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PEPTIC ULCER HAEMORRHAGE

with particular reference to Neodymium Yag laser photocoagulation

by

Ian Alexander MacLeod
MB ChB FRCS (Glasg.)

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SUMMARY

This thesis is concerned with a series of personal studies on acute upper gastrointestinal haemorrhage carried out over a period of several years in two different hospitals.

The first part presents the results of two policies of diagnosis and management of patients admitted to the Western Infirmary, Glasgow. The initial group of patients were admitted to individual units and barium meal examination was the main diagnostic procedure; the second group were admitted to a single medical unit, early endoscopy was used for diagnosis and a haematemesis team was available.

From comparison of the results in those two groups, it was concluded that early endoscopy was an accurate means of identifying the site and cause of bleeding but that this knowledge was not associated with improvement in outcome. Despite improvements in medical care, there was no evidence that this reduced mortality and blood loss remained the main cause of death. Emergency surgery had an appreciable mortality and it was concluded that there was a need to have a non-operative technique to treat or prevent further haemorrhage.

The second part of the thesis is concerned with an investigation into the application of the neodymium

YAG laser to endoscopic therapy in Glasgow Royal Infirmary. Preliminary animal studies were performed to assess the safety and efficacy of the neodymium YAG laser using prototype equipment. The effects of the radiation on the rabbit stomach were assessed by varying the different parameters of radiation and observing the resultant tissue changes by macroscopic and histological assessment. It was concluded that the tissue effects were predictable and within the range of radiation likely to be used for photocoagulation, the risk of visceral perforation was minimal. A further study was performed to see if the extension of tissue necrosis could be reduced by a prostaglandin analogue or a H_2 receptor antagonist but the results were inconclusive.

The ability of the neodymium YAG laser to arrest haemorrhage was assessed in an acute dog model with the splenic artery brought up to a hole in the stomach wall. Arterial haemorrhage was produced by fenestrating the vessel and within the limitations of the study the active bleeding could be arrested by laser photocoagulation.

A pilot study of laser photocoagulation was then performed on a group of patients, many of whom were poor surgical risks. The purpose of this pilot study was to improve the laser and ancillary equipment and assess whether it was worthwhile proceeding to a controlled trial. It was concluded that within the limits of an uncontrolled assessment, the laser could reduce further haemorrhage but

that objective assessment would be required to provide the answer.

A prospective controlled trial was performed to assess the efficacy of the neodymium YAG laser in patients bleeding from peptic ulcers and single vessels. Entry criteria consisted of clinical features (shock, blood transfusion, haemoglobin concentration $<10 g.dl^{-1}$) that conveyed an increased risk of further haemorrhage and endoscopic appearances (gastric or duodenal ulcer with either an artery or spot in the floor or a single vessel).

Of 657 patients admitted with acute non variceal haemorrhage, 184 were bleeding from peptic ulcers and single vessels; 130 of them were ineligible for study inclusion and all of them settled. Fifty four patients were eligible but 9 were excluded. Forty five patients were included in the study, 25 of whom were bleeding from ulcers with spots and irrespective of therapy, they all settled. Of the 20 who were bleeding from arteries, all 8 who were allocated to the control group underwent emergency surgery and 2 died. Four of the 12 patients who were allocated to receive laser therapy did not receive it and did as badly as the controls. Of the 8 who received laser therapy, only one required emergency surgery.

It was concluded that neodymium YAG photo-coagulation could reduce the need for emergency surgery

but within the experience of the study, it was not applicable in those who had brisk arterial haemorrhage or who had ulcers in positions that were inaccessible to the laser beam.

In general, it was concluded that by identifying those patients who had bled from arteries, it was possible to identify those who require emergency surgery. Furthermore if early semi elective surgery or laser photocoagulation was performed on these patients before further haemorrhage had occurred, then the mortality might be reduced in those bleeding from peptic ulcers. With this information available, there would be no need to provide special care for all patients admitted with acute upper gastrointestinal haemorrhage because the high risk group could be identified.

CHAPTER ONE

HISTORICAL REVIEW

I. INTRODUCTION

In this review of the literature relating to upper gastrointestinal haemorrhage, an attempt is made to trace the evolution of the approach to diagnosis and treatment from the time of Hippocrates. In relation to diagnosis, particular emphasis is placed on the development of fibreoptic endoscopy because its use is central to the applications of therapeutic endoscopy. Although the section on diagnosis is separated from that on therapy, this division is incomplete because in reality the two are complementary, and thus there is some duplication of information.

Although a considerable portion of the section on therapy is concerned with the first half of this century, this is intended so that the evolution of the approach to therapy of today can be examined, particularly since the clinician of today has been influenced by men who were taught in the nineteen thirties. Furthermore, the solutions to the problems of this condition can be found in the writings of men of that period who by convention might be considered to be ahead of their time but were merely of their time because they had come to the correct conclusions from the knowledge that was then available to them.

2. EARLY DESCRIPTION OF CONDITION AND MORBID ANATOMY

"And yet there is no new thing
under the sun"[1]

Although the vomiting of blood or passing of black stools is not mentioned in the Bible[2], this condition has been described from the dawn of medical writings. Hippocrates bequeathed the term melaena to us, however in the 'Corpus'; this word actually means the vomiting of blood in its pure or altered form[3].

Because of their religious laws forbidding dissection, the Greeks were unaware of the morbid anatomy of this condition[4]. It was not until the renaissance of science that pathological causes for blood loss were described. Littre in 1704 first documented a case in which death followed haemorrhage from a gastric ulcer[5]. In 1825 Broussais in his treatise "Sur la duodenite chronique" described a fatal haemorrhage from a duodenal ulcer[6]. Carswell in his "Pathological Anatomy" published in 1838 depicted bleeding from acute gastric ulcers[7]. According to Stacey Wilson, bleeding from oesophageal varices was described by Fauvel in 1838[8]; however, John Abercrombie described gastric varices as a source of haemorrhage ten years earlier[6]. In 1857, Brinton described post-mortem findings of gastric erosions[9].

However, within the context of clinical practice, the physician had no objective means of identifying the

source of blood loss until fibreoptic endoscopy became a routine procedure.

3. DIAGNOSIS - with particular reference to endoscopy.

It is only in the last decade that endoscopy has become the prime means of identifying the source of blood loss in the upper gastrointestinal tract, and in order to understand why it has taken a century to reach this situation, it is necessary first of all to review the development of the endoscope itself.

(i) Technical development of the endoscope.

This has depended on two facets: first, an appreciation of the topography of the stomach in relation to the gullet and second the application of the physics of light transmission and illumination. At each stage of the endoscopic evolution, progress occurred only when physicians, physicists and technicians worked in conjunction with one another.

Although Kussmaul was the first person to inspect a stomach with an endoscope in 1868, the first recorded attempt occurred in Glasgow some 20 years earlier when a Dr. Campbell invited a sword swallower to swallow his tube. The gentleman is reputed to have replied "I know I can swallow a sword, but I'll be (expletive deleted) if I can swallow a trumpet !" Kussmaul's endoscope was a straight tube. He abandoned the procedure because of

poor illumination of the stomach[10].

Mikulicz in 1881 published his paper on endoscopy. In it he described the angulation between stomach and gullet and hence the need for an angulated endoscope. His instrument had an angle of 30^{o} at the junction of lower one third and upper two thirds. Despite describing gastric pathology he eventually discarded the instrument because of poor optics and inadequate illumination[10].

Eddison invented the miniature electric bulb in 1879 but it was not utilised in the endoscope until 1895 by which time the endoscope makers had reverted to using straight tubes thus forgetting the necessity for tube angulation that Mikulicz had shown was so necessary[10].

In 1911 Hoffman theorised that it was possible to look through a curved tube by the use of prisms. However, when Wolf constructed an instrument utilising this principle it was found that the system absorbed too much light[10].

In the late 1920s Wolf and Schindler solved the problem by utilising prisms and lenses with short focal lengths. By 1932 they had produced the Wolf Schindler endoscope, a semi-flexible instrument which was the basic endoscope design used up to the early nineteen sixties when the fibre optic endoscope was introduced[11].

The idea of utilising the phenomenon of light transmission through a flexible fibre was conceived in Glasgow by John Logie Baird, the idea being patented in 1927[12]. It is of interest to note that a Doctor Lamm from Munich suggested to Schindler in 1928 that they should construct a gastroscope based on this principle. However, Schindler was too busy constructing his lens gastroscope[13], and the principle of fibre optics was forgotten until 1954 when Van Heel reported a technique of fibre cladding[14] and in the same year Hopkins and Kapany working in Reading developed the technique of fibre bundling[15]. Hirschowitz thought of the possibility of using this technology in an endoscope and working in conjunction with Curtis, produced the first flexible fibre optic endoscope[13].

In 1961 Hirschowitz published his early experience with the fibroscope and suggested that it might be used as a means of early examination of the upper gastrointestinal tract in bleeding patients. This instrument was introduced to Britain in 1961, and Burnett reported its use in 44 bleeding patients in 1962[17]. This early instrument was deficient in that it was difficult to visualise the duodenum[17], and it was not until the introduction of the end-viewing gastroduodenoscopes in 1969 that the whole of the upper gastrointestinal tract could be inspected visually[18].

(ii) The need for a diagnosis.

The requirement of a means of visualising the site and source of blood loss depended on the realisation by physicians that not all patients bled from gastric ulcers. This fact was not generally appreciated by physicians in the last century because of their conviction that haematemesis and melaena were symptoms of gastric ulcers.

Despite this belief, Brinton in 1857 had suggested that not all bleeding ulcers were symptomatic[9]. By 1900, 32 emergency operations had been performed for upper gastrointestinal haemorrhage, and in six of these cases no ulcer was found in the stomach[17]. As a result of this experience, Moynihan made the fundamental statement that bleeding was a complication and not a symptom of peptic ulceration[20]. Hale White in 1901 reasoned that patients, especially young women who had mild bleeding episodes, were in all probability bleeding from erosions and not ulcers[21].

Einhorn[22], Rodman[19], Mayo Robson and Moynihan[20] claimed that there was a need to diagnose the source of blood loss, however they all felt that the endoscope was not yet of any service because of the difficulty and potential danger in using it.

Although the need for a suitable instrument had arisen, it was not until 1932 when the Wolf Schindler

gastroscope was introduced that endoscopy became feasible[11].

In 1935 Jennings in a letter to the Lancet made a strong plea for diagnostic endoscopy[23]. Despite this, the prevailing consensus was that the source of blood loss could be diagnosed by bed end declaration after a suitable history had been taken[24].

Some physicians employed radiology approximately two to three weeks after the bleeding had stopped. If the x-ray was negative, it was reasoned that either the ulcer had healed or it had been missed[25].

It is apparent that only a few centres used endoscopy and then only in selected cases after the bleeding had stopped[26]. This was because of the difficulty experienced in using the instrument and the fear that the procedure might restart bleeding[27].

In 1952 Palmer published his observations on a vigorous diagnostic approach to severe upper gastro-intestinal haemorrhage in which a diagnosis was achieved in 74% of patients in the first week[28]. This approach was adopted in only a few centres and up to 1960 selective gastroscopy was performed sparingly elsewhere[29].

Apart from the risks of the procedure, the lens gastroscope could not visualise the fundus or the antrum

and it was not long enough to intubate the duodenum[17].

With the introduction of the fibre endoscope, it was quickly realised that a high degree of diagnostic accuracy could be achieved[16]. Hirschowitz reported a 90% diagnostic rate in patients endoscoped in the first 24 hours after admission. However due to technical limitations it was seldom possible to intubate the duodenum and the diagnosis of duodenal ulceration as a source of blood loss tended to be made by exclusion[30]. With the advent of the end viewing gastroduodenoscopes it became possible to visualise the whole upper gastrointestinal tract[18].

In the last decade, the adoption of early fibre optic endoscopy has become widespread[31] and diagnostic accuracy rates in excess of 90% have been reported[32,33,34]. Despite the high diagnostic accuracy, the mortality of this condition has not fallen[35] and doubts have been cast upon the necessity for early endoscopy[36].

However, in the last few years reports have been published on the stigmata of bleeding[37] and the presence of vessels in ulcer bases[38].

It is with this information that the request of Moynihan may be met when he said that medicine "must find a way of diagnosing the size of vessel that has been

perforated so that a rational plan of management can be adopted"[20]. Moynihan's thesis was that open vessels in the bases of ulcers were liable to produce continuing or further haemorrhage and if the patients who had open vessels could be identified prior to further haemorrhage then surgery could be undertaken more safely.

It has taken 77 years to provide this information. The question that remains, however, is what to do with this information.

4. THERAPY

(i) Ancient Medicine

The Hippocratean Corpus suggested initial starvation followed by cold milk and then a light diet avoiding greasy and sweet food. Evacuants were used and advice on convalescence was offered. Venesection was a part of the therapy but only if the patient was not too feeble[3].

Erasistratus of the Alexandrian school treated the condition according to the anti-Phlogistic theory, that is, by rest of the inflamed part (starvation) and relief of phlegmasia by venesection or by applying ligatures to the extremities[39].

Celsus in addition to advising rest to the stomach, suggested the induction of vomiting by the use of emetics such as rue or frankincense. If necessary, he prescribed

astringents such as turpentine, plantain or pomegranate rind. An infusion of wormwood was used to treat dyspepsia[40].

Therefore, prior to the eclipse of early rational medicine, the essential treatment for haematemesis or melaena was, rest to the stomach, relief of dyspepsia, venesection, styptics and appropriate convalescence.

(ii) Nineteenth century

After the renaissance of science, the morbid anatomists identified the sources of blood loss in this condition, but despite this knowledge, the prevailing outlook was to deny the existence of individual diseases and accept that maladies were manifestations of inflammation[39]. This paradoxical situation was typified by Broussais who first described a fatal case of bleeding from a duodenal ulcer but advocated the anti-Phlogistic approach, using leeches for blood letting.

John Abercrombie of Edinburgh described the symptomatology of peptic ulceration but his treatment was no different than the Greeks except that he had a more comprehensive list of styptics to offer[6].

Cruveilhier described the symptoms of gastric ulceration about the same time as Abercrombie and suggested that an ulcer of the stomach should be treated in the same way as a leg ulcer, in that it should be protected from

irritants (acid) and allowed to rest. Although he had applied a rational approach to the treatment of bleeding gastric ulcers (rest, starvation followed by milk) he was not in effect providing anything new[41].

Brinton writing in 1857 attempted to correlate the severity of bleeding with the calibre of gastric vessel eroded. He suggested that the stomach should be kept empty to prevent clot dislodgement. He advised a styptic plan of therapy except when a large vessel had been eroded (no advice was given on how to diagnose this clinically). He advised the use of ice placed on the epigastrium; however, venesection was no longer encouraged. The patients were given brandy and beef tea per rectum[9].

By the eighteen seventies, ice cold drinks had been added to the therapy[42], but others suggested that hot water taken either by mouth or per rectum was better[19]. In the eighteen nineties, morphine was administered to allay anxiety[43].

Thus, by the turn of the century, although there was better understanding of the pathophysiology of the condition, in essence there had been no fundamental change in medical therapy.

(iii) Early 20th century - feeding and antacids

In 1904 Lenhartz introduced the concept of early feeding which was totally against the conventional approach

already described[44]. His thesis was that most of the patients treated by traditional means were malnourished, anaemic and subject to delayed healing. Furthermore, if the patient continued to lose blood, he was less able to withstand the continued stress. The Lenhartz regime consisted of immediate feeding with frequent small quantities of egg and milk. He also prescribed bismuth to promote ulcer healing[45]. Spriggs in 1909 analysed the available data and claimed that the Lenhartz regime did not increase the incidence of further haemorrhage or perforation[46]. Despite these claims, many physicians were still fearful that early feeding would induce bleeding[44,47].

In 1915 Sippy published his work on the use of antacids for healing ulcers. In effect, this was a logical extension of Gruveilhier's concept that ulcers would heal if free gastric acid was removed from the stomach. The patients were fed hourly on a diet of eggs, milk and cream. In between each meal, antacids (systemic and non-systemic) and bismuth were given. For the first few nights the stomach was aspirated to remove acid. This control of free acid continued for four weeks[48].

It is possible to take stock of the situation in the period after the First World War by reviewing the discussion held at a meeting of the Royal Society of Medicine in 1924[49]. Despite the reports of Lenhartz and then Sippy, the agreement in opinion was that patients should still be subjected to initial starvation for a period of days, and then offered modifications of either the

Lenhartz or Sippy regimes. Some still favoured abdominal ice packs and others rectal infusions of hot water. If bleeding continued, some advocated gastric lavage followed by the instillation of a variety of haematinics of unproven value.

(iv) Advent of surgery and blood transfusion

At this point, it is worth considering aspects of therapy which are of cardinal importance, surgery and blood transfusion.

The advent of emergency surgery for bleeding peptic ulcers occurred in the latter part of the last century because of two discoveries, general anaesthesia and antisepsis[50]. Although ether and chloroform had been introduced in the eighteen forties, abdominal surgery did not become established until antiseptic techniques had been adopted. Lister reported his observations on the use of antisepsis in 1867. However, it was only after the Franco-Prussian War when the appalling extent of wound sepsis had been appreciated that the German Medical School applied Lister's techniques and pioneered gastric surgery[51].

Mikulicz performed the first operation to arrest gastrointestinal haemorrhage in 1887. At operation, he found a high gastric ulcer and applied cautery to the vessel in the ulcer base. Although the patient did not rebleed, she succumbed 48 hours later[52].

By 1900 there were 25 reported operations on bleeding peptic ulcers in the literature[19], the first in Scotland being performed by Pringle at Glasgow Royal Infirmary in 1899[53]. The overall mortality of these 25 cases was 40%[19]. These operations had been performed on patients who either had profuse haemorrhage or continuing episodes of small haemorrhages[19]. By 1900 surgeons were of the opinion that surgery was only of benefit in those patients who had repeated small bleeds and in effect all patients should have a trial of conservative therapy first and if that failed, then surgery should be considered[19,20, 54,55,56]. Dieulafoy disagreed with this policy[54], and advocated surgery on all patients who lost more than half a pint of blood. Contrary to folklore, simple drainage was not the most common operation performed[19]; instead, most of the eminent surgeons of the day advocated a direct attack on the bleeding vessel[19,56].

The experience of the First World War taught surgeons the value of blood transfusion. A special report was issued by the Medical Research Council in 1920 identifying the problems of shock and the methods of resuscitation particularly with blood transfusion[57]. At the Royal Society of Medicine's meeting in 1924, surgeons pointed out the value of blood transfusion, not only because it improved the patient's condition but also blood was thought to improve clotting. Some physicians were against blood transfusion because it would raise the patient's blood pressure and blow the clot out of the eroded vessel in the

ulcer. Others were extremely cautious and advocated transfusion of small volumes of blood (e.g. 250 mls). Despite the advent of blood transfusion, surgery was still considered a last resort, because medical therapy was thought to be successful and that the results of operation were poor[49].

(v) Critical reappraisal and refinement of therapy

Despite the claims that the mortality of this condition was rare[58], several series appeared in the British literature from 1927 to 1934 reporting mortality rates from 13 to 25%[25,59-64]. A strongly worded annotation in the Lancet of 1934 suggested that because of the high mortality, there should be a critical reappraisal of the time honoured conservative methods of treatment[65].

In relation to the dissatisfaction with the mortality rates, two authors made comments relevant to the problem. Chiesman writing in 1932[61], identified the high risk group of patients as those who continued to bleed despite medical therapy and showed that in 82% of deaths, the cause of blood loss was an eroded artery in the ulcer base. His conclusion was that there was an argument for surgery in carefully selected cases. Aitken writing two years later claimed that blood transfusion was still not widely practised in Britain[64].

In 1935 and 1936, three publications appeared in the British literature which were of great importance in

the treatment of this condition. In 1935 Marriott and Kekwick published their work on the value of "Continuous Drip Blood Transfusions"[66]. They demonstrated how large quantities of blood could be easily transfused by their method.

In the same year, Meulengracht reported a 1.2% mortality in a series of 251 cases who had been treated by immediate feeding. His arguments for feeding were not dissimilar to those of Lenhartz. In essence, his regime consisted of a full puree diet together with antacids. Instead of being fed small amounts at frequent intervals, the patients were allowed to eat as much as they wanted at regular meal times. Blood transfusion was given when necessary[67]. After this report, many physicians started prompt feeding[68].

The third paper was one by Finsterer in 1936, replying to criticism of the approach to early surgery that he had advocated[69]. Gordon Taylor writing in 1935, had claimed that Finsterer's "first 48 hours" was the optimum period for surgical attack in haematemesis[70]. This statement was misunderstood by some physicians. In particular Tidy[71], claimed that it was absurd to suggest that all cases of haemorrhage from chronic ulcers should be operated upon immediately. Finsterer in his article pointed out that he was talking about profuse acute gastric haemorrhage. In 52 resections he had a mortality of 4%. Thus he showed the importance of early rather than

late operation, when the patient was exhausted and was less able to withstand stress. Finally he made a fundamental statement that the mortality in medically treated cases depended primarily on the number of cases with an erosion of a large artery. This statement is probably true today.

Despite the dissatisfaction that had been expressed about the traditional methods of treatment[65] and the advent of immediate full feeding[67], continuous drip transfusions[66] and early surgery[70], eminent physicians, for example Hurst, still advocated the time honoured methods[72]. However, in 1937 Witts published his method of treatment which served as a reference for physicians up to the nineteen fifties[73]. In essence, he warned of the dangers of dehydration and uraemia, advocated a modified Meulengracht feeding regime, and cautious use of blood transfusion. He emphasised that the prevention and treatment of recurrent haemorrhage was the key to the reduction of mortality, but suggested that surgery was not the answer to this problem.

Bennett in 1938 provided firm data on the blood volume changes in haemorrhage and the inaccuracy of haemoglobin estimations. He showed that almost half the patients admitted with severe bleeding had lost more than 50% of their blood volume[74]. Following on from this Avery Jones[75] in 1939 reported on a study of blood transfusion and laid to rest the fear that transfusion would raise a

patient's blood pressure and cause further haemorrhage.

In an extension of this 1938 report, Bennett in 1942[76] claimed that blood transfusion was the most important factor in saving life.

In 1947, Avery Jones published his classical paper on gastrointestinal haemorrhage[77]. He alluded to the statistical errors in the literature of this condition and pointed out that some authors had excluded fatalities in their reports. He made a plea for a standardisation of the factors to be utilised in reporting so that the intrinsic variations in a given series could be determined from which inferences regarding therapy might be drawn. In particular he suggested that the proportion of elderly patients in a series should be known. He treated his patients according to the guidelines of Witts. The mortality in his series was 8% and he emphasised the adverse effect age had on the outcome. Only 3% of his patients underwent emergency surgery with a 14% post-operative mortality. He suggested that there was an argument for operating more often in selected cases; in particular those patients over 50 who had further haemorrhage.

Despite the therapeutic improvements in the late 1930's that Jones utilised, 71% of his deaths were due directly to blood loss, and at post-mortem, an eroded vessel was commonly found in the ulcer base. These findings lend support to his suggestion for more surgery.

Similar experiences occurred elsewhere in Britain. In 1949 reports from Oxford and Aberdeen showed operation rates of 3 and 2% of the populations respectively[78,79]. In Aberdeen, blood loss was the cause of death in 71% of the cases. It is apparent from these and subsequent reports in the early 1950's that there was a need for closer cooperation between physicians and surgeons, and this point was referred to in a British Medical Journal annotation of 1950[80].

In 1956, Avery Jones presented an extension of his experience. Apart from the adverse effect advancing age had on mortality, he identified other groups at risk such as those patients who had co-existent cardiovascular and respiratory disease. The site of blood loss was also important in determining the outcome and he suggested a need for diagnosing the site. Although surgery was used slightly more often than before, there had been no fundamental change in policy and there was no apparent improvement in overall mortality[81].

(vi) Different approaches to surgery.

Tanner, writing in 1949, published his results on different operating policies carried out at sequential periods of time. He suggested that Finsterer's approach of early operation for massive bleeders carried the lowest mortality[82].

In America, two publications appeared in 1948, proposing different attitudes to surgery. Dunphy and Hoerr in Boston[83] suggested that the crux of the problem regarding emergency surgery was to identify those patients who needed operation. They suggested that the rate of blood loss was the determining factor and advocated surgery in those patients who could not be stabilised with a replacement of 1.5 litres of blood in 24 hours. They added the riders that age in itself was not an indication for surgery and that there was a need for a preoperative diagnosis. Cooperation between physician and surgeon existed in Boston in that they had a team of doctors to look after their patients.

On the other hand, Stewart in Buffalo estimated red cell volumes in massive bleeders, advocating immediate surgery after resuscitation in those patients who had lost more than 30% of their red cell volume[84]. Both these centres performed partial gastrectomies.

From the 1930's, gastric resection had been the operative procedure of choice. However, in the late 1950's and early 60's, several publications advocated a more conservative surgical approach. Smith and Farris from Los Angeles writing in 1958[85] and 1960[86] advocated vagotomy and pyloroplasty with undersewing of the bleeding duodenal ulcer. Dorton writing in 1961[87], published his results using this technique. With 42 consecutive cases he had no deaths and no postoperative haemorrhage.

Foster writing in 1965 published his results on a sequential study of gastric resection versus undersewing plus vagotomy and drainage. The mortalities were 32 and 12% respectively, and there was no difference in the post-operative rebleeding rates[88].

In 1967, Carruthers advocated conservative surgery for both gastric and duodenal ulcers. Although his results showed a lower mortality with conservative surgery, his series was not controlled. Postoperative haemorrhage was more common after conservative surgery, and he suggested that this was due to poor technique[89].

In the 1950's and 60's, the literature on different operative techniques is voluminous and no firm conclusions can be inferred. It is possible that changes in operations reflect, in part, the changing attitudes towards elective surgery for uncomplicated peptic ulcers. In general terms, it was felt that particularly with the elderly, a more conservative procedure might reduce the mortality[90].

(vii) Early diagnosis in relation to treatment.

With the increasing acceptance of emergency surgery, it was felt that there was a need to identify those patients who were bleeding from chronic peptic ulcers so that an early decision regarding surgery could be made[81,90]. Palmer's vigorous diagnostic approach has been alluded to already[28], however, early diagnostic techniques were not generally employed and great reliance was placed on

eliciting a history of dyspepsia[91]. This may be one reason why patients with no dyspeptic history of bleeding from peptic ulcers had a higher mortality than those who did[92].

In the 1950's and early 1960's various early diagnostic techniques were reported. Chandler and Watkinson writing in 1953 and 1959 advocated the use of gastric aspiration[90,93]. Cantwell in 1960 reported on early bedside barium meals[94]. In the same year Chandler proposed a combination of diagnostic techniques[95]. In 1964 and 1965, Katz and Mailer put forward a case for early gastroscopy[96,97].

Schiller reported a large series from Oxford in 1970. His results showed the increasing use of early barium meals. Despite this, there was a fall in the proportion of patients undergoing emergency surgery within the 15 year period studied. He reiterated the need for more emergency surgery and the adoption of more conservative procedures particularly in the elderly[98].

At the beginning of the 1970's the panendoscopes were introduced[18,99] and in the last decade, early endoscopy became established as the prime means of identifying the source of blood loss[100]. By the end of the decade, 82% of centres in Britain had adopted the policy of early endoscopy[31]. At first, it was hoped that objective knowledge of the source of blood loss would improve the mortality[27, 30,98,101], however, it is apparent that with conventional

management, this has not happened[35], possibly because the proportion of patients who are elderly and have significant co-existent disease has risen[98,102,103].

(viii) Management of patients.

In relation to the conventional approach of early diagnosis, vigorous resuscitation and judicious surgical intervention, the most important advances have occurred in the organisation of medical management. Hellers and Ihre reporting in 1975, demonstrated that early diagnosis, vigorous resuscitation and early surgery performed by a team reduced mortality[104]. More recently, Hunt reporting on the experiences of a haematemesis unit, showed that mortality could be reduced[105].

However, in 1979, Dronfield reported on the causes of death in a series and showed that most of the potentially avoidable deaths occurred in those patients who underwent emergency surgery and suggested that mortality might be reduced if effective non operative means of controlling haematemesis could be used[106].

(ix) Non operative control of bleeding.

Prior to the advent of fibre optic endoscopy, clinicians began to assess methods that would arrest haemorrhage and prevent emergency surgery. These techniques have included gastric cooling[107,110], systemic hypothermia[111,112], the use of a G-suit[113], instillation of

adrenaline[114] and levanterol[115,116].

With the introduction of the H_2 receptor antagonists, several trials have been performed to assess the effect of cimetidine in its ability to prevent further haemorrhage. There is, however, no firm evidence that there is any benefit once bleeding has occurred[117-120].

Similarly, somatostatin has been used without proven benefit[121-124].

In 1972, Amdrup reported on the use of bentonite but no further reports have appeared[125].

In conclusion, although the concept of preventing clot dissolution is attractive, to date there is no convincing evidence that any of these methods are of any benefit[126].

(x) Therapeutic endoscopy.

The notion of controlling upper gastrointestinal bleeding by utilising an endoscope is not new. Kelling in 1900 described how he packed the gullet with gauze to staunch the bleeding from varices. He suggested that bleeding from a source in the stomach could be controlled by the same technique[127]. However, with peptic ulcers, direct therapy did not become feasible until the advent of the panendoscope when the exact source of blood loss could be visualised. The biopsy channel of these endoscopes

provided direct access to the site of bleeding and the concept of arresting haemorrhage was a logical progression from the diagnostic function of the instrument. The principle of applying cautery to a bleeding vessel in an ulcer base was first used by Mikulicz in 1887[52]. Youmaus in 1970 passed a cystoscope through a small gastrostomy and successfully applied electrocautery to bleeding ulcers in two patients[128]. The following year, Blackwood and Silvis reported on the use of electro-coagulation with a fibreoptic endoscope[129]. In the next few years several reports appeared from other centres using the same technique[130-134]. All these reports described successful cessation of bleeding in a variety of lesions in the upper gastrointestinal tract.

Since 1970, a variety of techniques have been assessed with the endoscope to arrest haemorrhage such as heater probes[135], electro-fulgaration[136], magnetic fields[137], glues[138] and clotting factors[139]. The most commonly used technique is that of the laser.

Maiman in 1960 reported in 'Nature' on the first laser (Ruby)[140]. The principle of light amplification by the stimulated emission of radiation was promulgated by Einstein in 1917[141].

The Neodymium Y.A.G. laser was first described in 1964 and the argon ion the following year[142].

Nath and Gorisch working with Kiefhaber in Munich reported on the coupling of argon laser radiation to a flexible fibreoptic system in 1973 and postulated that such a system could be passed down the biopsy channel of a fibreoptic endoscope[143]. Kiefhaber first used the Neodymium Y.A.G. laser to treat a patient bleeding from the stomach in 1975[144]. In the same year, Fruhmorgen in Erlangen used an argon laser[145]. Since then many patients have been treated with laser photocoagulation. Most of the work has been performed with the Neodymium Y.A.G. laser particularly in West Germany where the Messerschmidt Company produced a commercial laser specially adapted for use with endoscopes.

As with virtually every other therapy used in this condition, no scientific assessment of its efficacy had been performed.

CHAPTER TWO

CLINICAL STUDIES

I. INTRODUCTION

It has been estimated that in Britain, acute upper gastrointestinal haemorrhage accounts for a yearly admission rate of approximately 50-100 per 100,000 of the population[92]. Despite improvements in diagnosis, resuscitation and general medical therapy, mortality has remained in the region of 10%[98]. Several explanations have been proferred for this lack of improvement in mortality rates, the most cogent of which has been the rising proportion of elderly patients[102].

In the Western Infirmary, Glasgow, four aspects of medical care have changed in the last decade and might be expected to improve the outlook for patients admitted with gastrointestinal bleeding. The first was the setting up of a Shock Team in 1971 to investigate and manage patients with traumatic, septic and haemorrhagic shock. The second was the opening in 1973 of an acute medical receiving unit into which most of the patients with gastrointestinal bleeding were admitted. The third was the advent of an emergency endoscopy service in 1976 to provide early accurate diagnosis, and the fourth was the establishment of a Haematemesis Management Team (HMT) in 1977 to provide continuity of care.

In this chapter, the effect of these changes will be assessed by analysis of two patient populations; the

first admitted with acute upper gastrointestinal haemorrhage in the period 1968-1972, the second admitted during the period 1.1.77 - 31.12.77. In addition to establishing the causes of upper gastrointestinal bleeding, the studies will be used to address the following questions:

(i) Does early endoscopy improve the accuracy of diagnosis and so reduce mortality ?

(ii) Has there been any change in the major causes of death from gastrointestinal haemorrhage ?

(iii) Does emergency surgery offer a satisfactory means of arresting haemorrhage ?

(iv) Does a haematemesis management team provide an improvement in outcome ?

In relation to section (iv), only patients in the second study period and a further 20 patients admitted in December 1976 are used to address the question of management.

2. PATIENTS, MATERIALS AND METHODS

(i) Methods of Data Collection.

Study Period 1.1.68-31.12.72 (First Study Period).

Data was collected from patients admitted to the Western Infirmary, Glasgow because of bleeding from the upper gastrointestinal tract. Patients admitted for other reasons and who developed bleeding while in hospital have not been included in this study.

Data were compiled from the following sources.

Hospital Diagnostic Index Cards. It was the practice in the Western Infirmary for unit secretaries to complete a diagnostic index card on each patient at the time of completing the discharge summary. Diseases have been classified according to the International Statistical Classification of Diseases (8th Revision 1967) and the following codes were used to identify patients for inclusion in the present study.

456.0	Varicose veins of the oesophagus
530.9	Diseases of the oesophagus
531.9	Ulcer of the stomach (without mention of perforation)
532.9	Ulcer of the duodenum " " " "
533.9	Peptic ulcer " " " "
534.9	Gastro-jejunal ulcer " " " "
784.5	Haematemesis - excludes haematemesis from ulcer of stomach (531), duodenum (532) and peptic ulcer (533)
785.7	Melaena - excludes melaena of newborn (778.2).

The patient's full name, data of birth and hospital case sheet number were obtained from the cards and used to trace the patient's case record.

Hospital Death Certificate. A handwritten copy of the death certificate diagnosis is kept in the Western Infirmary by the Head Porter. The copies for the five-year period in question were scrutinised to identify patients with haematemesis, melaena or bleeding ulcers, and those individuals who died within hours of admission.

Hospital Theatre Books. The theatre books from the five surgical units in the hospital were inspected and the names and hospital numbers (if inserted) of all patients undergoing emergency gastroduodenal surgery for bleeding or an unspecified emergency gastroduodenal operation were obtained.

Information Recorded. A proforma was prepared and completed with data extracted from the case sheets. If the patient continued to bleed, underwent emergency surgery or died, additional information was appended to the proforma.

Study Period 1.1.77-5.9.77 (Second Study Period).

During this period of time, all patients bleeding from the upper gastrointestinal tract were admitted to one of three units; the acute medical receiving unit, the acute surgical receiving unit or the professorial

medical unit. The majority of patients were admitted to the acute medical receiving unit. Retrospective data was collected from the following sources.

Endoscopy Forms. Endoscopies were performed in one room. A standardised form was completed after each endoscopy and a copy of the form was retained in the Endoscopy Room. Details recorded included the patient's full name, date of birth, hospital case sheet number, reasons for endoscopy and endoscopic findings.

Ward Admission Book. A book was kept in the acute medical receiving unit which recorded details of the patient's name, sex, age and reason for admission.

Discharge Sheets and Letters. These were inspected to identify patients admitted with acute upper gastro-intestinal haemorrhage to the three units specified. The patients' names and case sheet numbers were extracted.

Management Team Cards. If the care of a patient had been taken over by the Haematemesis Management Team, a card was filled out and this contained the patient's name and case sheet number.

Hospital Theatre Books and Death Certificates. These were examined as in the 1968-72 study.

Computerised Diagnostic Index Printout (1977).
This was run by the medical records department of the Western Infirmary. Data was extracted from the hospital five-part admission set by the records staff and the patient's diagnosis was classified according to the International Statistical Classification of Diseases and entered into the computer.

The printouts were inspected as a cross check for the other methods and it allowed an assessment to be made of the accuracy of this method of data storage (see later).

Information Recorded. A proforma was prepared and the information recorded.

Prospective Study 6.9.77-31.12.77 (Second Study Period).

From 6.9.77 to 31.12.77 a prospective survey was performed. Data was collected of all patients admitted to the Western Infirmary with upper gastrointestinal haemorrhage. The data was collected by daily visits (usually twice a day) to the Receiving Units. The in-patient progress of each patient was documented.

(ii) Definitions.

Inclusion into Study: A patient was only included in the study if haematemesis and/or melaena or the presence

of melaena on rectal examination was observed by a reliable witness (general practitioner's letter, hospital medical and nursing staff), or if the case sheet recorded a definite history from the patient. If the history was vague and the patient's clinical course did not suggest bleeding, then the patient was excluded.

Alcohol Consumption: If the patient gave a history of alcohol consumption within 24 hours of his bleeding episode, or it had been recorded in the case sheet that the patient smelt of alcohol.

Alcoholic: If the patient gave a history of excessive alcohol consumption or had received medical care for alcoholism.

Salicylate ingestion: If the patient gave a history of having consumed a salicylate containing preparation within 24 hours of the bleeding episode.

Previous known pathology: Documentation of previous peptic ulcer disease and/or previous bleeding episodes.

Previous gastric surgery: Documentation of previous elective and emergency gastroduodenal surgery. Surgery for bleeding was recorded.

Shock on admission: Documentation of a systolic blood pressure under 100 mmHg and a pulse rate greater than 100 beats/min.

Source of bleeding: (A) Endoscopy. A lesion was regarded as the source of blood loss if at least one of the following criteria was fulfilled: active bleeding, adherent blood clot, altered blood or a protruding vessel in the base of an ulcer. If a single lesion was identified without any of the above stigmata, it was assumed that it was the source of bleeding if blood was present in the lumen of the stomach or duodenum, the patient had a definite history of haematemesis or melaena, or the clinical course in hospital indicated that he had bled.

(B) Barium meal. Lesions reported by the radiologist that could conceivably be a source of blood loss were regarded as potential rather than actual sources of blood loss.

(C) Clinical impression. Because of the inaccuracy of clinical assessment in determining the source of blood loss, the source of loss was regarded as unknown if the patient had not been endoscoped or had barium meal examination.

Further haemorrhage. (A) Further haemorrhage was assumed if there were continuing signs of blood loss requiring further blood transfusion with (or occasionally

without) haematemesis and melaena.

(B) After a period when there was no evidence of further bleeding, there was (a) vomiting or naso-gastric aspiration of fresh blood or (b) renewed evidence of hypovolaemic shock or rapidly progressive anaemia[146].

(C) Reappearance of fresh melaena after the faeces had returned to a normal colour or continuing fresh melaena over a period of days with either a drop of haemoglobin of at least 2 gm dl^{-1} more than 48 hours after the index bleeding episode or a failure of the haemoglobin to rise despite adequate blood transfusion.

Emergency surgery. Operation performed to arrest continuing or further haemorrhage.

Other illnesses. Documentation of significant cardiac, respiratory, renal or arthritic disease.

3. RESULTS

Number of patients in study period 1.1.68 - 31.12.72.

The relevant diagnostic cards provided the names of 1019 patients. Inspection of their case sheet records revealed that 933 (92%) had bled from the upper gastro-intestinal tract whereas the remaining 86 had not.

The hospital theatre books and death certificates provided a further 78 cases and thus 1011 patients were available for study.

Number of patients in study period 1.1.77 - 31.12.77.

The endoscopy forms provided 253 cases, the discharge letters and admission book 30 and the death certificates one. The prospective survey provided a further 106 cases, and thus 389 patients were available for study.

Accuracy of hospital diagnostic index.

The hospital diagnostic computer print-out for 1977 had the names of 284 patients coded for acute upper gastro-intestinal haemorrhage. Inspection of the case sheet records revealed that 243 (86%) patients had bled from the upper gastrointestinal tract, whereas the remaining 41 had not. Thus the diagnostic computer print-out had information of 243 (63%) of the 389 patients known to have been admitted to the Western Infirmary in 1977.

Demographic variables for study period 1.1.68 - 31.12.72.

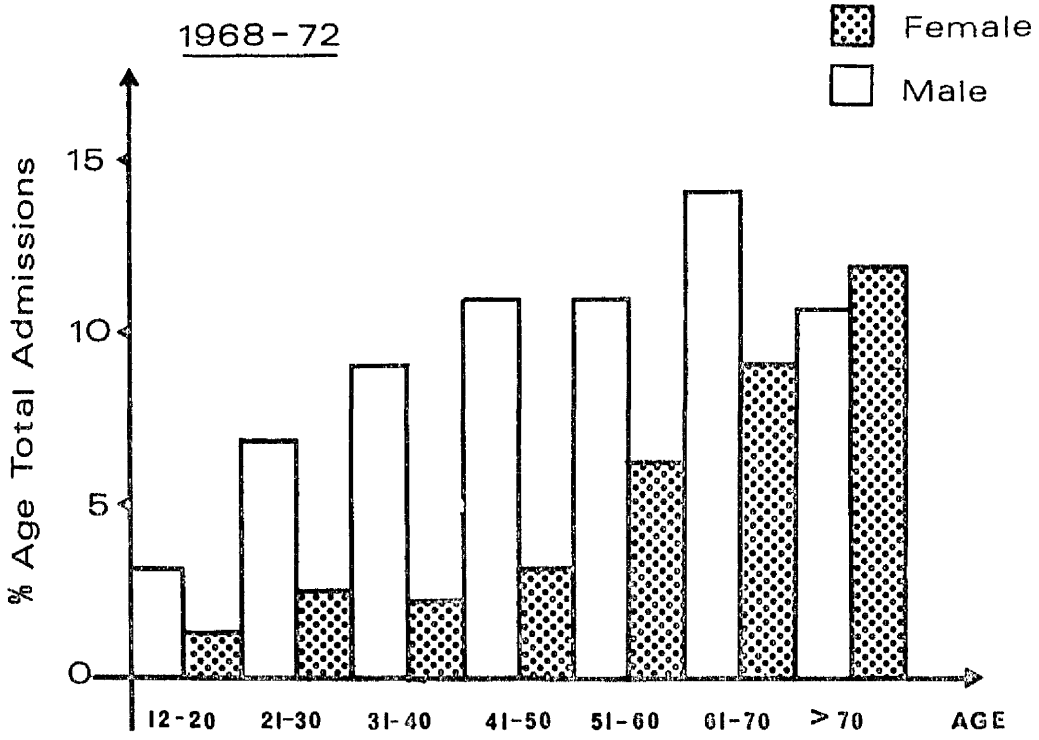
Nine hundred patients accounted for 1011 admissions. Six hundred and sixty seven (67%) were male and 344 (34%) female. The age range varied from 13-91, and 483 (48%) were over the age of sixty. Figure 1 depicts the age and sex distribution in decades.

Demographic variables for study period 1.1.77 - 31.12.77.

Three hundred and fifty eight patients accounted for 389 admissions - 246 (68%) were male and 123 (32%) female. Their ages ranged from 15 to 94 with a mean of 51.7. One hundred and fifty six (40%) of the total were over sixty years of age. The age and sex distribution in decades is shown in Figure 1.

4. DISCUSSION

The main sources used to identify the patients admitted with acute upper gastrointestinal haemorrhage in the two study periods were different. In the first (1.1.68-31.12.72) the hospital diagnostic index card system was the main source, but in the second (1.1.77-31.12.77) the discharge letters, admission book and endoscopy forms were the predominant ones and their accuracy was confirmed when it was found that the number of patients retrieved, matched the number in the prospective survey (6.9.77 -



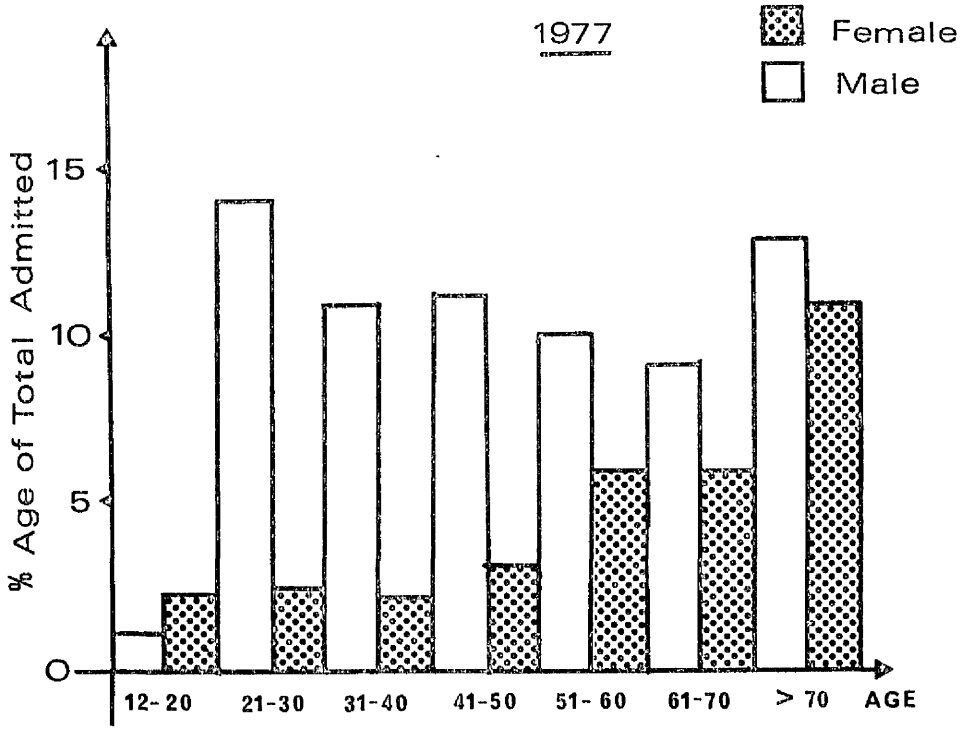


Figure 1. Age and sex distribution of patients in both study periods. Each column denotes the percentage of the total number of patients admitted in that study period.

31.12.77). Thus the number of patients in the second study period (389) was in all probability the actual number admitted.

The computerised diagnostic printout for 1977 contained information on 243 admissions which was only 63% of the known total of 389 and thus was not an accurate source of data. If it is assumed that the diagnostic index cards inspected in the first study had a similar inaccuracy, then the patients included in that study did not represent the total hospital admissions with acute upper gastrointestinal haemorrhage during that period of time. The actual number admitted might have been just under 1500.

It is therefore apparent that absolute comparisons cannot be made regarding the total hospital experience, for example mortality rates, during the two study periods.

The hospital theatre books and copies of the death certificates held by the Head Porter were found to be accurate sources of data regarding the patients who were operated on and those who died. Thus it was possible to make comparisons between the surgical experience and mortality in the two study periods.

DIAGNOSTIC TECHNIQUES

1. RESULTS

Number having investigations. In the first study period only 629 (62%) of the admissions had a diagnostic procedure performed compared with 350 (90%) of those admitted during the second study period ($p<0.001$). Of those investigated in the first study period, a barium meal was the main investigation and this was performed in 622 patients and an endoscopy was only performed on 51 (5%) patients. In contradistinction, endoscopy was performed on 350 (90%) of the admissions in the second study period ($p<0.001$).

Timing of procedure. Tables 1a and b show the timing of the diagnostic procedures. In the first study period, just over a half (56%) had a barium meal within one week of admission but only 27% within three days, and only 5 (10%) had an endoscopy performed within 72 hours. In the second study period, 315 (90%) were endoscoped within 24 hours of admission, and by 72 hours, 99% had the procedure performed ($p<0.001$).

Barium meal findings. In the first study period, barium meal examination failed to reveal any abnormality in 221 (36%) cases and in a further 76 (12%), a hiatus hernia was the only abnormality demonstrated. Thus no active pathology was found in 297 (48%) of cases. The

TABLE I(a). Time interval after adnission (in days) that endoscopy and barium meal were performed in study period 1.1.68 - 31.12.72.

Time (days)	Barium meal		Endoscopy	
	Number	(%)	Number	(%)
1 - 3	168	(27)	5	(10)
4 - 7	180	(29)	16	(31)
> 7	168	(27)	22	(43)
Unknown	106	(17)	8	(16)
Total	622	(100)	51	(100)

TABLE I(b). Time after admission (hours) that endoscopy was performed in 350 patients during 1977.

Time (hours)	Number	Percentage
< 12	133	38
12 - 24	182	52
24 - 48	21	6
48 - 72	10	3
> 72	4	1
	350	100

potential sources of blood loss found are shown in Table II. Duodenal ulcers were found in 212 (34%) and gastric ulcers in 44 (7%).

Endoscopic findings. In the first study period, the endoscopist identified a source of bleeding in 22 (41%) cases whereas in the remaining 29 (59%), the endoscopist reported a normal upper gastrointestinal tract (26) or failed to pass the instrument (3) (Table II).

In the second study period, a source of bleeding was identified in 309 (88.3%) patients. In 34 (9.7%) no source of bleeding was identified, and in the remaining 7 (2%) the endoscopist failed to pass the instrument. Chronic duodenal and gastric ulcers were found in 117 (38%) of patients, acute mucosal lesions in 105 (34%), Mallory Weiss tears in 16 (5%), oesophageal varices in 12 (4%) and carcinoma of the stomach in 3 (1%). Other lesions accounted for 24 (8%) cases and multiple causes were responsible in 32 (10%) patients. Details of these findings are shown in Table III.

Accuracy of investigation. In the first study period, 114 of those who had a barium meal examination, also had an endoscopy, underwent subsequent surgery or died and had a post mortem and thus it was possible to assess the accuracy of radiology. In 45 (39%), the barium meal report gave the wrong diagnosis, 24 of them being false negative. The most commonly missed lesion was a

TABLE II. Endoscopic and barium meal findings of patients having these procedures in study period 1.1.68 - 31.12.72.

	Barium		Endoscopy	
	n	(%)	n	(%)
Oesophagus				
Oesophagitis	1		3	(6)
Stricture	2		1	(2)
Ulcer	3		1	(2)
Varices	19	(3)		
Hernia	76	(12)	1	(2)
Stomach				
Ulcer	44	(7)	8	(16)
Gastritis	2		5	(10)
Carcinoma	6	(1)	1	(2)
Duodenum				
Ulcer	212	(34)	1	(2)
Other				
Stomal ulcer	6	(1)	1	(2)
Diverticulae	15	(2)		
Miscellaneous	2			
Multiple	13	(2)		
Normal	221	(36)	26	(51)
Fail			3	(6)
	622	(100)	51	-

TABLE III. Source of blood loss identified by endoscopy in 1977. The table shows the sources identified. The percentages relate to proportion of positive diagnosis and not total numbers endoscoped.

Lesion	Number	Percent
Oesophagus		
Oesophagitis	21	7
Ulcer	13	4
Mallory Weiss	16	5
Stricture	4	1
Varices	12	4
Stomach		
Chronic ulcer	43	14
Acute ulcer	9	3
Erosive gastritis	48	16
Carcinoma	3	1
Polyp	1	< 1
Intussusception	1	< 1
Volvulus	1	< 1
Duodenum		
Chronic ulcer	74	24
Acute ulcer	10	3
Duodenitis	14	5
Stoma		
Ulcer	4	1
Inflammation of	3	1
Multiple	32	10
TOTAL	309	100

gastric ulcer (7). In the same study period, 9 of those who had an endoscopy, also underwent a subsequent operation and in 5 of them, the endoscopist failed to find any abnormality in the upper gastrointestinal tract.

In the second study period, it was possible to assess the accuracy of endoscopy in 46 patients who came to surgery and 11 who died and had a post mortem performed. Endoscopic assessment proved inaccurate in 2 patients diagnosed as having a gastric ulcer but who proved to be bleeding from a duodenal ulcer. One patient thought to be bleeding from a stomal ulcer at endoscopy was found at operation to be bleeding from gastric erosions with no evidence of a stomal ulcer. One patient thought at endoscopy to have a duodenal ulcer was found to have a gastric ulcer at operation. Thus endoscopic diagnosis was inaccurate in 4 (7%) patients when comparison was possible.

Thus endoscopy was accurate in 93% of patients in the second study period compared with 44% in the first study ($p<0.001$). Even though a barium meal examination was accurate in 61% of cases in the first study period, this also was less accurate than endoscopy in the second study period ($p<0.001$).

Complications of procedure. In the second study period, early endoscopy produced complications in only two patients. One patient found at endoscopy to have a

duodenal ulcer, developed symptoms and signs of perforation shortly afterwards. At operation a perforated duodenal ulcer was found. Almost certainly, gas insufflation of the duodenum at endoscopy had re-opened a sealed perforation.

One moribund 78 year old patient with an advanced reticulum cell sarcoma of the stomach died with respiratory failure a few hours after endoscopy and it was considered that he may have aspirated following the procedure.

Diagnostic procedure in relation to outcome. In the first study period, only 50 (35%) of those undergoing surgery had a diagnostic procedure prior to operation compared with all of those undergoing surgery in the second study period ($p<0.001$).

Of those who died, 80% in the first study period and 42% in the second, had no diagnostic procedure prior to death ($p<0.001$).

With regard to those admitted in hypovolaemic shock, 36% and 42% were investigated in the first and second study periods respectively.

Accuracy of clinical history. In the second study period, 84 patients were known to have had a duodenal ulcer at some stage prior to their bleeding episode (diagnosed by barium meal or endoscopy). Seventy eight underwent

endoscopy after admission and 36 (43%) were found to have bled from duodenal ulcers and a further 5 from duodenal ulcers and another lesion. Thus 41 (53%) of those endoscoped were bleeding from duodenal ulcers.

2. DISCUSSION OF RESULTS

The results of the two studies showed a change in the approach to diagnosis. During 1968-72, almost a third had no diagnostic investigation performed and the remainder had a barium meal, usually after the diagnosis was required by the clinician, that is after further haemorrhage was likely to have occurred. The investigation had a low diagnostic yield which was inaccurate particularly with reference to false negative reports. Endoscopy was performed sparingly and usually supplementary to radiology, and had the same deficiencies as the barium meal reports. Thus the patients in this study had at best a potential rather than actual source of blood loss identified and in most cases no diagnosis at all.

In 1977, the approach had changed to early diagnostic endoscopy which provided a high diagnostic yield, was accurate and had a low associated morbidity. However, a number of patients who required early accurate diagnosis, for example those shocked on admission, were not endoscoped.

3. GENERAL DISCUSSION

The advent of fibre optic endoscopy has shown that clinical assessment is an inadequate means of identifying the source of blood loss. Several reports have shown it has a diagnostic accuracy between 36 - 45%[32,36,147,148]. The main reasons for this are that a history of dyspepsia does not mean that a peptic ulcer is the source of blood loss. Cotton[32] found that 25% of patients presenting with this symptom were bleeding from other lesions and conversely, 30% of patients bleeding from ulcers were asymptomatic. Graham[36] showed that 54% of patients bleeding from duodenal ulcers and 77% from gastric ulcers were asymptomatic. In addition, a history of known peptic ulcer disease does not indicate the patients are bleeding from that lesion. This was demonstrated in the 1977 study where 47% of patients with a history of duodenal ulceration were bleeding from other lesions.

Thus, in 1968-72 the source of blood loss in those who did not have a diagnostic investigation was unknown.

The results show that a barium meal examination is an unsatisfactory method of determining the source of blood loss. The low yield of positive findings is in keeping with the reports of Hoare and Fraser[149,150] but lower than the 45 and 57% reported by Dronfield and Cantwell[151,94]. A high proportion of the lesions reported were peptic ulcers. However the figures were lower than

the 86 and 87% reported by McGinn[152] and Dronfield[151]. The problem with this is that even if a peptic ulcer is present, it may not be the actual source of blood loss. Cotton[32] found that 29% of the duodenal and 6% of the gastric ulcers in his series were not the sources of blood loss.

Controlled trials comparing the accuracy of endoscopy with radiology have shown that endoscopy is significantly better than a barium meal in detecting the actual source of blood loss[36,151,153,154].

The small number of patients endoscoped in the 1968-72 study is surprising because in 1962 Burnett[17], working in the Western Infirmary, reported on the potential benefit of fibre optic endoscopy in upper gastrointestinal haemorrhage and Mailer writing in 1965 reported on its value[97]. The delay in performing a diagnostic procedure in the first series may in part explain the low diagnostic yield from endoscopy but not with the barium meal. Allen[155] has shown that diagnostic accuracy of endoscopy falls if the procedure is performed more than 48 hours after the bleeding episode and this is due to the rapid healing of mucosal lesions which are seldom identified by barium meals.

The experience of early endoscopy in 1977 is comparable to that of other British series (Table IV). Only Hoare had a higher diagnostic yield but the total

TABLE IV. The endoscopic experience of 7 British series. The Table shows the diagnostic yield, accuracy and limitations of the procedure. The study period where known is given in brackets below the author.

	Total	Diagnosis n	%	Accuracy[1] %	Fail[2] n	%	Blood[3] n	%	Complication n	
Cotton[32] (1971-72)	208	177	80	?	4	2	8	4	1	Perforation
Forrest[157] (?)	111	88	80	?	2	2	3	3	1	Aspiration
Hoare[149] (1973-74(	52	51	98	100	1	2	-	-	-	
McGinn[152] (1972-74)	138	118	86	?	1	1	1	1	1	Perforation
Lee[158] (1973-76)	108	94	87	?	?		?		?	
Dronfield[151] (? 1976)	162	108	67	81	-	-	5	3	-	
Morgan[159] (1975-76)	64	59	92	?	?		?		?	
MacLeod (1977)	350	309	88	93	7	2	2	<1	2	Perforation Aspiration

1. Comparison of endoscopic findings with surgery and/or post mortem.
2. Failure to pass endoscope.
3. Numbers in each series where blood obscured vision in stomach.

number of patients endoscoped was small[149]. There are however, several large American series with diagnostic yields in excess of 90%[33,34,156]. The only way of assessing the accuracy of endoscopy is to compare it with surgical and post mortem findings. The accuracy in this series compared favourably with the figure Dronfield[151] reported but lower than Hoare's[149], but comparison was only made with 14 patients.

Although the instrument was not passed in 7 patients, this experience is similar to others. The other main reason for failure to obtain a diagnosis is the presence of excess blood in the stomach and the British experience shows that this is an infrequent problem.

Complications arising as a result of endoscopy are unusual. Only 5 of the 1193 patients in Table IV had complications (0.4%), three of whom perforated and two aspirated.

The conclusion from this study and a review of the literature shows that early endoscopy is an accurate means of identifying the source of blood loss. Its value in relation to outcome will be discussed in the conclusion to this chapter.

MORTALITY

1. RESULTS

Deaths in those not submitted to operation. In the first study period, 87 died of whom 57 (66%) were male and 30 (34%) female. Sixty five (75%) were older than 60, eight (9%) had significant coexistent respiratory disease and 19 (22%) had a known cardiac disorder. Thirty eight (44%) patients were shocked on admission and 70 (80%) of those who died either continued to bleed or had a further haemorrhage after admission.

In the second study period, 24 (7%) of those not operated on died. Fourteen (58%) were male and 10 (42%) female. Twenty (83%) were older than 60, 5 had significant coexistent respiratory disease and 7 had a known cardiac disorder. Ten (42%) were shocked on admission and 20 (83%) either continued to bleed or had further haemorrhage.

Table V shows the major causes of death in both study periods. In relation to those who had further haemorrhage, blood loss was the most common cause of death in both studies and accounted for approximately three-quarters of the deaths in each. Twelve (23%) and 5 (36%) of those in the first and second study period respectively were not transfused. Furthermore, 25 (48%) and 9 (64%) of those dying of blood loss did so within 24 hours of admission. However, no patient in either study died within

TABLE V. Major causes of death in patients not undergoing emergency surgery in both study periods. The figures are divided into those who settled and those who had a further haemorrhage (FH). The percentages related to the total in each group.

	1.1.68 - 31.12.72					1.1.77 - 31.12.77.				
Cause	FH	(%)	Settle	(%)	Total	FH	(%)	Settle	(%)	Total
Blood loss	52	(74)	0		52	15	(75)	0		15
Cardio resp. failure	10	(15)	9	(53)	19	2	(10)	1		3
Liver failure	3	(4)	3		6	1	(5)	0		1
Cerebro vasc.	2	(3)	2		4	0	-	1		1
Sepsis	1	(1)	0		1	1	(5)	1		2
Malignancy	2	(3)	1		3	1	(5)	1		2
Diabetic coma	0	-	1		1	0	-	0		0
Unknown	0	-	1		1	0	-	0		0
	70	(100)	17		87	20	(100)	4		24

3 hours of admission.

Overall mortality. One hundred and forty nine (15%) of the 1011 admissions included in the first study died compared with 36 (9%) of the 389 admissions in the second study. If it is assumed that the actual number of patients admitted in the first study was approximately 1500 then the mortality rate might have been in the region of 10%. The causes of death in both studies are denoted in Table VI and it shows that blood loss was the most common cause of death in each study period and accounted for about half the deaths in each. Although cardiorespiratory failure was the second most frequent cause in the first study, sepsis held this rank in the second study.

Source of blood loss. In the first study period, 73 (49%) of those who died had bled from peptic ulcers. However, because a diagnostic procedure was only performed in 20% of those who died, this figure may have been higher.

In the second study, endoscopy was performed in 90% of admissions and with additional information obtained from surgery and post mortem, the source of bleeding was known in 94% of patients (Table VII). Six (13%) of those bleeding from chronic gastric ulcers and 9 (12%) from duodenal ulcers died.

TABLE VI. Major causes of death in study periods 1.1.68 - 31.12.72 and 1.1.77 - 31.12.77. This includes both those who underwent emergency surgery and those who died without undergoing surgery.

	1.1.68 - 31.12.72.		1.1.77 - 31.12.77.	
Cause	n	(%)	n	(%)
Blood loss	60	(40)	18	(50)
Cardiac failure	21	(14)	1	(3)
Respiratory failure	17	(11)	3	(8)
Liver failure	13	(9)	3	(8)
Cerebro vasc.	4	(3)	1	(3)
Sepsis	19	(13)	6	(17)
Malignancy	4	(3)	2	(6)
Pulmonary embolism	3	(2)	2	(6)
Diabetic coma	1	(<1)	0	-
Anaesthetic/Op.	5	(3)	0	-
Unknown	2	(1)	0	-
	149	(≃100)	36	(≃100)

TABLE VII.

Sources of blood loss in those who died during 1977. The figures are obtained from the final diagnosis.

Source	Total n	Death n %
Oesophagus		
oesophagitis	21	-
ulcer	13	2 (15%)
tear	16	-
stricture	4	-
varices	17	7 (41%)
Stomach		
chronic ulcer	46	6 (13%)
acute ulcer	9	-
gastritis	47	1 (2%)
carcinoma	4	4 (100%)
Duodenum		
chronic ulcer	76	9 (12%)
acute ulcer	10	1 (10%)
duodenitis	14	-
Stoma		
ulcer	5	1
infl.	3	-
misc.	3	1
Multiple	33	-
Unknown	68	4 (6%)
	389	36 (9%)

2. DISCUSSION

The findings suggest that there was no difference in the mortality rates or main cause of death (blood loss) in the two studies. In the introduction to this chapter, reference was made to four aspects of medical care which had been changed and might have been expected to improve outcome. Although the Shock Team was available in 1977, none of the patients in this second study were seen by members of that team. The first conclusion that must be reached is that resuscitation of these patients was inadequate and this is supported by the fact that some patients died without receiving a blood transfusion although no patient died within 3 hours of admission, and this suggests that the lessons learned by the Shock Team had not been disseminated adequately to the medical staff concerned with the initial care of these patients. The second conclusion is that surgical intervention should have occurred more often and this suggests that the surgeons were not involved in the care of these patients early enough and even if they were, then surgery was not performed soon enough.

The third conclusion reached was that knowledge of the source of bleeding in 1977 did not appear to influence the outcome of the patients who died or that it did not alter therapy.

The influence of the management team on mortality will be discussed in the fourth section of this chapter.

EMERGENCY SURGERY

1. RESULTS

(i) Study Period 1.1.68 - 31.12.72.

Sixty four patients bleeding from duodenal ulcers and 36 from gastric ulcers underwent emergency surgery because of continuing or further haemorrhage.

Duodenal ulcers. Forty eight (75%) were male and 16 (25%) female. Thirty two (50%) were over sixty years of age, 14 (22%) were shocked on admission, 36 (56%) smoked, six (9%) had significant respiratory tract disease and 4 (6%) had known cardiovascular conditions. Nineteen (30%) had a barium meal performed prior to surgery, whilst in the remaining 45 (70%), the surgeon had no objective diagnosis of the source of blood loss.

Undersewing of the ulcer with a vagotomy and drainage was performed in 47 cases with 13 (38%) deaths; a polya gastrectomy in 12 with 7 (58%) deaths and a simple ligation of the bleeding point in the remaining 5 with one death. Altogether 21 (33%) patients died (Table VIII).

Two of the patients who had a resection and 6 who had a vagotomy and drainage procedure died from septic shock as a result of bowel dehiscence. Cardio-pulmonary failure was responsible for 7 deaths and pulmonary embolism for a further 2. One patient who had a vagotomy

TABLE VIII. Emergency surgery for bleeding duodenal and gastric ulcers in study periods 1.1.68 - 31.12.72 and 1.1.77 - 31.12.77. Procedures performed and resultant mortality.

	1.1.68 - 31.12.72. (n)	Death	%	1.1.77 - 31.12.77. (n)	Death	%
Duodenal ulcer						
*V & drain & sew	47	13	(28)	14	2	(17)
Ligation	5	1	(20)	-	-	-
Partial gastrectomy	12	7	(58)	3	1	(33)
	64	21	(33)	17	3	(18)
Gastric ulcer						
Partial gastrectomy	20	7	(35)	5	-	-
*V & drain & sew	4	0	-	1	-	-
Ligation	8	4	(50)	-	-	-
Nil	2	2	(100)	-	-	-
Unknown	2	2	(100)	-	-	-
	36	15	(42)	6	(0)	-

* V = vagotomy.

and drainage procedure died from postoperative blood loss. Anaesthetic agents were probably responsible for a further 2 deaths (Table IX).

Gastric ulcers. Twenty three (64%) were males and 13 (36%) females. Twenty five (69%) were over sixty years of age. Ten (28%) were shocked on admission, 13 (36%) smoked, one had significant respiratory tract disease and 3 (8%) had known cardiovascular conditions.

Fourteen (39%) patients had a preoperative barium meal. However, 8 (57%) of the reports failed to demonstrate a gastric ulcer, therefore 30 (83%) of the patients went to surgery without any objective evidence of the source of blood loss.

Twenty patients had a partial gastrectomy and 7 (35%) died. Four had a ligation of the ulcer with a vagotomy and drainage procedure with no deaths, whilst 8 had a ligation of the bleeding point alone with 4 deaths. Overall, 15 (42%) of the 36 patients died (Table VIII).

Seven (19%) died from septic shock, 6 (17%) from cardio-pulmonary failure and the remaining 2 died as a result of exsanguination during surgery. No patient died of postoperative blood loss (Table IX).

Blood transfusion. Twenty four patients received 5 pints or less and 6 (25%) died. Forty eight received between 6 and 10 pints with 16 (33%) deaths whilst 13

TABLE IX. Emergency surgery for bleeding duodenal and gastric ulcers. Causes of death in those undergoing surgery in study period 1.1.68 - 31.12.72.

Procedure/Cause	n	Blood loss	Sepsis	Cardio/ Resp.	Pul/ emb.	Liver fail.	Anaesth/ Op.	Total
Duodenal ulcers								
Vagotomy & Drain & Sew	47	1	6	4	2	-	-	13
Ligation	5	-	-	-	-	1	-	1
Resection	12	-	2	3	-	-	2	7
	64	1	8	7	2	1	2	21
Gastric ulcers								
Resection	20	-	4	3	-	-	-	7
Vagotomy & Drain & Sew	4	-	-	-	-	-	-	-
Ligation	8	-	2	2	-	-	-	4
Nil	2	-	-	-	-	-	2	2
Unknown	2	-	1	1	-	-	-	2
	36	-	7	6	-	-	2	15

had more than 10 pints with a mortality of 39%. There was no different in mortality between the different groups (Table X).

Timing of surgery. Twenty nine had their operation within one day of admission and 13 (45%) died. By 48 hours, 44 had been operated on with 17 deaths. There was no correlation between the timing of surgery and mortality (Table XI).

Postoperative further haemorrhage. Of the patients who bled from duodenal ulcers, and had a vagotomy, drainage and undersewing of the ulcer, 4 (9%) rebled; 3 required further surgery to arrest the haemorrhage and 2 of them died. The fourth patient did not undergo surgery and she died from blood loss. One of the patients who had a partial gastrectomy for a bleeding duodenal ulcer died after re-operation.

One patient who had bled from a gastric ulcer, had further haemorrhage after a Billroth gastrectomy, and although he required a further operation, he survived (Table XII).

Anastomotic leak. Eight (13%) of those bleeding from duodenal ulcers and 7 (19%) from gastric ulcers developed septic shock as a consequence of anastomotic leakage after their operation and all of them died. This complication occurred in patients who did not have a gastric resection (Table XII).

TABLE X. Emergency surgery for bleeding peptic ulcers. The amount of blood transfused and the resultant mortality in study periods 1.1.68 - 31.12.72 and 1.1.77 - 31.12.77.

	1.1.68 - 31.12.72.				1.1.77 - 31.12.77.			
Blood (pints)	n	(%)	Deaths	(%)	n	(%)	Deaths	(%)
1 - 5	24	(24)	6	(25)	7	(30)	1	(14)
6 - 10	48	(48)	16	(33)	13	(57)	2	(15)
> 10	13	(13)	5	(39)	3	(13)	-	-
unknown	15	(15)	9	(60)	0	-	-	-
TOTAL	100	(100)	36	(36)	23	(100)	3	(23)

TABLE XI. Emergency surgery for bleeding peptic ulcers in study periods 1.1.68 - 31.12.72 and 1.1.77 - 21.13.77.
Day of operation and respective mortality.

	1.1.68 - 31.12.72.			1.1.77 - 31.12.77.		
DAY	n	Death	%	n	Death	%
1	29	13	(45)	9	2	(22)
2	15	4	(27)	3	-	-
3	13	4	(31)	5	-	-
4	10	5	(50)	1	-	-
5	7	1	(14)	0	-	-
> 5	24	7	(29)	5	1	(20)
Unknown	2	2	(100)	0	-	-
	100	36	(36)	23	3	(13)

TABLE XII. Emergency surgery for bleeding duodenal ulcers. Occurrence of postoperative further haemorrhage (FH) and anastomotic leakage - study period 1.1.68 - 31.12.72.

Complication/OP	n.	FH	(%)	*F.op.	+(mort)	Death Total	Anas. Leak	(%)	Death
Duodenal ulcers									
V. & drain & sew	47	4	(9)	3	(2)	3	6	(13)	6
Ligation	5	-	-	-	-	-	-	-	-
Resection	12	1	(8)	1	(1)	1	2	(17)	2
	64	5	(8)	4	(3)	4	8	(13)	8
Gastric ulcers									
Resection	20	1	(5)	1	-	-	4	(20)	-
V. & drain & sew	4	-	-	-	-	-	-	-	-
Ligation	8	-		-	-	-	2	(25)	-
Nil	2	-		-	-	-	-	-	-
Unknown	2	-		-	-	-	1	-	-
	36	1	(3)	1	-	0	7	(19)	7

* F.op. = Further operation.

+ Mortality after further surgery.

(ii) Study Period 1.1.77 - 31.12.77.

Emergency surgery was performed on 17 (22%) of the 76 patients who were bleeding from duodenal ulcers and 6 (13%) of the 46 bleeding from gastric ulcers.

Overall, 14 (61%) were male and 9 (39%) female, 16 (70%) smoked, 3 (13%) had known respiratory tract disease and the same number had significant cardiovascular disorders. On admission, 5 (22%) were shocked and 8 (35%) had a haemoglobin less than 10 g dl^{-1}.

All 23 had endoscopy performed, and only two reports gave the wrong diagnosis (9%). The eneoscopist thought that both patients were bleeding from gastric ulcers; however, at surgery, duodenal ulcers were found.

The surgical procedures performed for both gastric and duodenal ulcers are shown in Table VIII. Fourteen patients bleeding from duodenal ulcers had a vagotomy and drainage procedure with undersewing of the bleeding point and 2 (14%) of them died. The remaining 3 patients had a polya resection with one death. Five of the patients bleeding from gastric ulcers had a Billroth resection and only one had a vagotomy and drainage procedure. None of these patients died, and no patient had a postoperative haemorrhage. However, 2 patients bleeding from duodenal ulcers required further surgery. One because of efferent loop obstruction (survival) and the other because of sepsis (died). Two patients developed

septic shock from bowel dehiscence and both died. The remaining death was due to pulmonary embolism.

Blood transfusion. Only 3 patients were transfused more than 10 pints of blood. There was no correlation between the amount transfused and mortality (Table X).

Day of operation. Nine patients were operated on within one day of admission with 2 (22%) deaths. There was no correlation between the time of surgery and mortality (Table XI).

(iii) Comparison of the Two Series.

The disparity with the numbers in the two studies is due to the fact that the first was a 5 year and the second a one year review.

In 1977, all the patients undergoing emergency surgery had a diagnostic procedure performed prior to theatre compared with 33% of those in 1968-72 ($p<0.001$).

Operative procedure. The same proportion of patients in each study had a vagotomy, drainage and undersewing for bleeding duodenal ulcers and had a partial gastrectomy for bleeding gastric ulcers.

Outcome. The mortality rates between the two studies was the same in relation to total number operated on,

source of blood loss and procedure performed.

Complications and cause of death. There was no difference between the two studies in relation to the occurrence of septic shock, further haemorrhage or death due to these complications.

Timing and amount of blood transfusion. There was no difference in either the day of operation or the amount of blood transfused between the two groups.

2. DISCUSSION

Emergency surgery is at present the accepted means of arresting continuing or further haemorrhage from peptic ulcers, but it has a significant postoperative mortality which was 36% in the 1968-72 series. This figure is higher than the experience elsewhere in Britain (Table XIII). The nearest figure is 24% reported by both P.F.[146] and F.A. Jones[81]. The most obvious reason for this high mortality is that the data may be inaccurate; however, it was obtained from the theatre books and not the diagnostic index. The 1977 series had a lower mortality but because of the small numbers, the difference is not significant.

Age appeared to be a contributory factor in the first study. Fifty seven percent of the patients were over 60 and 42% of them died compared with 28% of those under sixty.

TABLE XIII. Emergency surgery for bleeding peptic ulcers - British series (12). Shown are the postoperative deaths in each series. The percentage range and median are given below the Table.

Author	Number	Deaths	%	Locus	Years of Study
Parsons[160]	49	7	14	Birmingham	1946-69
Fraenkel[161]	76	7	9	Oxford	1948-52
Jones, F.A.[51]	85	20	24	London	1947-54
Coghill[162]	54	8	15	Middlesex	1947-58
Tibbs[163]	33	5	15	Newcastle	1953-57
MacCaig[164]	76	12	16	London	1957-60
Banning[165]	27	3	11	Essex	1960-64
Carruthers[89]	49	6	12	Aberdeen & Leeds	1960-65
Cocks[166]	367	62	17	London	1953-62
Jones, P.F.[146]	75	18	24	Aberdeen	1967-68
Allan[102]	76	8	11	Birmingham	1970-73
Dronfield[106]	110	22	20	Nottingham	1970-77
Total	1077	178	17		
Mortality	Range 9 - 24% Median 15%				

In 1968-72, the postoperative mortality for bleeding gastric ulcers appeared to be higher than the figure for duodenal ulcers and also appeared to be higher with resection for both lesions but the differences were not significant. Tables XIV and XV show the mortality for both lesions and procedures performed in the literature. With duodenal ulcers, the median mortality for gastric resection was 13% and vagotomy and drainage 6%. With gastric ulcers the median value for resection was 17% and for vagotomy and drainage 14%. The figures from the literature appear lower than those of the 1968-72 series.

Analysis of the causes of death in the first study revealed that septic shock due to anastomotic leakage was responsible for 42% of the deaths. Information regarding this complication with gastric ulcers is not readily available in the literature, but with duodenal ulcers, the median value for gastric resection was 5.1% and zero for vagotomy and drainage (Table XVI). These figures are lower than the Western Infirmary experience. Anastomotic leakage may occur because of a technical failure or a deficiency in the healing of the tissues. Operative inexperience was not a factor because these operations were performed by consultants or experienced senior registrars.

It is worthy of comment that surgery did not invariably prevent the recurrence of haemorrhage.

TABLE XIV. Emergency surgery for bleeding duodenal ulcers - mortality in relation to procedure performed. Shown are the mortalities for resection and vagotomy, drainage and undersewing of ulcer. The percentage range and median mortality for each procedure are given below the Table.

Author	Resection		%	Vagotomy & drainage		%	Year	Centre
	n	Mort.		n	Mort.			
Carruthers (89)	25	5	20	24	1	4	1960-65	Leeds
Stone (167)	101	7	7	18	1	6	1960-75	New York
Byrne (168)	53	9	17	16	4	25	1960-69	Boston
Hampson (169)	131	9	7	9	1	11	1955-66	Montreal
Foster (170)	73	8	11	61	8	13	1968-69	Connecticut
Buckingham (171)	29	4	14	32	3	9	1960-69	Minnesota
Hunt (172)	77	8	10	44	1	2	1972-78	Melbourne
Parsons (160)	16	3	19				1946-49	Birmingham
Tibbs (163)	24	3	13				1953-57	Newcastle
Palumbo (173)	81	10	13				1948-58	Iowa
Snyder (174)				131	22	17	1960'ies	California
Westhand (175)				30	1	3	1949-56	California
Dorton (176)				47	0	0	1947-60	Kentucky
Vogel (177)				34	2	6	1963-67	Ohio
Weinberg (178)				47	1	2	1947-60	California
	610	66	11	893	45	5		
Range	7-20%			0 - 25%				
Median	13%			6%				

TABLE XV. Emergency surgery for bleeding gastric ulcers. Mortality in relation to procedure performed. The percentage range and median mortality for each procedure are given below the table.

Author	Resection			V. & drain & sew			Year	Centre
	n	Mort.	%	n.	Mort.	%		
Stafford[179]	44	9	21	6	2	33	1958-63	Baltimore
Hampson[169]	47	1	2	4	0	0	1955-66	Montreal
Foster[88]	30	4	13	13	3	23	1956-64	Oregon
Foster[170]	33	8	24	26	3	12	1968-69	Connecticut
Dorton[180]	-	-	-	14	2	14	1947-60	Kentucky
	154	22	14	63	10	16		

Range	2 - 24%	0 - 33%
Median	17%	14%

TABLE XVI. Anastomotic dehiscence after emergency surgery for bleeding duodenal ulcers. Shown are the leakage rates for both resections and vagotomy, drainage and undersewing of the ulcer. Beneath the table are the percentage range and median for each procedure.

Author	Resections			Vagotomy & drain			Year	Locus
	n	leak	%	n	leak	%		
Hampson[169]	131	0	0	9	0	0	1955-66	California
Snyder[174]				131	3	2	1960'ies	California
Westland[175]				30	0	0	1949-56	California
Dorton[176]				47	0	0	1047-60	Kentucky
Foster[170]	73	8	11	61	0	0	1968-69	Connecticut
Palumbo[173]	81	4	5				1948-58	Iowa
Weinberg[178]				47	0	0	1947-60	California
Tibbs[163]	24	1	4				1953-57	Newcastle
Parsons[160]	16	0	0				1946-49	Birmingham
Buckingham[171]	29	3	10	32	0	0	1960-69	Minnesota
Total	354	16	5	357	3	1		
Range		0 - 11%			0 - 2%			
Median		5%			0%			

There was no apparent correlation between the timing of surgery and the amount of blood transfused in the 1968-72 series, and, in reality, it is difficult to establish such trends because further haemorrhage does not occur at a fixed time after admission and the amount of blood transfused does not always equate with adequate resuscitation.

In 1977, all of the patients bleeding from gastric ulcers survived but 3 (18%) of those bleeding from duodenal ulcers died and sepsis was the cause of death in 2 of them. The number operated on was too small to draw meaningful comparisons. The postoperative mortality in the latter series suggests that the outcome is improving but the case is not proven. The figures from the 1968-72 series are disturbingly high and although the figures in the literature may be lower, emergency surgery does not provide an entirely satisfactory answer to the problem of continuing or further haemorrhage.

PATIENT MANAGEMENT

1. INTRODUCTION

During 1968-72 patients with acute upper gastro-intestinal haemorrhage were admitted to one of the four medical units in the hospital. As a rule, the surgeons were only asked to see a patient if he continued to bleed or had a significant further haemorrhage. There was no guarantee that the same surgeon would be recalled to see that patient. In 1973 an acute medical receiving unit was opened and the patients were admitted to this unit. The acute medical receiving teams were on duty for 24 hour periods and thus the continuity of medical care declined.

In March 1977 a haematemesis management team was instituted. This consisted of a group of physicians, gastroenterologists and surgeons who had a particular interest in this condition. A team of three doctors was on duty for a week at a time. The team consisted of a surgeon and physician of consultant or senior registrar grade and a registrar. At least one of them performed the endoscopies. The practice was to take over the management of the patient only at the request of the physician under whose care he had been admitted. This usually occurred after endoscopy had been performed which was in most cases, the morning after admission. The object of the team was to provide a continuity of care.

However, there were no specific management or therapeutic protocols.

2. PATIENTS and METHODS

The total number of patients studied was 303, and they comprised three different groups. The first consisted of 103 patients who were admitted between December 1976 and March 1977, the period immediately prior to the introduction of the management team when the endoscopy service was available - 'the endoscopy alone group'. The second comprised the 104 patients who were looked after by the management team between March and September 1977 - 'the management team group', and third, all 96 patients admitted during the same period of time as the latter group but whose care was not taken over by the management team - 'the non-referral group'.

In order to assess whether the three groups were similar the factors delineated in Table XVII were used for comparison. In relation to each factor, the figures in each group were compared using the 'Chi' squared test with Yates correction; significance being taken at the five per cent level.

The management team patients were older ($p<0.05$) and had a higher proportion of patients older than 60 ($p<0.05$) than the 'non-referral' patients. There was also a difference between those two groups in relation to

TABLE XVIIa. Numbers, age and sex differences between the three groups. The ages are presented as mean (± SEM).

	Endoscopy	Non-refer.	Management Team
Number	103	96	104
Males	69 (67%)	62 (65%)	78 (75%)
Females	34 (33%)	34 (35%)	26 (25%)
Age > 60	46 (45%)	31 (32%)[1]	47 (45%)[1]
Mean age	53.9 1.8	48.3 2.1[2]	55.1 5.96[2]

1 $X^2 = 4.055$ ($p < 0.05$)

2 ($p < 0.05$)

TABLE XVIIb. Clinical presentation of the three groups.

Presentation	Endoscopy		Non-refer.		Management Team	
	n	%	n	%	n	%
Haematemesis	48	(47%)	55	(57%)	57	(55%)
Melaena	28	(27%)	16	(17%)	18	(17%)
Both	27	(26%)	25	(26%)	29	(28%)
Shock	6	(6%)	11	(12%)	6	(6%)
Hb < 10g.dl^{-1}	32	(31%)	23	(24%)	28	(28%)
Further haemorrhage	26	(25%)	19	(20%)	31	(31%)

TABLE XVIIc. Patients' history. Table shows the numbers in each group who had the factors shown in the left hand column.

History	Endoscopy		Non-refer		Management Team	
	n	%	n	%	n	%
Alcohol	33	(32%)	41[1]	(42%)	29[1]	(28%)
Alcoholic	24	(23%)	25	(26%)	18	(17%)
Salicylate	28	(27%)	20	(21%)	23	(22%)
Smoker	50	(49%)	54	(56%)	54	(52%)
Respiratory disease	10	(10%)	13	(14%)	13	(13%)
Cardiac disease	14	(14%)	17	(18%)	15	(14%)
P H. bleeding	28	(27%)	33	(34%)	33	(32%)
Gastric op.	22	(21%)	13	(14%)	22	(21%)
Duodenal ulcer	22	(20%)	19	(20%)	31	(30%)

1 $X^2 = 4.192$ ($p < 0.01$)

the proportion of patients consuming alcohol ($p<0.005$). Table XVIII shows the main sources of blood loss. The 'management team' group had more patients bleeding from duodenal ulcers than the 'endoscopy alone' group ($p<0.01$) and fewer patients bleeding from erosive gastritis than the 'non-referral' group ($p<0.01$). The source of blood loss was unknown in a higher number of the endoscopy and non-referral groups compared to the management team patients ($p<0.005$ and <0.0005).

The outcome of the three groups was assessed by estimating the mean length of stay in days (±SEM), overall mortality, death in those who were shocked on admission and in those who had a further haemorrhage after admission. Differences were also looked for in the causes of death, frequency of emergency surgery and amount of blood transfused.

The outcome of patients bleeding from chronic gastric and duodenal ulcers was also determined.

3. RESULTS

Endoscopy. One hundred and three (99%) of the management team patients underwent endoscopy compared to 79 (82%) of the non-referral ($p<0.0005$) and 91 (88%) of the endoscopy alone group ($p<0.005$). These differences explain in part the reason for the lower number of unidentified lesions in the management team group.

TABLE XVIII . The main sources of blood loss in the three groups. The percentages given are to the nearest whole number and relate to the proportion of the total number in each group.

Source	Endoscopy n	Endoscopy %	Non-refer. n	Non-refer. %	Management Team n	Management Team %
Duodenal ulcer	11	(11%)	12	(13%)[1]	28	(27%)[1]
Gastric ulcer	11	(11%)	8	(8%)	20	(19%)
Varices	5	(5%)	6	(6%)	4	(4%)
Gastritis	12	(12%)	17	(18%)[2]	7	(7%)[2]
Carcinoma	4	(4%)	1	(1%)	-	-
Multiple	10	(10%)	7	(7%)	13	(13%)
Unknown	18	(18%)[4]	25	(26%)[3]	6	(6%)[3,4]

1 $X^2 = 7.126$ ($p<0.01$)

2 $X^2 = 6.784$ ($p<0.01$)

3 $X^2 = 17.250$ ($p<0.0005$)

4 $X^2 = 8.114$ ($p<0.005$)

Length of stay. There was no difference between the length of stay in the three groups (Table XIX).

Mortality. There was no difference in the overall mortality between the three groups.

The mortality rate in those who had a further haemorrhage was higher in the non-referral group compared to the management team patients ($p<0.001$) and of those who were shocked on admission none of the management team group died compared to 6 of the non-referral ($p<0.005$) and 5 of the endoscopy alone groups ($p<0.025$) (Table XIX).

Cause of death. Overall, blood loss was the most common cause, but only one of the management team patients died from this cause compared to 9 of the non-referral group ($p<0.025$) (Table XX).

Blood transfusion requirements. Table XXIa shows the amount of blood transfused (units) in those who had a further haemorrhage. There was no difference between the three groups.

Emergency surgery. There was no difference in either the number operated on or the resultant post-operative mortality (Table XIX).

Day of death. Overall, half died more than 5 days after admission, but 2 of the endoscopy group, 6 of

TABLE XIX . Outcome of patients in three groups.

	Endoscopy		Non-refer.		Management Team	
Number	(103)		(96)		(104)	
Death - Total	10	(10%)	13	(14%)	5	(5%)
Shock						
Number	6		11		6	
Death	5	(83%)	6	(55%)	0	
Rebleed						
Number	26		19		31	
Death	8	(31%)	11	(58%)	3	(10%)
Surgery						
Number	7		6		13	
Death	2	(29%)	2	(33%)	2	(15%)
Length of Stay						
Days SEM	9.5 ± 8.3		8.5 ± 10.7		8.9 ± 7.5	
Peptic Ulcers						
Number	22		20		48	
Death	3	(14%)	6	(30%)	2	(4%)
Operation						
Number	4		4		9	
Death	1	(25%)	1	(25%)	0	

TABLE XX. Cause of death. The table shows the cause of death in the three groups.

Cause	Endoscopy	Non-refer.	Management Team
Blood loss	6	9*	1*
Respiratory failure	1	2	-
Liver failure	-	-	2
Sepsis	3	-	1
Pulmonary embolism	-	-	1
Malignancy	-	2	-
Total	10	13	5

* $X^2 = 5.773$ $(p < 0.025)$

TABLE XXIa. Blood transfusion requirements in those patients who continued to bleed or who had a further haemorrhage (F.H.) The table shows the figures for the three groups. The figures represent the number of 'units' transfused. Percentages are given to the nearest whole number.

	Endoscopy		Non-refer.		Management Team	
F.H.	26		19		31	
Blood (pints)	n	%	n	%	n	%
None	3	12%	5	26%	2	7 %
1-5	9	35%	4	21%	8	26%
6-10	7	27%	5	26%	12	39%
> 10	7	28%	5	26%	9	29%

TABLE XXIb. The time after admission (in days) that death occurred in the three groups.

Time (days)	Endoscopy	Non-refer	Management Team
	n	n	
1	2	6	-
2	2	-	1
3	-	-	1
4	-	1	-
5	1	-	-
> 5	5	6	3
Total	10	13	5

the non-referral group and none of the management team patients died on the first day of admission (Table XXIb).

Outcome of gastric and duodenal ulcers. There was no difference in the number of patients undergoing emergency surgery or in the resultant mortality. However, the overall mortality in the non-referral group was higher than in the management team group ($p<0.05$).

4. DISCUSSION

At first sight, the results presented would seem to suggest that the management team provided an improvement in the outcome of these patients. However, certain features of this study require further examination.

The management team and non-referral patients were admitted during the same period of time, March to September 1977 and as they were not allocated randomly to the two groups, a degree of selection took place. All patients on admission were initially in the non-referral group. Some physicians as a matter of policy, did not refer their patients to the team. The decision to refer patients to the team was usually taken after endoscopy had been performed which was usually the morning after admission and the patients taken over by the team tended to be the ones bleeding from peptic ulcers, hence the disparity with duodenal ulcers between the two groups.

Six of the non-referral group died within 24 hours of admission. All of them had been admitted between noon and 2 a.m. (5 in a state of hypovolaemic shock) and all of them exsanguinated between 10 p.m. and the following morning. Four of them had bled from peptic ulcers. Thus the timing of their death precluded their possible inclusion in the management team group. Their selection to the non-referral group because of early exsanguination tends to invalidate four of the significant differences between the two groups, that is, mortality related to shock on admission, further haemorrhage, death due to blood loss and the mortality of those known to have bled from chronic peptic ulcers.

The endoscopy alone and management team groups were admitted at sequential periods of time. The former group comprised the total hospital admissions during December 1976 to March 1977 whereas the management team patients as already shown did not. Because of the reasons already described, the selection of the team patients would tend to invalidate the significant difference with mortality related to shock on admission.

In conclusion, there is no firm evidence that the management team produced an improvement in the outcome of patients admitted to the Western Infirmary.

It is worthy of comment that during this period of time there was a shock team available in the Western Infirmary and it was not called to see any of the patients admitted in shock.

CONCLUSIONS

The results of this study show that early endoscopy provided an accurate means of identifying the source of blood loss but did not appear to improve overall outcome. Emergency surgery for bleeding peptic ulcers had a high postoperative mortality in the first series and although there appeared to be an improvement in 1977, the number of patients operated on was too small to reach significance. The availability of the shock and haematemesis management teams did not appear to reduce the overall mortality or change the main cause of death (blood loss).

Doubts have been cast on the value of early endoscopy in relation to patient outcome[36,181]. Four prospective randomised controlled trials have shown that accurate diagnosis of the source of blood loss does not reduce the overall mortality[36,151,153,154]. Sandlow published the results of his trial in 1974, and examination of his data reveals that the group submitted to aggressive diagnosis (endoscopy) had a higher incidence of further haemorrhage than the group submitted to a conservative diagnostic approach ($p<0.01$). Because the occurrence of further haemorrhage could not be influenced by any medical therapy administered, the conclusions from his results are not valid[153].

Dronfield in 1977, failed to show an improvement in outcome with the group submitted to early endoscopy. However, 95 patients were excluded from the study and 44% of the total deaths came from the exclusions. Furthermore, 9 of these patients were admitted with massive continuing haemorrhage and either exsanguinated or underwent emergency surgery[151].

Petersen reported the same results from a similar study but there was also a degree of patient selection[154].

Graham reported the results of a study which had been performed to assess whether the information provided by endoscopy produced a change in therapy and found that this occurred in only 12% of the patients[36].

Two points of importance emerge, the first is that the patients who might benefit from early endoscopy (the massive bleeders) are not having the procedure performed. This is evident in Dronfield's study and the same situation occurred in the Western Infirmary. Thomas and others reported in 1980 on a survey of upper gastro-intestinal haemorrhage management in Britain and showed that severe bleeders were endoscoped within 4 hours of admission in only 61% of centres[31].

The second point relates to the findings of Graham that knowledge of the source of bleeding seldom changes the plan of management. With the exception of

the placement of a Sengstaken-Blakemore tube in a patient bleeding from oesophageal varices, there is no specific medical therapy available of proven value which will prevent or arrest further haemorrhage and thus it is medical therapy and not diagnostic endoscopy that is at fault.

If it is accepted that the occurrence of massive continuous or further haemorrhage is not influenced by medical management, then the crux of management is the recognition and treatment of this situation. The finding that blood loss accounted for more than 70% of the non-operative deaths in both the Western Infirmary series suggests that either the volume and rate of blood transfused was inadequate or that emergency surgery was not employed often enough. These findings are similar to those of Devitt's who was of the opinion that the main problem was the physicians' infrequent exposure to severe bleeders, thus causing the lessons, errors and understanding to be forgotten between cases. He also felt that all too often the responsibility for clinical assessment and resuscitation was left to junior members of staff and concluded that there was a need for a haematemesis team to treat these patients[182].

Hellers and Ihre reported on the improvement in outcome produced by a policy of early and vigorous diagnosis and management by a surgical team. They found

that with this policy, failure to reach a diagnosis and blood transfusion requirements fell whilst the operation rate increased[104]. Hunt came to a similar conclusion with the results from patients admitted to a haematemesis unit with a defined management policy[105]. The Western Infirmary study of 1977 suggests that even with the availability of both a shock and haematemesis team, the patients who might have benefited from such expertise did not receive it.

The solution, however, is not so simple as it appears. It has been shown in this study that many of the patients bleeding from the upper gastrointestinal tract are elderly and have coexistent cardiopulmonary disease. Allan and Dykes showed that the proportion of patients over sixty has and is increasing[102]. It has already been stated that emergency surgery is the accepted means of arresting further haemorrhage; however, the results from this study and the literature show that there is a significant postoperative mortality and this is especially true with the elderly. Dronfield analysed the causes of death in a series of 484 patients and concluded that most of the potentially avoidable deaths occurred in those patients who had undergone emergency surgery[106]. It is therefore reasonable to suggest that the mortality of this condition might be reduced if adequate resuscitation is carried out and emergency surgery is avoided by preventing further haemorrhage.

If primary bleeders (patients admitted because of this condition) are considered alone, then, excluding oesophageal varices, patients bleeding from chronic peptic ulcers are most liable to continue to bleed or have a further haemorrhage. Emergency endoscopy is the only accurate non-invasive means of identifying these patients. The fibre optic endoscope also affords direct access to the source of bleeding and thus allows the possibility of non-operative arrest of haemorrhage. If an effective means of arrest can be found, then emergency surgery could be avoided, and hopefully, the mortality could be reduced. It is for this reason that one form of therapy utilising the endoscope has been assessed, the use of laser radiation transmitted through a flexible glass fibre that can be passed down the biopsy channel of an endoscope to deliver heat to the source of bleeding. Data on the assessment of this form of therapy are presented in the following chapters.

CHAPTER THREE

LASERS AND FIBREOPTICS - THEORY, SAFETY AND EQUIPMENT

1. INTRODUCTION

In order to develop a laser system for a clinical application in medicine, it is necessary for personnel of different disciplines to cooperate and communicate with one another to achieve the desired end result. Thus the clinician involved should have not only a knowledge of the basic medical sciences but a knowledge of laser physics and technology, classical optics and physical chemistry so that equipment can be modified first for animal and then clinical research before its true efficacy for the intended medical application can be assessed.

In this chapter, the basic principles of electromagnetic radiation, laser and optical physics is presented. The interaction of electromagnetic radiation with matter is presented in the chapters relating to the experimental work. The laser equipment used and safety aspects relating to its operation will be outlined; however, details of the latter are presented in Appendix I .

2. THEORY OF LASERS

(1) Electromagnetic Radiation.

Electromagnetic radiation exhibits both wave and particle phenomena neither being mutually exclusive but complementary to one another[183]. The wave model of classical optics permits a description of a variety of optical phenomena associated with the propagation of electromagnetic radiation such as reflection, refraction, defraction, interference and polarisation and within this context, it is adequate[184]. However, other pnenomena such as those associated with absorption and emission of radiation and interaction with matter show that the classical theory is incomplete. These phenomena exhibit the particle nature of electromagnetic radiation which can be explained by the quantum theory of radiation, the basic concepts of which evolved from the explanation of black body radiation, the photo-electric effect, the Compton effect and the derivation of the Maxwell Boltzmann distribution of energy in a molecular system[141].

In its particulate aspect, electromagnetic radiation acts as small discrete bundles of energy called quanta or photons and the quantity of energy in a given photon is directly proportional to the frequency of oscillation of a given wave and is related by the formula $E = h \nu$ where h is Plancks constant[185].

The energy of a photon can only produce an effect when it is absorbed by matter and the ensuing interactions conform to the physical laws of nature. As the frequency of the electromagnetic spectrum decreases, a region is reached in which the photon energy, under normal circumstances, is insufficient to dislodge orbital electrons, and in biological systems, this lower limit is 12 electron volts[186]. Thus radiant energies below this level are referred to as non-ionizing electromagnetic radiation. The spectrum below this level consists of ultra violet (180 - 400 n.m.), visible (400 - 780 n.m.), near infra red (780 - 2.5×10^4 n.m.), far infra red (2.5×10^4 - 1.25×10^5 n.m.), microwaves (3 mm - 100 cm) and radio and television waves (1 m - 1000 m).

2. Quantum Theory of Emission and Absorption.

An electron can go from one energy level to another ($E_0 \rightarrow E_1$) by the absorption or emission of photons characterised by electromagnetic radiation at a frequency given by the equation

$$\gamma_{10} = \frac{E_1 - E_0}{h}$$

thus radiation at frequency γ_{10} incident upon an atomic system which has the exact spacing $\delta E = E_1 - E_0$ between energy levels, will cause the electronic state to increase from energy level $_0$ to $_1$ and this process is called absorption. The lifetime of this state is short and the electron will fall to state E_0 spontaneously and the system

will emit a photon of frequency V_{10}. This process is called spontaneous emission[187].

This explains the emission of discrete frequencies (line spectra) and the resonance absorption phenomena (ie. absorption at specific wavelengths).

3. Fundamentals of Laser Action.

Einstein suggested that there are two competing processes by which quantized energy may be released from radiating systems, ie. spontaneous and induced (stimulated) emission. If absorption is included, then it can be assumed that there are three possible energy state transitions for a system in thermal equilibrium:-

(1) Spontaneous emission - a system in excited state E_1 with a finite lifetime (t), will degrade to E_0 with the release of a photon and the speed of the transition is expressed by its transition probability Ao per unit time. This transition occurs independent of an electromagnetic force.

(2) Stimulated emission - a system of energy state E_1 will degrade to E_0 when a beam of energy density I (γ) interacts with that system resulting in the release of two simultaneous photons of identical energy and the transition for this process is B10 per unit time per unit energy density.

(3) Absorption - a system in state E_0 will rise to E_1 when a beam of energy density $I(\gamma)$ interacts with it. The transition probability for this process is Bol per unit time per unit energy density.

A_{10}, B_{10}, B_{01} are Einstein's transition probabilities for each of the three processes[188].

Formulae derived from the above show that if a photon is incident upon a system with either the ground or excited state occupied, the probability of absorption or stimulated emission are equal, but the Maxwell-Boltzmann distribution shows that at thermal equilibrium, the higher energy levels are less populated and therefore absorption is more likely to occur[187]. It can also be shown that the probability for spontaneous emission increases with the Cube Root of the frequency (γ^3) thus in the visible spectrum at room temperature, stimulated emission is virtually impossible, and thus a means of increasing the probability of stimulated emission is required. This can be achieved by inverting the Maxwell-Boltzmann distribution of energy levels (population invertion). This condition is necessary but not sufficient for laser emission[187].

(4) Population Inversion.

The process of population inversion is called pumping and with the Neodymium (Y.A.G.) laser it is achieved by optical pumping[188]. A high intensity light source (xenon flash lamp) supplies a sufficient photon

flux in a given spectral range. Because this range is a small fraction of the total lamp emission, the process is very inefficient.

The description of the fundamental action of a laser described a two level energy system, but in practice, most laser systems use a multi-level atomic system so that population inversion is more easily and efficiently achieved. The Neodymium Y.A.G. laser uses a 4 level system where population inversion occurs between the two intermediate states with a small proportion of the total population[188]. The system operates by the pumping of atoms from the ground state to a broad energy level (3). A fast non-radiative relaxation occurs preferentially to level (2) which acts as the upper laser level and this level is usually metastable because of its long relaxation time and an accumulation of atoms occurs at this state. Level (1) serves as the lower laser level and has a fast non-radiative relaxation time and is appreciably above the ground state. The population in level (1) is therefore small in comparison to level (2) and this ensures a population inversion between the two[188].

5. Basic Laser System.

There are three basic components to a laser system.

(1) Laser Media. This can be a solid, liquid, gas or the junction between two dissimilar metals which

is capable because of its atomic or molecular structure of sustaining stimulated emission.

(2) The source of excitation energy. This provides energy to produce population inversion by pumping.

(3) A Fabry-Perot Interferometer. This device is a pair of mirrors aligned parallel to one another at either end of the laser media. One of the mirrors is a total reflector and the other a partial reflector to allow emission of the laser radiation[189].

6. Operation.

Optical pumping provides excitation energy to produce population inversion so that stimulated emission can occur. The emitted photon stimulates another excited atom to release a photon of excess energy and the two combine to produce a beam of twice the intensity. The summated photons have identical coherence properties (Phase relationships). The process is repeated and the beam amplitude is increased rapidly whilst the coherence remains intact. When the beam reaches the totally reflecting mirror, the beam direction is reversed and it passes back through the laser media and is amplified further. On reaching the partially reflecting mirror, a portion of the beam escapes and this is the active emission of the laser.

Oscillation in the laser cavity is maintained as long as the amplification through stimulated emission

is sufficiently high to balance the attenuation of the beam caused by scattering due to optical inhomogenities, absorption in the mirrors and laser medium and the emission of part of the beam[188].

7. Mode Configurations.

The spontaneous emission from a laser medium displays an electromagnetic field with a superposition of plane waves each of slightly different frequencies and this is due to the multiple energy levels of the media. However, the laser cavity only allows some of them to oscillate and the others degenerate. The different frequencies that are allowed to oscillate between the mirrors are called the modes of the laser cavity. Because the longitudinal axis (2) of the cavity is much greater than the transverse (x and y), the field configurations in the cavity can be separated into longitudinal and transverse modes. The modes that oscillate are limited to the z axis with energy distributions in the transverse plane that do not spread significantly by diffraction. The modes are characterised by the notation T.E.M. (transverse electromagnetic waves)[188].

The oscillating modes can be altered by mirror alignment. The fundamental mode of the cavity is denoted $T.E.M._{00}$. This has the lowest losses and has a guassian distribution of intensity. The mode with a doughnut distribution of intensity is $T.E.M._{01}$. Thus by altering the modes, beams with different distributions of intensity can be produced.

8. Characteristics of a Laser Beam.

An emitted laser beam has the following characteristics. Due to the phase relationships of the electromagnetic waves, it has a high degree of spatial and temporal coherence. The spatial coherence relates to the nearly uniphase wavefront which results in the high intensity of the beam and temporal coherence relates to the monochromatic (single frequency) or narrow bandwidth of the light. Depending on the type of laser, the electric fields may be plane polarised[190].

Although lasers are thought to emit parallel beams of infinite length, in fact they diverge. This is because the partially reflecting mirror is not of infinite size, and in accordance with Huygen's principle, diffraction effects occur at the mirror aperture. The divergence of the beam is related to its diameter (D) and wavelength (λ)

$$\theta = \frac{\lambda}{D}$$

where θ is the half angle divergence (radians). The solid angle (Ω) into which the beam projects is related to the divergence by:-

$$\Omega = \pi\theta^2$$

where Ω solid angle (steradians)[190].

Even a low powered laser can emit an extremely bright beam of light. For example, the brightness of a I.M.W. helium neon laser is two orders of magnitude greater

than the sun.

9. Focussed Laser Beam.

A laser beam can be focussed by a lens and the resultant beam radius (waist) is given by $d = F\theta$ where d is the spot diameter (cm), F is the focal length of the lens (cm) and θ the beam divergence (radians). The area of the spot (focussed point) is given by[191]

$$A = \frac{\pi F^2 \theta^2}{4}$$

10. Laser Beam - Parameter Characterisation.

The radiometric units used are defined by the Système International (S.I.). The laser source is characterised by :-

(1) Radiant energy - the total quantity of energy emitted. Units are Joules (J).

(2) Radiant power - the rate at which energy is emitted. Units = watts (w).

(3) Radiant intensity - the spatial distribution of the emitted energy. Units = watts per steradian ($w\ Sr^{-1}$).

(4) Irradiance (intensity, power density). The measure of how much power from the source is falling in unit area of receptor surface. Units = watts per square metre ($w\ m^{-2}$).

(5) Radiance (brightness). The radiant intensity of the beams per unit area of surface. Units = watts per steradian per square metre (w $Sr^{-1,-2}$).

(6) Spectral radiance. The radiance per unit frequency interval. Units = watts per steradian per metre squared per unit frequenty (Hertz) (w Sr^{-1} m^{-2} Hz^{-1}).

The wavelength of the emitted radiation is expressed in nano-metres (m^{-9}) or occasionally micrometres (microns) (m^{-6}).

11. Modes of Operation.

Lasers are operated in one of the following modes of operation:- continuous wave (CW), pulsed, Q switched, mode locked or cavity dumped[188]. These operation modes produce different power output envelopes. Continuous wave operation emits a wave of continuous power. Pulsed operation is characterised by emission of bursts of relatively high energy pulses at varying repetition rates. The power of the pulse in an idealised output is almost constant for its duration. Cavity dumping, Q switching or mode locking techniques produce extremely short duration, high peak power pulses, and the power obtainable in the short pulse greatly exceeds that which can be achieved during continuous wave or pulsed operation.

12. Neodymium Y.A.G. Laser.

This is a solid state laser in which the laser media is composed of the trivalent rare earth ion neodymium (Nd) in a host material of yttrium aluminium garnet (Y.A.G.). The media operates as a 4 level system and therefore has much lower threshold levels than a 3 level system, eg. a ruby laser.

The laser operates in the infra-red part of the spectrum and is therefore invisible and has a corresponding reductionin energy per photon compared to lasers operating at shorter wavelengths. The metastable upper laser level has a lifetime of approximately 0.25 ms and thus Q switching is possible (unlike the Argon laser). Laser transition normally occurs at a wavelength of 1064 n.m. with a line width (frequency spread) of approximately 13 G.Hz.[188]

The system can operate in continuous wave, Q switched or in a pulsed mode. It is also possible to repetitively Q switch the Y.A.G. with continuous pumping. The emission can be frequency doubled (second harmonic generation) but the efficiency of this is low.

3. FIBREOPTIC TRANSMISSION OF LIGHT

When light passes from one transparent material to another and its velocity changes, then refraction (bending) of the light occurs. The angle of refraction is governed by Snell's law.[192]

If light is refracted into a flexible light-guide (fibre) the necessary condition for propagation in that fibre is total internal reflection, otherwise the light refracts out. Total internal reflection at the fibre boundary occurs when the angle of refraction is 90^{o} (Sin. $\theta = 1$) and for this to occur, there is a critical angle of incidence upon the boundary which depends upon the refraction indices of the fibre and adjacent material[193]. The angle of incidence varies according to the angle of acceptance of the light upon the fibre end. For any fibre, there is a maximum angle of acceptance for light propagation and this is called the numerical aperture (N.A.). At angles greater than this, propagation does not occur.

$$NA = \text{Sin. } \theta = \sqrt{\mu_1^2 - \mu_2^2}$$

where θ = half the acceptance angle, μ_1 = refraction index of fibre and μ_2 refraction index of surrounding material[193]. If these conditions are met, then propagation occurs even if the fibre is bent.

In a simple fibre, the propagated light field extends beyond the boundary of the transmitting material and thus any contact with the fibre will disrupt the field. To remove this problem, fibres are clad with a material of lower refractive index so that total internal reflection occurs at the interface between the two materials. If the difference of the refractive indices is small, then the numerical aperture of the fibre is

increased[194]. This type of light guide is referred to as a single step index cylindrical fibre. The central section for light propagation is called the core and its coat, the cladding[195].

Attenuation of light within the core occurs as a result of intrinsic scattering and absorption by ions, and for a given core material, the attenuation has a spectral dependency. The efficiency of light transmission in a fibre is expressed as a percentage of the light source[196].

The materials used for fibre optics are glass, silica, quartz and plastic, each having particular characteristics for light propagation. The spectral range of light (electromagnetic radiation) that can be transmitted through a fibre varies from 0.25 - 2.5 μm[196].

When laser radiation is used as the light source, its radiation is focussed by a lens onto the fibre tip, the spot size of the focussed beam should be approximately half the core diameter[193]. Because of the radiation intensity involved, the position of the beam spot and the fibre tip has to be kept constant otherwise fibre tip damage occurs.

The exit beam divergence depends on:-

(1) the focal length of the lens. However this is negligible when it is greater than 25 mm;

(2) wavelength of laser radiation (refraction);

(3) mode of laser emission (TEM_{00} mode has lowest divergence);

(4) fibre core diameter.

In general there is an inverse relationship between core diameter and beam divergence in a cylindrical fibre. Because the exit beam divergence has a non homogenous energy distribution, the criteria for full angle divergence is where the beam intensity falls to $1/e^2$ of the maximum. With a divergent emission beam, the intensity varies with the distance from the fibre and the energy distribution in the beam itself which in turn is dependent upon the mode emitted from the laser.

Fibres used for light transmission in clinical practice require the following properties:

(1) high optical power performance;
(2) low optical attenuation;
(3) suitable intensity distributions and sufficient small beam divergences at the distal tip;
(4) sufficiently small fibre diameter for endoscope biopsy channels;
(5) sufficiently high fibre flexibility for endoscope biopsy channels;
(6) mechanical robustness for clinical use;
(7) sufficient thermal stability with the radiation intensities used;
(8) ease of fibre end preparation.

The first three properties have been referred to. Because of the radiation intensity of the Neodymium Yag laser emission, the smallest cylindrical fibre that can be used has a 200 μm core diameter. Fibres with smaller diameters are damaged at their proximal tip. The fibre requires a radius of curvature smaller than that of the distal tip of an endoscope and it has to be robust enough to withstand the stresses imparted by clinical use and finally it should be able to function despite changes in temperature caused by propagation of laser radiation.

The tip (face) of the fibre requires a flat perpendicular end face for efficient emergence of the beam to occur, otherwise light is scattered and equipment can be damaged by absorption of radiation. When a fibre is fractured, the face comprises three regions known as the mirror, the mist and hackle zones. The mirror zone allows the emergence of the beam; however, the hackle causes light scattering and the fibre has to be fractured in such a way as to minimise the hackle zone. The theory behind fibre cleaving has been documented[197], and for laboratory use, efficient fibre cleavage is necessary.

4. LASER RADIATION HAZARDS AND SAFETY CONSIDERATIONS

Laser systems are potentially hazardous because of the unique properties of the emitted radiation and the high electrical voltages required for operation, and thus aspects of safety are concerned with both these hazards.

The unique property of the non-ionising laser radiation is due to its spatial and temporal coherence which can propagate over large distances without major changes in its characteristics and because of the intensities that can be obtained. The eyes and skin are therefore at risk both from a direct or reflected beam. The beam can be diffusely or specularly reflected. However, even with diffuse reflection, the intensity of the radiation may be sufficient to produce irreversible damage. Radiation incident upon a cornea is either absorbed, back scattered or transmitted. The cornea is transparent to radiation between 300 - 1400 n.m. and the optical gain of the transmitted light varies from 2×10^5 - 5×10^5. The damage to the tissues of the eye or skin occurs as a result of absorption of radiation, which is converted to thermal energy. Two further mechanisms of tissue damage are photochemical reactions or the production of thermoacoustics.

Electrical hazards arise because of the high quantity required for optical pumping. The Neodymium YAG requires a three phase electrical supply with 50 amperes per phase. Appendix I outlines the safety measures required for the use of lasers in a University laboratory and in the clinical setting.

5. LASER EQUIPMENT USED FOR ANIMAL WORK

The laser used was a Neodymium YAG laser (λ = 1.06 μm) which was modified from 'bread board' type equipment. The system used in the animal work consisted of the power supply/cooler unit, the laser unit and control boxes. The laser unit (laser media and optical components) was placed in metal housing for reasons of safety. A helium neon laser (λ =.6328 μm) with a continuous wave output of 2 M.W. was incorporated in the Nd. YAG optics to provide a visible target marker. Throughout the experiments the laser was operated in the continuous wave mode of output and the laser cavity was adjusted to permit a mode configuration of TEM_{01} (doughnut). The exit beam of the laser was focussed with a lens held in an XYZ micropositioner onto the tip of a single step index glass fibre with a core diameter of 400 μm. This allowed efficient launching of the beam into the fibre optic. The fibre tip was held in a constant position by a metal block fastened to the end of the housing and the fibre itself was encased in a flexible metal tube which terminated in a 'pencil' (Figure 2) which facilitated holding and fibre cleavage.

The control boxes permitted variation of the peak power output and the time duration of the pulse. The system allowed a variation of peak power from 30 - 120 watts and pulse duration of 0.1 - 10 seconds. Two meters on the control measured the peak power (watts) and total energy

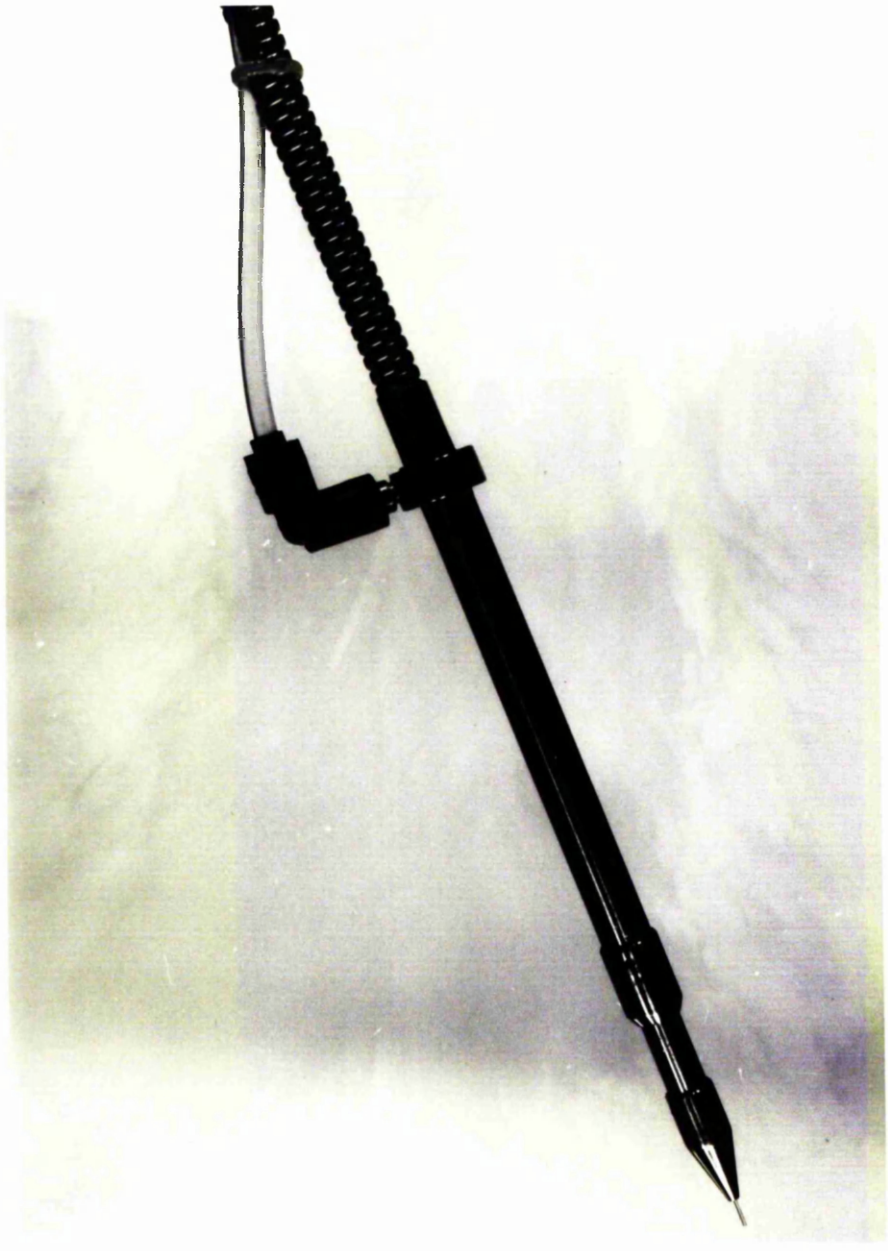


Figure 2. The laser pencil. At the lower extremity of the pencil, the glass fibre can be seen projecting from the pencil. The polyethylene tube connected to the pencil conveys the CO_2 to it. The helical coil connected to the pencil base is flexible and acts as a conduit for the fibre from the laser.

(Joules) emitted by the laser system itself. The peak power emitted at the fibre tip was measured with a coherent power meter. The exit beam divergence from the fibre had been measured by Barr and Strouds and was found to be 10^{o}.

The laser was fired by means of a pneumatic foot switch which activated lights on the control box and laser housing. It also activated a monotone sound of five seconds duration prior to the actual emission of the beam which was signalled by a second monotone sound of higher frequency which lasted for the duration of the emitted laser pulse. The laser could not emit radiation if any of the safety interlocks were in operation.

Carbon dioxide gas was delivered via a polyethylene cannula which was connected to the base of the laser pencil and this allowed emission of the gas coaxial to the fibre tip at a flow rate of 60 - 70 mls sec^{-1}. The flow of gas was controlled from the carbon dioxide cylinder.

The electricity supply to the laser power/coolant unit was obtained from a three phase system specially constructed for the laser and the water for the external cooling system obtained from the sink tap in the laboratory.

The laboratory had been altered to meet the safety requirements outlined in Appendix I[illegible]. The mod-

ifications made to the fibre optic system for the dog work and clinical use will be outlined in the respective sections.

CHAPTER FOUR

THE EFFECT OF NEODYMIUM YAG LASER RADIATION ON THE STOMACH WALL

1. INTRODUCTION

In order to obtain a basic understanding of the effects of laser radiation on biological systems, it is necessary to have an appreciation of the interaction between non-ionizing electromagnetic radiation and matter at the molecular, cellular and tissue level.

The energy of electromagnetic radiation can only produce an effect on matter when it is absorbed. The absorbed energy produces a change in either the electronic energies of its atoms or changes the rotational or vibrational energies of the molecules and these changes conform to the physical laws of nature[186].

The capacity of a molecule to absorb radiation of a particular wavelength is dependent upon its molecular configuration and the electronic configuration of possible higher energy states[198].

The modes of action of radiation on molecules are either photochemical or thermal. Electronic excitation produces a dissociation of molecules if the bonding electrons are involved and the excitation energy is

dissipated in the form of fluorescence, phosphorescence, free radical formation or degradation into heat. The photochemical responses of biological molecules occur primarily with radiations from the ultraviolet and visible parts of the spectrum because of their respective photon energies[186].

For thermal reactions to occur, the energy absorbed may be supplied either by the relaxation of excited electronic states into the vibrational modes of the molecule (internal conversion) or by direct excitation of the vibrational bands.

The photon energies of infrared radiation (λ = >700 n.m.) are insufficient under normal circumstances to produce a change in the electronic configuration of a molecule and absorption produces changes in the vibrational energy levels of molecules resulting in dissipation as heat and in relation to a large number of molecules, this change is realised by a rise in temperature[199]. Thus, the radiation emitted by the Neodymium YAG laser (λ = 1060 n.m.) produces a thermal mode of action on molecules.

The distribution of temperature change in tissue depends upon the parameters of the radiation, (wavelength, energy, power, intensity etc.), the distribution of the radiation within the tissue itself as a result of scattering, reflection, or absorption due to the fact that tissue is not a homogenous medium and finally because of

the intrinsic thermal paremeters of the tissue itself (specific heat, thermal conductivity etc.).

The physical and biological changes in tissue depend upon the rate and rise of temperature. The resultant rise in tissue temperature affects cells primarily by thermal denaturation of proteins and as a consequence of this, there are three basic modes of cellular reaction namely, immediate or delayed death which manifests as tissue necrosis, or a transient change in the functional state of the tissue[200].

As a prerequisite to the assessment of Neodymium YAG laser radiation as a means of arresting blood loss from a vessel in the upper gastrointestinal tract, it is necessary because of the high intensity of radiation involved to obtain an idea of the effects this radiation has on the stomach wall. This is of special relevance because of the possible risk of total thickness necrosis of the stomach wall and the attendant complications of a perforation in a patient.

Two sets of studies were performed to assess the effects of Neodymium YAG laser radiation on the gastric wall of an animal, and are presented separately as study I and II. The aims, materials and methods, results and discussion of each study are presented separately and finally, a general conclusion appears at the end of the chapter.

2. STUDY I.

The assessment of the effects of Neodymium YAG laser radiation on the stomach wall of New Zealand white male rabbits.

(1) AIM.

The aim of the study was to determine the effects of Neodymium YAG Laser radiation on the stomach wall of New Zealand white male rabbits and to see if the resultant tissue changes occurred in a predictable way. The parameters of the emitted radiation were varied and the resultant tissue changes were assessed immediately and at four days by recording the visual and histological appearances.

(2) MATERIALS and METHODS.

The laser equipment used has been described in Chapter 3. Transmission measurements of the exit beam showed a fibre transmission efficiency in excess of 90%. Calibration checks were made at the end of each experiment and in all cases, the peak power error was $<\pm 5\%$.

The laser equipment and laboratory safety measures satisfied the University laser safety regulations (Appendix I).

ANIMAL EXPERIMENTS

Twenty New Zealand white male rabbits weighing 3 - 3.5 kgms. were used. Food but not water was withheld for 18 hours before each experiment. Anaesthesia was induced and maintained with Halothane and Oxygen. The abdomen was opened through a midline incision and an anterior gastrostomy was performed. Laser induced lesions were produced at eight specified sites in each animal (Figure 3).

Three sets of experiments were performed.

Experiment A - Acute lesions.

Eight animals were used. Lesions were induced with varying peak powers at 8 increments of 10 watts from 40 - 110 watts. These powers were allocated randomly to the different sites in all eight rabbits. In each instance the time duration of the power was 1 second. The laser pencil was kept at a distance of 1 cm from the mucosal surface in four rabbits and 2 cm in the remaining four.

In addition coaxial carbon dioxide was allocated randomly to four of the rabbits.

The animals were all sacrificed within 2 hours of the start of each experiment.

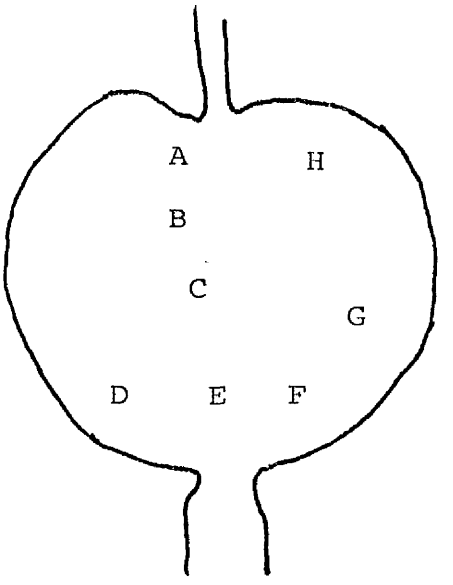


Figure 3.

Standard sites of laser induced lesions in rabbit stomach.

Site A = anterior wall of body, 1 cm distal from oesophago-gastric junction

B = anterior wall of body (lesser curve aspect) distal to A

C = lesser curve of stomach on incisura

D = antrum - anterior wall

E = antrum - lesser curve

F = antrum - posterior wall

G = body - posterior wall

H = body - posterior wall proximal to G.

Experiment B - 4 day lesions.

Eight animals were used and the same protocol as experiment A was used. The animals were sacrificed four days after induction of the laser lesions. All eight animals survived for four days.

Experiment C - constant energy lesions.

Four animals were used. Lesions were induced at the eight sites by the laser pencil which was kept at 1 cm distance from the tissue. Coaxial carbon dioxide was used throughout. Two animals were assigned to receive a total incident energy at each site of 60 joules. The peak power was varied from 30 - 120 watts, with an appropriate exposure time. In the remaining two animals a total incident energy of 120 joules was used at each site.

Each animal was sacrificed within two hours of the start of each experiment.

Assessment of Lesions.

Each lesion was excised from the stomach and pinned onto cork. The specimens were preserved in 10% buffered formalin. The specimens were examined by (SSR) without the prior knowledge of the laser parameters used.

The specimens were examined using a hand lens and the macroscopic changes documented. The surface area of each lesion was measured. If circular by $A = \pi R^2$ or

ovoid by $A = \frac{\pi ab}{4}$ where a and b represented the orthogonal diameters of the lesion[201].

For histology, each specimen was bisected at the site of the lesion. The sections were cut at three levels through the blocks and stained as follows:

1st level - haemalum - eosin (H & E), Gordon Sweet's Silver impregnation for reticulum and periodic acid Schiff (P.A.S.)

2nd level - haemalum - eosin (H & E) Elastic van Gieson (EVG) and Marche's Scarlet Red (MSR).

3rd level - haemalum - eosin (H & E).

The sections were examined for depth of tissue necrosis, loss of tissue and evidence of inflammatory reaction.

Treatment of Results.

Means, standard deviations and standard error of the means were calculated for each group of results. Students t tests (unpaired) were used to test for significant difference between groups. Correlation coefficients and regression line analysis were used for correlation of data. For comparison of absolute figures, chi squared test with Yates correction was used. Significance was estimated for $p<0.05$.

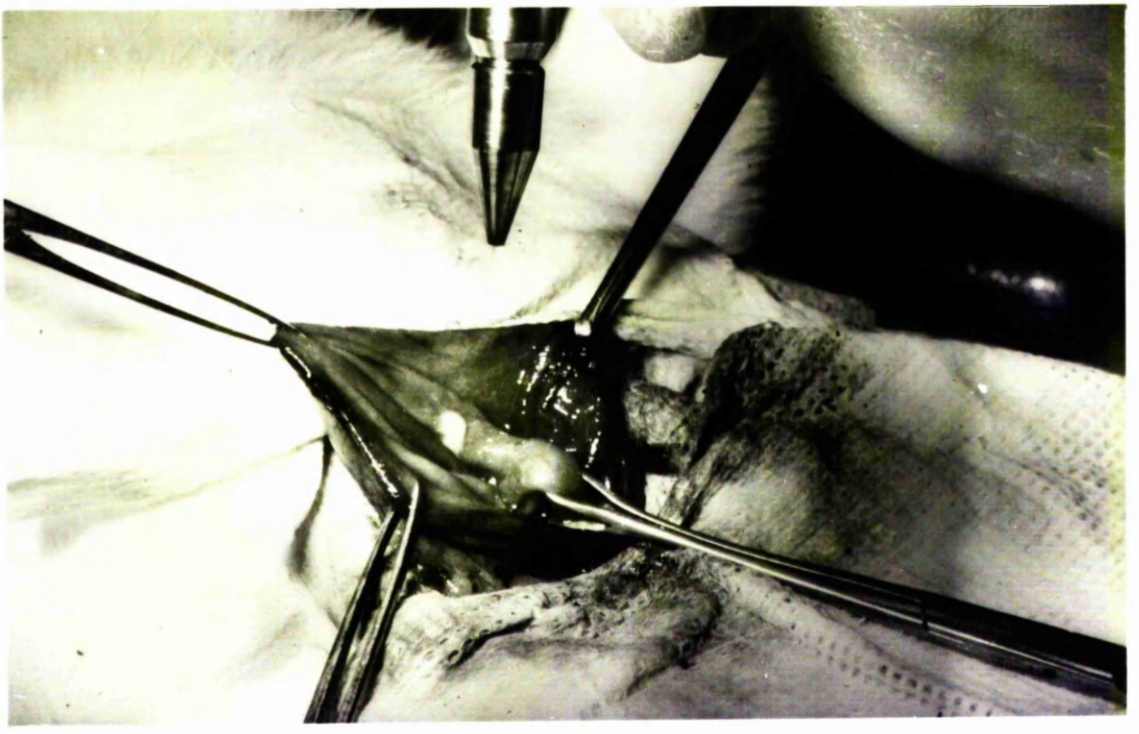


Figure 4. Acute lesion in rabbit stomach.
Shown is the laser pencil pointing at the rabbit stomach which has been held open with tissue clamps. Directly beneath the pencil is a circumscribed area of pallor on the mucosa. In this particular picture, the halo of hyperaemia is not readily apparent.

(3) RESULTS

Figure 4 depicts a typical acute lesion produced by the laser radiation. It shows a central pallid area surrounded by a halo of hyperaemia. At the 64 sites in the acute study, 26 of the lesions were circular and 26 ovoid, and at the remaining 12 sites (19%) there were no apparent visual changes in the mucosa. In each instance, the laser emitted the appropriate peak power and total incident energy. At one site there was loss of mucosal substance.

Surface area of lesions.

Study A. The results are denoted in Table XXIIa. The mean surface area of the lesions produced with the fibre tip 1 cm from the mucosal surface was 21.7 ± 3.1 mm^2 (mean ± S.E.M.) compared to 12 ± 2.7 mm^2 with the fibre tip held at 2 cm ($p<0.05$).

With the fibre tip held 1 cm from the mucosal surface, the addition of coaxial carbon dioxide reduced the surface area to 10 ± 1.7 mm^2 ($p<0.001$). However, at 2 cm it made no difference.

There was a positive correlation between the surface area of the lesions and the incidental peak power ($r = 0.86$; $p<0.01$) (Figure 5).

TABLE XXII.

A. Surface area of gastric mucosal coagulation produced by Nd. YAG laser radiation immediately and at 4 days. Shown are the respective surface areas ($mm^2 \pm 1$ SEM) produced by the laser pencil tip held 1 or 2 cm from the mucosal surface with or without coaxial carbon dioxide (50 - 60 mls.min^{-1}).
Differences calculated by students t-test (unpaired) with significance at the 5% level.

LASER		SURFACE AREA (mm^2)	
Distance	$\pm$ CO_2	Acute	4 days
1 cm	-	21.7 ± 3.1 (1,2)	21.3 ± 2.4 (3)
1 cm	+	10 ± 1.7 (1)	10.6 ± 2.3 (3)
2 cm	-	12 ± 2.7 (2)	20.2 ± 4.7
2 cm	+	9.8 ± 2.4	14.4 ± 4

(1) $p < 0.001$ (2) $p < 0.05$ (3) $p < 0.02$

B. Surface areas of lesions produced by Nd. YAG laser radiation with constant radiant energies of 60 or 120 joules. The peak powers used were low (30-60 watts) or high (75-120 watts).

Energy (joules)	n	Power (watts)	Surface Area (mm^2)
60	8	30-60	4.3 ± 0.8 (4,5)
60	8	75-120	8 ± 1.1 (4,6)
120	8	30-60	15.3 ± 2.5 (5)
120	8	75-120	19.8 ± 1.5 (6)

(4) $p < 0.025$ (5) & (6) $p < 0.001$.

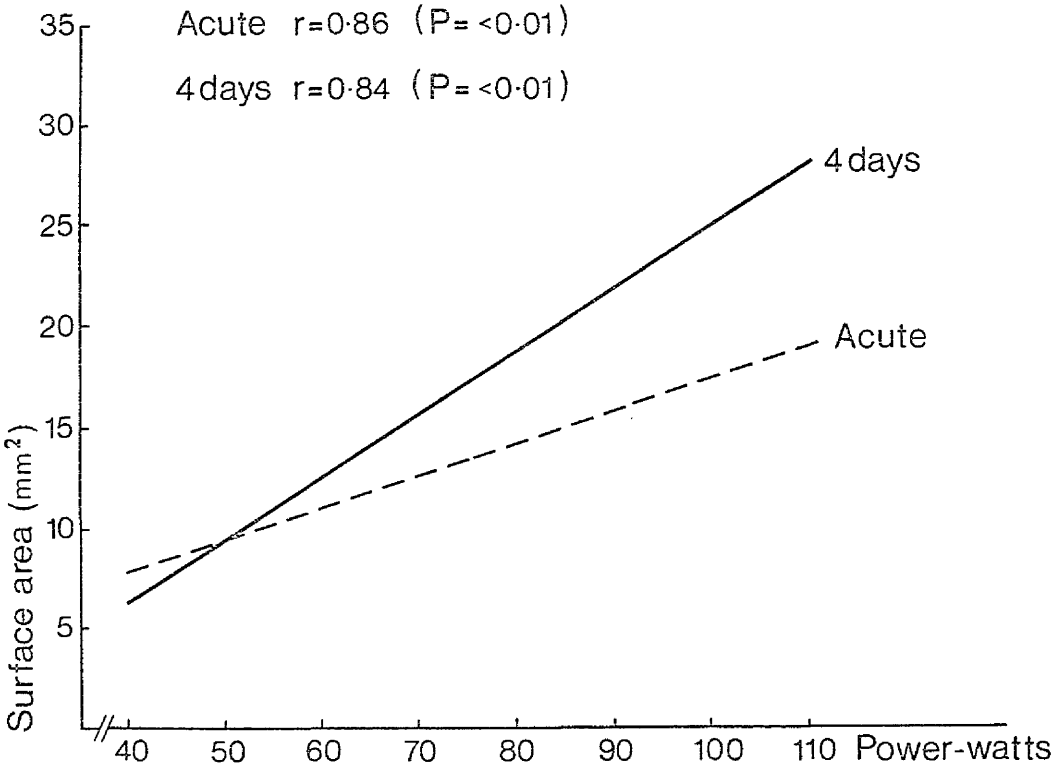


Figure 5. Correlation of surface area of mucosal lesions and increasing peak powers of radiation, immediately and at 4 days. The surface areas of the lesions (mean mm^2) are plotted against increasing peak powers from 40-110 watts in 10 watt increments.

Study B. The results are denoted in Table XXII(a). There was no difference in the surface area of the lesions in relation to the distance of the fibre tip from the mucosal surface. However, the addition of coaxial carbon dioxide reduced the surface area from 21.3 ± 2.4 mm^2 to 10.6 ± 2.3 mm^2 when the fibre tip was held 1 cm from the mucosal surface ($p<0.02$). At 2 cm the addition of the gas made no difference.

There was a positive correlation between the surface area of the lesions and increasing incidental peak powers ($r = 0.84$; $p<0.01$) (Figure 5).

Comparison of Studies A & B. There was no significant increase in the mean surface areas of the lesions between the acute and four-day studies, and this was irrespective of the parameters of radiation used.

Study C. Table XXIIb shows the surface area (mean ± SER) of lesions produced with the incident radiant energies kept constant at 60 or 120 joules with varying low (30-60 watts) or high (75-120 watts) peak powers. At 60 joules, the surface areas of the lesions produced with high powers were larger (8 ± 1.1 mm^2) than those using low power (4.3 ± 0.8 mm^2) ($p<0.025$). At 120 joules, there was no difference between the low or high power groups.

Histological Appearances and Depth of Necrosis.

Study A. The major pathological change observed by histology was a coagulative necrosis of the stomach wall extending to different depths of the tissue and this was seen at 52 (81.3%) of the sites. In addition, there was evidence of capillary congestion in 49 (77%), extravasation of red cells in 24 (38%) and tissue oedema in 6 (9%). At the remaining 12 sites (19%) there was no evidence of coagulation necrosis or any of the other changes observed.

Table XXIII depicts the extent of coagulative necrosis in relation to the radiation intensity and coaxial carbon dioxide. The absence of coagulative necrosis was seen more frequently when the laser pencil - mucosa distance was 2 cm and coaxial carbon dioxide was applied compared with the application of the laser and gas at 1 cm ($p<0.05$).

The occurrence of full thickness muscle necrosis was reduced from 5 of 16 sites to none when coaxial gas was added at 1 cm ($p<0.05$). However, at 2 cm there was no difference when the gas was used. Overall full muscle thickness necrosis occurred in 10 (16%) of the lesions but in none of them was there evidence of serosal damage.

Figure 6 shows the distribution of the depths of necrosis of the lesions produced in relation to the

TABLE XXIII.

The effect of power density and coaxial carbon dioxide on the depth of coagulative necrosis in the stomach wall immediately and at 4 days. The results are expressed as the actual number of sites at which there was no evidence of necrosis, the occurrence of full muscle tissue necrosis or serosal damage with each parameter used. X^2 squared test with Yates correction used to test statistical significance.

Fibre Distance	CO_2	No.	No necrosis		Full muscle necrosis		Serosal damage	
			Immed.	4 days	Immed.	4 days	Immed.	4 days
1 cm	-	16	0	0	$5^{(2,4)}$	$13^{(3,4)}$	0	1
1 cm	+	16	$1^{(1)}$	1	$0^{(2,5)}$	$8^{(5)}$	0	2
2 cm	-	16	4	0	4	$3^{(3)}$	0	3
2 cm	+	16	$7^{(1)}$	4	1	5	0	0
		64	12	5	$10^{(6)}$	$29^{(6)}$	$0^{(7)}$	$6^{(7)}$

Significance:-

(1) $p < 0.05$
(2) $p < 0.05$
(3) $p < 0.005$
(4) $p < 0.025$
(5) $p < 0.005$
(6) $p < 0.001$
(7) $p < 0.05$

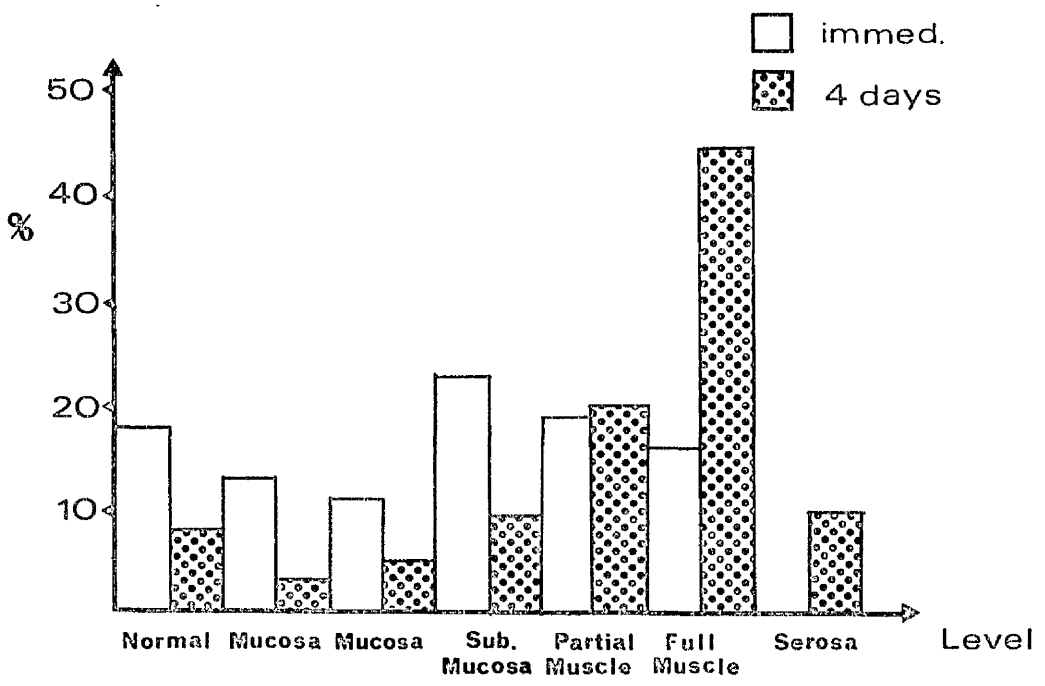


Figure 6. Depth of necrosis within the gastric wall immediately and at 4 days. Shown is the percentage of the total number of lesions occurring at each level of the stomach wall.

different layers of the stomach wall and shows that the most common level of necrosis was the submucosa with a decreasing proportion in the layers superficial and deep to it.

There was no correlation between peak powers and resultant depth of necrosis.

Study B. There was histological evidence of tissue coagulative necrosis of varying depths at 59 (92%) of the sites. The other changes seen were capillary congestion in 21 (33%), extravasation of red cells in 49 (77%) and localised oedema in 18 (28%). Fourteen of the lesions (22%) had loss of tissue substance (ulceration). Acute inflammatory cell infiltration of the necrotic zone was observed in 28 (48%) of the sites with necrosis. With the exception of coagulative necrosis, the occurrence of these pathological features was not influenced by any of the parameters used.

Table XXIII depicts the extent of coagulation necrosis in relation to radiation intensity and coaxial carbon dioxide. The absence of necrosis was not affected by any of the parameters used. Full muscle thickness necrosis was found in 29 (45%) of the lesions and increasing the laser pencil-mucosal distance from 1-2 cm reduced its occurrence from 13 to 3 ($p<0.005$). However, the addition of coaxial carbon dioxide did not influence the occurrence of full muscle necrosis at either distance.

At 6 sites (9%) there was evidence of damage to the serosa in addition to full muscle necrosis but at no site was there evidence of perforation.

There was a positive correlation between the occurrence of full muscle thickness necrosis and incidental radiation peak powers between 40 and 110 watts (Figure 7) ($r = 0.74$; $p<0.05$).

Figure 6 shows the percentage of the total number of lesions occurring with a maximum depth of necrosis corresponding to a given tissue layer and that the most common depth was down to but not including the serosa.

Comparison of Studies A and B. By 4 days, the occurrence of full muscle necrosis had increased from 10 to 29 ($p<0.001$) and at 1 cm there was also an increase with or without the use of coaxial carbon dioxide ($p<0.025$ and $p<0.005$ respectively).

In the acute study, there was no serosal damage but by 4 days it had occurred at 6 sites ($p<0.05$). Loss of tissue substance had also increased from 1 to 14 by 4 days ($p<0.001$).

Study C. At each energy level used, there was no difference in the distribution of full muscle thickness necrosis but when the energy level was 60 joules, it occurred at only 3 sites (19%) compared with 11 (69%) when

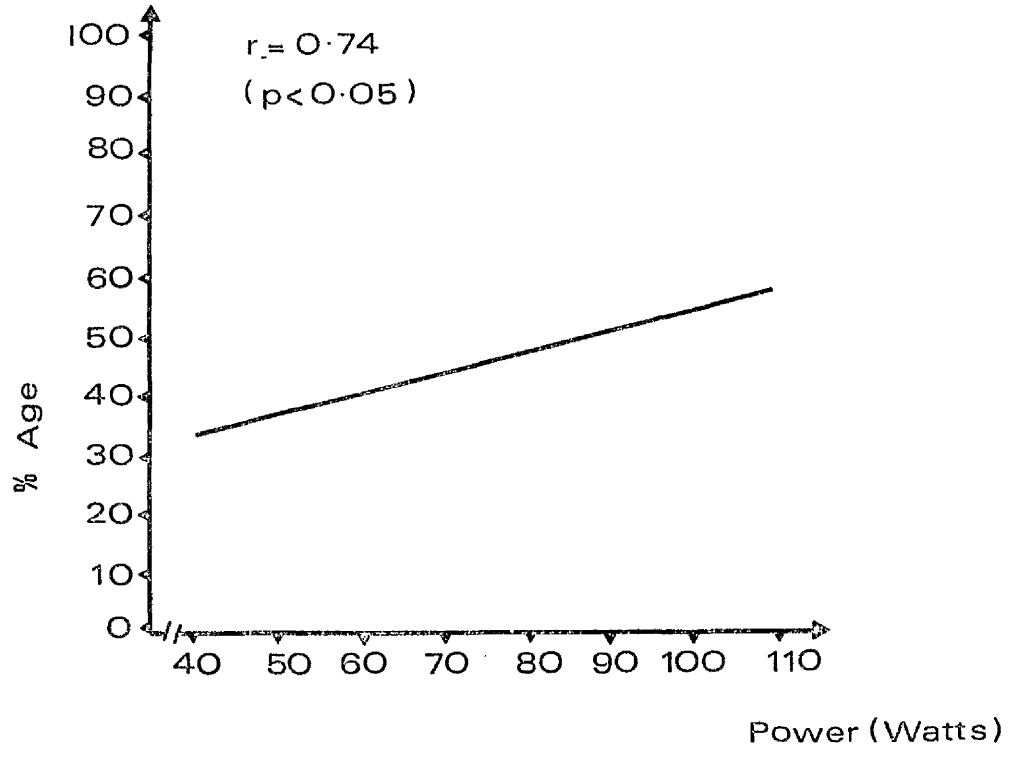


Figure 7. Correlation between full muscle thickness necrosis and incremented peak power 4 days after laser radiation.

120 joules was used.

Comparison of surface area in relation to depth of necrosis.

Figure 8 depicts the surface areas (mean ± SEM) for each level of necrosis immediately and at 4 days. There was a progressive increase in depth of necrosis with increasing surface area of coagulation in the acute study. The mucosal necrosis surface area was 8.3 ± 2.3 mm^2 as compared to 18.7 ± 3 mm^2 at partial muscle and 22.4 ± 3.9 mm^2 at full muscle necrosis levels ($p<0.02$ in both).

Although the 4 day results show a trend towards an increase in surface area in relation to depth of necrosis none of the values showed a significant difference.

There was no difference in the surface area values between the acute and 4 day groups at any of the levels of necrosis depicted.

(4) DISCUSSION

The spectrum of visual changes seen on the mucosa (hyperaemia, pallor and loss of substance) result from a thermal stimulus. They are not specific to laser radiation and can also be seen in other tissues, for example, skin, liver or muscle. For a given quantity of radiant energy, the degree of tissue change depends upon the rate and actual rise of temperature and upon the intrinsic thermal

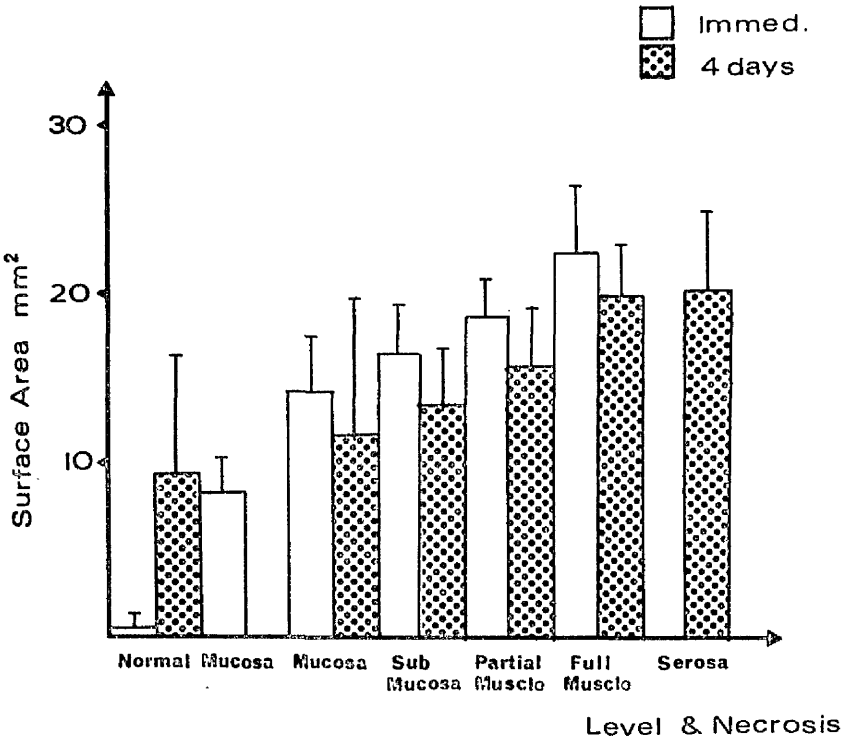


Figure 8. Comparison of surface area and corresponding depth of necrosis immediately and at 4 days.

factors of the tissue which may vary from site to site in relation to its thickness and cellular components, variations in existing temperature gradients, differences in tissue blood flow[202] and overlying mucus. Furthermore, the distribution of energy within the tissues depends upon the intrinsic optical properties of that tissue[203].

The sites lacking visual changes, probably received thermal stimuli below the threshold necessary to produce a vascular reaction.

The hyperaemia represents a dilatation of the superficial mucosal vessels and this change occurs below the thermal threshold necessary for epithelial necrosis[204].

The most frequent change observed was the discrete area of pallor with a surrounding halo of hyperaemia. The pallor represents a thermal denaturation (coagulation) of the tissue which is produced before there is time for a vascular reaction to occur[204] and the visual appearances are due to a change in the optical properties of the cells caused by a denaturation of intracellular proteins which produce a scattering of the incident light[205]. The halo of hyperaemia is caused by a slower rise of temperature to a level below that necessary for denaturation.

With the laser pencil held 1 cm from the mucosal surface, the surface area of the beam on the mucosa is 2.4 mm^2 (spot size diameter = 1.8 mm). However, the

resultant mean surface area of denaturation was 21.7 ± 3.1 mm^2, that is, 9 times the area of the beam. This increase is due to redistributive internal scattering of the radiation within the tissue causing an increase in the area of absorption[206] and to thermal conduction of heat within the tissue.

The reduction of the denatured surface area when the laser pencil - mucosal distance was doubled to 2 cm. occurred despite the surface area of the beam increasing to 9.62 mm^2. This is due to the fact that with a given radiant energy, when a beam is divergent, doubling the distance reduces the energy density fourfold.

When the laser was fixed at 1 cm from the mucosal surface, the addition of coaxial carbon dioxide reduced the surface area of denaturation and this probably occurred as a result of the gas producing a reduction in the mucosal surface temperature[207]. The presence of the coaxial gas at 2 cm did not reduce the surface area, possibly because at that distance the effect of the gas would be much less.

That increasing incidental peak power should produce an increasing area of denaturation is borne out by the positive correlation determined in this study.

By four days, the surface areas of the lesions had not increased in comparison with the values found

immediately after laser irradiation and this was the case irrespective of the radiation intensity (distance) or the presence or absence of coaxial carbon dioxide. The only difference between the values found at 4 days was the reduction in mean surface area of lesions produced when the laser was fixed 1 cm from the tissue surface with the presence of coaxial carbon dioxide and this appears to mirror the findings of the acute experiments.

The typical histological change produced in the stomach wall was coagulation necrosis. That is, the general architecture of the tissue remained with a homogenicity of the cytoplasm and nuclear karyolysis or pyknosis. The capillary congestion, extravasation of red cells and oedema at the edge of the coagulative necrosis zone is a vascular reaction to a thermal stimulus below the threshold necessary for coagulation[204]. The finding that the presence of coaxial carbon dioxide could reduce the occurrence of full muscle thickness necrosis at 1 cm distance but not 2 was the same as that in relation to reduction in surface area. This finding is at variance with that of Silverstein who found that it made no difference. However, the fibre-mucosa distance in his studies was between 2 and 3 cm, a distance at which the gas may have no cooling effect[208].

Although full muscle thickness necrosis occurred at 16% of the sites in the acute study, serosal damage did not occur even with peak powers of 110 watts and

radiation intensities of 4.5×10^3 watts cm^{-2}. The reason for this may be that the serosa has an increased resistance to a thermal stimulus[209] but this has not been verified experimentally. However, this may in part explain why serosal perforation is uncommon despite the frequent occurrence of full muscle thickness necrosis[208].

It was not possible to determine whether there was any correlation between actual depth of necrosis and the incidental peak powers used because the actual histological slides or prints were not made available.

The histological changes seen 4 days after the thermal insult were essentially the same as the immediate changes, but more extensive. However, by 4 days, an acute inflammatory reaction was apparent. Thermal injury to the skin can induce a leucocyte reaction within a few hours and by 24 hours the inflammatory reaction can delineate the zone within which the plane of irreversible injury subsequently becomes stabilised[204].

By 4 days, coaxial carbon dioxide did not appear to retain its effect of reducing the occurrence of full muscle thickness necrosis. However, by this time, a decrease in radiation intensity appeared to have produced a reduction in the occurrence of full muscle thickness necrosis. Comparison of the acute and 4 day studies showed that there was an obvious overall increase in extent of necrosis which was revealed by the increase in

occurrence of full muscle thickness necrosis, serosal damage and ulceration. This difference, however, was only apparent because the visual and histological techniques used to detect necrosis revealed morphological rather than functional change. The change in cellular function brought about by an increase in temperature cannot readily be appreciated by techniques such as fixation of tissue which in itself produces protein denaturation[204].

The occurrence of maximal damage at 4 days has been demonstrated by Bown[210] and is probably a result of the initial thermal insult rather than secondary tissue changes. Increase in ulceration is not brought about by autolysis because tissue that has undergone coagulation necrosis does not autolyse[205,211].

Within the limits of these studies it is apparent that perforation does not occur. The pilot studies showed that when neodymium YAG laser radiation is applied to the rabbit stomach, the minimum energy required to produce perforation is approximately 200 joules.

3. STUDY II.

The effect of Cimetidine and 15(S) Methyl Prostaglandin E_2 on the healing of Neodymium YAG laser induced gastric mucosal damage.

(1) INTRODUCTION

It was shown in Study I that the extent of coagulative necrosis produced by the laser was greater at 4 days than immediately after the application of radiation. This finding has been reported elsewhere and it was also shown that maximum damage is apparent at 4 days[210]. One possible cause for this observation is that maximal necrosis occurs immediately after the thermal stimulus but that some irreversible changes that occur in cells are not immediately recognisable with the methods of histology used. One other possible cause for this change is that the breach in the gastric mucosal barrier produced by the laser radiation allows the potentially damaging properties of gastric acid to extend the necrosis.

If the latter sequence of events is the correct one, then substances which inhibit or reduce gastric acid secretion may reduce the extension of necrosis and accelerate the healing of the gastric wall subjected to laser radiation.

Two groups of substances known to inhibit gastric acid secretion are the H_2-receptor antagonists such as

cimetidine[212,213] or prostaglandins of the E_2 series[214,215]. This study was set up to define the effect of cimetidine and a prostaglandin analogue (15S 15 methyl prostaglandin E_2) on the healing rate of rat gastric mucosa injured by laser photocoagulation.

(2) MATERIALS and METHODS

Fifty four male Sprague-Dawley rats weighing 250-350 gm. were starved for 18 hours. Following Halothane and oxygen anaesthesia, the abdominal cavity was opened through a midline incision and an anterior gastrostomy was performed. The stomach was emptied of any residual fluid and the laser pencil was aimed at a position on the lesser curve midway between the rumen and pylorus.

The laser equipment used has been described in Chapter 3. The radiation package delivered to the site was kept constant at 80 watts for one second at 1 cm from the surface (radiation intensity = 3327 joules cm^{-2}).

Following recovery, six rats were sacrificed at two hours. The remaining animals (n = 48) were then allocated randomly into three groups and received either (a) twice daily intraperitoneal injections of saline (n = 18); (b) saline plus 15 mg kg^{-1} cimetidine (Smith, Kleine and French, U.K.) (n = 18) or (c) saline plus 50 µg kg^{-1} 15(S) 15 methyl prostaglandin E_2 (Upjohn Co., Kalamazoo) (n = 12). The first injection was given two

hours after the operation. Six animals from each group were sacrificed at 4 days and a further six from each at seven days. The remaining six animals in groups (a) and (b) were sacrificed at 10 days. The surface area of the defect in the gastric mucosa was calculated using the method of Sonnenberg by measuring the largest orthogonal diameters (a,b) and the surface area = $\frac{\pi ab}{4}$[201]. Macroscopic examination of the mucosal damage was made with a hand lens (X10 magnification).

Carefully orientated sections were then processed by standard histological methods and routinely stained with haemalum and eosin. Light microscopic assessment was performed by a histopathologist (F.D.L.) who had no prior knowledge of the duration of the experiment or of the drugs used. Evidence of healing was assessed by presence of collagen or elastica formation using Van Geisen and Weigent's elastica stains.

Statistical analysis where applicable was performed using non-paired t-test.

(3) RESULTS

Macroscopic assessment.

The surface areas of the lesions are shown in Table XXIV. Immediately after application of the laser, the surface area of the lesions was 15.2 ± 1.4 mm^2.

TABLE XXIV. Mean surface area of gastric mucosal lesions in mm^2 ± SEM immediately after application of laser radiation and at 4, 7 and 10 days, following injection of saline, cimetidine and 15S 15 methyl prostaglandin E_2.

	Time Days			
Group	0	4	7	10
Control	15.2 ± 1.4	29.1 ± 7.3	23.9 ± 7	15.1 ± 3
Cimetidine	-	33.9 ± 8.7(1)	17.1 ± 7	10 ± 2(1)
15S Me PGE_2	-	27.6 ± 7	21.3 ± 3.3	-

(1) $p < 0.025$

At 4 days, the saline treated control group showed an increase in size of the lesions to a mean area of 29.1 ± 7.3 mm^2 with a reduction to 23.9 ± 7 mm^2 on the seventh day and to 15.1 ± 3 mm^2 on the tenth day. In animals treated with cimetidine and prostaglandin analogue, the mean surface areas followed a similar pattern of increase at the fourth day with a reduction in size by the seventh and tenth day (cimetidine alone). There was no significant difference between the groups on the fourth, seventh or tenth days.

In cimetidine treated animals, the surface area of the lesions at 4 days was 33.9 ± 8.7 mm^2. By seven days, the surface area had reduced to 17.1 ± 3 mm^2 and by 10 days to 10 ± 2 mm^2, an area significantly smaller than at 4 days ($p<0.025$).

In the prostaglandin treated group, the mean surface area on the fourth and seventh days were 27.6 ± 6.8 mm^2 and 21.3 ± 3.3 mm^2 respectively.

Macroscopic examination using a hand lens (X10 magnification) of the areas of damage in those animals sacrificed immediately following laser irradiation demonstrated mucosal lesions similar to those seen in the rabbit stomach, namely, a circumscribed area of pallor with a central punctum surrounded by a halo of hyperaemia. In each stomach, there was also a discrete area of serosal pallor directly under the mucosal lesion.

At 4 days, the saline treated control group had developed punched out ulcers with little evidence of healing, and two of these ulcers were penetrating through the serosa. The other four had coagulative necrosis extending down to the serosa. The cimetidine treated group demonstrated ulcers that were similar in nature, but none of them extended down to the serosa; however, there was some heaping of the mucosa suggestive of healing. The prostaglandin treated group at four days had two ulcers that penetrated through the serosa with free perforation. The remaining ulcers extended to the muscle layer.

At seven days, the control and prostaglandin groups had punched out ulcers with slough in the base with minimal evidence of healing whereas the cimetidine treated rats had shallower ulcers with clean bases and evidence of healing in five.

At ten days the control group had shallow ulcers with slough in the bases and evidence of healing in four whereas all the cimetidine treated group had very superficial ulcers with clean bases and evidence of healing.

Light microscopic appearances.

In all animals sacrificed two hours after laser irradiation, there was evidence of full muscle thickness coagulative necrosis with serosal damage. At four days, all the animals had similar appearances to the acute

lesions. Furthermore, serosal penetration and free perforation was confirmed in two of the six controls and the same number of prostaglandin treated rats. There was evidence of acute inflammatory cell infiltration in all of the lesions and there was some evidence of early fibroblast proliferation and collagen deposition at the base of the ulcers but there was no demonstrative difference between the animals.

At seven days, two of the control group had evidence of serosal necrosis which was not apparent in any of the cimetidine or prostaglandin treated rats. There was a subjective impression that the fibroblast proliferation was more pronounced in the cimetidine treated group compared with the other two.

At ten days, histological differences between the controls and cimetidine treated rats were more pronounced. The control group had evidence of more marked coagulative necrosis with slough in the ulcer bases, whereas the cimetidine treated rats had ulcers with clearer bases and very marked fibroblastic proliferation. In both groups, however, there was evidence of early epithelial regeneration at the ulcer edges.

(4) DISCUSSION

This study has shown that with the particular parameters of laser radiation used, a reproducible lesion could be made in the stomach wall of a rat in order to

assess the effects of cimetidine and a prostaglandin analogue (15S $MePGE_2$) on the extension of necrosis and healing.

Within the limitations of the study, it was shown that maximum damage occurred at four days and this has subsequently been confirmed by others using the Neodymium YAG laser[216].

The results would appear to indicate that the increase in damage at four days is unaffected by treatment with cimetidine or 15S Me PGE_2 and would suggest that the damage which is apparent at four days is initiated at the time of exposure to laser radiation and is therefore the result of thermal rather than chemical (acid and pepsin) injury.

At both four and seven days, there was no objective evidence that repair (fibroblastic proliferation) was more marked in any of the groups. However, by ten days, there appeared to be a difference between the controls and the cimetidine treated group in that the latter had evidence of greater fibroblastic proliferation and had less slough in the base.

Re-epithelialisation was only really apparent at ten days which is slower than that found in the dog stomach by others. Rutgeerts found that re-epithelialisation was complete between ten and fourteen days in dogs not

treated with cimetidine[217]. Kiefhaber claimed that a complete covering by a single layer of epithelial cells is complete between ten and fifteen days and there is a covering of mucosa with specialised glands between 20 and 25 days[218]. Apart from the species difference, it would appear that the lesions produced in this study were more marked than those produced in the dog by Rutgeerts and Kiefnaber.

The limitations of this study were that more animals could have been used in each group and that assessment could have been performed at more frequent intervals. Furthermore, no objective technique was used to assess the quantity of fibroblastic proliferation present.

Although this work must be considered inconclusive, it does suggest that a H_2 receptor antagonist (cimetidine) or a prostaglandin analogue (15S Me PGE_2) do not appear to reduce the extension of tissue damage as a result of laser radiation.

4. CONCLUSIONS

The aim of the work presented in this chapter was to obtain an appreciation of the effects of neodymium YAG laser radiation on the intact (non-ulcerated) stomach of an animal and thus minimise the potential risk of visceral perforation in a patient in whom this laser would be used to arrest haemorrhage.

At the time this work was conceived and executed, Kiefhaber had published results on the use of this laser on patients bleeding from the upper gastrointestinal tract with a low incidence of perforation[144]. However, detailed information regarding the effects of this radiation on the intact stomach was lacking in the literature and it was therefore felt necessary to investigate this in animals prior to assessing the efficacy of the neodymium YAG laser in arresting haemorrhage.

In a homogeneous medium, the attenuation of a particular radiation follows an exponential decay of intensity. Radiation with a wavelength of 1.06 μm (neodymium YAG) has a penetration depth of 9.1 cm in water (absorption coef. = 0.11 cm^{-1})[206]. Clearly, if Beers law was to hold true in tissue such as the stomach, then this radiation would be unsuitable for photocoagulation because of the depth of penetration and consequent damage to important structures outwith the stomach. Tissue such as the stomach is a highly structured heterogeneous 'optical' medium which produces a redistributive internal scattering of this radiation due to the multiple reflections, diffractions and scattering modes. The resultant effect on the incidental beam is to produce diffuse back scattering out of the tissue, forward scattering and beam broadening within the tissue. As a result of these effects, the site of maximum temperature is not on the tissue surface but beneath it[206]. This last phenomenon is of crucial importance in relation to the arrest of haemorrhage

and will be discussed in the next chapter.

Thus the extinction (damping) of radiation in tissue depends on both the absorption and scattering coefficients of that tissue for a particular wavelength of radiation, and with a wavelength of 1.06 μm, only a fraction is actually absorbed in the tissue. The penetration depth of this particular radiation into the stomach wall is said to be 1.75 mm, which is five times that of the Argon laser radiation[144].

The surface area of damage observed in the first study can be explained by redistributive internal scattering and the variation in depth of damage produced by a given parameter of radiation by tissue inhomogeneities producing variations in the coefficients of absorption and scattering. Trends in extent of damage (surface area and depth) were looked for by varying the peak powers, total incident energy, power density and the presence or absence of coaxial carbon dioxide.

In relation to surface area of damage, it was found that it increased with increasing peak powers and power density but was decreased when carbon dioxide was used when the fibre-mucosa distance was 1 cm. Bown found an increase in width of mucosa damage with increasing peak powers (25-75 watts) but this was independent of the fibre-mucosa distance[216], a finding at variance with the results of the first study. Unlike depth of damage, the surface

area of damage did not increase by four days. It was also found that there was an arithmetical association between surface area of coagulation and its depth. The extent of surface damage in relation to the parameters of radiation may be of importance in relation to the photocoagulation of vessels and this will be discussed further in the next chapter.

The major deficiency of the first study was that absolute depths of necrosis, and stomach wall thickness at each site, were not measured. It was intended to do this but unfortunately neither the histology nor photographic prints of it were made available to me. The results, however, did show trends of increasing depths of necrosis with increasing peak powers and this was more marked when the fibre-mucosa distance was 1 cm.

Bown found a general tendency for the depth of damage to increase in the normal stomach as the energy density increased but there were marked anomalies, whereas, irrespective of peak powers or energy density, total energy was a more important parameter[216]. These results, however, are difficult to interpret because of insufficient data.

What is more important in relation to depth of damage, is the occurrence of full thickness muscle necrosis and visceral perforation. In Study I, acute full muscle thickness necrosis occurred at 16% of the sites. There was no correlation between its occurrence and incidental

peak powers but coaxial gas reduced the occurrence when the fibre-mucosa distance was 1 cm. Rutgeerts found that with 50 or 60 watts, continuous exposures of 10-12 seconds were required (600-720 joules) whereas with 1 second interval exposures with 60 watts the energy required was double that, (1200 joules). The reason for the discrepancy is almost certainly due to the reduction in tissue temperatures between each pulse[217].

In the studies where the quinton ulcer[219] is used to assess the efficacy of photocoagulation and depth of damage together, the laser is fired at various bleeding sites within the ulcer base which vary in thickness from ulcer to ulcer. The ulcer, because it is made immediately before using the laser, has none of the histological features of repair seen in an ulcer in a patient. The amount of blood present in the ulcer base will affect the extent of tissue damage because, although the radiation of the neodymium YAG laser is less well absorbed in haemoglobin compared with the Argon ion laser, it is still appreciable. In a 150 μm thick layer of whole blood, only 60% of the radiation is transmitted (11.6% for the Argon laser)[220]. These factors have to be taken into account when discussing the extent of damage produced in a 'quinton ulcer'. Much of the concern in relation to full muscle thickness necrosis emanated from the study of Silverstein in which he reported an occurrence of this depth of necrosis in over 50% of the ulcers that had been photocoagulated, and this was irrespective of peak powers used (15-55 watts),

the presence or absence of coaxial carbon dioxide or the exposure time utilised (0.5 and 1 second or continuous)[208].

Johnston who used a similar animal model found no difference in the occurrence of full muscle necrosis between the various parameters of radiation used. These lesions were assessed by histology at 7 days[221]. In the 4 day lesions in the first study, although full muscle thickness occurred at 45% of the sites, there was a positive correlation with incidental peak powers (40-110 watts). From this it would appear that using peak powers of 85 watts, 50% of the lesions produced would have full thickness muscle necrosis.

This depth of necrosis has to be placed in its proper context. Firstly, this does not indicate visceral perforation, secondly, the serosa may have an increased resistance to this wavelength of radiation[209], and thirdly, in order to achieve protein denaturation within a source of bleeding it is necessary to achieve the requisite temperatures within the tissue and not on its surface.

In the first study and pilot study, visceral perforation did not occur in the rabbit stomach with peak powers of 110 watts and total incident energies of 200 joules. In relation to an intact dog stomach, Rutgeerts determined the parameters necessary to produce an acute perforation. With peak powers of 50 and 60 watts perfor-

ation occurred when continuous exposures of between 12 and 16 seconds were used. This gives a total incident energy range of 720-960 joules. The power densities for 50 and 10 watts were 1100 and 1300 w cm^{-2} respectively. With peak powers of 60 watts and repetitive exposures of 1 second, 24 exposures were required to perforate the stomach. This gave a higher total incident energy of 1440 joules. With 70 watts and 0.5 second exposures, 28 pulses were required (980 joules)[217].

Using the 'quinton ulcer' model, Dixon produced perforations with a peak power of 55 watts after 9.6 ± 1.5 seconds of continuous exposure[209]. Silverstein, using the same model and peak power level, failed to find perforations when energies up to 2,200 joules were used and the stomachs were examined after 7 days[208].

Kiefhaber used individual pulses with low energy levels and claimed that the perforation of a dog stomach could only be produced with energy densities greater than a factor of 7 compared to the values necessary for coagulation of bleeding sites[144].

In summary, the first study and the literature referred to have shown that full muscle thickness necrosis is a common occurrence with the various parameters of radiation used; however visceral perforation does not occur unless extreme parameters of radiation are used. The 'quinton ulcer' is a poor model to assess the risk of

perforation for the reasons already alluded to and it is not valid to extrapolate the experimental findings using the model to the clinical situation. Dennis and others recently reported on the depth of damage produced when using a single vessel as the source of bleeding. Sixteen ulcers were produced. Peak powers of 55 watts and time exposures of 0.5 seconds were used to assess blood loss. The maximum total energy used was 412 joules and none of the ulcers had evidence of full muscle thickness necrosis[222].

In the clinical situation, laser radiation could potentially produce a perforation at two sites, the normal gut wall and an ulcer base. If individual pulses of radiation used to arrest haemorrhage have energies between 40 and 60 joules then even in a distended stomach the risk of perforating the intact wall is negligible. In relation to the other situation, the base of a chronic peptic ulcer has copious granulation and fibrous tissue with serosal thickening underneath. Stewart found that 28% of peptic ulcers are firmly adherent to either the pancreas or liver and adhesions are present in 46 and 42% of gastric and duodenal ulcers respectively[223]. All these features of peptic ulcers would tend to reduce the occurrence of perforation. In reality, the laser radiation is directed at a vessel in an ulcer base and not the base itself.

The final evidence supporting the contention that the risk of perforation with the neodymium YAG laser is low

comes from the clinical experience of Kiefhaber. By 1979, he had treated 627 patients with this laser, and he reported six perforations (1%). Analysis of his data shows that in four, gas insufflation re-opened sealed perforations (0.6%) and in only two cases could the laser radiation be implicated (0.3%). However, in both cases, the laser was used twice on the same site on successive days[224]. It would therefore seem that when correct energy levels are used, the risk of perforation with this laser is low. It is of interest to note that the risk of perforation from emergency diagnostic endoscopy in Britain is 0.4% (Table IV).

The results of the second study presented in this chapter suggested that the extension of laser induced damage was not influenced by cimetidine or a prostaglandin analogue. It was worthwhile investigating the effects of cimetidine since most people admitted to hospital with acute upper gastrointestinal haemorrhage receive cimetidine.

CHAPTER FIVE

THE EFFICACY OF THE NEODYMIUM YAG LASER IN AN ACTIVE ARTERIAL BLEEDING MODEL

1. INTRODUCTION

Most of the animal experiments investigating the efficacy of the neodymium YAG laser for bleeding in the stomach have used a standardised canine gastric ulcer model[208,209,216,217,221], which was described by Protell and others in 1976[219]. However, the 'Quinton ulcer' has several deficiencies:

(1) Too much emphasis is placed on the reproduceability of the ulcer diameter and depth which is of little relevance to the source of bleeding. Peptic ulcers which are the site of major bleeding, vary in size and depth[225].

(2) The Quinton ulcer maker fenestrates several vessels within the submucosa which are of different size. Several vessels can be transected within each ulcer and they tend to retract under the ulcer rim[222].

(3) The actual size of vessel fenestrated is small and the rate of bleeding is low and variable. Dixon reported a bleeding rate of 1.5 ± 0.9 ml. min^{-1} with a range of 0.6 - 6.2 mls. min^{-1} in 40 ulcers[209]. Furthermore, many ulcers stop

bleeding spontaneously; Protell had a spontaneous cessation rate of 42% within 37 minutes[219]. Therefore the animals are heparinised, but even then, the flow rate diminished by 60% in 10 minutes[209].

(5) The 'Quinton ulcer' has none of the histological features of inflammation or repair seen in an acute or chronic peptic ulcer in a patient[223].

(6) Little attention is paid to the actual source of bleeding, namely, the vessel itself.

Clearly then, a more realistic model is required to assess the efficacy of this laser, and in order to produce one, several points have to be considered. Patients bleeding from peptic ulcers and who continue to lose blood or have a further haemorrhage are probably bleeding from a single sizeable vessel in the ulcer base. Griffiths showed that patients who had vessels visible in the ulcer base at the time of endoscopy all re-bled[38]. Savariaud examined the sources of bleeding in patients who had exsanguinated from peptic ulcers. Most of them had bled from single arteries in the ulcer base and only 11% had no evidence of a single vessel as the source of bleeding[56]. Thus, the first requirement of a bleeding model which is relevant to the clinical problem is that the source of blood loss should be a single vessel.

The histological features of acute or chronic peptic ulceration have been well described[223] and even if they could be produced in an animal model, it would not be possible to produce a reliable acute bleed[219]. Key performed micro-angiography on specimens of gastric ulcers removed at operation and found that there was complete absence of all but fine vessels in the ulcer floor[226]. Because the blood vessels intrinsic to the stomach wall are small[227], the ideal bleeding model would therefore require the presence of an abnormally large vessel in addition to the histological features of peptic ulceration.

There is a misconception that patients who have bled from vessels within ulcer bases are actively bleeding at the time of endoscopy. In the retrospective study reported by Griffiths, although 28 patients had vessels in ulcer bases, and all of them had further haemorrhage, only 11 were actively bleeding at the time of endoscopy, whereas the remaining 17 were not[38]. Thus, there is the choice of assessing the efficacy of the laser on a vessel which is either actively losing blood or not.

In the Department of Surgery laboratories, only acute experiments could be conducted on dogs. It was therefore decided to produce an acute model with an active arterial bleed in the dog stomach in an attempt to simulate the active arterial bleed in a patient who was liable to continue bleeding. The major part of the study consisted

of using the splenic artery as the source of bleeding. However, a second pilot study was performed to assess the use of the gastric submucosal arteries as a source of bleeding. The sources of bleeding used had none of the histological features of peptic ulceration and no long term assessment was made of the control of bleeding.

The purpose then of this study was to assess the ability of the Neodymium YAG laser to arrest active arterial haemorrhage and also to make an assessment of the laser fibre delivery system, the use of coaxial carbon dioxide and the venting system via a fibre optic endoscope.

2. MATERIALS and METHODS

(a) Splenic artery model.

Six dogs varying in weight from 15 - 28 kg were starved overnight and anaesthetised with thiopentone and maintained by pentobarbitone sodium and oxygen. The pulse rate, arterial pressure and blood gases were monitored. A laparotomy was performed through a midline incision and the greater omentum was opened to allow identification of the splenic vessels. The splenic artery was dissected free from the vein up to its splenic bifurcation and the anterior adventitia opened longitudinally. An incision was made on the posterior surface of the stomach adjacent to the artery. The incision extended down to the mucosa. An anterior gastrotomy was then performed and a circle of mucosa approximately 1.5 cm in diameter was excised over

the mid-point of the posterior gastric incision. The arterial adventitia was then sutured to the muscularis of the gastric incision using interrupted 0000 silk sutures, thus tethering the splenic artery to the base of the 'ulcer' (Figure 9a). A suitably sized electro magnetic flow probe (Stratham, Fenwick Electronics, Glasgow) was then placed on the splenic artery distal to the ulcer (Figure 9b). After the arterial spasm had ceased, the mean and peak flow rates were obtained.

(b) Submucosal single vessel model.

In the last three dogs used for the splenic artery model, a total of 14 submucosal single vessel lesions were produced. The sites at which branches of the left gastric artery penetrated the muscularis were noted on the serosal surface of the lesser curve, and by transillumination the course of these vessels in the submucosa could be identified. By lift and cut technique, a circle of overlying mucosa was excised and by sharp dissection the underlying artery was isolated.

Laser and endoscope.

The basic laser equipment used has been described in Chapter Three. Instead of the laser pencil, the fibre-optic was placed in a 3 mm diameter polyethylene cannula, the end of which had a 3 - 4 mm length metal cylinder to hold the fibre tip in a central position and allow a free flow of coaxial carbon dioxide. The emergent beam had a

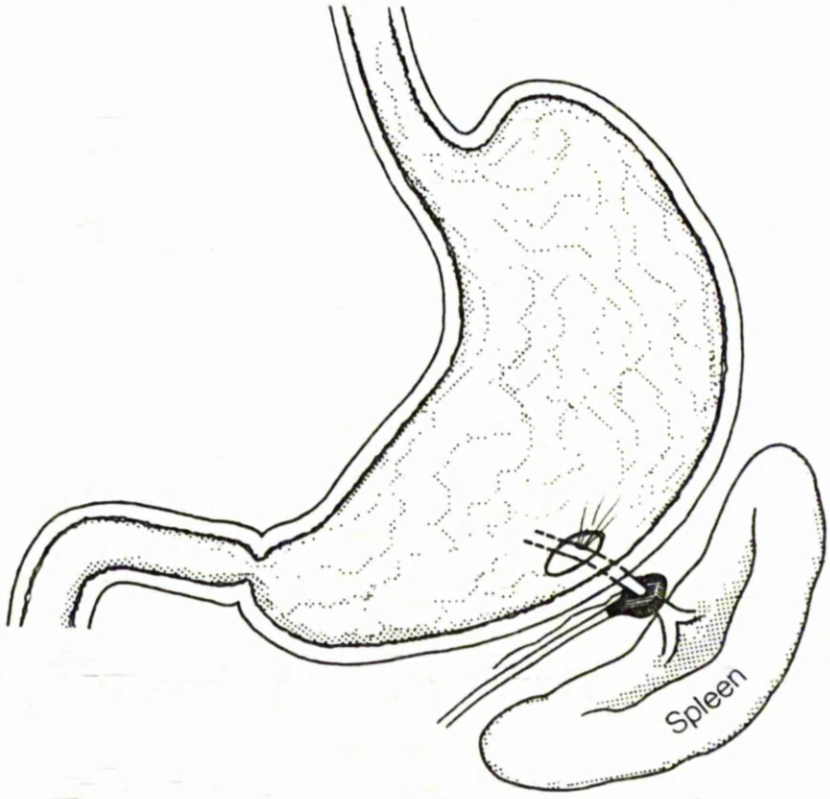


Figure 9a. Schematic representation of splenic artery model.

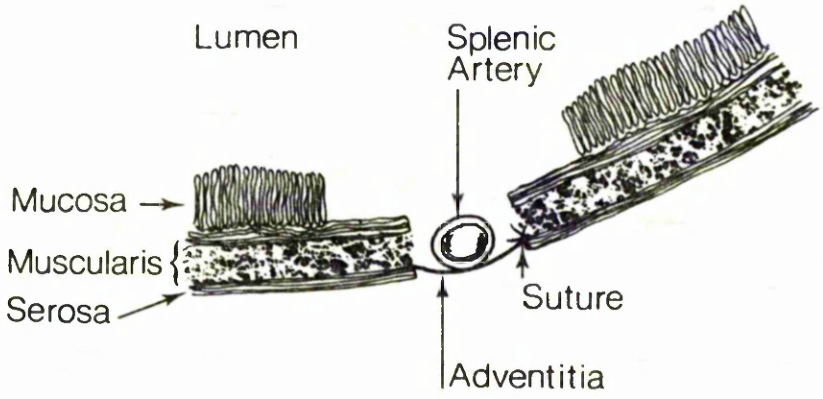


Figure 9b. Schematic representation of position of electromagnetic flow probe in splenic artery model.

10^{o} divergence. A twin channel Olympus TGF-2D endoscope (Key Med) was passed perorally into the dog stomach as for a routine endoscopic procedure. The glass fibre cannula was dedicated to the larger of the two biopsy channels and the tip could be passed beyond the distal end of the endoscope. The smaller biopsy channel was used for suction and venting of the carbon dioxide.

Because of the risk of reflected radiation passing up the endoscopic optics[228], transparent safety goggles were worn.

3. RESULTS

The splenic artery flow rates were measured continuously in all six dogs. The mean flow rates varied from 50 - 120 $ml.min^{-1}$ with the splenic artery diameters varying from 2.5 - 3.5 mm. In all animals, fenestration of the artery produced a marked arterial spurt. The coaxial carbon dioxide could divert and diminish the blood flow thus allowing visualisation of the source of bleeding. Despite the red colour of the helium neon target marker beam, it was possible to see it on blood, however visualisation of the beam could be improved by reducing the intensity of the Olympus light source.

With free venting and active suction, over distension of the stomach could be avoided.

In five animals, the laser was successful in arresting haemorrhage using peak powers of 70 watts and exposure times of one second. In the remaining dog, a second application of laser radiation was necessary to arrest haemorrhage.

With the submucosal artery model, fenestration produced a small spurt of blood and in all cases the laser was effective in arresting haemorrhage.

The major problem encountered with the equipment was the use of the goggles. This reduced the acuity of vision.

4. DISCUSSION

The splenic artery model provided a reproducible intra-gastric arterial bleed which was quantifiable and simulated more closely the active arterial bleed encountered in patients who may require emergency surgery.

The submucosal artery lesions produced active spurting, but this was of lesser severity than the splenic artery model.

The results show that the laser equipment could be used with a fibreoptic endoscope to stop severe intra-gastric bleeding. However, it was concluded that the equipment would require modification. A transparent filter

would have to be inserted into the endoscope optics to improve acuity of vision and allow photography and the use of a fibreoptic teaching aid. The gas venting system would have to be improved for use in the clinical setting and this will be discussed further in the next chapter.

The models used in this study only assessed the efficacy of the laser with an acute actively bleeding vessel. It was not possible to determine whether any late recurrence of bleeding would have occurred and no histological assessment was made of laser induced damage of the stomach wall.

5. CONCLUSIONS

This study and others reported in the literature have shown that the neodymium YAG laser can arrest active bleeding from splenic artery and submucosal artery lesions[222] and from Quinton ulcers[208,209,216,217,221]. Because of the restraints of the laboratory regulations it was not possible to determine whether re-bleeding would have occurred from the splenic artery. However, it was felt that this model most closely simulated the type of bleeding that might occur in a patient who was liable to continue bleeding.

Recently, Dennis and others have described the use of a submucosal artery lesion similar to the one used in this study. The bleeding rate from 29 vessels was

2.3 ± 1.7 ml.min^{-1} (mean ± SE) in the first minute. The laser was effective in arresting blood loss but re-bleeding from one lesion caused one of the dogs to ex-sanguinate. Of the remaining 16 ulcers that were examined at 7 days, none had re-bled[222]. There are several criticisms which apply to both the 'Quinton ulcer' and submucosal artery models described in the literature. All the animals were anticoagulated and thus the natural haemostatic processes are affected. Despite the fact that 42% of the Quinton ulcers in animals that were not anticoagulated stopped bleeding spontaneously in 37 minutes[219], it would have been more realistic to have assessed the efficacy of the laser in both models with animals that were not anticoagulated, in order to determine the re-bleeding rate over a period of days in ulcers receiving either laser or sham therapy.

Although the bleeding rates for the single vessels and Quinton ulcers in Dennis's study were the same, the actual rate of blood loss in the latter lesion must be lower because several vessels are fenestrated in any given ulcer[222]. Furthermore, because the single vessels are not transected, retraction does not occur as it does in the Quinton ulcer. Thus, of the two models, the single vessel is the more realistic.

Unfortunately neither this study nor the others alluded to have examined the mechanisms of photocoagulation in a bleeding vessel. This has to be considered further.

In general, the effects of the laser have to be considered on three facets of a bleeding lesion, namely, blood, the vessel itself and the tissue surrounding the vessel.

Blood when heated coagulates. Despite the presence of plasma proteins and platelets, haemoglobin is the only constituent to exhibit sizeable absorption of 'light' and is thus the most important agent in relation to absorption of laser radiation. The absorption spectrum of haemoglobin shows strong absorption bands at 414.5 and 550 n.m.[229]. The critical temperatures at which haemoglobin denatures as a result of heat is $65^{o}C$[230]. Because the Argon ion laser emits radiation between 444 and 520 n.m., it is highly absorbed in haemoglobin; 75% of its radiation is absorbed in a 100 μm thick layer of oxy-haemoglobin. Although the neodymium YAG radiation is outwith the visual spectrum, its radiation is still absorbed to an appreciable extent, being 16% in the same thickness of oxy-haemoglobin[231]. In whole blood, erythrocytes increase the scattering of radiation[232] and thus in a 150 μm thick layer of whole human blood, 88% of Argon and 44% of neodymium YAG laser radiation is absorbed[220]. The carbon dioxide laser radiation is totally absorbed in 14 μm of whole blood.

Coagulation of blood itself can arrest haemorrhage from a small vessel in which the pressure and flow rate is low. However, in the clinical situation blood in the stomach is altered and a clot can disintegrate[233] and

thus clotting of blood itself is insufficient. This is the probable reason why the Argon laser can only arrest bleeding from a vessel of less than 1 mm in diameter[234,235]. Because of the high absorption in blood of the radiation from both the Argon and carbon dioxide laser, little energy is left to affect the source of bleeding, namely a vessel.

There are five basic component parts of a vessel wall, namely, endothelium, basement membrane and ground substance, elastic tissue, collagen and smooth muscle. Depending on the type of vessel, these components are present in varying proportions[236]. In a muscular artery, collagen comprises approximately 21% of the total composition[237]. When laser radiation is absorbed by collagen, the resulting heat produces a thermal denaturation between 60-70^{o}C[238].

The net result of denaturation is to produce a shrinkage which follows a first order reaction[239]. The shrinkage temperature is about 67^{o}C and at this level collagen changes from a predominantly crystalline to an amorphous state[240] and contracts to approximately a quarter of its original length[238]. Although shrinkage is a rate process, when collagen is 'shocked' with a temperature above the shrinkage temperature, contraction is almost instantaneous[238]. The shrinkage of collagen is the principle cause for shrinkage of vessels when sufficient heat is applied.

Gorisch has performed studies on the effects of heat and neodymium YAG radiation on intact blood vessels of the rabbit mesentery[234,241]. With laser radiation, shrinkage occurs when temperatures of greater than 76^{o}C are reached. Hydrothermal studies showed that at 82^{o}C veins shrunk within the rise time of the temperature jump, and with arteries the temperature necessary was 90^{o}C and above. Keifhaber has shown that surface temperatures in excess of 100^{o}C can be achieved with the neodymium YAG Laser using powers of 90 watts and time exposures of 0.5 seconds[242]. Gorisch found that vessels up to 5 mm in diameter could be shrunk with the neodymium YAG laser, however, they were in the rabbit mesentery[234,241]. One point of importance from this study was that effective shrinkage was influenced by beam diameter and hence surface area of coagulation.

In vitro studies performed by myself on post mortem specimens of gastric arteries which were filled with blood showed that contraction of the vessels occurred when the neodymium YAG laser was fired at the vessels using peak powers between 70 and 90 watts and time exposures of 0.5 - 1 second.

Only a certain amount of information can be obtained from studying the effects of laser radiation on intact vessels that are isolated (e.g. mesenteric arteries) either in vitro or in vivo. The distribution of radiation on a vessel embedded either wholly or partially in tissue

(e.g. ulcer base) will be different because of the heat sink effect of the tissue. In this situation the theoretical requisites for effective haemostasis are that sufficient energy is imparted on the vessel wall, lumen and surrounding tissue to produce thermal shrinkage of the vessel wall, endothelial damage, coagulation of the luminal blood and oedema of the surrounding tissue[242]. Because of the high absorption coefficient of Argon laser radiation in blood, little energy is left to affect the vessel wall and this occurs both extra and intra-luminally. When further energy is delivered, vaporisation of blood occurs which produces vessel disruption because of the 20-fold increase in volume[231]. The radiation from the carbon dioxide laser is totally absorbed in the first 14 μm of tissue irrespective of its constituents, and in order for sufficient energy to pass through the vessel wall and lumen, the rise of temperature is such that carbonisation and vaporisation will occur. Instead of coagulation, cutting will occur[206]. The energy from other thermo-active techniques are maximally absorbed on the tissue surface[243] and the same problem exists particularly when it is difficult to control the amount of energy imparted upon the tissue[244].

Neodymium YAG radiation is less preferentially absorbed in blood or tissue and as a result, penetration is deeper and maximal temperatures occur below the surface. As a result, volume heating occurs. So the increased coagulation necrosis is an advantage rather than

a disadvantage[231]. The ideal degree of necrosis that should be achieved within a vessel wall is a coagulation necrosis that retains the connective tissue architecture. If the necrosis becomes amorphous, then the tensile strength is greatly reduced[245].

Despite the theoretical and experimental considerations that have been outlined and because there is no ideal animal model that reproduces exactly the clinical situation, the only effective way of assessing the efficacy of the neodymium YAG laser is to use it on patients with objective assessment and if possible histological confirmation of the effects.

CHAPTER SIX

NEODYMIUM YAG LASER PHOTOCOAGULATION IN PATIENTS - A PILOT STUDY.

1. INTRODUCTION

By September 1979, neodymium YAG laser photocoagulation had been performed on 1533 patients bleeding from a variety of lesions in the upper gastrointestinal tract, and it was claimed that bleeding had been controlled in 89% of them[224]. However, up to that time, there had been no reports on how effective this technique actually was. The purpose of this research project was to assess the efficacy of the neodymium YAG laser for this condition, but before this could be done it was necessary to perform a pilot study and the experience obtained from it is presented in this chapter.

The aim of this pilot study was to gain experience in the technique of laser photocoagulation which entailed identifying the actual source of bleeding at endoscopy, and learning to use the laser and the ancillary equipment, and to modify the equipment if necessary.

If the initial experience obtained from this pilot study was encouraging, then the intention was to proceed to a controlled trial and assess the efficacy of this form of therapeutic endoscopy.

2. PATIENTS and METHODS

Patients.

Eleven patients were included in the pilot study and their basic clinical features are outlined in Table XXV. Eight were male and three female. Their mean age was 57.7 ± 4.1 years (mean ± SE) and only four were over 60.

Seven of the patients were admitted because of acute upper gastrointestinal haemorrhage but four were not and bled subsequent to admission. One of them bled 5 days after a Whipple's procedure for pancreatic cancer and another 2 weeks after oversewing of a perforated gastric ulcer. The third patient was admitted for respiratory investigations and the fourth, for treatment of a Stage IV Hodgkin's disease.

Eight of the eleven patients were known to have had peptic ulcer disease and five of them had a previous episode of upper gastrointestinal haemorrhage (two requiring emergency surgery).

Two patients had chronic bronchitis, one had previously undergone surgery for mitral valve disease and was on anticoagulants. The patient who had been admitted with a perforated gastric ulcer had evidence of a severe chest infection and congestive cardiac failure at the time of referral.

TABLE XXV. Basic clinical features of the eleven patients.

Patient	Sex	Age	Reason for admission	History of G.I. disease	P.H. of G.I. bleed	Other Diseases	Drugs
1	M	57	G.I. bleed	Cirrhosis			Salicylates
2	M	76	Resp. invest.	D.U.		Chron.Bron.	
3	F	56	Ca. pancreas	Ca. pancreas			Indocid
4	M	37	G.I. bleed	D.U.	+		
5	M	53	G.I. bleed	D.U.	+		
6	M	76	Perf. G.U.	G.U.		(Chest infection (C.C.F.	Digoxin
7	M	66	G.I. bleed	G.U.	+ (op.)	Chron. Bron.	
8	M	66	G.I. bleed	D.U.			
9	M	40	Hodgkin's	-		Hodgkin's	Chemo Rx.
10	F	42	G.I. bleed	D.U.	+	Mitral valve	Warfarin
11	F	55	G.I. bleed	G.U.	+ (op.)	Arthritis	Indocid

The clinical presentation of bleeding is depicted in Table XXVI. Six were shocked as a result of their initial bleeding episode, four had an initial or subsequent haemoglobin of less than 10 $g.\alpha l^{-1}$. The first manifestation of bleeding had occurred at times varying from less than 12 hours up to 13 days prior to referral. Ten of the patients last bled within the preceding 12 hours. In the interval between admission or onset of bleeding and referral, ten of the patients had further episodes of haemorrhage (seven with hypovolaemic shock), and all had received blood transfusions in amounts varying from 2 - 20 units.

Laser Equipment.

A room was set up to house the laser equipment and both fulfilled the hospital safety regulations (Appendix 1). The laser equipment had been modified after its use in the surgical laboratories and a new control box had been designed for clinical use. It had a visual display for peak power (watts), total incident energy (joules) per pulse and number of pulses used. Dials allowed pre-setting of the peak powers between 20 - 110 watts and time exposures varying from 0.1 - 2.9 seconds. A white button allowed firing of the laser lamp and an orange button activated the laser system. A third button (red) when pressed, disabled the laser. When the laser was fully activated, it was fired by means of a pneumatic foot switch. When it was pressed, the laser emitted a monotone sound lasting five seconds which

TABLE XXVI. Clinical presentation of bleeding in the eleven patients.

Patient	Shock	Hb. <10g.dl^{-1}	Blood before laser	Time after ad/	Time after last bleed (hrs)	Time from first bleed	Bleeding subsequent to admission and before referral.
1		+	6	8 hrs.	<12	12-24 hrs.	Continuous
2			3	6 days	24-48	72-96 hrs.	Haem. shock X 2
3	+	+	6	50 days	<12	13 days	Intermittent.
4			2	5 hrs.	<12	48-72 hrs.	Shock.
5	+	+	6	27 hrs.	<12	12-24 hrs.	Haem. X 2, shock.
6	+		5	17 days	<12	48-72 hrs.	Haem. X 5, shock X 2
7	+		5	4 hrs.	<12	<12 hours	Haem. shock
8		+	8	3½ hrs.	<12	9 days	Haem. X 3.
9	+		20	14 days	<12	11 days	Haem. X 4, shock X 3.
10		+	6	14½ hrs.	<12	12-24 hrs.	-
11	+		10	10 hrs.	<12	<12 hrs.	Haem. X 2, shock X 2.

preceded the actual firing of the laser. This was followed by a tone of different frequency which lasted for the duration of the laser pulse. After the first patient, the warning sound was removed from the system. The exit beam from the laser was launched into a 600 μm single step glass fibre (Pilkington P.E. Ltd., U.K.) which was enclosed in a 3 mm diameter polyethylene cannula. The end of the cannula had a 7 mm long metal cylinder fitted onto it which held the fibre tip in a central position, and protected it from damage and allowed a free flow of carbon dioxide. A connection was screwed into the port of the large biopsy channel of the endoscope. The female counterpart of the connection was on the laser cannula and when the cannula was passed into the large biopsy channel, it was screwed onto the connection to provide an air and fluid seal around the cannula. The female component also had a 4 cm long spring to prevent acute flexion of the cannula at the level of the connection.

In order to measure the peak power of the beam emitted from the fibre, a peak power sphere meter was produced by Barr and Stroud which had an entrance port for the fibre tip. The peak power was measured before and after each patient and when this was done, safety goggles were worn (Glendale Optical Co., New York).

Carbon dioxide.

The gas was supplied from a standard 1800 L. carbon dioxide cylinder (British Oxygen Company). The

gas flow rate was regulated by a valve system designed by Barr and Stroud which provided a constant low flow (25 ml.sec.$^{-1}$) through the cannula. Pressure of a button on the valve system produced a high flow (100 ml.sec.$^{-1}$) which lasted as long as the button was pressed. The high flow of gas was used to clear the endoscope biopsy channel when inserting the cannula and also, if necessary, to blow blood off the target lesion.

Endoscope.

The instrument used throughout the study was a twin channel Olympus TGF-2D (Key-Med) which had a transparent Schott glass filter (Barr and Stroud) inserted into the endoscope eyepiece to protect the operator's eye from back reflection of the neodymium YAG radiation.

The laser cannula was dedicated to the larger of the two biopsy channels and its distal tip could be passed beyond the end of the endoscope.

The smaller biopsy channel was used for suction, water lavage or venting of carbon dioxide.

Gastric lavage.

Depending on the circumstances, two different techniques of gastric lavage were used. The first utilised the small biopsy channel of the endoscope. The system devised consisted of a Vygon neutripak (Vygon, U.K.)

which acted as a reservoir for 1500 mls of cold tap water. An intravenous blood administration set (Travenol, Norfolk, England) was attached to the bag and the leur fitting was inserted into the small biopsy channel. Water was allowed to flow at a low constant rate by opening the 'giving set' clamp. If a jet of water was required, then this was produced by pressure infusion. This technique was used to clear blood from a particular site in the upper gastrointestinal tract or to reduce oozing from a lesion.

The second technique was used when a large amount of fresh or clotted blood was present in the stomach. Polyvinyl tubes with outside diameters of 13 or 18 mm were passed into the stomach and with a filter funnel, cold water was poured into the stomach. The gastric contents were evacuated by gravity (syphoning) or by suction. The procedure was repeated until the aspirate was clear.

Venting.

The system devised for this purpose consisted of connecting a length of argyle tubing to the small biopsy channel of the endoscope and placing the other end into a jar of water which was positioned at the same level as the patient's trolley.

When carbon dioxide was passed into the patient's stomach, a rise in intragastric pressure allowed the gas

to pass through the small biopsy channel into the argyle tubing and escape by bubbling through the water in the jar. If necessary, venting could be augmented by using the endoscope suction system.

Ethical Committee approval and patient consent.

Approval for the clinical research project was granted by the Hospital Ethical Committee (30th April 1979). Patients entering the study were informed of the nature and purpose of the study and gave written informed consent. Laser photocoagulation was performed in accordance with the local hospital rules (Appendix 1.) which were displayed on one of the laser room walls. The nurse present with each patient was also informed of the procedure.

Procedure.

Before the patient entered the laser room, the laser and endoscope were checked and the laser exit beam peak power was checked with the power meter.

Endoscopy was performed with the patient on a trolley with brakes. The patient was sedated with intravenous diazepam (Roche) 10-40 mgm. i.v. and placed in the left lateral position. Endoscopy was performed to identify the site and source of bleeding. If necessary, one of the techniques of gastric lavage described was performed. The venting tube was connected to the small biopsy channel and the laser cannula was inserted into the

larger biopsy channel and passed right down until the tip could be viewed through the endoscope. 20 mgm. of hyoscine butylbromide (Boehringer) was then given intravenously to produce gastric relaxation. The helium neon target marker beam was then checked by aiming it at the stomach wall or at the lesion. If the beam could not be seen, a pulse of high flow carbon dioxide was passed through the cannula to make sure no debris had covered the tip. If it still could not be seen, the cannula was withdrawn for inspection. If there was difficulty in seeing the beam, the intensity of the endoscopic light source was reduced. The laser was then activated and fired. After photocoagulation had been performed, the lesion was observed to see if bleeding had been induced and to note what tissue changes had occurred. Before withdrawing the cannula, the laser was deactivated.

Documentation.

Proformas were prepared for recording details of the patients' clinical history, progress, endoscopic findings and laser therapy applied. Whenever possible photographs were taken of the lesions at the time of laser therapy and if the patient was re-endoscoped. The camera used was an Olympus Pen-F (Key Med). Because of the light intensity from the endoscope light source, shutter speeds of 0.25 seconds were used.

3. RESULTS

Endoscopic findings.

These are depicted in Table XVII. All of the patients had blood present in the upper gastrointestinal tract; however, one of them had only a small quantity of fresh blood in the duodenum. Of the remainder, four had fresh blood and five had clots in the stomach.

Although seven of the patients were actively bleeding at the time of endoscopy, only two had actively spurting arteries; the others had a non pulsatile flow or oozing of blood.

Gastric tube lavage was performed in six patients because of the presence of clots or a large amount of fresh blood. Endoscopic lavage was performed in another four patients to identify the exact source of bleeding.

Five of the patients were bleeding from gastric ulcers and three from duodenal ulcers. One patient was bleeding from a gastric varix and another from a single artery pouting through the gastric mucosa. The remaining patient was bleeding from two gastric ulcers, each of which had histological evidence of Hodgkin's disease in the ulcer base. The site of these lesions is shown in Table XXVII. Seven of the nine gastric lesions were found in the proximal part of the stomach and only two were in the antral region. Two of the duodenal ulcers

TABLE XXVII. Endoscopic findings in the eleven patients. Shown are the site and character of blood present, and whether lavage was performed. Also shown are the lesions responsible for blood loss, their site and the stigmata present.

Patient	Blood				Lavage[1]	Lesion	Site[2]	Stigmata
	oes.	stom.	duod.	Descript.				
1	+	+	+	clotted	tube	varix	post. wall 50 cm.	vein - ooze
2			+	fresh	-	D.U.	ant. wall	B.S. ooze
3		+	+	clotted	tube	G.U.	ant. wall G.C.	vessel A.B.
4		+	+	fresh	end.	D.U.	post bulbar	vessel A.B.
5		+	+	fresh	end.	D.U.	ant. wall	R.S.
6		+	+	clots	tube	G.U.	ant.wall pre-pyl.	vessel
7		+	+	fresh + clot	tube	G.U.	post. wall 50 cm.	vessel ooze
8	+	+	+	fresh + clot	tube	G.U.	L.C. 45 cm.	vessel - spurt
9	+	+	+	fresh	end.	(G.U. (G.U.	(L.C. 41 cm. (G.C. 65 cm.	(B.S. (B.S.
10	+	+		fresh	end.	G.U.	L.C. post. wall 45 cm.	R.S.
11	+	+	+	fresh	tube	vessel	post. wall G.C. 42 cm.	Vessel - spurt

1. End. = endoscope lavage
2. Distances are measured in cm. from the incisors.
3. A.B. = active flor (non pulsatile) of blood.

G.C. = greater curve
L.C. = lesser curve

were on the anterior wall and the other was barely visible in the post bulbar region.

A vessel was the source of bleeding in seven patients (six arteries and one vein). In the other four, red or black spots were present in the ulcer base.

Laser therapy.

It was possible to aim and fire the laser exactly at the source of bleeding in eight of the patients, but there was difficulty in aiming at the lesion in the other three for the following reasons. In the case of the patient who had the post bulbar ulcer, it was extremely difficult to actually see it because of the size of the endoscope used and respiratory movements. The laser was fired once at the lesion but it was doubtful whether the radiation hit the target. Patient number eight was actively bleeding from a gastric ulcer high up on the lesser curve and although the endoscope was retroflexed, it was not possible to fire the laser at the vessel. The laser was fired once but the radiation hit the ulcer rim. Patient number eleven was bleeding from a single artery on the posterior wall aspect of the lesser curve only 3 cm from the oesophago-gastric junction. Although the laser could be aimed at the vessel, the angle between the beam and the mucosal surface was approximately 10^{o} and thus the radiation was absorbed more on blood than the vessel itself. However, the spurting was reduced to a non pulsatile flow of blood.

In each patient, peak powers of 70 watts and time exposures of 0.5 - 1 second per pulse were used. In none of the patients was bleeding actually induced or made worse with the laser.

The high flow coaxial carbon dioxide was used in only those patients who were actively bleeding.

Clinical course.

Table XXVIII details the clinical course of the patients. Of the eight patients in whom the laser was fired at the source of bleeding, one re-bled but the other seven settled. The patient who bled again (Number 3) did so seven hours after laser therapy and was submitted to emergency surgery. The surgeon who performed the operation was also present at endoscopy and was of the opinion that the source of bleeding at operation was an acute ulcer adjacent to the one that had been photo-coagulated. This patient died six days later as a result of sepsis and intraperitoneal bleeding. Of the seven who settled, three died. One died from bronchial carcinoma one month later (Number 2) and another died 15 days later from respiratory complications of his Hodgkin's disease (Number 9). The other patient who died (Number 7), had been weaned off a ventilator with difficulty two weeks earlier in another hospital. He had poor respiratory function and died three days after admission as a result of respiratory failure.

TABLE XXVIII. Clinical course of patients. Shown are the occurrences of further haemorrhage, operations performed and causes of death. Also shown is the amount of blood transfused (units) after laser therapy and total amount transfused. Length of stay in those admitted for reasons other than bleeding is taken from onset of bleeding in hospital.(2)

Patient	Lesion	Laser	F.H.[1]	Operation	Death	Blood transf. (units) after End.	Blood transf. (units) Total	Length of Stay (days)
1	Varix	+				0	6	21
2	D.U.	+			Bronchial Ca.	0	3	>30[2]
3	G.U.	+	7 hrs.	undersew	Sepsis	6	>10	19[2]
4	D.U.		24 hrs.	V & P + undersew		12	14	13
5	D.U.	+				0	6	9
6	G.U.	+				0	5	28[2]
7	G.U.	+			Resp. failure	0	5	3
8	G.U.		cont'd.	V & P + undersew		6	14	10
9	G.U.x 2	+			Hodgkin's	0	20	26[2]
10	G.U.	+				2	8	10
11	Vessel		6 hrs.	V & P + undersew		12	22	14

[1] F.H. = further haemorrhage.

The three patients who did not actually receive appropriate laser therapy either continued to bleed or had a further haemorrhage and underwent emergency surgery. The patient who had the post bulbar ulcer started bleeding again 24 hours after endoscopy and had a vagotomy, pyloroplasty and undersewing of the ulcer. The patients bleeding from the gastric ulcer and single vessel continued to bleed and underwent surgery within 6 hours of endoscopy. Both had the vessel undersewn and a vagotomy and pyloroplasty. All three patients survived and were discharged from hospital. Of the seven patients who settled after laser photocoagulation, only one received a further transfusion of blood. This was patient Number 10 who had a haemoglobin of less than $10g.l^{-1}$ and was transfused 2 units. The four patients who all re-bled, all received further transfusions varying between 6 and 12 units.

The mean length of stay of the eight patients who were admitted because of acute upper gastrointestinal haemorrhage was 11.4 ± 2.1 days (mean ± SEM) with a range of 3 - 21 days.

Endoscopic follow up.

Three patients were endoscoped four days and one month after laser therapy (Numbers 1, 5 and 6). The patient who was bleeding from a gastric varix had an acute ulcer at the site of photocoagulation with no sign of the varix. By one month, the ulcer had healed completely.

The other two patients had ulcers with clean white bases at four days which had both healed at one month.

4. DISCUSSION

The patients included in this pilot study of laser photocoagulation all had major episodes of bleeding as has been shown in Table XXVI . Nine of them were considered to be poor surgical risks and were referred because of this.

The results of laser photocoagulation were encouraging in that only one of the patients in whom the laser was actually fired at the lesion, re-bled, and even then there was some doubt if the site of re-bleeding was the same as that which had been photocoagulated. In none of the eleven cases was bleeding induced or aggravated by the laser and no perforations occurred. What is unknown, however, is how many of these patients would have re-bled if they had not received laser photocoagulation. All eleven patients had stigmata of haemorrhage but Foster's study showed that the presence of stigmata of bleeding could not identify the individuals who would re-bleed[37]. Griffith's study, although retrospective, suggested that patients who had visible vessels would all re-bleed[38]. In this pilot study, seven were bleeding from vessels and four had red or black spots in the ulcer base. The three patients who had lesions that the laser could not be fired at, all re-bled and they had vessels visible at endoscopy.

Of the eight who received laser therapy, four had vessels in the ulcer base. Although four had red or black spots in the ulcer base, one was on anti-coagulants and in the case of another, a decision had been taken to perform emergency surgery because of further haemorrhage (Number 5). However, after laser therapy, surgery was cancelled and the patient settled. The patient who had Hodgkin's disease and died, had a post mortem and histology showed tumour tissue in the ulcer base with dilated veins.

The endoscope used in this study had superior optics to the other standard Olympus endoscopes (GIFD series and GIFk) and was easy to handle; however, because of its outside diameter it was difficult to manoeuvre in the duodenum. The radius of curvature of the tip was less than that of the $GIFD_2$ and GIFT Olympus endoscopes (Key Med) and this limitation increased the difficulty of aiming at lesions high up in the stomach. The twin biopsy channels of the endoscope allowed simultaneous use of the laser cannula and either suction, venting or washing, and this obviates the need for a separate gastric tube to vent the carbon dioxide.

The system of producing a seal between the endoscope and the laser cannula at the biopsy part was cumbersome and time consuming and it was concluded that a simpler system should be devised so that the cannula could be introduced into the endoscope like biopsy forceps. The

laser cannula itself was robust and it appeared to be an advantage to be able to pass the cannula tip beyond the enclosure so that it could be seen. However, its diameter restricted its use to the larger biopsy channel and it was concluded that a narrower cannula would permit the use of the smaller biopsy channel which had a bridge that would increase the manoeuvreability of the cannula tip and would also allow the use of other endoscopes. The cannula system was different from the triconal fibre used by Kiefhaber which was dedicated to a twin channel endoscope and had a special quartz window inserted at the endoscope tip[144]. This system does not require carbon dioxide to protect the fibre tip, but the position of the cannula cannot be altered.

The coaxial carbon dioxide system was successful in that the fibre tip was not damaged as a result of blood covering it. However, the flow of gas induced gastric peristalsis and it was found necessary to give buscopam routinely. The venting system devised was adequate but not entirely satisfactory. When endoscopic suction was used, water was sucked out of the water seal jar. Other systems have been devised where there is a recycling system but this appears to have the disadvantage of being complicated and liable to blockage[246].

Gastric tube lavage was necessary when large clots of blood were present in the stomach and it was successful to this end. Fresh blood was easy to remove when the

large biopsy channel of the endoscope was used for the simple reason that it was liquid. It was found that the large biopsy channel could clear 900 mls of fluid per minute.

5. CONCLUSION

The pilot study of laser photocoagulation presented in this chapter included a group of poor risk patients who presented with major episodes of upper gastro-intestinal haemorrhage with a significant risk of re-bleeding. The experience obtained was encouraging and it seemed worthwhile to progress to a clinical trial to assess the efficacy of neodymium YAG photocoagulation. The actual technique of endoscopic photocoagulation was difficult and required learning.

Some of the prototype equipment would require modification and this has been discussed.

CHAPTER SEVEN

PROSPECTIVE SINGLE BLIND CONTROLLED TRIAL TO ASSESS THE EFFICACY OF THE NEODYMIUM YAG LASER FOR BLEEDING PEPTIC ULCERS AND SINGLE VESSELS

1. INTRODUCTION

In the last chapter, data was presented from a pilot study of neodymium YAG laser photocoagulation which suggested that this form of therapeutic endoscopy might reduce further haemorrhage. But because bleeding peptic ulcers have a natural tendency to stop bleeding spontaneously it is necessary to assess the efficacy of this laser under the constraints of a controlled trial. Furthermore, because of this spontaneous cessation of bleeding, large numbers would be required to show any benefit of therapy that might exist and thus the study was designed to include only those patients who had a high risk of further haemorrhage, and cognisance was therefore taken of the patients' clinical status in addition to endoscopic appearances.

2. PATIENTS and METHODS

Patients.

The patients considered for the study were those who were admitted to hospital because of acute upper gastrointestinal haemorrhage with evidence of blood loss

within the preceding 24 hours. Patients admitted for other reasons and who developed upper gastrointestinal bleeding in hospital were not considered.

Criteria for entry into the trial.

A patient was eligible for the study if he or she fulfilled at least one of the following clinical features:

(1) Presence of shock as a result of blood loss on or subsequent to admission. Shock was defined as the presence of pallor, cold and clammy extremities with a systolic blood pressure of less than 100 mmHg and pulse rate greater than 100 beats $minute^{-1}$.

(2) An initial or subsequent haemoglobin concentration of less than 10 $g.dl^{-1}$.

(3) Blood transfusion judged necessary in preceding 24 hours by clinician responsible for management.

(4) If none of these clinical features were present, a patient could still enter the study if active haemorrhage was encountered at endoscopy.

Entry was also based on fulfillment of one of the following endoscopic criteria:

(1) Presence of a gastric or duodenal ulcer considered to be the source of haemorrhage with either an artery or a red or black spot in the ulcer base.

(2) Presence of a single vessel (bleeding or not) which was considered to be the source of haemorrhage.

According to the trial protocol, fresh clot could be washed away to define the underlying situation, but no attempt was made to dislodge firm clot. It was accepted that patients with firm clot could be re-endoscoped if bleeding recurred.

The protocol was approved by the District Ethical Committee and all patients gave written informed consent before inclusion.

Trial design.

If the study entry criteria were fulfilled, the patient was allocated by random card selection to receive laser or sham therapy. Gastric ulcers, duodenal ulcers and single vessels were regarded as separate groups for randomisation purposes. Laser photocoagulation was carried out by one clinician (I.McL) to ensure uniformity of therapy. This individual was not allowed to divulge whether laser therapy had been used and was not concerned in subsequent clinical management. On completion of endoscopy, the patient was returned to the care of the referring

clinician with a letter explaining that the patient had entered the laser trial, and defining the source of bleeding. The letter did not state whether the patient had received laser therapy but requested that the patient should be commenced on cimetidine in a regime of 200 mgm i.v. bolus injection six-hourly for 24 hours, then 1 gm. day^{-1} orally for one month. All decisions on further management (e.g. blood transfusion, surgical referral) were the responsibility of the physician in charge of the patient's care.

If there was doubt that an episode of further haemorrhage had occurred, then repeat endoscopy was performed to see if this had occurred and to determine the source of bleeding.

After discharge from hospital, the patients were endoscoped between 4-6 weeks later.

Method of Assessment.

Success or failure of laser or sham therapy was assessed according to the following criteria by one of two independent observers unaware of the patient categorisation and not concerned in the patient's management.

(1) Further haemorrhage after the index bleeding episode as indicated by:

overt haematemesis

aspiration of fresh blood from a nasogastric tube

passage of fresh blood per rectum

fall in haemoglobin concentration $3g.dl^{-1}$ within 48 hours in the face of continuing melaena.

shock in the face of continuing melaena

presence of fresh blood in the stomach or duodenum at repeat endoscopy.

(2) Performance of emergency surgery to arrest continuing or further haemorrhage.

(3) Death of the patient.

Exclusions and withdrawals from the trial.

A patient was excluded from the study if he was unwilling to give informed consent or if at endoscopy the pylorus was too narrow to allow duodenal intubation when bleeding was judged to be due to duodenal ulceration.

A patient was withdrawn from the study if the rate of blood loss was such that the delay entailed by endoscopy was adjudged to constitute an unacceptable risk to life.

Endoscopy and Laser Technique.

The technique of endoscopy and lavage was the same as described in the previous chapter.

Three different laser cannulas were used. The one used in the pilot study was replaced after the third patient by a cannula which could be passed through a standard biopsy valve into the large biopsy channel. The third cannula had a 400 μm glass fibre and was only 2.5 mm in diameter and thus could be passed down the smaller biopsy channel. This provided the potential for using other standard endoscopes (e.g. Olympus GIFT, GIFD series and GIFK).

For photocoagulation, peak powers of 60-90 watts were used with total incident energies of approximately 40-50 joules with each pulse. The operation of the laser conformed to the local hospital regulations.

Documentation.

A proforma was prepared for recording the patients' clinical data, progress, endoscopic findings and photocoagulation and another to be used by the assessor to document success or failure of therapy. Photographs were also taken of the source of bleeding in each patient.

Statistical analysis.

For analysis of data from two independent samples, unpaired students t-tests were used.

Because of the small numbers involved in each treatment group, Fisher's exact probability test was used

(two tailed) for comparison of outcome.

For comparison of attributes between different groups, X^2 test with Yates correction was used.

3. RESULTS

The trial commenced in October 1980, and during the subsequent 20 months, 657 (94%) of the 698 patients admitted with acute non variceal upper gastrointestinal haemorrhages were considered for the study. The remaining 41 not considered were admitted whilst the trial was in abeyance because of holidays, meetings or repair and modification of laser equipment.

One hundred and eighty four of those considered were bleeding from duodenal ulcers (118), gastric ulcers (64) or single vessels (2). Fifty four (29%) fulfilled the study entry criteria but 9 were not included for the following reasons. Two patients bleeding from duodenal ulcers had a pylorus too narrow for duodenal intubation with the endoscope; both settled on conservative management. One patient was bleeding from a duodenal ulcer with an artery in the base that was missed at endoscopy but found at surgery which was performed for recurrent bleeding. Another patient had terminal cardiac and cerebrovascular disease and a decision was taken not to endoscope him. He died from blood loss, and post mortem examination revealed a duodenal ulcer with an artery in the base. Two patients had posterior wall duodenal

ulcers with firm clot in the base and both re-bled; one was not referred for further endoscopy and the other died from blood loss before further endoscopy could be arranged. The other three patients were excluded because of massive recurrent haemorrhage; one died from blood loss and the other two underwent emergency surgery and one of them died.

Of the 130 patients who did not fulfill the study entry criteria, all settled with conservative management. Forty five patients entered the study. Twenty eight (62%) were male and 17 (38%) female. Their ages ranged from 22 - 88 with a mean of 57.2 SD ± 16.4 years and 19 (42%) were over the age of sixty (Table XXIX).

Twenty one (47%) were shocked on admission and 31 (69%) had an admission haemoglobin of less than 10 $g.dl^{-1}$. Forty four (98%) had received a blood transfusion prior to study entry, 36 (80%) receiving less than 5 units and 8 (18%) between 5 and 10 units. No patient received more than 10 units before study inclusion.

Twenty three patients were bleeding from duodenal ulcers, 20 from gastric ulcers and two from single vessels. The patients bleeding from duodenal ulcers were younger than those bleeding from gastric ulcers and a higher proportion of them were male. There was no difference in severity of bleeding between the three groups in relation to the occurrence of shock, a low admission haemoglobin and the amount of blood transfused.

TABLE XXIX. Sex, age of patient, bleeding from duodenal ulcers, gastric ulcers and single vessels. Shown also is the presence of shock, Hb <10g.dl^{-1} and requirement of blood transfusion. Significance calculated by X^2 test with Yates correction and Students t-test.

Patients	D.U. n	%	G.U. n	%	Vessels n	%	Total n	%
Number	23		20		2		45	
Male : female	21:2[1]		5:15[1]		2:0		27:17	
Age - Mean SD	49.6 ± 15.8[2]		65.9 ± 12.4[2]		45 ± 21		57.2 ± 16.4	
- Range	22-77		48-88		30-60		22-88	
- > 60	7	(30%)	12	(60%)	0		19	(42%)
Shock	9	(41%)	12	(60%)	0		21	(47%)
Hb <10g.dl^{-1}	17	(74%)	14	(70%)	0		31	(69%)
Transfusion 0	0		1	(5%)	0		1	(2%)
<5	21	(91%)	14	(70%)	1		36	(80%)
5-10	2	(9%)	5	(25%)	1		8	(18%)

1 & 2 ($p < 0.001$)

Eighteen (90%) of the gastric ulcers were in the body of the stomach and only 2 in the antrum. Thirteen (56%) of the duodenal ulcers were on the anterior wall of the duodenal bulb, 7 (30%) on the posterior wall and 3 (13%) in the post bulbar region. One of the single vessels was on the anterior wall of the stomach and the other on the anterior wall of the duodenal bulb.

At endoscopy, blood was present in the stomach or duodenum in 32 (71%) and endoscopic lavage was used in all of them, but tube lavage was only required in 3 (7%). Active beleding was present in 13 (29%) at the time of endoscopy, but only 2 (4%) had active spurting from vessels. In the remainder, an active flow of blood was observed in 5 (11%) and oozing in 6 (13%).

An artery was adjudged to be the source of bleeding in 5 (22%) of the duodenal ulcers, 13 (65%) of the gastric ulcers and both the single vessels. Red or black spots were present in 18 (78%) of the duodenal ulcers and 7 (35%) of gastric ulcers.

Twenty one patients were allocated to receive laser therapy and twenty four sham therapy. The age, sex and severity of bleeding of patients allocated to each therapeutic group in relation to site and source of bleeding is shown in Table XXX and this shows that the mean age of the patients with gastric ulcer and arteries allocated to receive laser therapy were younger than the controls.

TABLE XXX. Details of patients entered into study.
Unpaired t-test used to estimate difference between means.

Bleeding lesion	M:F	Mean age (± SD)	Shock present	Hb.< $10g.dl^{-1}$	Mean no. units of blood transfused (± SD).
D.U.					
spots - control	10:0	48 ± 21	3	7	2.7 ± 1.4
- laser	8:0	48 ± 11	2	6	2.8 ± 1.7
arteries - control	1:0	60	1	1	3
- laser	2:2	54.5 ± 9.8	3	3	3 ± 2.5
G.U.					
spots - control	0:6	72.5 ± 12.3	4	5	2.5 ± 1.8
laser	1:0	69	0	1	2
arteries - control	1:5	69.8 ± 9.8) *	4	4	3.2 ± 3.1
- laser	3:4	56.4 ± 10.8)	4	4	4 ± 1.6
vessels					
control	1:0	60	0	0	4
laser	1:0	30	0	0	8

* ($p < 0.05$)

Otherwise, there was no difference between the groups. Tables XXXIa and b show the outcome of each therapeutic group in relation to site and source. Twenty five patients were bleeding from gastric or duodenal ulcers with spots in the base and irrespective of therapy they all settled, did not require emergency surgery and all survived. There was also no difference in the amount of blood transfused or length of in-patient stay.

Eight patients bleeding from arteries were allocated to receive sham therapy and all of them had further haemorrhage, underwent emergency surgery and two died, one as a result of blood loss on the operating table and the other from respiratory failure. This outcome pertained irrespective of whether the site of bleeding was a gastric or duodenal ulcer or a single vessel.

Twelve patients bleeding from arteries were allocated to receive laser therapy but four did not receive it for the following reasons. One patient was bleeding from the gastroduodenal artery and the bleeding was too brisk to allow adequate visualisation of the vessel. A second patient bleeding from a gastric ulcer would not tolerate a second endoscopy after he had been entered into the study.

The remaining two patients had gastric ulcers in locations that did not allow the laser to be aimed at the arteries. All four of these patients re-bled and underwent emergency surgery and one died as a result of sepsis and multiple organ failure.

TABLE XXXIa. Outcome of patients bleeding from spots and arteries.

	n	Rebleed n	Rebleed Time(hrs)	Emergency Surgery	Death	Blood Total (units)	Length of Stay (days)
D.U.							
Spots - control	10	0	0	0	0	4.7 ± 1.5	12.1 ± 5.6
- laser	8	0	0	0	0	5.5 ± 4.2	10 ± 2.6
Arteries - control	1	1	70	1	1	9	10
- laser	4*	1	1	1	1	7.5 ± 5.1	14.8 ±
G.U.							
Spots - control	6	0	0	0	0	3.8 ± 1	16 ± 10.8
- laser	1	0	0	0	0	3	8 ± 7.4
Arteries - control	6	6	9 ± 9.3	6	1	9.3 ± 2.2	15.5 ± 10.5
- laser	7+	4	55.3 ± 48	3	0	7.8 ± 4.4	12 ± 4.4
Vessels							
control	1	1	8	1	0	7	15
laser	1	1	101	1	0	22	20

* One patient did not receive laser therapy.

\+ Three patients did not receive laser therapy.

TABLE XXXIb. Outcome of patients bleeding from spots and arteries. Shown is the allocation of therapy in relation to their sources of bleeding and the occurrence of further haemorrhage, emergency surgery and death. Statistical significance calculated by Fisher's exact probability test (two tailed).

Spots	n	Rebleed	Emergency Surgery	Death
Control	16	0	0	0
Laser	9	0	0	0
	25	0	0	0
Arteries				
Control	8	8[1,3]	8[2,4]	2
Laser - Yes	8	2[1]	1[2]	0
- No	4	4[3]	4[4]	1
	20	14	13	3

1. ($p = 0.01$)
2. ($p = 0.001$)
3. ($p = 0.048$)
4. ($p = 0.02$)

Of the eight patients bleeding from arteries and who received laser therapy, two re-bled and one underwent emergency surgery seven days later to prevent further bleeding. None of the eight patients who received laser therapy died.

The re-bleeding rate in the treated arteries is significantly less than in the controls ($p = 0.01$), and the difference between the 12 patients in the laser treated group as a whole and the controls is also significant ($p = 0.048$). The emergency operation rate in the artery group who actually received laser therapy is significantly lower than the controls ($p = 0.001$) and the difference between the laser treated group as a whole compared with the controls is also significant ($p = 0.02$).

There was no difference in mortality between the two groups and the blood transfusion requirements and length of in-patient stay were the same.

4. DISCUSSION

Study design.

Patients who developed upper gastrointestinal haemorrhage subsequent to admission were not included in the study because the protean nature of their admission illness would have made randomisation extremely difficult. Only those patients with firm evidence of blood loss within 24 hours of admission and referral were considered

so that those admitted with chronic blood loss and those who had already settled would be excluded.

Although the neodymium YAG laser had been used to treat a variety of bleeding lesions in the upper gastrointestinal tract[144], it was decided to assess the efficacy of this laser with peptic ulcers and single vessels. Oesophageal varices were not considered because at the time the study was set up there was an ongoing study of sclerotherapy and oesophageal transection. Although acute mucosal lesions account for a significant proportion of patients admitted with acute upper gastrointestinal haemorrhage (Table III), only a small proportion of them have further haemorrhage (Appendix 2) and emergency surgery is seldom required to control the bleeding. Furthermore, the bleeding tends to come from diffuse rather than discrete sources and for these reasons this diagnostic group was not considered.

Gastric and duodenal ulcers were treated as separate groups for purposes of randomisation because of the different outcome of these conditions[146].

Because of the natural tendency for bleeding peptic ulcers to settle spontaneously, large numbers of patients would be required in a controlled trial of therapeutic endoscopy to show any benefit of therapy that might exist. To obviate the need for large numbers, it would seem reasonable to select patients for such a study

who had a reasonable chance of further haemorrhage. In order to identify factors which could be used to predict further haemorrhage, an analysis was made of the data obtained from the patients admitted to the Western Infirmary, Glasgow, in 1977 (Chapter 2) and the findings from this study are presented in Appendix 2.

From this study, it was decided that a patient should have at least one of the following clinical features to enter the trial, each of which conveyed an increased chance of further haemorrhage; shock as a result of blood loss on or subsequent to admission, an initial or subsequent haemoglobin of $<10 g.dl^{-1}$ or the requirement of a blood transfusion for resuscitation as opposed to the correction of anaemia. In order to include patients who had an initial minor bleed and who re-bled, it was decided that a patient could enter the study if he met any of the above clinical features subsequent to admission. Because it was conceivable that a patient might be found to have active haemorrhage at the time of endoscopy without possessing any of the above clinical features, this was included as a criterion of entry to the study. In this context, the term active haemorrhage indicates active flow or spurting of blood as opposed to a mere ooze.

In assessing each patient for the study, it was important to be satisfied that at least one of the clinical features was present. In particular, if a patient was

said to be shocked, this was checked personally, and if there was any doubt that the shock was due to blood loss, then a tube was passed per orally into the stomach and the contents aspirated to see if blood was present. If blood was absent, then it was usually found that the hypotension was due to other causes e.g. myocardial infarction, alcohol excess or withdrawal, or viral infection. If a patient had been transfused blood then the reasons for transfusion were examined. In a few cases, it was found that there had been no good reason for giving blood and these patients were excluded. The most important criterion to assess was the evidence for blood loss within the preceding 24 hours. Melaena itself was insufficient evidence and a patient was only considered if blood was present in the stomach or an episode of shock had occurred.

These clinical features appear to have been successful in selecting patients for the study to the extent that all of them who failed to meet the entry criteria settled with conservative management, and many of them had ulcers with raised spots in the ulcer base. The two British studies of argon laser photocoagulation relied mainly on endoscopic stigmata of bleeding for patient selection and this is why they both included a much higher proportion of patients bleeding from peptic ulcers[247,248].

It is necessary in a study of therapeutic endoscopy to define the endoscopic appearances of the sources

of bleeding that are included. The stigmata of recent haemorrhage outlined by Foster and others indicate the result of bleeding rather than its source with the exception of presence of a vessel[37]. However, the appearances of a vessel were not described and the problem when using this term is that it may be an artery, arteriole, capillary, venule or vein, each of which may have different appearances and re-bleeding rates. Vallon and others included vessels as part of their endoscopic criteria, but no description was given[247]. Swain and his colleagues also included vessels as one of their treatment groups and defined them as 'a red or blue raised spot protruding from the ulcer crater, resistant to washing and often associated with a red clot'[248]. Other studies did not define sources of bleeding[249,250]. In this study, the endoscopic sources of bleeding in peptic ulcers were divided into two distinct groups. The first comprised those ulcers which appeared to have an artery in the base and they had three different appearances: (a) a whitish or cream coloured protuberance which often had a thin film of blood on its surface; (b) a pearly grey polypoid lesion in the ulcer case which was interpreted as being a false aneurysm; (c) a red or bluish black punctum in the ulcer base which had a halo.

The second group of endoscopic appearances were described as spots which were red, blue or black and either raised or flat. No attempt was made to make anatomical deductions from these appearances even though some

of them may have been small vessels (arterioles or venules). It is probable that some of the vessels described by Swain would have been included in this group.

Apart from gastric and duodenal ulcers, a third diagnostic group was included in the study, namely patients bleeding from single vessels. The appearance at endoscopy was of an artery pouting through the gastric or duodenal mucosa without surrounding ulceration. This entity has been described by Goldman[251] and Jones[252]. Some have described these lesions as gastric artery aneurysms[253-255], but it is probable that they are abnormally large submucosal muscular arteries that have pouted up through the mucosa[251]. Although they may be an uncommon cause of bleeding, they may be an important cause of major blood loss especially since they accounted for 10% of the patients bleeding from arteries in this study and because they are difficult to identify at endoscopy.

In this study, if firm clot was adherent to an ulcer, then this was left, but a request was made to the referring physician that if the patient re-bled he should be referred back for possible study inclusion. Although these patients as a rule did not re-bleed, two who had posterior wall duodenal ulcers with adherent clot did, and this will be discussed later. This attitude towards firm clot was different from that of Swain[248] and was complied with to allay the fear of some that removal of clot might start bleeding.

In relation to the trial design, all patients were commenced on Cimetidine to ensure uniformity of therapy and not because of any possible haemostatic effect of reducing intragastric acid secretion[233]. The relevance of one person performing laser therapy will be discussed later.

The factors used to assess the success or failure of laser or sham therapy were the occurrence of further haemorrhage, the performance of emergency surgery to arrest continuing or further haemorrhage, and death as a result of the admission illness. Blood transfusion requirements and length of in-patient stay were also recorded. Of the three main factors used for assessment, the softest was the occurrence of further haemorrhage. The definition used was a refinement of that of Jones, P.F.[146]. However, it was decided that if there was any doubt whether this had occurred, then endoscopy should be repeated to see if there was any evidence of recent bleeding in the upper gastrointestinal tract and also to ascertain whether there was objective evidence that the blood had come from the lesion that had been adjudged to be the source of bleeding at the time of entry to the study. The experience obtained from the study however was that in only one patient was there any doubt that re-bleeding had occurred and endoscopy showed that further haemorrhage had not occurred and the ulcer had a clean white base.

The randomisation of therapy to the three diagnostic groups was done by using an ordered card system in blocks of 40 for each group. There was no stratification of therapy in relation to endoscopic appearances, but the results were stratified retrospectively and that is why there was some disparity of numbers in relation to the endoscopic appearances (spots and arteries).

Results.

The groups appeared to be similar in relation to age, sex, severity of bleeding, except that the patients allocated to receive laser therapy and who were bleeding from gastric ulcers with arteries in the base were younger than the controls (Table XXX). However, there is no evidence that older patients with arteries in the ulcer base have a higher chance of re-bleeding than their younger counterparts but it is more likely that an older patient is less likely to withstand the stress of re-bleeding or emergency surgery[102,256].

In this study, patients who were bleeding from gastric or duodenal ulcers with spots in the base and who received sham therapy, settled and did not require emergency surgery. This finding pertained even if there was active bleeding at the time of endoscopy and irrespective of the severity of the index bleeding episode. It was found that those bleeding from gastric ulcers with spots were older than the patients with duodenal ulcers and spots and despite the disparity with age, both diagnostic

groups settled. The outcome of patients bleeding from arteries and who received sham therapy was different. Irrespective of the age of the patient, the site of bleeding or the severity of the index bleeding episode, an artery always re-bled and to an extent which required surgical control. This outcome occurred even if the artery was not bleeding at the time of endoscopy. The spontaneous re-bleeding rate of arteries in this study was the same as that of the visible vessels in the retrospective review of Griffiths[38]. However, the spontaneous re-bleeding rate of non spurting vessels in the studies of Vallon and Swain and their colleagues was 50 and 54% respectively which is significantly different from the outcome in this study (both $p<0.025$)[247,248]. This suggests that some of the vessels in these two studies may not have been arteries.

In an attempt to see if the presence of a vessel in an ulcer base is as important as these findings seem to suggest, the reports of all the post mortems performed in Glasgow Royal Infirmary during the ten year period 1971-1980 were inspected to obtain information on all patients who died as a result of blood loss from peptic ulcers. These reports were inspected to see how many of the ulcers had a single vessel in the ulcer base. A total of 34 patients were found and the pathologist had noted that a vessel was present in 30 (90%). Where histology was available, the vessel was found to be an artery. None of the arteries had evidence of arteriosclerosis and the only vascular pathology noted was end arteritis obliterans,

a condition which is dependent on the ulcer and not the age of the patient[5].

The evidence that the vessels seen at endoscopy in this study were in fact arteries is as follows. Thirteen of these patients underwent emergency surgery and the surgeons who performed the operations concluded that the vessels seen were arteries. Histology was obtained in four and the pathologist confirmed the presence of an artery in each. The seven patients who did not undergo surgery had endoscopic appearances similar to those operated on and it would seem reasonable to suggest that the vessels called arteries at endoscopy were what they appeared to be.

Two major questions arise from the above, namely, do patients who bleed from arteries always re-bleed, and if a patient is not bleeding from an artery, will he re-bleed. In relation to the first question, the results of the study showed that they do, and the post mortem study lends support to this. In addition, of the seven patients who were not included in the study but fulfilled the entry criteria and re-bled, the ulcer base was seen in six, either at surgery or post mortem, and in each an artery was seen. In relation to the second question, none of the patients bleeding from peptic ulcers and who were not included had arteries in the ulcer base and none of them re-bled. These findings are at variance with the commonly held belief that patients who re-bleed do so because they

are elderly and bleed from vessels that have arteriosclerosis and are therefore less able to constrict[257]. The findings from this study suggest that the size of vessel involved is the important factor in relation to further haemorrhage. It is accepted that extra gastric arteries such as the splenic, gastroduodenal or left gastric[56] can be the source of blood loss and this was the case with five patients bleeding from gastric ulcers. However, eight other gastric ulcers had arteries in the base which seemed to arise from within the stomach wall itself and they appeared to be much larger than the size of the normal intragastric vessels described by Piasecki and Barlow[227,258] and this suggests that these arteries are abnormal. Inspection of the photographs which were taken at endoscopy shows that these ulcers were superficial and small and this raises the possibility that the single vessels and the ulcers with intragastric arteries were part of a spectrum of the same condition caused primarily by an abnormal submucosal artery which had pouted up through the mucosa and in some cases caused surrounding mucosal ulceration as a result of ischaemic necrosis. If this is correct, then these ulcers are not peptic in origin. This hypothesis applies to a sub-group of gastric ulcers and does not suggest that all gastric ulcers are caused by this process but the inference from this is that if a gastric ulcer does not involve a sizeable extra gastric artery or an abnormal intragastric artery, then if bleeding does occur it is unlikely that it will be major and it is probable that bleeding will stop

spontaneously as a result of intravascular thrombosis. Because of spontaneous cessation of bleeding, it is unusual to obtain histology of such gastric ulcer bases shortly after the bleeding episode and it can only be assumed that some of the spots seen in ulcer bases at endoscopy represent the normal sized intragastric vessels.

Some studies have made a distinction between vessels that are either actively spurting or not at the time of endoscopy[247,248,250] but despite the high spontaneous re-bleeding rates of spurting vessels reported by Vallon and Swain[247,248], analysis of their data shows that there is no significant difference in re-bleeding rates between spurting and non spurting vessels. Although a few patients bleeding from ulcers with vessels continue bleeding after admission, the majority stop bleeding for a period of time before further haemorrhage occurs[38] and this is the reason why only one artery in this study was actively spurting at the time of endoscopy. Thus, it would appear that the occurrence of active spurting at endoscopy is related more to the timing of endoscopy after the index bleeding episode than the presence of two distinct groups of vessels. Furthermore, the presence of spurting blood does not imply that the source of bleeding is an artery because pulsatile flow can occur in vessels as small as arterioles and unless the magnitude of spurting is measured or the nature of the vessel from which it has arisen is described then this is not an absolute indication of arterial haemorrhage in itself. If every patient was endoscoped at the time

of the index bleeding episode then presumably active bleeding would be seen in all cases and perhaps some ulcers with spots would have a fine spurt of blood issuing from it.

The patients bleeding from peptic ulcers with spots and who received laser therapy, all settled and there was no difference between the treated and control group in relation to total amount of blood transfused or length of in-patient stay.

Twelve patients bleeding from arteries were allocated to receive laser therapy and efficacy for this group has to be assessed in relation to those who actually received laser therapy and the laser treatment group as a whole. Eight patients actually received laser therapy, only two re-bled compared with all eight of the controls ($p = 0.01$) and only one of those who re-bled underwent emergency surgery compared with all eight of the controls ($p = 0.001$). In relation to the laser treated group as a whole, the occurrence of further haemorrhage was reduced ($p = 0.048$) as was the need for emergency surgery ($p = 0.02$). Further analysis showed that there was no difference in the timing of further haemorrhage, total amount of blood transfused, length of in-patient stay or mortality.

Although this study has shown that the neodymium laser reduced the occurrence of further haemorrhage and requirement for emergency surgery, these results have to be

interpreted in relation to the total experience gained from the study. The arteries that were actually treated by the laser were all medium sized and did not include any of the major extra gastric arteries (splenic or gastro-duodenal). In this context, the study was incomplete because an insufficient number of patients bleeding from larger arteries were allocated to receive laser therapy. Thus the maximum size of artery that the laser could photocoagulate successfully remains unknown. Theoretically, the limiting factor in relation to maximum size is likely to be the vessel wall to lumen diameter ratio and thus it is improbable that the laser could prevent further haemorrhage from a dilated thin walled splenic artery. Even if more of the larger arteries had been treated, the answer would to a certain degree remain empirical because if re-bleeding was prevented, then it is improbable that histology from that vessel would be available. This problem is compounded by the fact that the ulcers with the largest arteries allocated to receive laser therapy did not receive it because of brisk bleeding and inaccessability of the artery in relation to the laser beam. The impression gained from the study was that the ulcers which had the largest arteries tended to be in locations within the stomach that made it more difficult to aim the laser beam at the artery. Although one of the patients in the laser treatment group would not tolerate a second endoscopy, the impression was that the ulcer was in a position that might have caused difficulty in aiming the laser at the vessel.

The study was also incomplete in that the patients excluded produced an alteration in the study clinical mix. Of those excluded, six were bleeding from posterior wall duodenal ulcers and the ulcer base was seen in five either at operation or post mortem and all of them had gastroduodenal arteries in the base. The question is not what would have happened had they been allocated to sham therapy but what the outcome might have been had they been allocated to the laser group. Five of the six were endoscoped, one had an ulcer which was missed at endoscopy, two had posterior wall ulcers with firm clot in the base and the remaining two had massive active bleeding at the time of endoscopy which precluded accurate location of the site of bleeding. It would appear that it might have been extremely difficult to have aimed the laser beam at the sources of bleeding in these patients because of the position of the ulcer within the confined space of the duodenal bulb. Furthermore, when massive active bleeding is present, it is not possible to clear the upper gastrointestinal tract sufficiently in a short period of time and the conclusion in the light of present experience must be that these patients should be referred for surgery without delay. The presence of firm clot on a posterior wall duodenal ulcer requires further discussion. Both patients who had this appearance were not referred back in time for possible trial inclusion. There is an argument for removing the firm clot at endoscopy to see if an artery is underneath, and even if it is not possible to aim the laser at it, then

the patient could be submitted to operation without delay thus avoiding the risk of waiting for further haemorrhage to occur.

Comparison with other studies.

It is difficult to compare the results from this study with those from others using the Neodymium YAG laser. Ihre showed no benefit in therapy in a group of patients who had massive upper gastrointestinal haemorrhage, but there was no separation of the diagnostic groups in relation to therapy and no description of the sources of bleeding were given. In particular, it is not possible to interpret the results for bleeding peptic ulcers[249]. Vantrappen showed that the Neodymium YAG laser reduced the occurrence of further haemorrhage in patients with peptic ulcers with either active bleeding or fresh stigmata present but there was insufficient information on the endoscopic appearances[250].

Two controlled trials of argon ion laser photo-coagulation have been reported and aspects of the study protocols have been alluded to already[247,248]. The study conducted in Barcelona failed to show any benefit with laser therapy[247]. Analysis of the data from the study of Swain and others shows that the argon laser did not reduce the re-bleeding rate in those bleeding from vessels irrespective of whether they were bleeding or not at the time of endoscopy. Although the mortality was higher in the control group who were bleeding from vessels, it is

difficult to interpret why this difference should have occurred when the re-bleeding rate was not reduced by the laser[248].

Execution of study.

Although the main purpose of the study was concerned with the efficacy of the Neodymium YAG laser and not with the total hospital management of upper gastro-intestinal haemorrhage, this was of relevance in relation to the patients entering the study. Five of the patients who were excluded might have entered the study had they been referred sooner after admission. The three who were excluded because of massive active haemorrhage all fulfilled the clinical features on admission but were not referred at that time. These patients settled and were only referred after their second or third episodes of further haemorrhage, when they were moribund. The two patients with posterior wall duodenal ulcers with adherent clot were not referred back in time for study inclusion and aspects of this have been discussed already.

The practice of some of the patients being endoscoped by the duty endoscopist before referral made therapeutic endoscopy more difficult because of the patients' reduced tolerance to further endoscopy, and trauma to the site of bleeding by the endoscope. When this practice occurred, the endoscopy was performed to suit routine endoscopy lists. For these reasons, this factor more than anything else made the running of the study

more difficult than it might have been. The problem was compounded because of the occasional difficulty in obtaining a trained nurse to assist in the laser room.

It was intended to endoscope patients one month after discharge from hospital to see if laser photocoagulation affected the ulcer healing, but unfortunately some physicians would not refer their patients for endoscopy and this aspect of the study was not considered.

Technique of endoscopy and laser therapy.

With most patients, the use of diazepam provided satisfactory sedation. However, a proportion of the patients who had consumed alcohol prior to their admission became disorientated rather than sedated. This was a definite problem with these patients and raised the question of using general anaesthesia. This practice has been used elsewhere but was not adopted during the study[224].

Tube lavage was necessary with only three (7%) patients. However, the total experience gained from this procedure during two years was that the technique evolved was effective in removing sufficient clot to examine the stomach. The experience has also shown that it is not necessary to perform lavage on every patient who has had a major bleed. The technique of endoscopic lavage which was described in the previous chapter was found to be extremely efficient in cleaning ulcers and to stop active oozing of blood.

The lesson learned from endoscoping patients who had brisk active haemorrhage was that the procedure should in reality be confined to localising the site of bleeding. If the procedure is prolonged, it is conceivable that a significant proportion of a patient's blood volume could be sucked from the upper gastrointestinal tract and this plus the delay in active resuscitation and surgical control of the bleeding could affect the patient's prognosis. The modified 2.5 mm diameter laser cannula was as simple to introduce into the small biopsy channel of the endoscope as biopsy forceps. This permitted the use of the forceps bridge which made it easier to aim the laser beam at some of the lesions particularly on the anterior wall of the stomach and duodenum. But the bridge did not improve the aiming of the beam at lesions on the posterior wall of the stomach and duodenum. The advantages and disadvantages of the twin channel endoscope have been outlined in the previous chapter and it was hoped that this new cannula would allow the use of other endoscopes but in practice, it was difficult to obtain them for use in the study. In retrospect, it might have been better to have acquired an Olympus GIFQ (Key Med) instead of the TGF-2D because of the better manoeuvreability of that instrument.

Although the coaxial carbon dioxide tended to keep the laser fibre tip clean, it failed to do so in two cases when the fibre tip was damaged. In one of these patients, the tip of the cannula melted and fell off and

was lost. Within the confines of the study, high flow coaxial gas was seldom used to clear the source of bleeding and this raised the possibility of developing a system similar to but simpler than that used by Kiefhaber[144]. In vitro studies were performed with a water filled balloon on the endoscope to protect the fibre tip and allow compression of an active bleeding source but it was never used in the study. Other modifications of the fibre tip were considered, e.g. prisms for angular projection of the beam, but this is outwith the remit of this study.

The gas venting system devised and used in the study was never entirely satisfactory primarily because of the problem of back suction of water from the water seal jar. A Heimlich valve (Vygon) was inserted into the system but tended to become blocked with blood.

Whenever the laser cannula was inserted into the endoscope it was necessary to administer buscopam to reduce gastric peristalsis and eventually this drug was given routinely just before the cannula was inserted.

In this study, only one person performed therapeutic endoscopy so that uniformity of therapy was maintained. Despite this, the number of patients treated during the two years that the laser was in use was small and thus the experience obtained was limited. This made learning difficult despite this experience and in vitro

studies with post mortem specimens of arteries, evolution of the actual technique of laser photocoagulation must be considered incomplete.

CHAPTER EIGHT

GENERAL CONCLUSIONS

1. DIAGNOSTIC ENDOSCOPY

In Chapter Two it was shown that early fibre-optic endoscopy provided an accurate means of identifying the site and pathological causes of bleeding. However, there was no firm evidence that this information resulted in an improvement in outcome. At first this conclusion appears confusing but analysis of the possible reasons for this provides the probable solution. Although 90% of the patients included in the 1977 study were endoscoped, analysis of those who were not shows many of them were high risk patients who did badly. In particular, 42% of those shocked on admission were not endoscoped and the same proportion of those who died were also not endoscoped. If knowledge of the site and cause of bleeding makes any difference in outcome, then endoscopy must be performed on high risk patients and not just on those who will do well anyway.

The second possible reason relates to medical therapy proferred as a result of endoscopic findings. With the exception of oesophageal varices, knowledge of the cause of bleeding does not alter the medical management of patients. In essence, the basic medical treatment for acute upper gastrointestinal haemorrhage consists of bed rest, initial starvation followed by feeding, administration

of antacids or H_2 receptor antagonists. If the patient is anaemic or continues to bleed, then blood is transfused. To a certain extent, confusion exists between treating the pathological cause of bleeding and attempting to prevent further haemorrhage. With regard to the former, the first three facets of medical therapy will accelerate the healing of most of the causes of upper gastrointestinal haemorrhage with the exception of oesophageal varices and carcinoma. However, it does not follow from this that these measures will reduce the occurrence of further haemorrhage and in fact there is no firm evidence that they will. Even so, because most patients will settle spontaneously after their index bleeding episode, many clinicians believe that these simple measures are efficacious in reducing rebleeding. The simple conclusion that must be reached from this is that because the natural course of events of this condition is not altered, then diagnostic endoscopy in itself has not altered outcome.

If the conventional role of endoscopy is accepted as a means of providing information on the site and cause of bleeding, then any improvement in outcome must result from improvement in management of these patients and surgical arrest of further haemorrhage if it occurs. The purpose of the management team in the Western Infirmary was to provide a continuity of care by clinicians who had a special interest in this condition and who could operate on those who had significant further haemorrhage. Within the context of the findings of the 1977 study, there was

no evidence that the availability of the team provided an improvement in outcome. The reasons for this are two-fold. As the care of patients was taken over by the team after endoscopy, some of the high risk patients were either operated on or died before the management team took over their care and to a certain extent, natural selection provided the team with a group of patients who had a high probability of settling without requiring any special care. The second reason is that although resuscitation was improved and documentation better, there was no medical therapy available to prevent further haemorrhage and thus any improvement must come about by reducing postoperative mortality. The evidence that the postoperative mortality was reduced is lacking. Dronfield showed that most of the potentially avoidable deaths occurred in those who were operated on and from this it follows that if any significant reduction in mortality is to be achieved, then emergency surgery has to be avoided.

The key to this problem lies with the event of further haemorrhage. In all probability, the occurrence of further haemorrhage is the most important factor in determining the outcome of patients admitted with acute upper gastrointestinal haemorrhage for once it occurs, then a patient's chances of dying rise tenfold (appendix). Thus further haemorrhage has to be prevented but how is this to be achieved?

The first step must be to identify these patients who will have further haemorrhage. In terms of clinical history and presentation, only groups of patients with a high probability of further haemorrhage can be identified and data on this is presented in Appendix 2 . Allied to endoscopic information of the cause and site of bleeding, patients with a high risk of further haemorrhage could be operated on early and to a certain extent, this approach can be successful as has been shown from the results of the haematemesis unit in Melbourne. However, within the context of the patient population in the West of Scotland, some patients fulfilling the Australian criteria would undergo surgery without requiring it and may succumb.

2. PROGNOSTIC ENDOSCOPY

This leads to the third possible reason why diagnostic endoscopy has not provided a reduction in mortality. The real value of this procedure lies in the possibility of identifying the individuals who will have further haemorrhage. At the time of the 1977 study in the Western Infirmary, little attention was paid to the actual source of bleeding, and to endoscopic stigmata of haemorrhage which might indicate an increased risk of rebleeding. Prior to the publication of Foster's study relating to stigmata of recent haemorrhage, I attempted to determine whether the presence of active bleeding, altered or fresh blood, or clot adherent to an ulcer conveyed an increased

risk of further haemorrhage (Appendix 2). The results failed to show any increased risk of rebleeding if these stigmata were present, but the essential factor missing from the analysis was documentation of the source of bleeding (type of vessel). One possible reason for this lack of documentation may have been that vessels were not there but they were seen at surgery and post mortem. The other and more likely reason for the failure to document the presence of vessels was because of the organisation of the endoscopy servicein the Western Infirmary at that time. It consisted of 6-8 endoscopists each of whom was on duty for a week at a time. Thus each endoscopist would performed approximately 50 endoscopies per year and only a few of the patients would have a visible artery in the ulcer floor, and thus the relevance of the source of bleeding was not appreciated. In retrospect this was surprising since it was long known by surgeons and pathologists that arteries were commonly found in the ulcer floor of patients undergoing emergency surgery or post mortem after death due to blood loss.

The paper by Foster was a landmark to the extent that it showed that it was possible to identify groups of patients who had an increased risk of further haemorrhage. However, in some ways it was misleading since it detracted from the importance of identifying the source of bleeding. Minds were concentrated on the presence of blood in its various states, or active bleeding in the upper gastro-intestinal tract. The problem with these appearances is

that they are transient and thus, the timing of endoscopy after the index bleeding episode will affect the presence or absence of them. In particular, if all endoscopies were to be performed at the time of the index bleeding episode, all patients would have active bleeding, but it is well known that most patients stop bleeding spontaneously. Although the presence of a vessel was considered to be a stigma of bleeding, unfortunately no precise description of their visual appearances was given and no separate data was provided on the rebleeding rate of patients who had visible vessels. The publication of Griffiths, although a retrospective survey, was probably more important than Foster's because it focussed on the visible vessel and the possibility of identifying the individual who would rebleed. Unfortunately like Foster's study, no precise description of a vessel was given and this raised problems. It is apparent that the meaning of the term and the visual appearances are different to different people. The data from the studies of Vallon and Swain show that not all patients who have visible vessels in ulcer floors rebleed.

The fact that all patients who have arteries present in ulcer floors, rebleed is the most important finding from the data presented in this thesis, since it shows that it is possible to identify the individual who will rebleed. The reason for the disparity in outcome between the vessels of Swain and Vallon was presented in the last chapter and this difference highlights the

necessity for standardising the visual description of an artery.

With the importance of the presence of an artery being realised, the real potential of diagnostic fibre-optic endoscopy can be achieved because the procedure can become prognostic (prognostic endoscopy) and the natural history of acute upper gastrointestinal haemorrhage can be changed.

3. THERAPEUTIC ENDOSCOPY

In the first chapter of this thesis, reference was made to the various techniques that have been used to prevent further haemorrhage but there was no evidence that any of them were of value because their efficacy had not been tested under the constraints of a controlled trial. The controlled trial of Neodymium YAG photocoagulation for bleeding peptic ulcers presented in chapter seven showed that the occurrence of further haemorrhage and the need for emergency surgery was reduced and thus the natural history of the condition had been altered. However, because of the numbers involved, the mortality had not been reduced. Furthermore, within the limits of experience gained, this form of therapeutic endoscopy was not applicable in those who had brisk arterial haemorrhage at the time of endoscopy or had ulcers in situations that were inaccessible to the laser beam.

Although little reference has been given to other techniques of therapeutic endoscopy, the fact remains that

none of them are of proven value and just because equipment such as multiprobe diathermy is cheap does not mean that it is efficacious.

4. EARLY SEMI-ELECTIVE SURGERY

The ability to identify the individual who will rebleed means that surgery can be performed on these patients in semi-elective rather than emergency circumstances and it might appear to be logical to suggest that the postoperative mortality will be reduced. However, it may be that the patients who undergo semi-elective surgery after their bleeding has settled are a different population from the ones that undergo emergency surgery and it does not therefore follow that the latter will have as low a mortality as the former. If, however, the mortality for surgery is reduced in these patients, then the value of therapeutic endoscopy may be reduced especially if non-operative therapy delays surgical intervention in those who rebleed because of failed endoscopic therapy. It would therefore appear that the true value of identifying those who will rebleed and prevent its occurrence has yet to be determined.

5. FUTURE MANAGEMENT POLICIES

From the foregoing conclusions, it is possible to suggest a more satisfactory method of looking after patients with acute upper gastrointestinal haemorrhage.

On admission to hospital, a patient is examined to determine if he has a high risk of further haemorrhage or not. If he is shocked, has a haemoglobin of less than 10 $g.dl^{-1}$ or requires colloid or blood for resuscitation then his care should be taken over by a team of surgeons who are at least of post-fellowship grade and resuscitation is carried out. All of these patients should then be endoscoped as soon as they have been resuscitated, preferably within 4 hours of admission. The number of endoscopists should be restricted to 2 or 3 so that they each have sufficient experience to be able to diagnose the cause, site and source of bleeding. If brisk arterial haemorrhage is encountered, then immediate surgery should be undertaken. If an ulcer is found with a non-bleeding artery in the base that is inaccessible to laser therapy, then immediate semi-elective surgery is performed. If there is a posterior wall duodenal ulcer with a firm clot in the base, then the clot should be removed. If brisk arterial haemorrhage ensues then immediate surgery should be undertaken. If arterial bleeding does not occur, then laser therapy could be performed. If any ulcer has an artery in the base which is accessible to the laser beam, then laser photocoagulation should be performed.

Of the remaining patients, ideally they should all be endoscoped within 24 hours of admission and if any ulcer is found with an artery in the base, then either laser photocoagulation or immediate semi-elective surgery should be performed. The remaining patients could then be returned to the referring physician.

6. FUTURE STUDIES

Because the true role of therapeutic endoscopy and early semi-elective surgery has to be resolved, it will be necessary to perform a controlled trial of neodymium YAG laser photocoagulation versus immediate semi-elective surgery in patients who have ulcers with arteries. The appropriate surgical procedure for gastric ulcers has yet to be determined and to a certain extent this depends on elucidating the aetiology of gastric ulcers with arteries in the ulcer floor. However, it may be that simple ligation and ulcer closure or exclusion is all that is required for ulcers that have arteries intrinsic to the stomach wall and either this is tested in a controlled trial versus ligation and a peptic ulcer operation or a series of the former are performed to assess the efficacy of such a procedure. With regard to other forms of therapeutic endoscopy, no comments can be made until the results of valid controlled trials are reported.

Finally, the long-term benefit of therapeutic endoscopy and early semi-elective surgery has yet to be assessed.

STATEMENT OF COLLABORATION

The original idea of looking at the haematemesis admissions to the Western Infirmary during the five year period 1968 - 1972 was Dr. A. Patel's, and his main reason for looking at this group of patients was to investigate the epidemiology of alcohol ingestion. The proforma for this study was drawn up by myself. The case sheets were retrieved by Dr. Patel's secretarial staff but the collation of data presented in this thesis was entirely my own work.

The idea of comparing the different groups in relation to patient management was Mr. C. MacKay's. However, it was my prior expressed intent to look at this group of patients. The construction of the proforma and extraction of data was entirely my own work. The endoscopies that were performed on the patients concerned in this second study were performed by the various members of the endoscopy service including myself. The patients whose care was taken over by the haematemesis team were looked after by the members of that team which also included myself.

The laser photocoagulation project in the Royal Infirmary was first proposed and funded by Barr and Stroud Ltd. and the laser equipment was provided by and modified by their employees. The methodology of the animal experiments was devised by myself with the exception that

Dr. David Hole gave advice on the randomisation of laser radiation parameters in the first experiment.

All the animal experiments were performed by myself with the exception that Mr. H. Lewi injected a small proportion of the rats in the second experiment. Dr. Charles Bow operated and calibrated the laser apparatus throughout the animal studies and Mr. R. Wright set up the anaesthetic and flow probe equipment for the dog studies.

The histology of the animal work was performed by Drs. Rao and F. Lee.

The ancillary equipment devised for the clinical studies was designed by myself; however the modifications to the laser equipment were carried out by Barr and Stroud as a result of the feedback from the clinical pilot study.

The protocol for the controlled trial was drawn up in collaboration with Drs. Mills, MacKenzie and Russell. However, the original idea for the clinical and endoscopic criteria were my own. The construction of the protocol and the execution of the trial was performed under the guidance of Professor D.C. Carter.

All the endoscopies in the laser studies were performed by myself.

All the references cited in the text have been read by myself.

I C Macleod

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APPENDIX I.

LASER SAFETY

1. INTRODUCTION

The regulations covering the use of laser equipment in Britain are contained in British Standard Institution 4803 published in 1972 (UDC 614.875: 534.374) entitled "Guide on protection of personnel against hazards from laser radiation". However, these regulations are dated with regard to the advances in laser equipment and knowledge of exposure limits to radiation. At present, there is a fifth draft of the revisions and the regulations are derived mainly from "American National Standards for the Safe Use of Lasers" published by the American National Standards Institute Inc. (ANSI 2136.1 - 1976).

In practice, the safety codes for the use of lasers in hospitals in this country are drawn up locally. In the Royal Infirmary, Glasgow, they were drawn up by the Department of Clinical Physics and Bioengineering after consultation with Barr and Stroud Ltd. and the medical staff involved with the laser project.

Laser equipment used on University premises has to comply with "Safety in Universities Notes of Guidance, Part 2.1 Lasers" published by the Association of the Commonwealth Universities for the Committee of Vice Chancellors and Principals. Guidelines from these

regulations were drawn up by the University laser safety officer.

The American legislation divides laser equipment into four classes according to their potential hazard and the Neodymium YAG laser is defined as a Class 4 laser, which means that it is a high risk laser and that there should be no direct intrabeam viewing and that precautions should be taken against retinal exposure to diffuse reflection of the beam. This class of laser is also a potential fire hazard and precautions should be taken to remove this risk.

Class 4 lasers must have certain safety features incorporated in the equipment, namely, protective housing for the laser, safety interlocks, a remote control connector, key lock control of the equipment, a laser radiation emission indicator on both the laser and power supply unit and an intracavity electro mechanical shutter.

The helium neon laser incorporated with Nd. YAG laser system is defined as a class 3A laser which means that intrabeam viewing should be avoided.

As the eye is the most vulnerable organ to laser radiation, personnel using laser equipment should undergo eye tests (including retinal photography) before using the equipment and at three year intervals to check that damage has not occurred.

Because most laser equipment makes use of high voltages, there are potential electrical hazards and installation of such equipment must comply with British Standards Institution 5724 "The specifications for safety of medical electrical equipment" published in 1979.

2. SAFETY FEATURES OF THE LASER ROOM IN THE UNIVERSITY LABORATORY

The following changes were made in accordance with the guidelines made by the University safety officer.

1. The room was defined as a laser designated area (LDA) and entry was restricted to authorised personnel only and a sign indicating this was placed on the outside of the door.

2. An illuminated sign was placed on the outside wall adjacent to the door with the warning DANGER - HIGH POWER LASER - NO ENTRY. This sign was interlocked with the laser so that it came on when the laser was operational.

3. An interlock was installed on the door which was connected to the laser so that it would be inactivated if the door was opened when the laser was operational. An interlock button was placed on the wall outside the room to inactivate the laser if required and a further two were positioned on the wall inside the room. These were connected in series with the door interlock.

4. The inside of the door and lower part of the laboratory windows were lined with matt finished metal

sheets and the walls and upper parts of the windows were painted with pale blue matt paint to reduce specular reflections and maintain a high level of background illumination to prevent pupillary dilatation.

5. All unnecessary equipment was removed from the room and any polished or metal surfaces were either painted or covered with tape.

6. A clearly marked isolation switch for the 3 phase electricity supply was installed outside the room so that the laser could be shut down from outside if necessary.

7. The laser equipment was modified to comply with the regulations covering Class IV lasers (e.g. metal housing).

8. The safety goggles used at first had an optical density of 16 for Nd. YAG radiation and a 37% transmission of light (Glendale Optics, U.S.A). However, because the visor was green, goggles with transparent glass were used. The glass used was Schottglass BG18 with an O.D. of 17.1 at 1060 N M. The glass was tested at Barr and Stroud Ltd. before use. With continuous wave peak power of 100 watts, flaring of the glass occurred after one minute exposure, and transmission of radiation did not occur until several seconds of flaring had elapsed.

Because the laser was being operated in 'open' conditions in the laboratory, a sequence of events was developed to obviate the risk of retinal exposure to radiation and they were as follows:-

(1) Only personnel authorised to be in the room were admitted.

(2) The tap for the laser water coolant system was turned on.

(3) The mains electrical supply switch was turned on.

(4) The laser power supply - coolant unit was turned on and a check was made to see that none of the interlocks were operating.

(5) Safety goggles were put on and the laser lamp was fixed.

(6) The laser was activated and the exit beam was checked for calibration with the peak power meter.

(7) Experiments were performed.

(8) Exit beam peak power calibration checked.

(9) Laser was deactivated and the power supply unit was turned off.

(10) Mains electrical supply and water tap turned off.

3. SAFETY PRECAUTIONS FOR USE OF THE LASER IN THE HOSPITAL

The room that was to be used as a laser designated area was modified according to the regulations referred to in the introduction. The main modifications were as follows:-

The doors were modified so that no laser radiation could escape to the outside and an interlock was fitted onto the outside so that the laser could only be activated when the doors were closed. An illuminated sign was placed on the outside wall adjacent to the doors and it only came on when the laser system was on. The sign indicated that entry to the room was forbidden when the laser was on. A black blind was fitted to the room window and this was to be drawn when the laser system was on.

The electrical modifications made were in accordance with B.S. 5724.

Because of specular reflection from the stomach wall, a Schott glass filter was incorporated into the eye piece of the endoscope. The local rules for the use of the laser in the clinical setting were drawn up as shown on the following page and a copy was placed on the laser room wall.

Local Rules for the use of the Nd-YAG Laser in the Endoscopy Theatre Ante-Room, Glasgow Royal Infirmary.

This laser can cause injury from both the direct beam or its specular reflections and from diffuse reflection. It also presents a potential fire hazard. Safe use of the laser depends upon strict adherence to the following rules:

1. A register shall be kept of personnel authorised to operate the equipment (Appendix).

   One authorised operator shall be nominated to ensure that the register is maintained and assume overall control of the installation and its safe operation (Laser Safety Officer).

2. It is the responsibility of the Operator to be aware of the nature of the hazard involved, to be familiar with the Operator's Notes, to ensure that persons assisting in the procedures are fully trained in the safe performance of their duties and to ensure that the requirements are being observed for the safety of himself/herself, the patient and any other staff or visitors who may be present.

3. When the laser is in operation the number of people in the room shall be kept to a minimum.

4. When the laser is operated under "Closed" conditions there is no external hazard to persons within or outside the room and safety goggles are not required. Under "Open" conditions the laser must only be operated whilst all persons present in the room are wearing goggles designed to protect against 1.06μ radiation and the windows are blacked out.

5. The following operating procedure shall be observed:

   (a) Close the key switch and verify that the warning light above the door is ON.

   (b) Close the doors.

   (c) Insert the endoscope into either the patient or the power meter and then insert the fibre connected to the laser into the endoscope ("Closed System".

   (d) Ensure that the illumination channels of the endoscope are connected or blanked off.

   (e) Press the enable switch only when ready to lase.

   (f) Operate the footswitch as necessary.

   (g) Disable the laser between treatments, or if it is necessary to withdraw the endoscope from the patient or the power meter ("Open" System).

6. In case of emergency the "Emergency Stop" shutter mounted on the Laser Head Unit should be closed or the switch on the power supply set to laser OFF.

7. Whenever the equipment is unattended by an authorised operator the power must be switched off and the key withdrawn and kept in safe custody by the authorised operator.

8. Operators must sign statements that they have read and understood these Local Rules. The completed statements will be sent to the Secretary of the Radiological Safety Committee.

APPENDIX 2.

FACTORS IDENTIFYING PROBABILITY OF FURTHER HAEMORRHAGE AFTER ACUTE UPPER GASTROINTESTINAL BLEEDING

Patients and Methods

All patients admitted to the Western Infirmary during the second study period (1.1.77 - 31.12.77) were included in the study.

The incidence of further haemorrhage was determined for the factors tested in tables I - IV to ascertain whether the presence or absence of a factor influenced the occurrence of further haemorrhage. Statistical analysis was by X^2 test with Yates' correction.

Certain of the factors require clarification and are defined in chapter 2.

Results

Ninety-five (24%) of the 389 admissions had a further haemorrhage during the period of in-patient care and 28 (30%) of them died compared with 8 (3%) of those who settled. Rebleeding was most likely to take place within 24 hours of admission and this occurred in 46 (48%). By 72 hours, 71 (75%) had rebled.

The predictive value of the factors examined in identifying those patients at risk from further haemorrhage are documented in Tables I - IV.

TABLE I.

Incidence of further haemorrhage in relation to the presence or absence of factors in the patient's history

Factor		Total n	Further haemorrhage n	Further haemorrhage %	Significance
Dyspepsia	Yes	108	25	23%	N/S
	No	281	70	25%	
History of peptic ulcer	Yes	83	22	27%	N/S
	No	306	73	24%	
Previous GI haemorrhage	Yes	129	27	21%	N/S
	No	260	68	26%	
Peptic ulcer surgery	Yes	78	16	21%	N/S
	No	311	79	25%	
Cardio-vascular disease	Yes	54	16	30%	N/S
	No	345	79	23%	
Respiratory disease	Yes	47	14	30%	N/S
	No	342	81	24%	
Alcohol	Yes	137	20	15%	$p<0.001$
	No	252	75	30%	
Salicylate	Yes	86	23	27%	N/S
	No	303	72	24%	
Smoking	Yes	206	48	23%	N/S
	No	183	47	23%	

N/S = not significant.

TABLE II.

Estimation of the significance of the patient's admission status in relation to incidence of further haemorrhage

Factor	Total n	Further haemorrhage n	%	Significance
Male	266	59	23%	N/S
Female	123	36	29%	
Age <60	233	42	18%	p<0.02
Age >60	156	53	34%	
Shock: present	29	20	69%	p<0.0001
absent	360	75	21%	
Hb <10 g/dl	104	51	49%	p<0.0001
Hb >10 g/dl	285	44	15%	
Haematemesis	209	35	17%	
Melaena alone	72	23	32%	p<0.01
Both	108	37	34%	

N/S = not significant.

TABLE III.

Further haemorrhage in relation to main sources of blood loss found at endoscopy.

Site.	Total n	Further haemorrhage n	%
Oesophagus			
Oesophagitis	21	2	(10)
Ulcer	13	4	(31)
Mallory Weiss Tear	16	2	(13)
Varices	12	5	(42)
Stomach			
Ulcer	52	25	(48)
Gastritis	47	3	(6)
Carcinoma	3	1	(33)
Duodenum			
Ulcer	84	27	(32)
Duodenitis	14	2	(14)
Multiple lesions	33	5	(15)
Miscellaneous	14	1	(7)

TABLE IV.

Incidence of further haemorrhage (F.H.) in those patients bleeding from gastric or duodenal ulcers. Also shown is the incidence of further haemorrhage in each lesion in comparison with age and the finding of stigmata of haemorrhage at endoscopy.

	G.U.			D.U.		
	n	F.H.	(%)	n	F.H.	(%)
Age						
< 60 years	23	10	(45)	53	13	(25)
> 60 years	29	15	(52)	31	14	(45)
Total	52	25		84	27	
Stigmata						
Presence	29	13	(45)	45	17	(38)
Absence	23	12	(52)	39	10	(26)
Total	52	25		84	27	

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