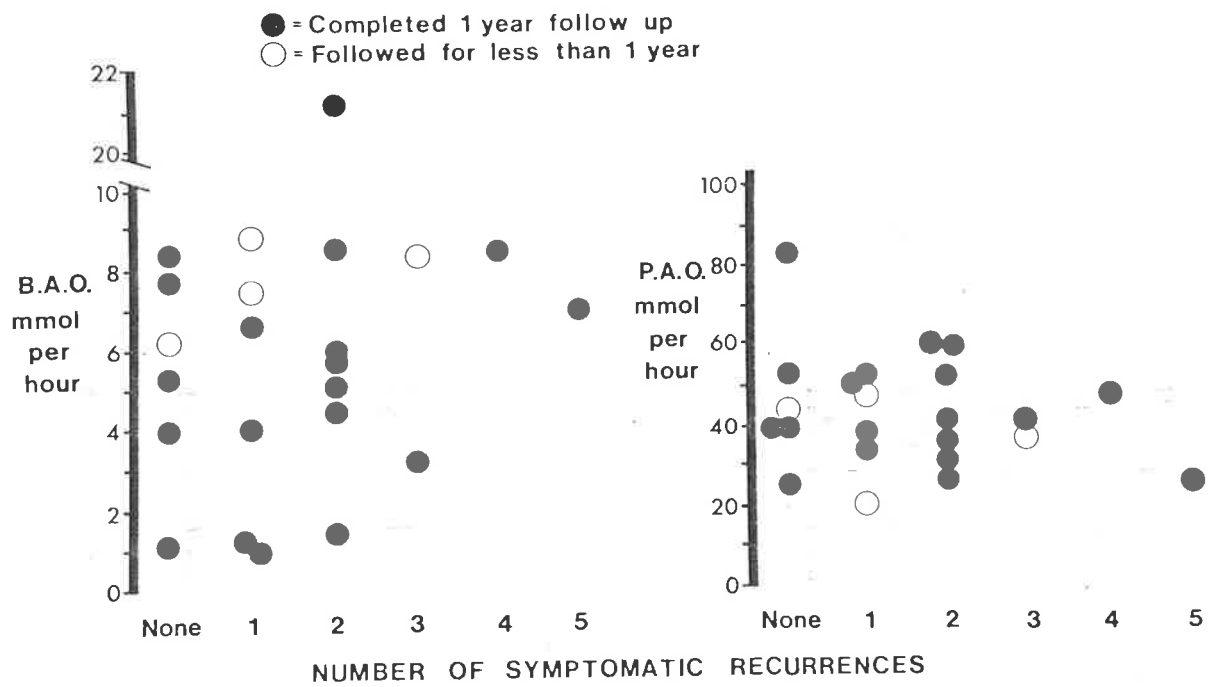


FIGURE 9.3. Intermittent treatment group. Pretreatment basal acid output (BAO) and peak acid output (PAO) in 23 patients, related to their clinical course during the following year.



during the follow-up year. In individual patients there was no close relationship between the length of the first and subsequent remissions. Consequently the length of one remission period could not be used to predict the future pattern of relapses and remissions.

No side effects were encountered in patients in either group. At the dose levels chosen, the total amount of cimetidine used in the continuously treated group (28 tablets per patient per week) was three times that used in the intermittently treated group (an average of 9 tablets per patient per week).

Discussion

The results in patients receiving continuous maintenance therapy confirmed our previous findings (Hetzl, Shearman, Hecker, Sheers, 1979). Cimetidine 400mg twice daily prevented recurrence of symptoms in over 90% of patients who took it regularly for 1 year, although only 75% of patients remained ulcer-free.

The alternative approach of 'intermittent therapy' as used here in a group of 24 patients referred to hospital was satisfactory in 6 who suffered no further relapse during the year following the initial healing course. A further 7 patients suffered only one more symptomatic relapse during the follow up year and thus 13/24 (55%) would probably have been satisfactorily treated within the limits of the Australian pharmaceutical benefits scheme current at that time. However, it should be noted that we used 6 weeks as the duration of our short course of treatment. It is possible that 4 week courses, as currently subsidised, might provide a less satisfactory result.

Three patients of the 18 who suffered clinical recurrences required more than 6 weeks treatment to produce complete healing. This was not unexpected as our previous double blind studies had shown that 15% of patients failed to heal their ulcers during 6 weeks therapy with cimetidine (Hetzl, Taggart, Hansky et al 1977). However the prolonged treatment necessary for this minority reduces the proportion of patients who could be managed by two short courses per year to approximately 40% of the group. If these data on hospital referred patients could be extrapolated to all patients with duodenal ulcer it suggests that the Commonwealth Government pharmaceutical benefits limitations were set at an unrealistically low level.

Even though asymptomatic ulcers occurred with continuous treatment, it should be noted that they were more common with intermittent treatment. Their clinical significance is uncertain, but it is recognised that complications may occur in the absence of symptoms.

From the viewpoint of the general practitioner it is important that symptomatic recurrence of ulcer (defined as symptoms similar to those previously experienced, on 3 days out of 7) in all cases was confirmed to be ulcer recurrence by endoscopy. Thus a clear history of typical recurrence in patients with known duodenal ulcer provides good evidence of ulceration, but absence of symptoms does not imply freedom from ulcer.

Two other hospital based studies, one from U.K. and one from Denmark have also assessed intermittent treatment with cimetidine (Bardhan 1980, Rune et al 1980). Differences in

the design of these from our own study are shown in table 9.2.

Bardhan's results are difficult to interpret as his methods are inadequately described. For example although his patients' progress was followed for "up to 22 months" the exact duration of observation for each patient and the group is not stated. His patients were not followed up in any predetermined way but referred themselves back "if their symptoms became troublesome". At the time of final assessment "those who had not recently had a relapse were recalled for interview". He does not state whether all responded to this request, although this seems unlikely as he admits that of "83 patients who relapsed, 21 defaulted". Some of the 42 patients who are classified as having no relapse might just have defaulted. Overall it seems likely that his method would lead to an underestimate of the number and duration of recurrences.

The methods of Rune et al are more clearly stated, although they do not comment on patients who defaulted or define exactly how often patients were reviewed. They relied entirely on symptoms to define relapse and did not use endoscopy even in the initial diagnosis of their study group.

If these differences in design are taken into account there is reasonable agreement between the studies on the expected outcome of a group of patients followed for 1 year after initial healing of the ulcer with cimetidine (Table 9.3).

As expected, Bardhan's estimates when compared with the other two studies show that a rather higher proportion of patients had no recurrence of symptoms (36%) and fewer suffered three or more bouts of pain (7%). Conversely fifteen percent of Rune's patients had no recurrence while thirty percent had three or more bouts of pain.

Table 9.2 A comparison of the designs of three studies assessing intermittent treatment with cimetidine

	<u>Hetzel et al</u>	<u>Rune et al</u>	<u>Bardhan</u>
Study design	Prospective	Prospective	Retrospective
Study duration	13.5 months	12 months	Up to 22 months
Duration of each course	6 weeks	4 weeks	1 to 2 months
Patient review	Monthly	Frequent visits	At patient discretion
Criterion of recurrence	Pain 3 days of 7	Pain 5 days of 7	Troublesome symptoms
Endoscopy	Yes	No	Usually
Patients entered	24	65	125
Patients defaulted	3	Unstated	21 of 83 who relapsed
Pentagastrin test	23	56	Nil

Table 9.3 Three studies of intermittent cimetidine treatment for duodenal ulcer. Frequency of symptomatic relapse during 1 year after initial healing with cimetidine.

Number of relapses per year	Percentage of patients studied by		
	Hetzel et al	Rune et al	Bardhan
0	24%	15%	36%
1	24%	32%	37%
2	33%	23%	20%
3	10%	22%	7%
4	5%	6%	
5	5%	2%	

Which patients are not suitable for intermittent treatment? In our own study four of the patients suffered three or more clinical relapses, in addition to the attack which led to their referral to hospital. Two additional patients required prolonged therapy to effect healing. These six patients, 35% of group B, could be considered the failures of intermittent treatment. It seems likely that they would have suffered fewer symptoms with continuous treatment. In the study of Rune et al nineteen patients (30%) suffered 3 or more clinical relapses in addition to the initial attack. That these patients were considered failures of intermittent treatment can be judged by the fact that ten were subsequently sent for operation compared with three of the forty six patients who suffered fewer relapses. Bardhan of course found intermittent treatment satisfactory in a greater proportion of patients.

A disappointing feature of our own results and those of Rune was the inability of any readily determined clinical parameter to predict the number of relapses. Neither acid secretion nor duration of ulcer disease had any prognostic value. Other authors have also found acid secretion tests unhelpful in determining which patients might require medical or surgical treatment (Baron 1978). None of the three studies of intermittent treatment found any correlation between duration of first and second remissions.

There is a small but unavoidable risk of complications with ulcer recurrence. One patient of Rune et al developed pyloric stenosis and a frail 76 year old patient of Bardhan perforated his ulcer (while on the way to the pharmacy to collect some cimetidine) and died five days postoperatively.

Patients in whom complications might be disastrous are therefore not suitable for intermittent treatment. These include the very old and those with other severe disease, such as cardiorespiratory problems. Patients who have had major haemorrhage previously have an increased risk of subsequent haemorrhage and avoidance of recurrence is desirable particularly if they live in a geographically remote area.

There is no clearcut evidence from these studies as to how patients with chronic duodenal ulcer might be best managed in the medium to long term. A case can be made for an initial trial of intermittent therapy. The pharmaceutical benefits regulations current at the time our study was carried out and published, allowed only two subsidized courses of cimetidine treatment annually and only about 50% of our patients would have been adequately treated by such an arrangement. In December 1980 the regulations were changed to allow up to 900 tablets per annum in the year following demonstration of a duodenal ulcer. This seems adequate to allow effective intermittent treatment in most patients.

For those patients having frequent relapses, long term maintenance treatment offers a satisfactory alternative in most. However further information on long term safety and comparisons with other treatments including surgery is required. Although we have used a dose of cimetidine 400mg twice daily there is evidence to suggest that 400mg at bedtime will produce similar results (Berstad, Aadland, Carlsen et al 1979, Burland 1978b) especially in the elderly in whom the bio-availability of the drug is increased (Redolfi et al 1979). At present, apart from clinical trials, we reserve continuous maintenance therapy

for patients over 70 and those with other diseases who have an increased operative risk.

Other authors have attempted to assess the relative merits of intermittent and continuous treatment by making mathematical models of the two strategies (Pounder 1981, Wyllie 1981). Each model makes a number of assumptions (some of dubious validity) and uses published rates of short term healing and subsequent ulcer recurrence during cimetidine or placebo treatment to estimate numbers of patients requiring full dose or low dose treatment each week. Unfortunately Pounder miscalculated the monthly frequency of relapse in patients receiving placebo maintenance therapy.

Wyllie has correctly calculated the outcome using the same treatment model and the accurate monthly relapse rates from published data, which range from 10.5-26.2% (mean 18.3%) for placebo maintenance and 0-5% (mean 3.0%) for cimetidine maintenance. His predictions of cimetidine consumption using an intermittent treatment model agree remarkably well with the findings of the three published investigations (Table 9.4).

Wyllie notes that the strategy of intermittent cimetidine treatment would, according to the model, keep patients symptom free only 75-88% of the time while continuous treatment shows a more favourable outcome with 94-100% of patient-months symptom free. He (and Pounder) feel that despite the cost advantage of intermittent treatment, most hospital-referred patients with duodenal ulcer should be managed by continuous treatment. Bardhan and Rune et al conclude that intermittent treatment is a cheaper and adequate alternative in most patients. I believe that continuous treatment gives the most satisfactory result for

Table 9.4 Approximate annual consumption of cimetidine per patient using different treatment strategies.

<u>Intermittent treatment</u>		
Author	Weeks of treatment per year	Cimetidine, grams per year
Hetzel	Initial course + 13 weeks	93g
Rune	Initial course + 8 weeks	55g
Bardhan	Initial course + 12 weeks	84g
<u>Calculated from treatment models</u>		
Pounder	Initial course + 5.2 weeks*	36g*
Wyllie	Initial course + 6.2-13 weeks	43-91g
<u>Continuous maintenance treatment</u>		
Author	Cimetidine dose	Cimetidine, grams per year
Hetzel	400mg bd	291g
<u>Calculated from treatment models</u>		
Pounder	1.6 weeks at 1g/day, remainder 400mg/day.	153g
Wyllie	1.6-3.2 weeks 1g/day, remainder 400mg/day	153-159g

* This is an underestimate. Pounder miscalculated the mean monthly frequency of ulcer recurrence in placebo treated patients in published maintenance trials. Although approximately 68% of patients relapsed in 6 months the curve (as seen in our own actuarial graphs) is an exponential one. Thus the monthly rate of relapse is not simply 68% divided by 6 (=11.3% as Pounder assumes) but 15.7% of those patients who remain in remission each month.

hospital-referred patients but is probably unnecessary for many patients when first seen by their family doctor. The controversy is ultimately more likely to be decided on grounds of efficacy and safety of long term exposure to H₂-receptor antagonists rather than by cost factors.

CHAPTER X

CIMETIDINE: SAFETY, SIDE EFFECTS AND DRUG INTERACTIONS

Introduction

If the dictionary definition of "safety" as "freedom from danger or risk" is accepted it is axiomatic that no pharmacologically active drug can be totally "safe". Whenever a therapeutically effective drug is prescribed it is, or should be, the result of weighing the expected benefits against the known risks. Most drugs are selected for development because of their desirable therapeutic effects; to clarify the risks attached to their use is more difficult although just as important to the patient.

If it is accepted that "safety" is a relative and not an absolute concept, where then is the dividing line between "safe" and "unsafe" to be drawn? Jick has suggested an arbitrary definition of "low risk" to mean that significant drug-induced illness occurs in less than 1 instance in 10,000 (patients? or therapeutic episodes?) per year (Jick 1977). If this were fully accepted then no new drug and few existing potent drugs would qualify for this description - which already contains a value judgement about what is "significant".

Because risk cannot be measured precisely, the acceptability (or not) of any adverse effect must be considered with respect to the natural history of the disease in question, the effectiveness of the drug in influencing the disease and individual risk factors related to the patients who might be treated.

Peptic ulcer is seldom life threatening and in large patient populations there is no evidence that the disease shortens life expectancy. No matter how efficacious a drug is for the treatment of peptic ulcer, it will be suitable for most patients only if the risk is relatively low. Even if one does not completely

accept Jick's definition of "low risk", it is apparent that to establish risks of that order of magnitude, then studies of tens of thousands of patients are necessary. Ironically this represents far more patients than the number necessary to demonstrate drug efficacy.

The process of establishing the risks of treatment must therefore involve the collection of individual reports from a variety of sources which might represent an adverse reaction to cimetidine. These have to be related to the pattern of other reports and, if possible, a reasonable conclusion is drawn. This has then to be communicated to doctors to form part of their judgement of benefit and risk in treating individual patients.

Because the question of side effects requires study of large numbers of patients, this chapter will be largely based on published data. However the question of the interaction of cimetidine with other drugs will be discussed in some detail with emphasis upon our own results.

Methods for assessing drug safety and adverse reactions.

A variety of sources must be used for assessing the safety of drugs (Table 10.1).

A. *Animal Toxicology.* The toxicology of cimetidine was discussed briefly in Chapter 3 but a number of points are worth repeating in view of their possible relationship to clinically observed side effects.

Extensive 12 month toxicological studies in rats and dogs were carried out with daily doses up to 950mg kg^{-1} (rat) and 504 mg kg^{-1} (dog), about 150 and 200 times the oral ID_{50} for inhibition of histamine stimulated acid secretion on those

Table 10.1 Methods for assessing drug safety

A. Preclinical: animal toxicology

Acute dosing

Repeated dosing

Reproductive studies

Interaction studies

B. Preclinical: animal pharmacology

Effects on target system

Effects on other physiological systems

C. Clinical: human studies

Pharmacological studies

Clinical trials

Post marketing surveillance

Published reports

Spontaneous reports - to manufacturer

- to a government agency

- of accidental overdose

species (Leslie, Walker 1977). At these high dose levels the only important finding was a weak antiandrogenic effect with reversible retardation of the growth of prostate and seminal vesicles. There was no effect on breasts, male mating performance or fertility, and no evidence of feminisation of the male foetuses of female rats treated throughout pregnancy. Some dogs on the 336 and 504 mg kg⁻¹ daily dose developed transient tachycardia (presumably in response to vasodilatation) and 2 animals from the top dose group became unwell after 6 months and had to be killed. Minor lesions of liver and kidney were found which were not apparent in animals sacrificed after 12 month's treatment.

After the occurrence of granulocytopenia with metiamide the possibility that cimetidine might also cause this was of great concern. However unlike metiamide, cimetidine did not cause granulocytopenia or change in the bone marrow appearances in any of the test animals. Also unlike metiamide ³H-labelled cimetidine was not taken up into bone marrow cells (Cross 1977).

Acute interaction studies with a wide array of therapeutic drugs in the rat showed no effect of other drugs on the acute intravenous toxicity of cimetidine or vice versa (Brimblecombe et al 1978). It was difficult to kill animals with cimetidine. In dogs the LD₅₀ value of cimetidine after oral dosing with solution was approximately 2.6 grams per kg body weight. (By extrapolation this would require a 70 kg man to take over 900 of the 200mg tablets to achieve a similar dose!) Death occurred within 4 hours of dosing and was preceded by clonic convulsions indicating the possibility that some cimetidine had penetrated

the central nervous system at these high dose levels. The animals which died had peak blood levels of cimetidine in excess of $770\mu\text{M}/\text{l}$ (Brimblecombe et al 1978).

B. *Animal pharmacology.* The effects of cimetidine on gastric acid secretion and other physiological systems in animals and man has been covered in Chapter 3. It is important to re-emphasize that histamine H_2 receptors have been demonstrated in a wide variety of tissues including mast cells, T-lymphocytes, brain, reproductive organs, heart, blood vessels and smooth muscle as well as stomach. Whether histamine receptors at these sites have a physiological (rather than pharmacological) role is uncertain.

The pharmacological effects of cimetidine in man have been very similar to those seen in animals, with a similar potency in terms of blood concentration (Brimblecombe, Duncan 1977). The absorption, metabolism and excretion of cimetidine is similar in man, rat and dog, and in all species studied a blood concentration of cimetidine of about $2\mu\text{mol}/\text{l}$ is associated with a 50% inhibition of maximally stimulated acid output. Doses sufficient to inhibit gastric secretion were without measurable effects on other physiological systems (Brimblecombe et al 1978).

At much higher doses the only system in which any acute changes could be demonstrated was the cardiovascular system. Experiments using the perfused hind-quarters of anaesthetized rats showed that high doses of cimetidine caused vasodilatation (Brimblecombe, Duncan 1977).

In intact conscious dogs, large doses of cimetidine (1.5mmol kg^{-1} by mouth) 150 times the ID_{50} for inhibition of gastric acid secretion, caused transient bradycardia and slight hypotension

only in untrained animals, while dogs accustomed to blood pressure and heart rate recording showed no cardiovascular response to $1,3 \text{ mmol kg}^{-1}$ (Brimblecombe, Duncan 1977).

Clinical studies

Clinical trials. The advantages of clinical trials include the close care with which patients are supervised and events recorded, the scientific quality of the data and the presence of controls. The latter are particularly valuable in allowing assessment of whether minor events occurred more or less frequently than might be expected in everyday life.

Pooled data from clinical trials in the U.K., continental Europe, Scandinavia and South Africa obtained during the $2\frac{1}{2}$ years up to 31st August 1977 have been reviewed and safety aspects of short term and longer term treatment considered (Burland 1978a).

In *short term* clinical trials (800mg-2g/day for 4-8 weeks) review of 3206 patients showed that side effects were infrequent and mainly mild and transient. Of these, 2182 had received cimetidine, 884 had received placebo and 140 had received some other form of treatment. A summary of the untoward clinical effects or abnormal biochemical findings is given in tables 10.2-10.4 which are constructed from Burland's data.

No coherent pattern of side effects causing withdrawal of cimetidine was encountered. Early in the course of the trials 6 patients were withdrawn because of rash. The rashes were variable in appearance and distribution and it is unlikely that most patients developing a rash would now be withdrawn for that reason alone.

Table 10.3 illustrates the similar frequency of minor side effects not leading to withdrawal of treatment, which occurred

Table 10.2 Overall incidence of side effects occurring during short term (4-8 weeks) cimetidine or placebo treatment

	Cimetidine		Placebo	
	Number	%	Number	%
Patients monitored	2182	100	884	100
Untoward clinical events leading to withdrawal	24	1.1	10	1.1
Abnormal biochemistry leading to withdrawal	10	0.4	1	0.1
Minor effects not leading to withdrawal	365	17	170	19

Table 10.3 Incidence (%) of minor untoward clinical effects not leading to withdrawal from short term treatment

Untoward effect	Cimetidine	Placebo
Headache	3.1	3.6
Diarrhoea	1.8	1.0
Tiredness	1.7	1.6
Dizziness	1.3	1.0
Drowsiness	1.3	0.9
Rash	1.2	1.0
Constipation	1.0	2.8
Muscular pain	0.8	0.6

Table 10.4 Incidence (%) of abnormally high values of blood biochemical indices during short term treatment (and % in which values returned to normal during continued treatment).

	Cimetidine	Placebo
Plasma creatinine	10.6 (4.7)	5.9 (2.7)
Plasma urea	4.0 (2.0)	4.0 (2.6)
Serum GOT	6.9 (3.0)	4.8 (2.5)
Serum ALP	4.7 (2.1)	3.1 (1.4)
Serum bilirubin	3.2 (1.6)	2.2 (1.0)
Serum GPT	5.8 (1.7)	2.7 (0.7)

in cimetidine and placebo treated groups. There was no relationship between the doses of cimetidine and the occurrence of untoward clinical events or minor side effects.

Abnormal elevations of blood biochemistry occurred at some stage during short term treatment in both cimetidine and placebo treated groups (table 10.4). Raised levels of plasma creatinine, serum transaminases and alkaline phosphatase occurred slightly more frequently in cimetidine treated patients. Of these abnormalities only the change in serum creatinine appeared to be dose dependent. Approximately half of all the abnormal biochemical values returned to normal despite continued cimetidine or placebo therapy. No clinically significant haematological abnormalities, and no neutropenia in particular, were reported.

The modest elevations in serum creatinine were also found in our own six week studies (Hetzl, Taggart, Hansky et al 1977) and further commentary has been made on this point in pooled data from North American studies (Kruss, Littman 1978). Although this aspect has been widely confirmed as occurring in around 60% of cimetidine treated patients (and 37% of controls) it seems to have virtually no clinical importance. The changes in creatinine seldom raise the level above normal and vanish with the end of therapy. There are no accompanying changes in blood urea, urine microscopy or proteinuria. The mechanism is unclear but it cannot be explained by drug interference with the laboratory test, changes in glomerular filtration, or increased creatinine production. There is no evidence of serious nephrotoxicity and it is possible that cimetidine

interferes with the renal tubular handling of small amounts of creatinine (Burland, Gleadle et al 1977, Dubb et al 1978).

In summary, it seemed from the data on short term treatment obtained in clinical trials that no side effects that might limit the clinical use of cimetidine had been found.

The process of clinical drug development continued with longer term studies many of which used smaller doses of cimetidine. In the longer term European and South African studies, 1124 patients were reviewed (Burland 1978) 657 who received cimetidine and 434 who received placebo. A summary of the untoward clinical effects or abnormal biochemical findings is given in tables 10.5 to 10.8. It must be noted that cimetidine treated patients were under monitored observation for much longer periods of time than placebo treated patients, as the latter were withdrawn earlier because of ulcer recurrence. Therefore data should be examined in relation to duration of patient exposure to treatment, as shown in table 10.7.

Two patients were withdrawn because of increases in serum transaminases (table 10.5). In both of these and 5 patients in whom this had happened in short term treatment, values for SGOT and SGPT returned to normal within 12 weeks of stopping cimetidine. As shown in table 10.8, abnormal values of bilirubin and SGPT occurred more frequently in cimetidine than placebo treated patients although more than two thirds of the abnormal values returned to normal during continued treatment. Only one patient became jaundiced and all cases remained clinically well. Liver biopsies taken

Table 10.5 Overall incidence of side effects occurring during longer term cimetidine or placebo treatment

	Cimetidine		Placebo	
	Number	%	Number	%
Patients monitored	657		434	
Untoward clinical events leading to withdrawal	12	1.8	8	1.8
Abnormal biochemistry leading to withdrawal	2	0.3	0	-
Minor clinical effects not leading to withdrawal	145	22	66	15.0

Table 10.6 Overall incidence (%) of minor untoward clinical effects not leading to withdrawal from longer term treatment

Untoward effect	Cimetidine	Placebo
Headache	2.6	3.7
Tiredness	3.5	0.9
Musculoskeletal pains	2.2	1.3
Constipation	1.5	1.2
Diarrhoea	1.5	1.8
Rashes	1.7	0.8
Nausea	1.1	2.1
Vomiting	1.2	1.4
Flatulence	1.1	0.4
Dizziness	0.9	1.4
Depression	1.1	0.2

Table 10.7 Incidence of all untoward symptoms or signs calculated according to number of patient-months of exposure to cimetidine or placebo treatment during the longer term European studies.

Cimetidine 400 mg daily	2.2
Cimetidine 400 mg bd	3.7
Placebo	3.4

Table 10.8 Incidence (%) of abnormally high values of blood biochemical indices in patients with normal indices prior to long term treatment (and % in which values returned to normal during continued treatment)

	Cimetidine	Placebo
Plasma creatinine	8.6 (6.5)	7.6 (5.3)
Plasma urea	4.4 (2.3)	4.3 (3.7)
Serum GOT	7.9 (5.8)	6.7 (5.8)
Serum ALP	5.5 (3.2)	4.4 (2.3)
Serum bilirubin	4.1 (3.2)	1.8 (1.6)
Serum GPT	8.3 (5.6)	2.8 (2.3)

from seven patients with abnormal liver function tests were reported as showing centrilobular necrosis in three, and fatty infiltration and slight inflammatory changes in four.

Overall these European clinical trials suggested that increases in serum transamines and bilirubin occurred occasionally during cimetidine treatment but marked increases were very rare. There was no relationship with dose or duration of treatment and the role of other drugs (which a few patients were taking), alcohol, diet or other factors (such as blood transfusion after haemorrhage) could not be determined. Changes in liver function were not considered limiting factors in the use of cimetidine in peptic ulceration.

The North American experience of changes in liver function during short term clinical trials produced similar conclusions (Kruss, Littman 1978). In 536 cimetidine treated patients and 310 controls SGOT levels exceeding 100 units occurred in 18 cimetidine treated patients (3.4%) and 11 controls (3.5%). In most patients elevations were slight and transitory and no clinical significance was attributed to them. Four cimetidine treated patients showed substantial rises. In two of them clinical and laboratory data were typical of viral hepatitis. In the other two there were "moderate increases during or after treatment, with insufficient collateral information available to allow confident interpretation. An effect of the drug cannot be excluded". In the placebo group, of the five significant elevations of SGOT, two were attributed to post transfusion hepatitis and in the remainder levels of 132, 390 and 450 occurred only at the two week post therapy tests. It is salutary that one of these

patients later died with fulminant hepatitis; had they been in the cimetidine group the presumption of drug toxicity might have been made.

Spontaneous reporting of adverse reactions

Following satisfactory completion of clinical trials, cimetidine was released for clinical use in the United Kingdom in November 1976, in Australia in May 1977 and in the U.S.A. in August 1977. In January 1980 "Tagamet" was marketed world wide in 113 countries and it was estimated by Smith, Kline and French Laboratories that over ten million patients had received the drug. Clearly the largest potential source of data on adverse events is this pool of patients for whom cimetidine has been prescribed in normal clinical use.

There are obvious problems in relying on the system of spontaneous reporting. Under-reporting is known to be considerable (Inman, Evans 1972). The observations are usually anecdotal, often poorly documented and subsequent analysis of the outcome often inadequate because of the difficulties of government or pharmaceutical agencies obtaining follow-up information.

Smith Kline and French have adopted a system in the major countries in which they operate of assessing all adverse events reported to them. Medically qualified personnel review each report individually. These are collated, added to their world wide data base and automatically notified to the drug regulatory authority in the country concerned, e.g. the Committee on Safety of Medicines in the

U.K. and the Adverse Drug Reaction Committee in Australia (Davis et al 1980).

Despite the shortcomings of spontaneous reporting these data have proved very useful in identifying a number of uncommon adverse effects and allowing modification of prescribing information. For example, interaction of cimetidine with oral anticoagulants was identified in this way and allowed Smith Kline & French to warn doctors on this point (Flind 1978).

Journal reports

Case reports in the medical press reflect interest particularly in new drugs. Their status as a source of information is no different from reports to the pharmaceutical companies or to government agencies. They must be judged on the facts of the case rather than on opinions presented, and must be assessed in the context of all other known information. Their publication acts as a useful stimulus to further reports of similar events which may have occurred. An example with cimetidine was a report in the Lancet of mental confusion (Grimson 1977). This triggered off a number of other reports (Delaney, Ravey 1977, Menzies-Gow 1977, Robinson, Mulligan 1977) and more scientific appraisal of cimetidine's possible effects on the central nervous system (Nuotto et al 1980, Schentag et al 1979).

Post marking surveillance (PMS)

The study and testing of new drugs does not end when they reach the market but goes into a new phase. In order to improve on the necessarily haphazard process of awaiting spontaneously reported adverse effects, a number of methods

of post marketing surveillance of cimetidine are being assessed. Their advantage over clinical trials is that they involve a larger population of patients who are systematically monitored for drug safety rather than efficacy.

The U.K. cimetidine PMS scheme is the largest ever undertaken in that country and uses entirely new methods (Colin-Jones, Langman, Lawson, Vessey 1980). It has registered 10,000 patients, with a control population of similar size, at four centres and will monitor adverse events serious enough to lead to hospital attendance, withdrawal of treatment and any patient dies. No results are yet available from this study.

The U.S.A. surveillance program involves 10,000 outpatients treated with cimetidine. These were recruited by 1000 doctors - a mixture of family practitioners, internists and gastroenterologists who each prospectively provided data on 10 patients treated by them during a 3 month period. Interim results using the information available at the end of that three months, have been published (Gifford et al 1980). The nature and incidence of side effects reported seem very similar to those found in pre-marketing clinical studies. The absence of a control group limits the certainty with which events can be attributed to cimetidine, but does provide a reasonable way of assessing the incidence and timing of uncommon side effects. For example, gynaecomastia was reported 18 times and was the most common late onset adverse effect. The timing was reported in 11 cases. In only one 80 year old male was the onset in less than 8 weeks, in another

6 between 2 and 6 months and in 4 patients the onset was after 6 months of treatment.

One of the purposes of the surveillance programme was to search for important events that might not be attributed to cimetidine by the prescribing physician. Therefore all hospitalisations, consultations, changes in associated conditions or new conditions which occurred during or after therapy were recorded. Careful examination of these revealed no events which were judged to be additional adverse reactions not previously observed.

Sixty five deaths occurred during the surveillance period. These cases were given special attention and as far as could be assessed, none were due to cimetidine therapy. Most deaths were in the elderly. Nineteen were related to pre-existing tumours, and sixteen to pre-existing cardiovascular disease. Other deaths were due to pulmonary embolus, vehicle accident, chronic pulmonary disease, complications of gastrointestinal disease or occurred after stopping treatment.

The longer term results are necessary before conclusions on the value of these expensive exercises can be drawn. I have some doubts about their worth. The absence of a control group (as in the U.S.A. study) is a handicap which will prevent the detection of any subtle effects on the incidence of common diseases. Despite the size of the American study it is only two or three times the number of patients studied carefully in the controlled trials and is unlikely to reveal the 'one in a million' unusual event that will probably be noted during clinical use.

Specific safety issues

Some specific topics which have caused controversy or are recurrent themes are worth discussing in more detail.

1. Bone marrow toxicity
2. Hepatotoxicity
3. Central nervous system
4. Cardiovascular system
5. Endocrine effects
6. Immunological effects
7. Gastrin, acid secretion and intrinsic factor
8. Gastric carcinoma
9. Drug interactions

1. Bone Marrow toxicity

The anxiety provoked by the occurrence of granulocytopenia with metiamide was only partially relieved by the toxicological studies in animals with cimetidine. These did not show the granulocytopenia or concentration of ^3H labelled material in bone marrow which had been found in equivalent studies with metiamide. The thiourea group in metiamide, known to be associated with blood dyscrasia in other drugs had, of course, been replaced by a cyanoguanidine residue in cimetidine.

The most important evidence that it was the thiourea group responsible for granulocytopenia came from clinical studies. Three patients recovering from agranulocytosis attributed to metiamide continued to improve when their treatment was changed to cimetidine (Burland et al 1975b, Fleischer, Samloff 1977). As mentioned above, in none of the short term clinical trials or surveillance studies involving many thousands of patients, had clinically significant haematological abnormalities been

found.

However, a number of cases of non-fatal granulocytopenia have been reported since general release of cimetidine. Over 100 cases worldwide had been reported to Smith Kline and French up to 1980 (Davis et al 1980). In all but one of these, other factors including serious illness, irradiation and concomitant drugs were associated. Evidence for a simple cause and effect relationship has not been conclusive. Whether cimetidine could have some potentiating effect on other bone marrow toxins remains to be clarified, although the presence of H_2 -receptors on marrow stem cells has been suggested as a mechanism for this hypothesis (Byron 1980).

It is encouraging the cimetidine associated granulocytopenia has rarely been reported in outpatients with uncomplicated peptic ulcer disease (Freston 1979). An anecdote recounted by Flind illustrates such a case where at first sight attribution of granulocytopenia to cimetidine treatment appeared clear (Flind et al 1980). A 54 year old man being treated for duodenal ulcer developed aphthous mouth ulcers and a check blood count showed a neutrophil count of $600 \times 10^6/l$ with a total white cell count of $2040 \times 10^6/l$. Although the counts rose on instructing the patient to stop treatment, it was later discovered that he had taken further cimetidine tablets during that week. When his ulcer dyspepsia recurred 3 months later, cimetidine was reintroduced with no effect on the white cell count and no recurrence of mouth ulcers. In retrospect, both might have been the result of a viral infection.

Reports of haematological side effects other than isolated granulocytopenia have been rare. Thrombocytopenia has been reported in a handful of patients, in whom factors other than cimetidine were also present (Isaacs 1980, McDaniel, Stein 1979). Autoimmune haemolytic anaemia (Rotoli et al 1979) and aplastic anaemia (Chang, Morrison 1979) have occurred in isolated patients receiving cimetidine. The latter patient died and although a temporal relationship with cimetidine was evident, the authors cautiously noted "given the widespread use of cimetidine and the known occurrence of aplastic anaemia of unknown cause, inevitably such a patient will receive cimetidine by chance".

2. Hepatotoxicity

The clinical trials reports outlined above clearly indicated that occasional significant (but usually mild) elevations of transaminases and bilirubin occurred during cimetidine (and placebo) therapy.

Individual case reports have confirmed the impression that hepatic injury may occur as a rare event. One patient showed elevations of SGOT, ALP and bilirubin which fell on discontinuing cimetidine only to recur on each of two separate rechallenges with the drug. In this instance a hypersensitivity reaction rather than direct toxicity was suspected (Villeneuve, Warner 1979). A few cases of reversible cholestasis in children (Lilly et al 1978) and an adult (Züchner 1977) have also occurred.

A number of patients with fulminant hepatic failure have been treated with cimetidine without evidence of drug associated deterioration when compared with controls

(McDougall et al 1977).

3. Central nervous system

Clinical trials did not reveal any important cimetidine related effects in the central nervous system (CNS). Since marketing, a small but appreciable number of patients have developed mental symptoms while taking cimetidine. An assortment of effects occurred including confusion, agitation, lethargy, restlessness, disorientation, hallucination, slurred speech, focal twitching and seizures (Delaney, Ravey 1977, Grimson 1977, Menzies-Gow, 1977).

Review of the Smith, Kline & French worldwide data in late 1978 found 57 reports and of the 44 providing enough information, 35 patients were over the age of 65 and had serious concomitant illness or other therapy to account for their abnormal mental state (Flind et al 1980). In many of these cases the impaired mental state improved when cimetidine was withdrawn. A comment on "reversible confusional states, usually in the elderly or very ill" was included in the U.K. drug data sheet.

The possible mechanisms by which cimetidine might influence brain functioning are of interest. Histamine H_2 receptors are present in the brain but their physiological role remains unclear (Burkard 1978, Sastry, Phillis 1976). Histamine may have a neurotransmitter role, exerting a depressant effect on the reticular activity system of cerebral cortex in rats, but H_1 -receptors as well as H_2 -receptors are involved.

Significant neurotoxicity of cimetidine had not been expected since initial autoradiographic studies in rats showed no central nervous uptake. However under certain

circumstances, for example in uraemic patients, the permeability of the blood-brain barrier is altered. In a recent prospective study, 6 of 36 (17%) critically ill patients given cimetidine developed changes in mental state which were attributed to cimetidine (Schentag et al 1979). A correlation was found between raised 'trough' concentrations of the drug in serum (exceeding 1.25 $\mu\text{g/ml}$) and the occurrence of mental changes. Patients with renal failure were particularly at risk and in the five patients where it was examined, cimetidine was found in the cerebrospinal fluid. This finding has been confirmed in three other patients with renal failure and cimetidine associated twitching or convulsions (Edmonds et al 1979). Development of unexplained CNS abnormalities in a patient taking cimetidine should be an indication to stop the drug or substantially reduce the dose.

The importance of concomitant illness (and presumably a 'leaky' blood-brain barrier) is confirmed by the fact that in several healthy patients massive cimetidine overdosage with blood levels up to 57 $\mu\text{g/ml}$ was associated with no apparent change in mental state (Flind, Rowley-Jones 1979). In healthy medical students sophisticated psychomotor and psychological testing was carried out after single 400mg doses of cimetidine (or placebo) or 1.6g daily for 2 days (Nuotto et al 1980). The tests had been found sensitive enough to detect drug induced psychomotor impairment after diazepam 10mg or alcohol 0.8-1.0g/kg, but no cimetidine related changes were found. The psychological testing (using visual analogue scales) suggested weak but positive changes in mood with

subjects feeling more kind and gay after cimetidine than placebo!

4. Cardiovascular system

The presence of H_2 receptors in vitro in peripheral blood vessels and the heart, and vasodilatory effects of large doses of cimetidine in experimental animals was mentioned earlier in this chapter. Recent data have shown a dose dependent increase in pulse rate in healthy volunteers after undiluted intravenous bolus injections of 200mg, 400mg and 800mg cimetidine intravenously. The changes (statistically significant only at 2 minutes after 800mg compared with controls) were not accompanied by changes in blood pressure and returned to basal levels within 20 minutes (Smith Kline & French data file 1980).

Infusion of histamine and also the selective H_2 agonist impromidine causes dose dependent vasodilatation, increase in heart rate and reduction in blood pressure in most species including man (Hunt et al 1980). These are a summation of direct responses of heart and blood vessels and secondary reflexes (e.g. tachycardia following fall in blood pressure or vasodilatation).

H_1 antagonists predominantly act to reduce the early effects of histamine on blood pressure and heart rate while H_2 antagonists affect the later changes in diastolic blood pressure and heart rate. The effects of impromidine are competitively inhibited by cimetidine and confirm that H_2 receptors in peripheral blood vessels mediate vasodilatation and those in the heart mediate positive inotropic and chronotropic influences (Boyce et al 1980).

Clinical experimentation has not yet shown a clear cut physiological role (as opposed to pharmacological) for H₂ receptors in the cardiovascular system. An infusion of 300mg cimetidine in 10 healthy volunteers did not affect heart rate, sinus node recovery time or sino-atrial conduction (Engel, Luck 1979). Cardiac output, heart rate and blood pressure were measured in 10 intensive care unit patients on intermittent positive pressure ventilation given 400mg of cimetidine by rapid intravenous injection. No changes were seen in 9 of the patients, while one (who required positive end expiratory pressure ventilation) showed a 30% reduction in blood pressure within 5 minutes of the injection and this persisted for an hour (Samuel, Dundee 1980). The reason for this unusual response is unknown.

Cimetidine has been widely used intravenously and adverse cardiovascular effects are rare. A small number of cases of bradycardia with or without hypotension, hypotension alone, other arrhythmias and cardiac arrest have been reported (Cohen et al 1979, Jeffreys, Vale 1978, Shaw et al 1980). It is well documented data of this sort which are perhaps the most important in assessing the safety of cimetidine in a variety of clinical settings. To date it seems that the cardiovascular problems that have occurred were in elderly patients, those with renal impairment or those who have just received large intravenous boluses (400mg or more) of cimetidine. The most recent recommendations therefore suggest that when intravenous cimetidine is necessary, it should be diluted and given as an infusion during 15-30 minutes rather

than as a bolus injection, particularly in the elderly or patients with known cardiovascular disease.

5. Endocrine effects

An assortment of endocrine abnormalities have been found in association with cimetidine treatment. These include gynaecomastia, elevations of serum prolactin, galactorrhoea, impotence, changes in sperm count and reductions in blood levels of parathyroid hormone. These effects are not necessarily interrelated and their relationship to the antiandrogenic effects of cimetidine found in animal experimentation remains uncertain.

Gynaecomastia is the commonest clinically apparent side effect. Its incidence varies with the age of the patient and the duration of treatment. In the post-marketing surveillance studies (see above) it was reported 18 times in 10,000 patients (0.18%) and usually occurred in elderly males after 2-6 months of treatment (Gifford et al 1980). Other authors confirm this predilection for the elderly (Kruss, Littman 1978) and the delayed onset. The first patients in whom this was noted suffered from the Zollinger-Ellison syndrome which is itself occasionally associated with gynaecomastia (Hall 1976). Since then many more cases have been reported, most with no evidence of the Zollinger-Ellison syndrome. There may be a relationship with the dose of cimetidine: 5 of 25 male patients treated with 1.6g daily developed symptoms of breast swelling and tenderness of one or both nipples after 4-9 months of treatment. However in all cases gynaecomastia subsided spontaneously despite continued treatment (Spence, Celestin 1979).

Our experience within the Royal Adelaide Hospital is very similar. At least 5 patients, all elderly men, have developed transient breast swelling and tenderness which they thought was a minor nuisance for which they did not wish to stop treatment (Hetzel, unpublished observations). The only hazard is that doctors who are unaware of the drug association may proceed to unnecessary excision biopsy.

The cause of the breast changes is uncertain. Other clinical effects (such as impotence, reduced libido, changes in body hair etc) to suggest feminisation have not been found in these patients although one patient noted cessation of nocturia and relief of symptoms related to benign prostatic hypertrophy (Hetzel, unpublished observations). Plasma levels of testosterone and gonadotrophins have usually been normal when measured. Despite the other evidence relating prolactin release to intravenous cimetidine (see below) most patients with gynaecomastia have had normal prolactin levels, and this is probably not the mechanism. If gynaecomastia is the result of an anti-androgenic effect of cimetidine, then it is likely to be a local alteration of the oestrogen/testosterone ratio at the androgenic receptor (Spence, Celestin 1979). Cimetidine has certainly been shown to occupy androgen receptors in mouse kidney preparations but to have no affinity for rat uterine oestradiol receptors (Funder, Mercer 1979).

It has been demonstrated that an intravenous bolus injection of cimetidine 200mg or more will cause an immediate, transient three-fold rise in serum prolactin levels in normal men (Carlson, Ippoliti 1977, Daubresse et al 1978). However when cimetidine is given orally at conventional doses an

association with elevated prolactin levels has not been established. A case report suggested an association (Delle Fave et al 1977) but other authors have been unable to demonstrate changes in prolactin production or release (Delitala et al 1978, Majumdar et al 1978, Spiegel et al 1978). The effect on prolactin is probably related to the cimetidine molecule itself rather than to H₂ blockade since other H₂ antagonists (oxmetadine and ranitidine) have failed to show it (Sharpe et al 1980).

Reports of sexual dysfunction in men receiving cimetidine raised controversy (Peden et al 1979, Wolfe 1979) but evidence for an effect of the drug on hypothalamic-pituitary-gonadal function is conflicting (Barber, Hoare 1979, Bohnet et al 1978, Delitala et al 1978). Impotence or loss of libido are not uncommon in the general population, increasing from 1% at age 30 to about 18% at 60 years (Kinsey et al 1948) and there is no evidence that these figures are increased in patients on cimetidine.

One group of workers reported reduced sperm counts in 7 men after treatment with cimetidine for 9 weeks (Van Thiel et al 1979). However the counts remained well within the normal range. As sperm counts vary considerably from day to day in normal men and no control group was studied, the significance of the results cannot be assessed.

There have been conflicting reports on the possible value of cimetidine in treating primary hyperparathyroidism and that secondary to chronic renal failure. Two groups of workers found that raised immunoreactive parathyroid hormone (PTH) levels returned to normal or showed substantial

reductions during cimetidine treatment (Jacob et al 1980, Sherwood et al 1980) and an inhibition of PTH synthesis or release by cimetidine was suggested. Another similar study in primary hyperparathyroidism failed to show this effect (Ljunghall et al 1980). Even when changes in PTH have been demonstrated, changes in clinical features or serum calcium and phosphate have been variable or absent. The significance of these findings in the small numbers of patients involved cannot be clearly evaluated.

6. Immunological effects.

The classical work of Dale and others firmly established a role for histamine as a mediator of immediate type hypersensitivity and inflammation. Histamine, largely via stimulation of H₁-receptors, can contract smooth muscle, increase vascular permeability, dilate arterioles and increase nasal and lacrimal secretion.

More recently, receptors for histamine have been identified on T lymphocytes, mast cells, basophils, eosinophils and neutrophils and stimulation of these by histamine produces inhibition of a number of components of the inflammatory response (Vickers et al 1980). This histamine seems to have a dual role as both a "pro-inflammatory" agent and also a regulator of cellular and humoral immune responses. Immune responses reported to be inhibited in vitro by histamine include antigen and mitogen induced T lymphocyte proliferation, lymphokine production, T lymphocyte mediated cytotoxicity, lysosomal enzyme release and IgE mediated histamine release.

Many workers have shown in vitro that cimetidine can block some of these regulatory actions and have concluded that H₂-receptors are the mediators of these effects. However, few have attempted to carry out dose response studies and hence obtain evidence of true competitive inhibition. Studies using specific H₂-receptor agonists (e.g. dimaprit) and chemically related compounds lacking H₂-receptor agonists activity (e.g. nor-dimaprit) indicate that the receptor at which histamine acts to regulate immunological responses is not identical to the histamine H₂-receptor as defined by Black in 1972 (Vickers et al 1980).

Regardless of the precise nature of the receptor involved, the fact that the H₂-receptor antagonists can block some of the immune regulatory actions of histamine has led to expressions of concern that administration of cimetidine to man might allow immunological response to be accentuated.

Immediate cutaneous hypersensitivity in man does not appear to be affected by cimetidine (Smith et al 1979, Wolfe et al 1979) and far from exacerbating bronchospasm, cimetidine may augment the beneficial effects of H₁ receptor antagonists (Eider et al 1978). Measurements of serum immunoglobulins, various auto-antibodies and leucocyte migration inhibition made before and after some weeks or months cimetidine treatment in ulcer patients have shown no change (De Pauw et al 1977, McGregor et al 1977). Phytohaemagglutinin (PHA) induced lymphocyte proliferation showed slight increases in 8 of 9 duodenal ulcer patients after 2 weeks'

treatment with cimetidine 800mg daily (Robertson et al 1979). However no control subjects were studied and the timing of blood sampling relative to the last dose of cimetidine was unspecified. If the serum contained appreciable quantities of cimetidine then a direct in vitro blockade of histamine mediated inhibition might explain the results.

The difficulty of interpreting some results is well illustrated by the paper of Avella et al (1978) who looked at delayed cutaneous reactions to PPD, Candida, Trichophyton and SK/SD in 16 duodenal ulcer patients before and after 6 weeks cimetidine or placebo treatment. A significant increase in erythema and induration responses was observed after cimetidine, while after placebo there was a tendency for responses to decrease. However, their "pre-treatment" baseline was read on day 1 and day 2 of cimetidine treatment and the second test was performed and read 2 and 3 days after the last dose of cimetidine. Thus it is possible to interpret the data presented in a completely opposite way. It was also pointed out that the increased induration seen at 48 hours was only seen with the SK/SD antigen (Jones 1978). Alternative mechanisms, other than immunological effects, for any change in skin reactions which occurred also have to be considered. Human skin blood vessels have H₂-receptors which can mediate vascular effects and skin contains the histamine degrading enzyme N-methyltransferase. Therefore vascular events and effects on histamine metabolism should be considered.

Wolfe et al also examined delayed hypersensitivity skin responses in 6 patients and 6 controls with allergic rhinitis treated for 5 days with cimetidine or placebo. An increased 48 hour induration reaction to SK/SD occurred in both groups suggesting that the first test had primed all patients (Wolfe et al 1979).

Preliminary results suggest that cimetidine may reverse previously negative skin tests of delayed hypersensitivity in patients with Crohn's disease or chronic mucocutaneous candidiasis (Bicks, Rosenberg 1980; Jorizzo et al 1980). Further controlled studies are needed before definite conclusions can be drawn on the effects of cimetidine on cell mediated immunity.

Results of the clinical use of cimetidine in renal transplant patients suggest that the drug has no influence on graft function and does not cause an increase in either the number or severity of rejection episodes (Charpentier, Fries 1978, Doherty, McGeown 1978, Jones et al 1978). The widespread use of cimetidine with few reports suggesting clinically apparent changes in immune responses or atopy is reassuring. Histamine may play a subtle regulatory role in immunity but H₂ blockade to date has not been associated with adverse immune reactions.

7. Gastrin, gastric secretion and intrinsic factor

Cimetidine treatment enhances postprandial gastrin release acutely by reducing antral acidity. In patients with duodenal ulcer treatment with maintenance doses of cimetidine for 6 months progressively increases this response (Forrest et al

1979, Hansky, Stern et al 1979) but gastrin release rapidly returns to pretreatment levels after treatment is stopped.

Reports of ulcer recurrence with perforation or bleeding soon after stopping raised the spectre that H₂-receptor antagonists might cause a subsequent increase in duodenal ulcer (Saunders, Wormsley 1977). Hypergastrinaemia, perhaps causing parietal cell hyperplasia and "rebound" of gastric acid secretion after treatment was invoked as a possible mechanism.

So far the evidence from pharmacological and clinical studies suggests that neither "rebound hypersecretion" nor aggravation of ulcer disease occur when cimetidine treatment is stopped. Review of 5 studies, including our own work, which made controlled observations on gastric secretion, showed no significant change after cimetidine in three, an increase in basal output after 2 weeks (but not 4 or 6 weeks) in one, and a statistically significant decrease in pentagastrin stimulated (but not meal stimulated) secretion in the other (Winship 1978).

An alternative approach designed to detect changes in parietal cell activity after cimetidine treatment also yielded negative results. The dose response curve relating gastric acid output to increasing submaximal doses of pentagastrin showed no changes after courses of cimetidine lasting up to 16 weeks (Aadland, Berstad 1979, Holden et al 1978).

The question of aggravation of ulcer disease after cimetidine treatment has been stopped has of course been covered in chapter VIII.

In addition to its capacity to inhibit acid secretion, cimetidine infusion acutely reduces parietal cell secretion of intrinsic factor (IF). The extent of this inhibition is controversial. Fielding et al found that cimetidine reduced basal and pentagastrin stimulated IF output in duodenal ulcer patients (Fielding et al 1978). Binder found no effect on basal IF output but abolition of betazole stimulated IF output in normal volunteers (Binder, Donaldson 1978). Burland et al found no significant effect of cimetidine infusion on pentagastrin stimulated IF release (Burland et al 1977). Sharpe et al found cimetidine infusion reduced peak and total IF output in response to either impromidine or pentagastrin, but the IF concentration was unchanged (Sharpe et al 1980). These responses were unchanged by additional administration of cimetidine 2g/day orally for 1 week. Secretion of intrinsic factor measured 12 hours after completing a 12 week course of cimetidine had returned to pretreatment levels in duodenal ulcer patients (Epstein et al 1978).

Normal IF secretion has been estimated to be 100 times more than is necessary to allow normal absorption of vitamin B₁₂. In view of this and the fact that long term maintenance doses of cimetidine produce only transient cyclic inhibition of IF secretion, the changes in IF release seem unlikely to be of clinical significance. No adverse effects involving vitamin B₁₂ have yet been reported. A recent paper indicated that cimetidine 300mg given 60-90 minutes before measurement of oral B₁₂ absorption by Schilling test produced a decrease if the B₁₂ was bound

to chicken serum, but not if given in crystalline form (Steinberg et al 1980). The biological significance of this observation is uncertain but the effect of long term cimetidine administration on vitamin B₁₂ stores needs further evaluation.

8. Gastric carcinoma

Cimetidine and the subject of gastric cancer are interrelated in a number of ways.

The distinction of benign and malignant gastric ulcers is sometimes difficult, and several cautionary reports document relief of symptoms and healing of a gastric ulcer with cimetidine treatment, followed at varying intervals by the discovery of gastric adenocarcinoma or lymphoma in the same patient (Taylor, Lovell, Menzies-Gow et al 1978). In many cases a short delay before accurate diagnosis and inadequate initial investigation make it clear that the problem is one of mistaken diagnosis. In other case reports more prolonged delay in diagnosis has occurred (Hecker, Horowitz 1979) sometimes after initial gastroscopy and biopsy had suggested benign ulcer (Taylor, Lee et al 1979). The possibility that cimetidine might have promoted tumour growth was raised (Elder et al 1979).

A flurry of correspondence in the Lancet followed this report which described the discovery of gastric cancer in 3 patients who had been receiving cimetidine for 10 weeks to 11 months. The authors expressed appropriate concern for the need to establish the correct diagnosis in patients with

gastric ulcer. In the same article they speculated that cimetidine might undergo nitrosation in vivo to form nitrosocimetidine which might have the carcinogenic properties found in other nitrosoguanidines. This juxtaposition of clinical anecdote with rather tenuous speculation generated considerable heat; there were further supporting case reports (Reed et al 1979, Taylor, Lee et al 1979) and rebuttals of their hypothesis (Hill 1979, Roe 1979, Ruddell 1979).

The nitrosamines are a group of compounds some of which have been shown to be carcinogenic in animals but their relevance to carcinogenesis in man remains uncertain after 30 years of investigation. We all ingest, inhale, form and detoxify nitrosamines each day. They are formed by interaction of nitrates and some amine compounds which are available in foods such as preserved meats and fish. Cimetidine, in addition to being "nitrosatable" itself, might in theory promote intragastric bacterial nitrosation by raising intragastric pH and allowing microbial colonization of the stomach.

In practice, there is little available to indicate whether or not nitrosocimetidine is formed in vivo, and even the influence of cimetidine on the gastric microflora is variable. Fasting bacterial counts rose after one month's cimetidine (Ruddell et al 1980) but healthy subjects on a normal diet rarely showed bacterial overgrowth or elevations of gastric juice nitrite (Muscroft et al 1981). Long term experiments with high dose cimetidine treatment in rats and dogs have produced no evidence of tumours (Crean et al 1979).

The nitrosation of foodstuffs and drugs is of great interest as many other drugs (e.g. chlordiazepoxide, tetracycline, chlorpheniramine, chlorpromazine) are nitrosatable and may be prescribed for long periods of time. It seems premature to single out cimetidine as a gastric carcinogen.

Drug interactions

Interaction studies in rats with a large number of therapeutic drugs showed no effect of these on the acute intravenous toxicity of cimetidine or vice versa (Brimblecombe et al 1978). However in 1978 it was observed coincidentally during studies of gastric mucosal clearance that cimetidine caused an increase in plasma levels of aminopyrine in rats (Puurunen, Pelkonen 1979) and in man case reports suggested that cimetidine, when prescribed for patients receiving a stable dose of warfarin, caused a 20-50% increase in prothrombin time (Flind 1978, Hetzel et al 1979, Wallin et al 1979). Haemorrhagic complications have been reported (Silver, Bell 1979).

Further investigation found that cimetidine inhibited the hepatic microsomal oxidation system in vitro and thus reduced clearance of drugs metabolised by these enzymes (Puurunen, Pelkonen 1979, Serlin et al 1979).

The following report of one of our own cases illustrated the interaction of varying doses of cimetidine with warfarin and examined the mechanism by measuring plasma levels of warfarin as well as prothrombin ratio (Hetzel, Birkett, Miners 1979).

A 45 year old woman presented in December 1978, with epigastric pain and nausea after the introduction of oral prednisolone for a severe attack of bronchial asthma. Endoscopy showed two large ulcers in the duodenal cap. She had been

chronically anticoagulated with warfarin since mitral and aortic valve replacement in 1976. This anticoagulation had been stable but cautious since a gastrointestinal bleed in 1977.

Cimetidine 200mg three times a day and 400mg at night was added to her usual medication which was continued unchanged (warfarin 7mg daily, digoxin 0.25mg daily, frusemide 40mg daily, aerosol beclomethasone and salbutamol). The changes in prothrombin ratio are shown in figure 10.1. To confirm that the rise in prothrombin ratio (PTR) was not due to improved patient compliance with the warfarin, cimetidine was twice stopped and the PTR fell both times. Endoscopy confirmed ulcer healing after 7 weeks' treatment, and the cimetidine was reduced to a maintenance dose of 400mg at night. The patient remained symptom-free until oral prednisolone 10mg daily was introduced in May, 1979. Because of dyspepsia the cimetidine dose was then increased to 400mg twice daily.

During the 7 months' follow-up blood samples were taken and deep frozen for subsequent measurement of warfarin concentration by specific high performance liquid chromatography (Bjornsson et al 1977). Results are shown in figure 10.1, and mean values before and during the different dose regimens of cimetidine are shown in table 10.9. Analysis of variance confirms that different doses of cimetidine produced statistically significant changes in PTR and serum warfarin.

These results suggested that doses of cimetidine 800-1000mg daily increased the PTR by 40-50% while 400mg at night produced only about 10% increase. The rise in total serum warfarin confirmed the study of Serlin et al in normal volunteers given subtherapeutic doses of warfarin which demonstrated that cimetidine

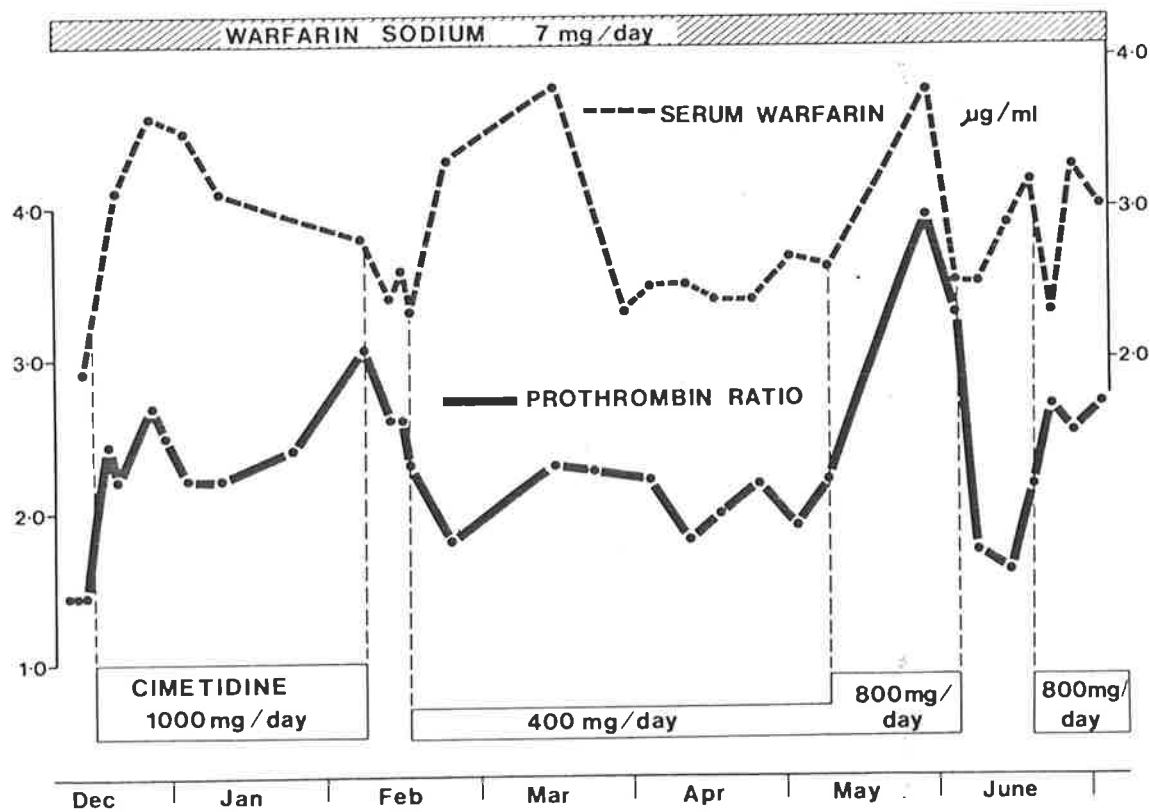


FIGURE 10.1 Prothrombin ratio and serum warfarin concentrations in patient A.T. on and off cimetidine treatment.

Table 10.9 Mean values of prothrombin ratio (PTR) and serum warfarin concentration in a single patient during prolonged treatment with varying doses of cimetidine. The number of observations are shown in parenthesis.

Cimetidine dose (mg/day)	PTR	Serum warfarin ($\mu\text{g/ml}$)
Before cimetidine	1.5 (2)	1.9 (1)
1000	2.8 (8)	3.2 (5)
400	2.1 (9)	2.7 (9)
800	3.0 (5)	3.0 (5)
Cimetidine stopped	2.1 (6)	2.6 (6)

inhibits the hepatic metabolism of warfarin.

Because initial anticoagulation in this patient was suboptimal no change in warfarin dose was necessary. However, the changes were large enough to make it important for physicians to monitor the effects of oral anticoagulants and be prepared to reduce the dose when cimetidine is introduced.

Other drugs which are metabolised by the hepatic microsomal oxidation system may be influenced by cimetidine but the clinical significance of the interaction will depend on the specific properties of the drug concerned. For example the same mechanism is thought to account for the observation that cimetidine increases the elimination half life of diazepam (Klotz, Reimann 1980) and chlordiazepoxide (Desmond et al 1980). In contrast no interaction with lorazepam or oxazepam has been demonstrated (Patwardhan et al 1980). These two drugs, which are also benzodiazepines, are metabolised by glucuronidation not oxidation. The interaction with diazepam and chlordiazepoxide has not been reported to cause any significant clinical problem although this possibility should be borne in mind.

Phenytoin, a commonly used anticonvulsant with a narrow therapeutic index is also metabolised by hepatic microsomal oxidation. We therefore investigated the effect of cimetidine on steady state plasma phenytoin concentrations in patients with longstanding epilepsy (Hetzel, Bochner et al 1981).

Serum phenytoin concentrations were measured in four epileptic volunteers (table 10.10 and figure 10.2) by EMIT^(R) (Syva, Palo Alto, California) on 3 to 5 separate days in the week preceding cimetidine administration, on 5 or 6 days during cimetidine

administration and up to 6 days afterwards. Blood samples were taken at 7 a.m., before breakfast, in the three inpatients and at 4.30 p.m. each day in the single outpatient (case 4). Cimetidine 200mg tds with meals and 400mg nocte was given for six days. Dosage of all other drugs was unchanged for the 2 weeks before and during the study. A 24-hour urine collection in each patient was obtained before and during cimetidine administration for measurement of free phenytoin and its main metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH). Urinary free phenytoin and total p-HPPH were measured by gas chromatography and mass spectrometry after preparation by the method of Sawchuk and Cartier (1980). Liver function values were normal in all patients. Renal function was normal in all except one patient, case 4, who had a steady serum creatinine of 0.19 mmol/l (normal range 0.05 to 0.12 mmol/l). The unpaired t statistic was used to analyse changes in serum phenytoin concentrations for individual patients, and the paired t statistic to compare urinary excretion of phenytoin and p-HPPH, before and during cimetidine treatment.

Cimetidine treatment resulted in statistically significant elevations of plasma phenytoin in each patient (table 10.10 and figure 10.2). Mean twenty-four urinary output of p-HPPH and of phenytoin increased from 122.5 to 201.5mg and from 6.8 to 12.0 mg respectively. One patient (case 1) developed symptoms consistent with mild phenytoin intoxication during cimetidine administration, which disappeared when cimetidine was stopped. When cimetidine was withdrawn, plasma levels of phenytoin tended to fall towards the values found before cimetidine administration (table 10.10 and figure 10.2).

Table 10.10 Patients studied and mean plasma phenytoin concentrations (\pm SD) before, during and after cimetidine (C).

Patient	Age (years)	Phenytoin dose (mg/day)	Other drugs	Mean plasma phenytoin, $\mu\text{mol/l}$ +		
				before C	during C	after C
1 (G.F.)	27	400	Carbamazepine	74.7 \pm 5.8	99.2 \pm 6.3*	89.4 \pm 11.0
2 (P.C.)	20	260	Valproate, primidone	63.8 \pm 3.1	82.6 \pm 6.7*	74.5 \pm 2.1
3 (I.R.)	33	300	Clonazepam, primidone	45.4 \pm 3.9	52.7 \pm 4.5*	48.0 \pm 0.7
4 (W.C.)	63	300	Phenobarbitone	33.8 \pm 3.8	40.3 \pm 3.5*	36.0 \pm 0.0

* $p < 0.02$ compared with pre-cimetidine treatment level

+ Therapeutic range = 40-80 $\mu\text{mol/l}$

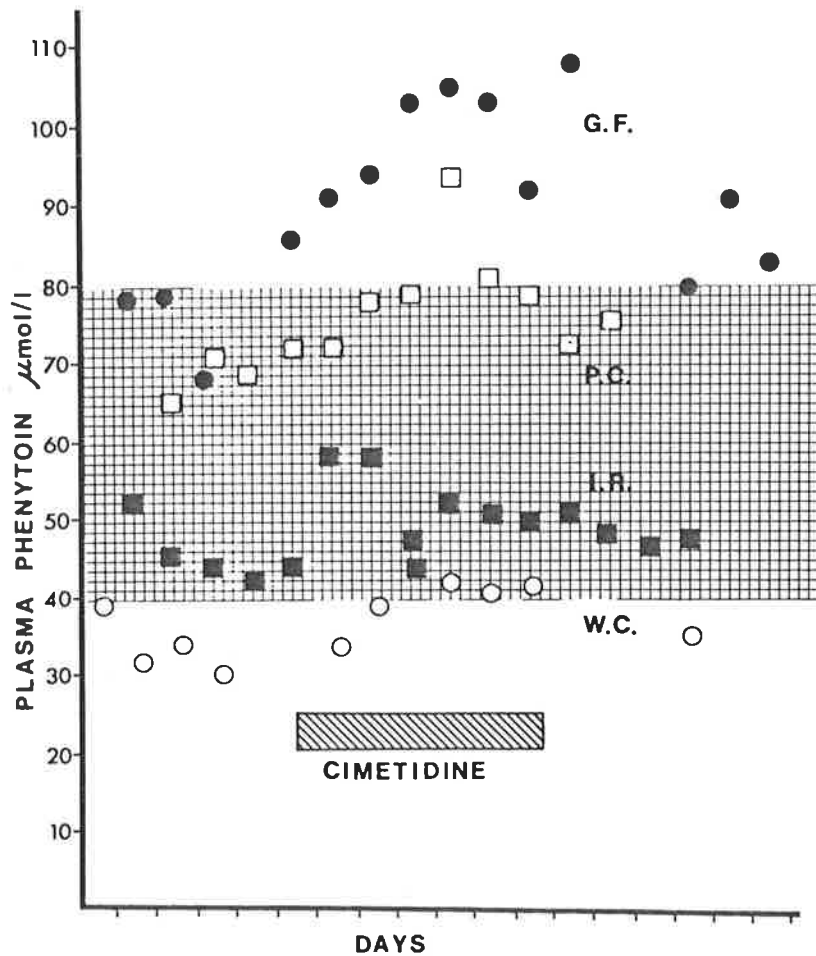


FIGURE 10.2 Plasma phenytoin concentrations in each of the four patients before, during and after the addition of cimetidine for 6 days. The shaded area indicates the therapeutic range.

The addition of a standard dose of cimetidine was associated with a 13-33% increase in mean plasma phenytoin levels. This effect was of clinical importance in one patient (case 1) who became mildly clinically intoxicated. A rise in plasma phenytoin concentration was seen in all patients within 48 hours of beginning cimetidine. Two patients (cases 3 and 4) appeared to achieve a new steady state of plasma phenytoin concentration after five days of cimetidine administration. A clear plateau was not obtained by the time of cimetidine withdrawal in patient 1 and 2 whose plasma phenytoin concentrations were in the higher range associated with changing elimination kinetics. In these patients, continued cimetidine administration might have resulted in even higher phenytoin levels.

Our results do not explain the mechanism of the interaction. An unexpected rise in urinary p-HPPH levels occurred in each patient and makes it unlikely that cimetidine inhibited metabolism of phenytoin to p-HPPH. It is possible that cimetidine blocked one of the other metabolic pathways responsible for phenytoin degradation. The rise in free urinary phenytoin would be consistent with this hypothesis. An alternative, but less likely, possibility is that cimetidine caused an increase in phenytoin bioavailability.

Cimetidine and phenytoin are frequently prescribed and concurrent administration will therefore occur in some patients. Our findings show that caution is necessary when adding cimetidine to phenytoin treatment, especially when plasma concentrations are already in the upper therapeutic range.

An interaction with cimetidine resulting in increased drug concentrations has now been reported for antipyrine (phenazone)

(Serlin et al 1979; Klotz, Reimann 1980), theophylline (Weinberger et al 1981) and also propranolol (Feely et al 1981, Heagerty et al 1981). The latter is interesting in that a further mechanism may be involved. Propranolol is efficiently extracted by the liver and after intravenous administration liver blood flow is the main factor determining its clearance. This high hepatic extraction is responsible for substantial "first pass" metabolism of propranolol after oral administration. Feely et al found that cimetidine in a single dose acutely reduced fasting liver blood flow by 25%. Cimetidine 1.2 g/day for 7 days reduced the flow by 33%. In addition to reducing the clearance of intravenous propranolol by decreasing hepatic blood flow, cimetidine also inhibited the metabolism of oral propranolol and thereby further reduced elimination. Pulse rates at rest were markedly lower after propranolol plus cimetidine than after propranolol alone. These observations have important implications for patients with altered liver and gastrointestinal blood flow, and when cimetidine is used with drugs such as morphine and lignocaine whose hepatic elimination depends on liver blood flow.

The inhibition of hepatic microsomal oxidation by cimetidine is not a consequence of H_2 -receptor blockade. Comparison of cimetidine with ranitidine, a potent new H_2 -receptor antagonist, has shown that the latter has no effect on aminopyrine or antipyrine half life or clearance (Henry et al 1980). In ranitidine a furan ring replaces the imidazole compounds ring present in cimetidine. Many other imidazole compounds are well known as inhibitors of microsomal oxidation (Wilkinson et al 1973) and it seems likely that it is this particular part of the chemical structure of cimetidine which is responsible.

Ranitidine and other H₂-receptor antagonists which lack an imidazole ring have an advantage over cimetidine in being free of this effect.

Conclusions

The introduction of a drug with a completely new pharmacological action into everyday medicine demands extensive evidence of its safety. Initial experimental and clinical studies revealed the weak anti-androgenic effects of cimetidine, but few other side effects. Minor untoward effects such as headache, tiredness and rash in patients receiving cimetidine during short term controlled trials in several thousand ulcer patients were just as frequent in those who received placebo. Small increases in serum creatinine were common but of no clinical significance. Longer term treatment gave rise to gynaecomastia in a small proportion of men and abnormalities of liver function were occasionally found. It was rarely necessary to stop cimetidine treatment because of side effects and in most patients the expected benefits of its use were believed to outweigh the small risk of side effects.

In the five years since its release for clinical use in November 1976, an estimated 20,000,000 patients worldwide have been treated with cimetidine and these provide the mass if evidence for its safety. In outpatients side effects are rare. Elderly patients and those with other serious illnesses such as renal or hepatic failure, may run a low but increased risk of developing mental confusion or gynaecomastia. Serious side effects are extremely rare and in only a handful of

patients has cimetidine been thought to be a factor that may have contributed to their death. Large overdoses in outpatients have been reported, with few ill effects.

Interaction of cimetidine with drugs metabolized by hepatic microsomal oxidation is well established and care should be taken when adding cimetidine to oral anticoagulants in particular. There are no absolute contraindications to the use of cimetidine although use in pregnancy and lactation is best avoided, as with most drugs. Intravenous administration is rarely necessary and slow iv infusion is advisable when parenteral use is indicated. Reduction of dosage in renal failure is important.

Some precautions, such as exclusion of malignancy in patients with gastric ulcer are important no matter what treatment is chosen. The safety of cimetidine as a life long term treatment for peptic ulcer remains to be demonstrated.

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