THE NEUTRAL RED TEST - A COMPARISON WITH THE INSULIN TEST IN 100 PATIENTS WITH DUODENAL ULCER TREATED BY TRUNCAL VAGOTOMY AND PYLOROPLASTY

A thesis submitted to the Faculty of Medicine of the University of Leicester for the Degree of Doctor of Medicine.

by

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THE NEUTRAL RED TEST - A COMPARISON WITH THE INSULIN TEST IN 100 PATIENTS WITH DUODENAL ULCER TREATED BY TRUNCAL VAGOTOMY AND PYLOROPLASTY

W. MORRIS-JONES

Over a period of nineteen years, one hundred patients were initially tested with the Neutral Red Test and with the Insulin Test. Twenty one patients died during the study, the main cause of death being cancer and cerebro-vascular disease. No increase in cancer of the stomach or colon was noted during the study. Sixty five patients were available for study (mean follow-up time - fourteen years, six months. The clinical outcome showed an 81.5% in the "successful outcome" (Visick I and II). The recurrence rate was 14%, the majority of these being treated medically. The study confirms the simplicity and safety of the Neutral Red Test with its ability to stimulate the vagal system centrally and thus produce a mild secretagogue effect. The Neutral Red Test confirms many of the features of the Insulin Test and there is a very high degree of agreement between the two tests. The classification of the Insulin Test into "early" and "late" is confirmed. The predictive value of these tests is relatively low but has clinical value. The fate of the "late" positive response is similar to the negative response. Therefore, the "late" positive response carries a good prognosis as far as future clinical outcome is concerned. Therefore, the ability of a few residual vagal fibres to re-innervate the gastric mucosa by collateral nerve regeneration or sprouting is insignificant, even over a long period of time. Therefore, this study makes a strong plea for maintaining or re-introducing tests to assess the completeness of vagotomy post-operatively in order to prognosticate clinical outcome and to assess the vagotomist.

"One thing I have learned in a long life: that all our science, measured against reality, is primitive and childlike - yet it is the most precious thing we have."

Albert Einstein

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CONTENTS

THE HISTORY OF THE VAGUS NERVE

In the first century A.D., Marinus of Alexandria described the paired arrangement of the cranial nerves. Galen (A.D. 129-199) of Pergamum, who had read the works of Marinus, described seven pairs of cranial nerves. He based his descriptive anatomy on the dissection of lower animals, particularly the African monkey and the Barbary ape. His sixth pair of cranial nerves included the glossopharyngeal, the vagus and spinal accessory nerves not because he could not distinguish between the nerves but because organisationally they could be treated as one. The recurrent laryngeal nerves he tied, thus demonstrating that the brain controls the voice. Galen was familiar with the oesophageal plexus, the formation of the anterior and posterior trunks and their division and he was particularly intrigued by the hepatic branch of the anterior trunk.

Thomas Willis in Cerebri Anatome, 1664, described nine pairs of nerves; the glossopharyngeal, vagus and cranial portion of the spinal accessory nerves were counted together as the eighth pair. The present system of twelve pairs of cranial nerves was accomplished by Soemmerring in 1778 but it was over a century later before it was widely accepted and the vagus or tenth nerve regarded as a separate entity.

Earlier, the vagus nerve had been described as the second or wandering part (Hunter, 1752). Early in the nineteenth century the term "pneumogastric" began to appear in the French and Italian literature while in Germany, the term "vagus" was always used. It is only in the latter part of this century that the term "pneumogastric" has disappeared from British and American text books.

In recent years, the anatomy of the vagus nerve in man has been described by Latarjet (1922), McCrea (1925), Mitchell (1938, 1940), Miller & Davis (1947), Bradley et al (1947), Dragstedt et al (1947), Jackson (1948, 1949), Griffith (1964) and Skandalakis (1974).

The left and right vagi enter the thorax and form the oesophageal plexus which lies on the oesophagus between the level of the bifurcation of the trachea and the diaphragm but it may occasionally extend below the diaphragm. Distally, the fibres of the plexus re-unite to form the anterior and posterior vagal trunks which then divide into four divisions. The anterior trunk divides into the hepatic division which innervates the liver and gall bladder and sends a branch which turns downwards to innervate the pylorus and duodenum. The other division, the anterior gastric division, follows the lesser curvature of the stomach. The posterior vagal trunk divides into the coeliac division, passing to the coeliac plexus and the posterior gastric divides with branches to

the posterior gastric wall. The vagal structures entering the abdomen through the hiatus may, therefore, be:

(a) portions of the oesophageal plexus

(b) trunks

(c) divisions

(d) branches of divisions

Skandalakis et al (1974) found in an examination of 100 cadavers, 2 vagal structures in 88, 4 vagal structures in 7 and more than 4 in 5 cadavers. Recently, Rosati (1976) and Johnson (1982) have stressed the importance of a vagal fibre which may emerge from the hiatus at a considerable distance from the oesophagus and enter the top of the fundus. Grassi et al (1972) described a nerve which is a branch of the posterior trunk which passes behind the oesophagus to innervate an area on the posterior wall of the stomach. This is often referred to as the "criminal nerve". It is not surprising, therefore, that small vagal fibres are missed at the hiatus at operation.

Further, there is some experimental evidence, though we could not confirm it in the rat (Jones & Griffith, 1970 (a) (b)), that the vagus does not provide the only cholinergic innervation to the stomach but that cholinergic fibres in the splanchnic nerves and in the anterior and posterior roots of the thoraco-lumbar cord can affect the function of the stomach (Jefferson et al 1965, Donahue et al, 1988).

During the past few decades there have been new concepts concerning the functional anatomy of the vagus nerve:

(a) The classical study by Agostini et al (1957) showed that at the level of the diaphragm the anterior and posterior vagus nerves contain a total number of 31,000 fibres in the cat. Only 10% of these fibres are efferent and consist of unmyelinated axons, small in number and slowly conducting. The remaining 90% of the fibres are afferent, myelinated axons, large in diameter which conduct more quickly.

(b) Gravgaard in 1968 showed in a cadaveric study that the diameter of the vagal trunk, the transverse area of the vagus nerves and the amount of typical nerve tissue within the nerve were all significantly greater in the duodenal ulcer group, especially when compared with the control group. There is thus an anatomic basis for the theory that hypersecretion in duodenal patients is due to vagal hyperactivity (Dragstedt et al 1944). There is no method available for directly determining vagal tone but there is an indirect method in which pancreatic polypeptide (PP), mainly released by vagal activation of PP secreting cells, can be measured in duodenal ulcer patients and in healthy controls. However, Schwartz et al (1979) could find no significant difference between these two groups.

(c) Studies on the target organ, namely the parietal cell, have shown that there may be further evidence for the anatomical basis for acid hypersecretion. Cox (1952), in a post mortem study, showed that the number of parietal cells counted in the stomach of patients with duodenal ulcer was double that of normal and that there was a threshold parietal cell count below which duodenal ulcers were not seen. The range of the number of parietal cells closely paralleled the range of peak acid output seen in a population of healthy controls and duodenal ulcer patients.

(d) Cannon and Rosenbleuth in 1937 postulated that autonomic nerves might supply only certain "key" cells and diffusion of transmitter substances from this region was able to influence nerve effectors. This clearly implied that partial division of the nerve supply of a gland would have little, if any, influence on the amount of secretion produced by a standard nervous stimulus. Even Dragstedt in 1947 wrote concerning incomplete vagotomy. "The remaining vagus nerve fibre appears to activate the entire glandular apparatus, acting presumably through the submucous plexus of Meissner".

However, in recent years it has been shown experimentally that this 'all or none' phenomenon is

incorrect. In 1949, Shay et al reported that acute unilateral abdominal vagotomy did reduce the rate of spontaneous gastric secretion in the pylorus-ligated rat to 78% of control levels. Rivilis et al in 1968 found similar results in the pylorus-ligated rat. Pritchard et al in 1968 using the basic dye, Neutral Red, was able to show in the dog the pattern of vagally innervated mucosa. Legros and Griffith (1968 and 1969) showed that segmental innervation also applied in the rat and again using Neutral Red were able to show areas of vagally innervated mucosa after various types of vagotomy. I was able to confirm this work in the rat (Jones, 1969, Jones and Griffith, 1970 (a) (b)), and used the areas of vagally innervated mucosa to assess the degree of collateral nerve regeneration or sprouting over a period of time.

Figures 1-5 show the types of vagotomy carried out in this rat study, the area of mucosal excretion of the dye and the acid output. The histological section of the oesophagus clearly shows the atrophy of the circular and longitudinal muscles when the anterior trunk is ligated and cut and the posterior drunk preserved.

Experimental studies in dogs, Legros and Griffith (1968 a, 1968 b), Stening and Isenberg (1969),

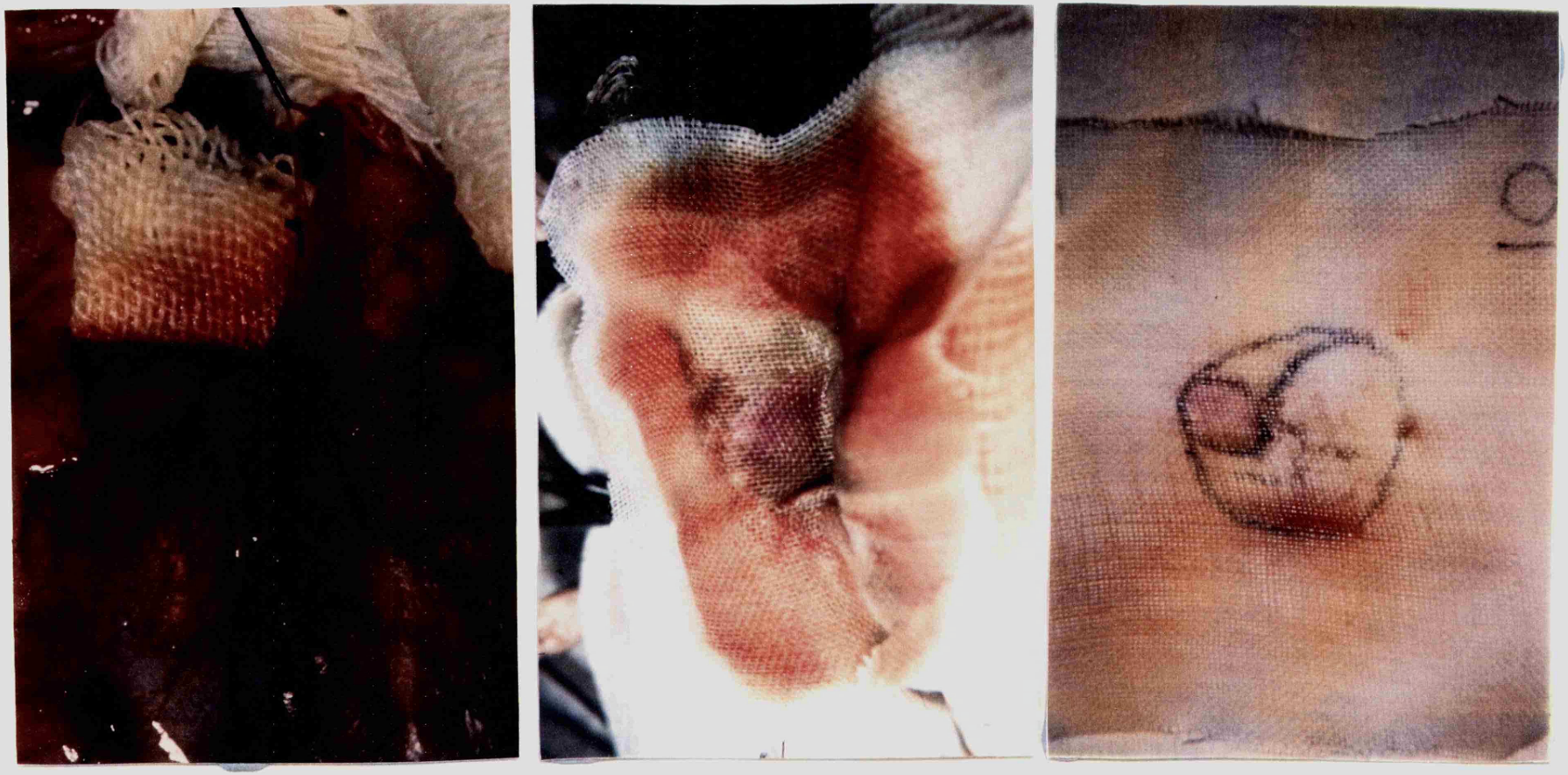


Fig. 1: Small intact fundic branch - area of excretion of neutral red is confined to this area.

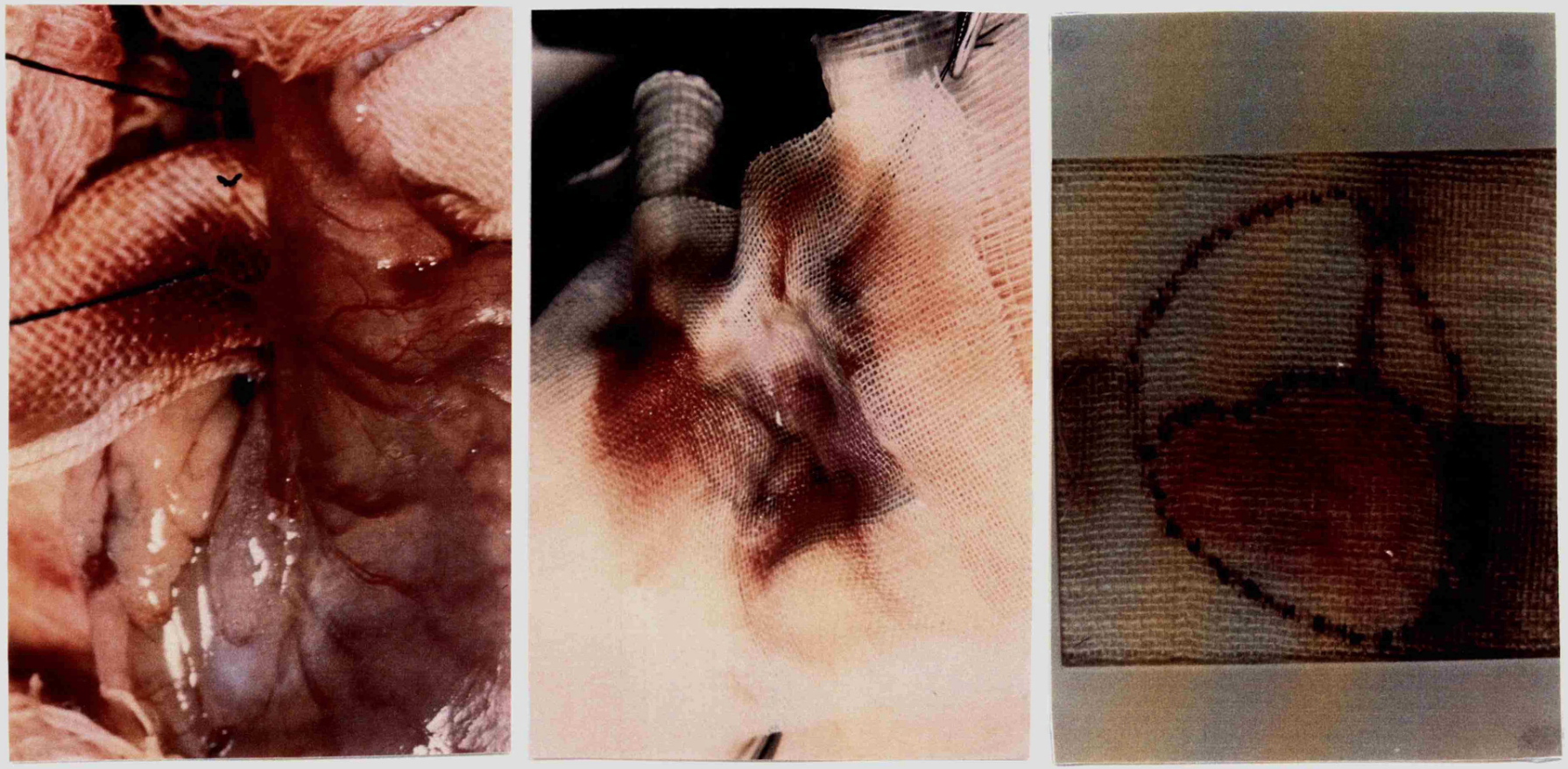


Fig. 2: Posterior vagal trunk intact - area of excretion of neutral red is confined to this area

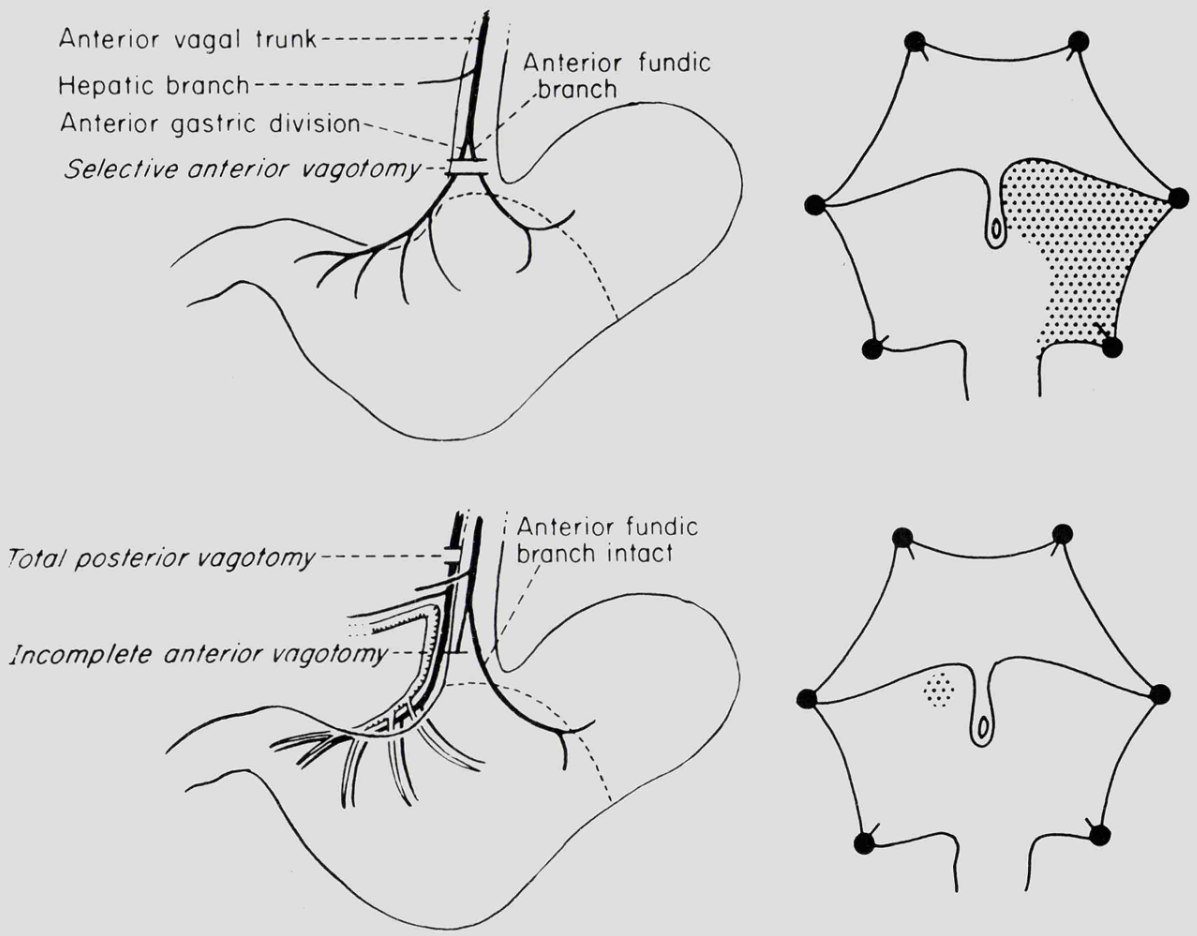


Fig. 3: Diagramatic representation of vagal nerve supply and resulting pattern of neutral red excretion.

Type of vagotomy	Weight Means ± S.D.	Vol. gastric juice Means ± S.D.	pH Means ± S.D.	mEq/L Means ± S.D.	mEq/7 hrs Means ± S.D.
Normal rats	330.0 ± 36.4	6.8 ± 3.0	2.3 ± 0.2	69.7 ± 18.9	.479 ± .259
Posterior trunk intact	366.5 ± 35.1	7.1 ± 3.0	2.7 ± 0.6	38.7 ± 14.7	.295 ± .201
Fundic branch intact	327.5 ± 34.0	4.7 ± 2.7	3.6 ± 1.3	27.5 ± 18.1	.156 ± .156
Total vagotomy	310.5 ± 42.0	3.4 ± 2.4	4.6 ± 2.0	16.4 ± 13.1	.052 ± .062

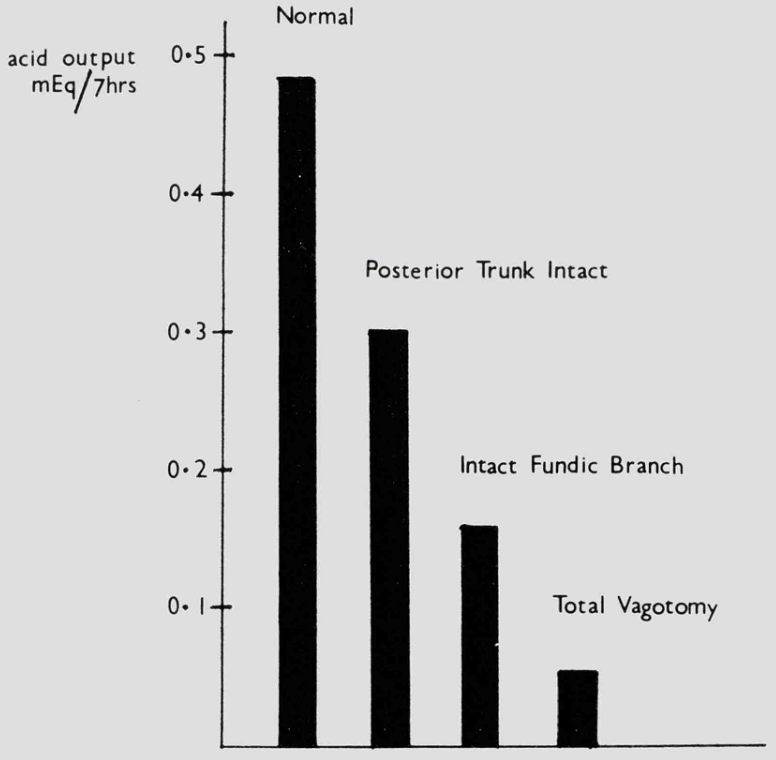
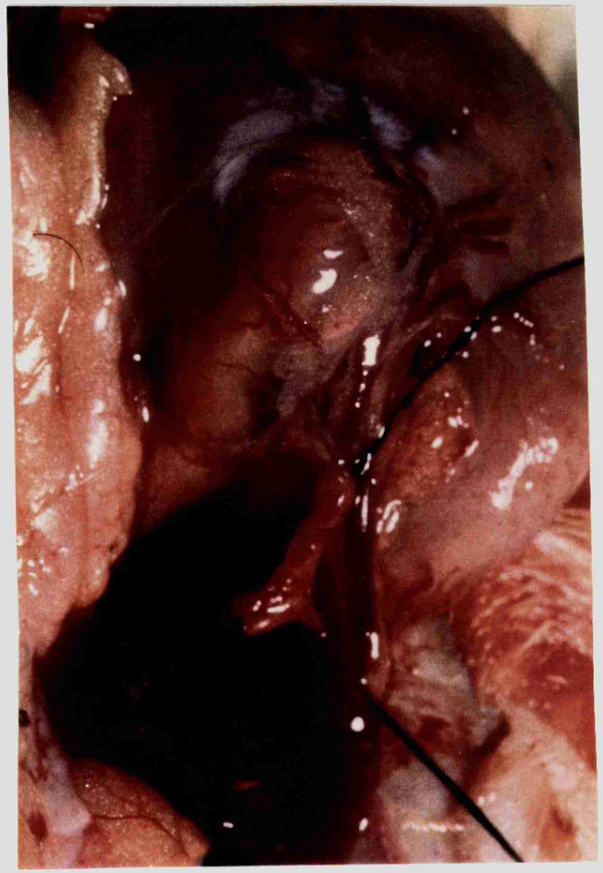


Fig. 4: Acid output in control rats after various types of vagotomy.



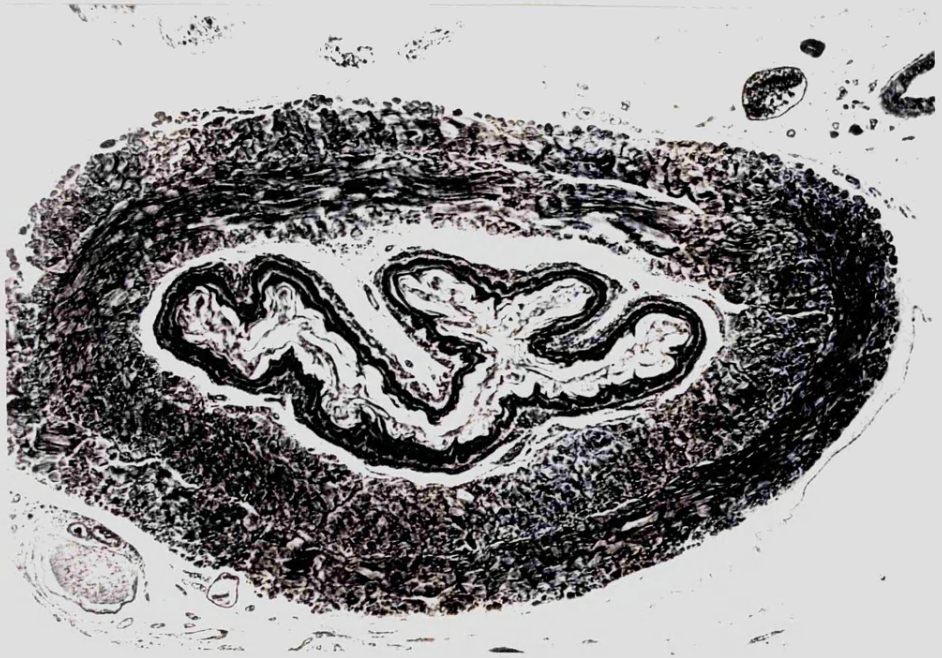


Fig. 5: Division of the posterior vagal trunk. Atrophy of the muscle fibres in the anterior half only of the oesophageal wall.

Stening and Grossman (1970), Nundy and Baron (1973, 1974), have all confirmed that partial vagotomy in animals produces partial reduction in acid output. Vagal innervation becomes segmental at the level of the oesophageal plexus. In other words, it is possible to have degrees of vagality.

THE HISTORY OF CLINICAL VAGOTOMY

In 1809, Sir Everard Home, a surgeon at St. George's Hospital, London and a relative of John Hunter was the first to demonstrate in the dog the effect of vagal section on gastric secretion. He wrote, "Suppression of secretion was to be attributed solely to the division of the nerves" (Taylor, 1983). His assistant, and later successor at St. George's Hospital, Sir Benjamin Brodie (1783-1862) also experimented with vagotomy in the dog. He found that arsenic poisoning caused a copious secretion of mucoid, watery fluid in the stomach which was abolished by vagotomy in the neck (Brodie, 1814). In 1858, Claude Bernard observed the total absence of contractions of the stomach after vagal resection. In 1904, Pavlov received the Nobel Prize for Physiology and Medicine for his work which demonstrated that the complete phase of gastric secretion could be abolished by vagotomy.

Earlier in 1901, the first vagotomy in man had been performed by Jaboulay in Lyon, France. The coeliac plexus was removed in an attempt to relieve the abdominal pain in a patient with tabes dorsalis. In 1919, Exner and Schwartzmann attempted to relieve the gastric crisis of tabes dorsalis with a vagotomy and a gastroenterostomy. In 1920 Bircher in Switzerland described a technique of selective vagotomy. He operated on 20 cases which resembled gastric ulcer. However, at operation one proved

to be an ulcer, in 6 the diagnosis was doubtful even at operation and in the remainder, no ulcer was present (McCrea 1925). The effective beginning of therapeutic vagotomy for duodenal ulcer came with the work of Latarjet and his co-worker Wertheimer from Lyon (1922, 1923). Latarjet was the first to apply this procedure systematically to patients with duodenal ulcer and even at this early stage in the development of vagotomy to recognise the complication of delayed gastric emptying and to add a drainage procedure in the form of a gastroenterostomy. The early types of vagotomy are depicted in Figure 6. The enormous contribution made by Latarjet, Figure 7, can be appreciated when one realises that he performed an anterior selective vagotomy and also a posterior selective vagotomy via the gastrocolic omentum, removing all the posterior gastric branches yet preserving vagal branches to the coeliac plexus. Thus, he was not only the first vagotomist but also the first selective vagotomist and yet his work was forgotten for the next twenty years.

The modern era of vagotomy began on January 18th, 1943 when Lester R. Dragstedt of Chicago (Figure 7) sectioned the vagus nerves above the diaphragm in a patient with acute duodenal ulceration who had refused the conventional surgical treatment of the time, namely partial gastrectomy. (Dragstedt and Owens, 1943).

Dragstedt had been interested in the physiology of gastric

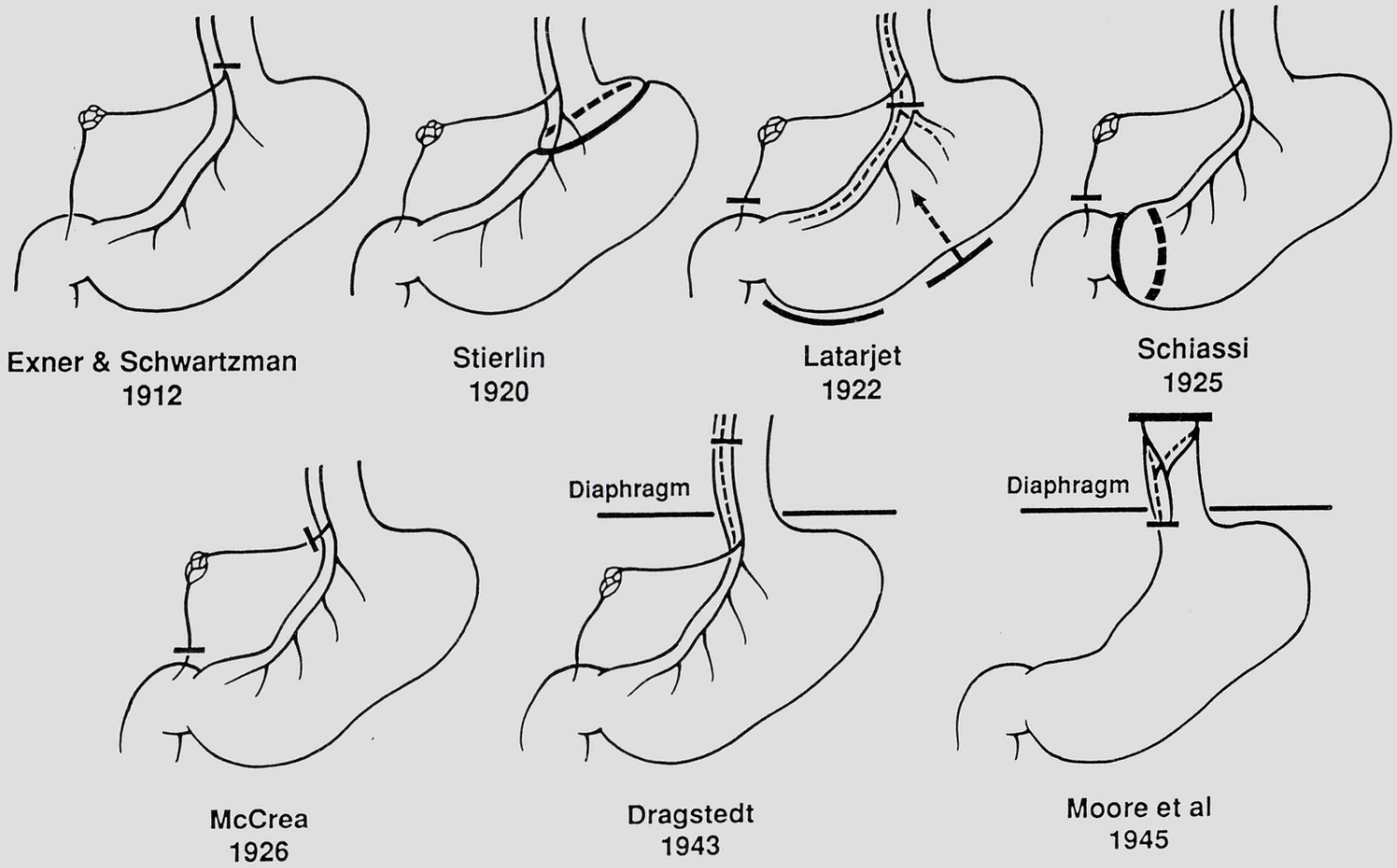


Fig. 6: Early methods of clinical vagotomy (after Jackson, R.C., 1948).

LESTER R. DRAGSTEDT

For Dr Wyn Morris Jones with best wishes and "great expectations".
Lester R. Dragstedt

Fig. 7: Lester R. Dragstedt of Chicago and A. Latarjet of Lyons, France - great pioneers in the surgery of vagotomy.

secretion and aetiology of peptic ulceration for many years. He had published his first paper on experimental peptic ulcers in 1917 while still a graduate student. He was impressed by Schwartz's famous dictum, "No acid, no ulcer". (Schwartz's, 1925). In 1935 he repeated and confirmed Claude Bernard's famous experiment with the legs of pithed, living frogs immersed in pure canine juice (Dragstedt, 1935). Later, he showed experimentally that pure gastric juice could destroy and digest living tissue including the wall of the stomach itself, producing a defect which was identical with the lesion found in man (Dragstedt, 1942). His hypersecretion theory was given further confirmation by the work of Wangensteen and his associates (Walpole et al, 1940). These workers had been able to produce perforating ulcers of the stomach and duodenum in dogs, cats and other experimental animals by the subcutaneous and intramuscular implantation of crystalline histamine incorporated in a mixture of mineral oil and beeswax. The gradual liberation of histamine provoked a long continued secretion of gastric juice which he was able to show occurred in patients with duodenal ulcer. Dragstedt had been so impressed by the work of two German doctors, Henning and Norpoth (1932) that he began to measure the twelve hour basal nocturnal gastric secretion in normal controls and in patients with duodenal ulcers. He found that normal controls secreted an average of 15 mEq of hydrochloric acid while patients with duodenal ulcers secreted an average of 60 mEq per twelve hour period (Dragstedt et al 1944). He theorised that the

basal hypersecretion at night in patients with duodenal ulcers was attributed either to a continuous formation of histamine like substances in the body or to the secretory hypertonus of the vagus. In his first two patients he was able to show a significant fall in the gastric secretion following vagotomy (Dragstedt and Owens, 1943), thus establishing the physiological basis for vagotomy.

The operation of trans-thoracic vagotomy became very popular and Dragstedt and his team operated on 82 patients in the next two years (Woodward, 1987). However, it soon became clear that many of the results were unsatisfactory due to gastric retention. Therefore, an abdominal approach to the vagotomy was required in order to add a drainage procedure in the form of a gastroenterostomy or pyloroplasty (Dragstedt, 1947). Even though a pyloroplasty appeared to be the more attractive procedure (Weinberg et al, 1956) in fact no significant difference was discovered when gastroenterotomy and pyloroplasty was subjected to a planned trial (Kennedy, Gillespie and Kay, 1968 , Kennedy et al, 1973). In this country, vagotomy was first carried out in 1945 by Orr and Johnson (1949) and by 1952 Pollock was able to review 1,524 cases collected from several major centres. Using the Visick grading which had also recently been introduced as a method of assessing patients post-operatively (Visick, 1948), he showed that in patients subjected to vagotomy alone, 44% had an unsatisfactory result. When a

gastro-enterotomy or pyloroplasty was added, the percentage of unsatisfactory results fell to 12% and 13% respectively. 35 years on, truncal vagotomy and a drainage procedure is still the most commonly performed operation for duodenal ulcer in Britain, especially in an emergency situation, despite the fact that it denervates not only the parietal cell mass but also the whole of the abdominal viscera with the exception of the hind gut.

As previously mentioned, Latarjet and Wertheimer in 1922 were the first to attempt a more selective denervation of the stomach. 25 years later, two papers were published which showed that technically a more selective vagotomy was possible (Franksson, 1947, Jackson 1948). However, no drainage procedure was performed at the time of vagotomy and poor results were again obtained due to gastric retention. Some years later, the concept of a more selective denervation was again introduced by Griffith (1969) and Sawyers et al(1968) in America and by Burge (1969) and Amdrup (1969) in Europe. At this point in time, it was realised that both truncal and bilateral selective vagotomies are complete gastric vagotomies and must, therefore, be complemented either by a drainage procedure or by antrectomy. The claim was made that bilateral selective vagotomy was superior to truncal vagotomy in two respects; **(a)** it permitted performance of a more reliable and complete vagotomy in that the nerves were sectioned below the hiatus where there are no

anatomical landmarks available to assure the accomplishment of complete or adequate vagotomy. It has been shown that failure to divide the posterior vagal trunk at the hiatus is the main weakness of truncal vagotomy; this is because the trunk may be multiple and lie behind and away from the oesophagus (Taylor et al, 1977). It was hoped that selective vagotomy would avoid this pitfall. **(b)** It was also hoped that preservation of the hepatic and coeliac branches would avoid some of the side effects of truncal vagotomy, especially diarrhoea.

The claims made by Burge and Griffith have been substantiated to some extent by controlled clinical trials (Sawyers et al, 1968, Kronberg et al 1970 , Kraft et al 1967, Kennedy 1973, 1974, Griffith 1963, Harkins et al 1963, Burge and Frohn, 1969, Amdrup and Jensen, 1970). These trials showed that the incidence of incomplete vagotomy and the incidence of diarrhoea was significantly less after selective vagotomy yet the overall clinical results obtained after selective vagotomy were only a little better than the clinical results after truncal vagotomy. These findings, together with the fact that the operation of selective vagotomy is technically more tedious and difficult to perform than truncal vagotomy, has ensured that this operation has not gained wide acceptance in Britain or in the United States.

An attempt to abolish the cephalic, vagally mediated phase of gastric secretion together with the hormonal phase arising from the release of antral gastrin was accomplished when in 1957 vagotomy and antrectomy was first performed in America (Farmer and Smithwick, 1952, Edwards and Herrington, 1957). This combined procedure results in a profound fall in acid output. Kay (1962), found that antrectomy alone reduced gastric secretion by 70% and vagotomy alone likewise reduced the acid output by 60%-70%. A combination of the two procedures resulted in a 95% reduction in acid output. It is, therefore, not surprising that this is the most effective anti-ulcer operation with a very low recurrence rate. The study by Herrington and Sawyers (1978) of 3,584 patients subjected to the operation showed a recurrent ulcer rate of only 0.6%. However, dumping was present in 25%, weight loss in 10% and severe diarrhoea in 1%. In the United States this operation has remained popular but due to the side effects listed above it has never gained widespread popularity in this country.

Therefore, removal of the antrum combined with vagotomy produces a very good anti-ulcer operation. What if the antrum was left innervated and the vagotomy was restrictd to the parietal cell mass? Vagal denervation of the antrum had always been regarded as essential because it was thought that gastrin release was thereby reduced (Forrest, 1956, Oberhelmann et al 1957, Nyhus et al,

1960). Griffith and Harkins from Seattle were the first to attempt denervation of the parietal cell mass (Griffith and Harkins, 1957). This was an experimental study in dogs in which the acid-pepsin secreting fundus and corpus was denervated preserving the vagal supply to the entire antrum, pylorus and duodenum. The operation they called "partial gastric vagotomy" and this showed that the cephalic phase of gastric secretion was abolished. They deduced that it could well have clinical application.

Highly selective vagotomy with pyloroplasty or antrectomy was first used in man by Holle and Hart from Munich (Holle and Hart, 1967). Vagotomy confined to the parietal cell mass without a drainage procedure was first performed by Johnston and Wilkinson (1969, 1970) in England and by Amdrup and Jensen (1970) in Denmark. The operation in this country goes by the name of "highly selective vagotomy". In Denmark it is called "parietal cell vagotomy". In the United States it is popularly called "proximal gastric vagotomy". This operation has been subjected to intense study during the last twenty years. The incidence of dumping, diarrhoea and vomiting are significantly less frequent than after truncal vagotomy (Stoddard et al 1984, Fraser et al, 1983) although in another study the difference was not very marked (Koffman et al, 1983). When all the evidence is considered, the clinical results appear to be better

after highly selective vagotomy (Johnston, 1980). Schirmer, in a collective review article (Schirmer, 1989) collected data from 26 studies. The Visick 1 & 2 groups (the satisfactory" result) varied from 59%-100% with a mean of 86.5%. In another collective review, 84.7% of 1,729 patients fell into the Visick 1 & 2 "satisfactory" result group (Hershlag, 1983). Therefore, most prospective randomised studies have concluded that highly selective vagotomy is equal or usually superior to most other operations with significantly less dumping, diarrhoea and epigastric fullness.

However, the long-term follow up of highly selective vagotomy is showing that it is associated with a high incidence of recurrent ulcer. In an 18 year follow up, Hoffman et al, 1987, reported on a 30% incidence of proven symptomatic recurrences. As Johnston wrote recently, "Recurrent ulceration is without doubt the potential Achilles heel of highly selective vagotomy". (Johnston & Blackett, 1988). One of the major factors for early ulcer recurrence is failure of technique. It is an operation that is technically more demanding than truncal vagotomy. Proximally, about 6cm of the distal oesophagus should be cleared of all fibres (Hallenbeck, 1976) and distally the dissection should extend to 5cm to 6cm of the pylorus (Johnson, 1982, Johnson & Baxter, 1977).

Using modern immuno-assay techniques, it has now been shown that preservation of innervation to the antrum does not alter the levels of circulating gastrin as they remained the same in patients subjected to truncal or highly selective vagotomy (Hansky and Korman, 1973). However, there are patients in which the antrum is the dominant factor in the hypersecretion (Gillespie and Kay, 1961). Conditions of G-cell hyperplasia or antral dominance are difficult to detect pre-operatively (Hansky, 1977) and probably account for 1%-2% of patients (Johnston and Blackett, 1988).

Another factor which could account for the incidence of recurrent ulceration is antral stasis, a result of leaving the pylorus intact, predisposing to excessive release of gastrin. Holle and Bauer (1974) have always advocated routine drainage of the antrum. A recent controlled trial comparing highly selective vagotomy with and without pyloroplasty has shown a lower recurrence - 8% compared with 20% in the pyloroplasty group (Emas, 1985). However, studies of gastric emptying using radio-labelled liquid and solid meals has shown no significant difference in patients with and without recurrent ulcers after highly selective vagotomy (Blackett, 1982).

The influence of the individual surgeon is a major factor in dealing with recurrences after surgery. Johnston and Goligher (1971) showed wide variations in the ability of

individual surgeons to achieve complete truncal vagotomy. The disturbing feature of this study was the finding that the completeness of vagotomy bore no relationship to the experience of the surgeon. Further studies have shown the same inter-surgeon variation in the performance of highly selective vagotomy (Adami et al, 1984), (Blackett and Johnston, 1981).

Another factor which must be considered is whether the individual surgeon has chosen the wrong operation. For example, highly selective vagotomy is not indicated for pre-pyloric ulcer, the recurrence rate is very high in the early post-operative years (Anderson et al, 1982).

The presence of pyloric and duodenal parietal cells is not taken into account in the operation of highly selective vagotomy. The presence of these cells has been well documented (Leela and Kanagasuntheram, 1968, Hoedemaeker, 1970, Johansen et al, 1973). More recently, Braghetto et al, 1987, showed the presence of parietal cells at the level of the proximal branch of the crow's foot of Latarjet. The "acid antrum" as a possible cause of recurrent ulceration after highly selective vagotomy was recently reviewed by Kirk (1988) and by Naik et al (1988), the latter study showing that the parietal cells extended all the way to the pylorus in 16% of stomachs. Therefore, it is possible to imagine these pyloroduodenal cells continuing to secrete locally damaging acid in

patients whose antrum has been kept innervated.

Partial denervation of an organ makes it susceptible to return of function by collateral nerve regeneration or "sprouting". C.G. Clark wrote recently, "I have often thought that parietal cell vagotomy (P.C.V.) was an operation with built in potential for collateral nerve "sprouting". Clark (1987), Murray and Thompson (1956, 1957) were the first to show the existence of collateral nerve regeneration in the autonomic nervous system. They clearly showed in this study that the degree of re-innervation is dependent on the number of remaining intact fibres. I confirmed this work (Jones, 1969, Jones & Griffith, 1970 (a) (b)). Studies in the rat showed that vagal re-innervation by collateral nerve regeneration depends on the anatomic type of incomplete vagotomy, i.e. on the size of the remaining intact vagal fibre. It was absent in a small vagal fibre (the intact fundic branch) but present at six months in a large vagal fibre represented in this study by an intact posterior trunk. Therefore, the potential for collateral nerve regeneration after highly selective vagotomy is great and has shown to be present in the dog (Cuesta, Valentin, 1987).

The quest, therefore, for newer techniques continues. Anterior highly selective and posterior truncal vagotomy without a drainage procedure has recently been decribed

by Hill and Barker (Hill and Barker, 1978). This operation keeps the antrum and pylorus intact and denerveates the posterior wall of the antrum, pancreas and small intestine. A very similar procedure is anterior seromyotomy and posterior truncal vagotomy and the results to date over the past nine years have been encouraging (Taylor, 1980, 1982).

Therefore, it can be seen that from the days of Latarjet, surgical technique based on sound anatomical knowledge is vital to the success of the operation of vagotomy. As Johnston and Blackett (1988) put it so well recently, "The fault lies not in the vagotomy but in ourselves". It is surprising, therefore, that so few surgeons test the completeness of the vagotomy either at the time of the operation or post-operatively. These will now be discussed.

INTRA-OPERATIVE AND POST-OPERATIVE TESTING AFTER VAGOTOMY

The truth of Johnston & Blackett's statement (1988) that the fault lies with the vagotomist becomes self evident from the work of Fawcett et al (1969) and Taylor et al (1977). Fawcett et al (1969) explored the oesophageal hiatus in 59 patients with recurrent ulceration after truncal vagotomy and drainage and found an intact trunk or trunks in 45% of cases and slender vagal strands in 15% of cases. Similar findings were reported by Taylor et al (1977). In this latter series, an intact posterior trunk was present in 54% of cases.

A few techniques have been developed to try and ensure that the patient leaves the operating theatre with a complete vagotomy. Burge and Vane (1958) developed first in cats and later in patients a technique of electrical stimulation of vagal nerves around the oesophagus. The stomach was isolated with an oesophageal balloon and a pyloric clamp. Any change in pressure inside the stomach on stimulation denoted the presence of residual vagal fibres under the electrodes and the quadrant relative to these fibres could be isolated and, therefore, the area for further dissection isolated. Burge et al (1970) used this test in a series of 700 selective vagotomies and claimed

that 80% would have had an incomplete vagotomy if the test had not been used. Clark and Murray (1963) had 93 technically successful tests in 100 vagotomies and in 8 patients missed nerve trunks were detected electrically, found and cut.

In a recent study in patients subjected to highly selective vagotomy there was an excellent correlation between the electrical test and the post -operative insulin test (Maybury et al, 1977). However, Watkin et al (1971) could find no correlation between electrical tests and the results of the insulin test at 1 week, 2 months and 6 months. Unfortunately, the test prolongs the operation and it is sometimes difficult if not impossible to pass the tube. It may also be based on a misconception in that it assumes that the vagomotor fibres and the vagosecretory fibres are identical. There has been a reported death (Coupland and Cumberland, 1972). Lythgoe (1961) considered the time devoted to the test would have been better employed looking for the residual nerves. Therefore, the test is rarely used these days in this country and in the United States (Williams, 1969).

The use of intra-gastric pH probes to delineate the antrum have been in use for some time (Amdrup and Jensen, 1970). Grassi (1971) used these probes to map out areas of intra-gastric acidity following an

apparently complete vagotomy of the parietal cell mass. Following an infusion of histamine or pentagastrin the mucosa is searched for areas with a pH below 5 so that residual vagal fibres can be detected. In one series two uncut nerves were found in 20 vagotomies (10%) (Grassi et al, 1971). However, Johnson & Baxter found residual nerves in 29 of 50 highly selective vagotomies, an incidence of 48% (Johnson & Baxter, 1977). Unfortunately, this test is again tedious, requires gastrostomy, prolongs the operating time and is associated with a post-operative infection rate of 23% (Johnson & Baxter, 1980). The test also assumes that complete vagal denervation abolishes the gastric secretory response to histamine and pentagastrin but it is known that histamine stimulated secretion in the post-operative period does not seem to be abolished by an adequate vagotomy (Hobsley, 1982). This test has again not become popular, perhaps because low recurrent rates can be achieved without the test (Johnson and Blackett, 1988).

Selective staining of the vagal fibres with leucomethylene blue (Lee, 1969) has not gained widespread use, basically because it is inaccurate (Cooke et al, 1970) and patients subjected to the test show no difference from control patients when studied post-operatively with the insulin test (Jensen et al, 1971)

The use of dyes in medicine has always attracted attention, especially if given intravenously as with Neutral Red. Excreted only by the parietal cells, it offers theoretically an excellent method for delineating areas of residual innervation at the time of operation. Pritchard et al (1968) and Nundy and Baron (1975) used is experimentally during theoretical innervation of the vagal nerves. Weber et al (1975) combined intravenous Neutral Red with 2DG pre-operatively, intra-operatively and post-operatively. In the intra-operative test the appearance of purple dye on the swabbing sponge within 30 minutes after injection of Neutral Red was considered positive. A significant correlation was found between the result of the intra-operative test and the insulin test performed 10 days post-operatively.

Therefore, several intra-operative tests have been designed to detect incomplete vagotomy, yet none has gained widespread popularity.

Post-Operative Testing

The same can be said for post-operative testing, certainly as far as this country is concerned (Baron and Williams, 1971). In this study carried out to evaluate the use of gastric function tests by British Gastroenterologists, only half the surgeons contacted

ever try to assess the completeness of their vagotomies and in only one third of this half is it their usual practice. Of the 41 surgeons who used post-operative testing, 38 (92.6%) used the Hollander or Insulin Test.

Incomplete vagotomy is usually defined by a gastric acid response to insulin hypoglycaemia according to the pioneer studies in dogs by Hollander who developed the Insulin Test in 1946, (Hollander, 1942, 1946, 1948). In 1927, it had been shown for the first time that intravenous insulin was a powerful hypoglycaemic stimulus of gastric secretion (Simici et al 1927). At first it was thought that the acid response after insulin was an all or none phenomenon. However, recently it has been shown that this is not the case (Baron, 1970, Spencer and Grossman, 1971). These studies clearly showed that insulin stimulated acid secretion is dose dependent, although the dose of insulin which produces the greatest acid output varies between individuals. An insulin dose of 0.2u/Kg is now recommended to produce sufficient hypoglycaemia to guarantee a near maximal vagal acid output and yet not to allow the blood glucose to fall so low that (a) hypoglycaemic inhibition of gastric secretion occurs and (b) dangerous side effects or even death occurs. The inhibition of gastric secretion by insulin has been studied extensively both in man and in animals.

Hirschowitz (1966) was of the opinion that this inhibition was associated with a fall in plasma and gastric juice potassium and was reversed or prevented by the intravenous injection of Potassium Chloride. The earlier insulins were contaminated with glucagon which would account for the inhibition of gastric secretion in early studies. However, no significant early inhibition was found when British insulins were used (Baron, 1970) and Kronberg et al, Sead J. Gastro - 9: 173-176, 1974). The dangerous side effects of insulin have been well noted and the Insulin Test should not be done in patients with heart disease, dysrhythmias or abnormal E.C.G's. and in diabetics and should be avoided in patients over 65 (Baron, 1978). Deaths have been reported after Insulin Tests and is probably due to dysrhythmias produced by hypocalcaemia and release of catecholamines, (Stempien, 1962, Decker and Myburgh, 1969, Kronberg, 1970).

Despite these worries, the Hollander or Insulin Test has been widely used and for the following reasons:

(1) to assess the efficiency of the surgeon's technique.

(2) as a means of assessing the likelihood of a patient developing recurrent ulceration, and

(3) to determine whether the dyspepsia following vagotomy is due to a recurrent ulcer and if so, whether there is still substantial vagal innervation

Criteria for the completeness of vagotomy have fallen into two groups, qualitative and quantitative criteria.

Qualitative Criteria

An Insulin Test was considered positive when an increase of 20mmol/l in titratable acidity in any two consecutive 15 minute samples in the 2 hours after the intravenous injection of insulin (provided the blood sugar fell below 50mg per 100ml) over the mean acidity of the two 15 minute basal samples. If the basal samples contained no free acid then the test was considered positive when post-insulin acidity was more than 10mmol/l. These were Hollander's original criteria (Hollander, 1946, 1948).

In 1964 Ross and Kay in Sheffield noted that the patients in the Hollander Test fell into two distinct groups. In the first group, the response occurred within 45 minutes (early positive) and in the second group the response occurred within 45-120 minutes (late positive). The 'early' positive patients showed higher basal secretion and greater response to both insulin

and the augmented histamine test than did the 'late' positive patients and these differences were statistically significant. It was further noted that the 'late' positive group approximated more closely to the negative response group (complete vagotomy) than to the early positive one. It was suggested that the 'early' response indicated an incomplete and inadequate vagotomy due to the presentation of a vagal trunk or large vagal branch while the late response indicated an incomplete but adequate vagotomy to be the preservation of a small vagal fibre. This concept has been confirmed experimentally by the work of Legros and Griffith (1968). Insulin tests were performed in dogs before and after two anatomic types of incomplete vagotomy. Results before and after incomplete vagotomy of an intact trunk were large and early while the response after incomplete vagotomy of an intact fundic branch was significantly decreased and delayed.

Johnston et al (1967) thought that even better differentiation could be obtained by extending the 'early' response to the first 60 minutes and the 'late' response to the second 60 minutes. I have followed these criteria in this thesis.

Quantitative Criteria

(1) Reduction in 12 hour overnight secretion of less

than 60% (Dragstedt et al, 1947).

(2) An increase in volume of gastric juice in any hour after insulin compared with the basal hour (Waddell, 1957)

(3) Output of acid in the 2 hours after insulin of more than 2mmol (Stempien, 1958).

(4) Output of acid in any of 3 hours after insulin of more than 1mmol, higher than in any of the 2 basal hours or basal acid output of more than 2mmol (Bachrach, 1962).

(5) Output of acid in the first hour after insulin 5 mmols more than the basal hour (Clark and Murray, 1963).

(6) A comparison of peak acid output during 2 hours after insulin before vagotomy, with peak acid output during 2 hours after insulin following vagotomy (Hubel, 1966).

(7) Output of acid in the first or second hour after insulin higher than basal acid output in the two 15 minute basal collections expressed as mmols/h. (Bitsch et al, 1966)

(8) Output of acid in any one hour after insulin of 2mmol more than in the basal hour (Bank et al, 1967).

(9) Basal acid output more than 0.25mmol/h or increase in any post-insulin hour over basal acid output more than 0.25mmol/h, any post-insulin hour more than 1mmol (Bachrach, 1967).

(10) An excess of 0.5mmol in 2 hours after insulin compared with 2 hours basal secretion (Stempien, 1968).

(11) An increased acid output after insulin in excess of three times the mean basal output (Gillespie et al, 1972).

Multiple Criteria

Since none of the above quantitative criteria have been shown to be superior to Hollander's original criteria (Kay, 1967), it has been suggested that the sum of five criteria should be used (Bank et al, 1967 and Ruckley, 1973). However, Decker (1969) and Hood et al (1976) did not find multiple criteria any more helpful than the Hollander criteria alone. Therefore, the Hollander criteria with the Ross and Kay or Johnston modification are still the most widely used internationally.

FRANKLIN HOLLANDER, PH.D.

Fig. 8: Franklin Hollander who pioneered the Insulin Test

Timing of the Hollander Test

Surgeons who adopt the practice of routine insulin testing after vagotomy have preferred to do the test before discharging the patient from hospital, otherwise one is faced with difficulty of persuading symptomless patients to return for secretion tests (Hood et al, 1976). However, a high incidence of change from negative to positive responses were noted in the weeks following vagotomy (Mason and Giles, 1968, 1969, Gillespie et al, 1970). The initial tests were probably unsatisfactory due to the large gastric residue or stagnation of food. The final pattern of the response to insulin seems to be established at 2 months after vagotomy and it is recommended that the Insulin Test be delayed until after this period (Watkin et al, 1971). Therefore, the early Insulin Test is of little value. It is interesting to note that even with early testing a review of the literature shows an overall incidence of incomplete vagotomy of 25% (Cox, 1970).

Assessment of Surgical Technique

There have been studies from four centres to try and assess the role of experience in producing a complete vagotomy. In three studies the role of experience seems to be paramount. In Sheffield, there were early

positive responses in 13 out of 54 patients whose vagotomies had been performed by surgeons in training but in none of 73 patients vagotomised by experienced surgeons (Kay, 1969). In Copenhagen, the recurrence rate of experienced vagotomists was half that of their inexperienced colleagues (Holst-Christensen et al, 1977). A study in Lund, Sweden, showed that 2 specialists in gastric surgery achieved lower acid responses to insulin immediately after surgery and 1 year later than their more general colleagues and this was reflected in less recurrent ulceration (Liedberg and Oscarson, 1976). However, in Leeds, Johnston and Golligher (1971) found 18% incomplete vagotomies among the consultant surgeons and 12% incomplete vagotomies among the senior registrar and registrars. These findings were similar both for truncal and selective vagotomy. However, Johnston recently has emphasised that "the Hollander Insulin Test provides good quality control and so exerts psychological pressure on the surgeon to achieve a complete vagotomy" (Johnston and Blackett, 1988).

Assessment of Prognosis of Patient

The second most important reason for performing an Insulin Test is to give the surgeon an idea as to the prognosis of the patient as far as recurrent ulceration is concerned. Hollander himself emphasised that it was

impossible in an individual patient to predict the occurrence of recurrent ulceration on the evidence of insulin test (Weinstein et al, 1950). At least 50% of patients will have a positive insulin test by Hollander's criteria (Hollander, 1948). Johnston et al, (1967) followed 286 patients after truncal vagotomy for 2 years and 134 (47%) give a positive response to insulin. However, as few as 60% of patients with recurrent ulcer have a positive response (Jordan and Condon, 1970, Kennedy et al, 1973, Ross and Kay, 1964, Watkin and Duthie, 1971, Johnston et al, 1967, Eisenberg, 1969). The insulin test is, therefore, an imperfect means of predicting recurrence.

Because of this, there has been a search for other tests. For example, the ratio of the peak acid output after insulin to the peak acid output after pentagastrin has been suggested as a quantitative index of vagal innervation (Venables and Johnston, 1969). This test has not gained acceptance, the main reason being that after vagotomy the peak acid output after histamine or pentagastrin is not a valid index of the stomach's maximal capacity to secrete acid because much higher doses are needed (Duthie et al, 1967) and the only way to achieve pre-vagotomy levels is to administer simultaneously a cholinergic drug (Payne and Kay, 1962).

Peak acid output (P.A.O.) is unsuitable for evaluation of completeness of vagotomy in the early post-operative period (Holst-Christensen, 1977). Recently, Primrose and Johnston, 1986, compared the Insulin Test with the basal acid output and peak acid output in 38 patients with recurrent ulceration after highly selective vagotomy and 101 patients without recurrent ulceration. This study showed that the Insulin Test was less sensitive than basal acid and peak acid output as indicators of recurrence was much more specific. Their conclusion was that it would be premature to abandon the Insulin Test.

Therefore, the ability of the Insulin Test to identify patients with incomplete vagotomy is well established although the relationship cannot be proved because until recently there was no other independent test for comparison. Sham feeding has been introduced recently to test for completeness of vagotomy (Stenquist et al, 1978, Athow et al, 1984, 1986). It is certainly a safer and simpler test than the Insulin Test and probably a purer vagal stimulant of acid than insulin. Kronberg was of the opinion that the Insulin Test should be abandoned and replaced by the Sham feeding test (Kronberg, 1981).

Kronberg's advice has certainly been heeded and the Insulin Test has been abandoned in many centres. The

reasons for this abandonment are listed below:

(1) The test can be dangerous, especially in elderly patients and those with a heart condition and fatalities have been recorded (Decker & Myburgh, 1969).

(2) Its predictable value is low.

(3) The insulin induced hypoglycaemia stimulates acid secretion by non-vagal as well as by vagal mechanisms (Read et al, 1972). This would explain its poor predictive value and the frequency with which positive results are recorded in asymptomatic patients. The non-vagal pathway suggested has been the sympathetic system.

(4) Insulin hypoglycaemia may release gastrin (Jordan & Condon, 1970) and this would explain the late response even in patients with complete vagotomy.

Therefore, the time seemed appropriate in 1971 to see whether the Neutral Red Test could be used to assess the completeness of vagotomy, to compare it with the Insulin Test and to see whether it had a better predictive value. The methods involved were developed from the large clinical experience of others in the

1920's and 1930's and from my own experimental observations gained in the Department of Surgery, University of Washington, Seattle (Jones, 1968, 1969).

THE EXCRETION OF NEUTRAL RED

The application of Neutral Red as an initial dye was first introduced by Ehrlich. Its use in the study of gastric secretory function dates from Fuld's work in dogs (Fuld, 1908). He demonstrated excretion into Pavlov pouches when the dye was instilled into the main stomach. This work was confirmed by Finkelstein in 1922 who went further and showed that the excretion of the dye occurred in the main stomach and in the Pavlov pouch after subcutaneous injection of the dye.

The first clinical application of the dye occurred in 1923 when Glaessner and Wittgenstein used it to assess gastric function. They performed the test in 40 patients, injecting 5cc's of a 1% solution of Neutral Red intravenously and found that in normal individuals the dye appeared within 10-15 minutes. In hyperacidity, the dye appeared sooner while in hypoacidity 50 minutes elapsed before the dye appeared in the stomach. They came to the conclusion that the dye was excreted only by the acid secreting cells. Davidson et al, 1925, investigated the excretion of the dye in 48 cases including normals and patients with peptic ulcer, gastric carcinoma, pernicious anaemia and microcytic anaemia. The actual quantity of the dye excreted during a two hour test period was measured. Again, the relationship between the appearance time and gastric

acidity was noted but that this relationship was too unreliable for it to be used as a diagnostic test.

Piersol et al, 1925, came to the same conclusion. They showed that only a small fraction of the intravenously injected Neutral Red appears in the stomach. In normal controls, only 1.2% of the dye was excreted into the stomach during a two hour test period. Therefore, it was concluded that the dye is largely eliminated by the other organs, the liver, kidneys and small intestine and that little reliance could be placed upon any quantitative method of testing the secretory function of the stomach. Further, they showed that there was a rough relationship between the amount of dye excreted and the degree of gastric acidity but also that the dye could be excreted in the absence of acid. This phenomenon had been previously shown to be possible. Hirbayash, (1924), experimenting with gastric cannula dogs had found that the stomach continued to eliminate dye after the hydrochloric acid was completely suppressed by silver nitrate solution. Therefore, the possibility was raised, even at this early stage, that the excretion of Neutral Red could be independent of the secretion of hydrochloric acid. This era in the clinical use of the Neutral Red test closed with another disappointing study from Guy's Hospital (Fairley and Ive, 1925). The results from this study showed that the excretion of Neutral Red was too irregular for it to be

considered as a test with clinical value. At this point in time, there was no proof, clinically or experimentally, that Neutral Red was solely excreted by the oxyntic cells.

Ingram and Visscher (1934) investigating the physiochemical characteristics of dyes excreted by the stomach had found that all dyes appearing in gastric juice after intravenous injection in the dog were characterised by having chromogen in the electro-positive ion under suitable conditions; this included Neutral Red.

Previously Kobayashi (1926) had found that only basic dyes such as Neutral Red are excreted by the stomach though Dawson and Ivy (1925) could find no physical or chemical characteristics that distinguished the dyes which appeared in gastric juice. However, these latter workers were the first to claim that Neutral Red could be detected by microscopic examination in the canaliculi of the oxyntic cells. However, they were unable to fix the dye in the oxyntic cell. This was accomplished by Morrison et al in 1936. By the use of a "Susa" mixture of Heidenhein, Neutral Red granules were found to be selectively eliminated by the oxyntic cells of the white rat's and dog's stomachs. The localisation of the Neutral Red granules corresponded exactly with the anatomic distribution of the oxyntic cells in the

phloxine-methylene blue preparations. Morrison (1938) in the clinical context had seen patients who demonstrated no secretion of hydrochloric acid in the fasting analysis or after a test-meal but did excrete Neutral Red. He, therefore, thought that the Neutral Red excretory test represented the last stage of mucosal activity before complete cessation of oxyntic glandular function.

Bradford and Davies (1949) from the Department of Biochemistry, University of Sheffield, showed that basic dyes of many chemical types were transported across acid-secreting frog and toad gastric mucosa and were concentrated in the secretions. On the other hand, some acid dyes were transported but were not concentrated in the secretions. These workers found that Neutral Red was especially suitable as it was possible to see that the gastric tubules and the canaliculi of secreting oxyntic cells were red with acid form of the dye whilst the cytoplasm of the oxyntic cells and the lower regions of the mucosa were yellowish and slightly alkaline. Experiments with Neutral Red showed that the acid is formed with a pH 6.8.

Experimental studies by Kolm, Komarov and Shay, 1945, showed in dogs that Neutral Red was excreted by the oxyntic cells and that it was not excreted by the pyloric mucosa. They showed for the first time that the

dye acted as a mild gastric secretagogue consistently producing a small increase in gastric secretion as well as an increase in the acidity or a decrease in the alkalinity of the juice. These effects were prevented by preliminary atropinization and to a lesser degree by vagotomy. They came to the conclusion that the major part of the secretagogue action of Neutral Red was due to stimulation of the vagal mechanism. Further proof of this mechanism was obtained by the observation that the intravenous administration of Neutral Red was always accompanied by slowing the heart rate and a decrease in the amplitude of the pulse, both effects abolished by vagotomy. They later showed (Komarov et al, 1949) that the liver plays a predominant part in the excretion of the dye, eliminating 28.2% in the first hour while the kidneys only excrete 2.4% during the same period.

The Neutral Red test was re-introduced as a clinical test of gastric function by Gillman (Gillman, 1943, 1944). In a study of 90 normal controls and 300 patients with gastric dysfunction, he came to the conclusion that the Neutral Red test was not only more reliable but also more sensitive than the acid secretion test as an indicator of gastric function. He also came to the conclusion that acid secretion and dye excretion do not necessarily parallel one another and that they are indicators of two apparently independent functions of the gastric oxyntic cell.

Sevitt and Jepson (1948) came to the same conclusion as Gillman that the Neutral Red test was superior and more reliable than the estimation of acid secretion. They also showed that there is a statistical correlation between normal acid production and normal Neutral Red excretion and between achlorhydria and lack of excretion of the dye. However, they also showed that patients with normal acid production failed to excrete the dye at all. They also showed that excretory activity of the dye is abolished by vagotomy and unaltered by lumbar sympathectomy, unilateral and bilateral and splanchnicectomy.

When Pritchard, Griffith and Harkins, 1968, re-introduced the use of Neutral Red experimentally, they were able to show that the old "all or none" theory was incorrect and that in the dog the vagus nerve was distributed segmentally. Legros and Griffith (1968a and 1968b) and I (Jones, 1969, 1970a, 1970b) were able to show that this also applied in the rat. My work in Seattle showed that in the rat the long-term fate of the residual vagus fibre depended on the size of the fibre. A small residual fibre as depicted by the intact fundic branch, had not changed over a period of a year in area, acid output or ulcerogenic potential, while a large residual fibre as depicted by a posterior vagal trunk showed evidence of increasing its influence through collateral nerve regeneration. Therefore, the findings

in this study suggested that an incomplete yet adequate vagotomy as represented by an intact fundic branch seemed destined to remain so even after an interval of time and that recurrent ulceration was a problem of incomplete, inadequate vagotomy at the time of the initial operation and not to be attributed to collateral nerve regeneration from a few residual vagal fibres.

At this point in time, it seemed an appropriate time to me to see whether the Neutral Red Test could be revived yet again and to see whether it had clinical application in three areas:

(1) To assess the completeness of vagotomy.

(2) To compare the Neutral Red Test with the Hollander or Insulin Test and to assess the ability of both to predict the outcome after truncal vagotomy.

(3) To assess the outcome of the 'late' positive response. Taylor wrote recently, "the significance and mechanism of the 'late' positive insulin response and its relation to recurrent ulcer is ill understood" (Taylor, 1987). I was especially interested to see whether an incomplete but adequate vagotomy as represented by the 'late' positive response carried a good prognosis on a long-term basis. In other words, to see whether in

the human a few small vagal fibres had the potential over a long period of time to regenerate significantly by collateral nerve regeneration or sprouting. Experimentally in the rat, this ability to regenerate over a period of a year had been shown to be of no significance (Jones, 1969, Jones & Griffith, 1970 (a) (b)).

MATERIALS AND METHODS

MATERIALS AND METHODS

The clinical and laboratory studies involved 100 patients suffering from duodenal ulcer, as diagnosed pre-operatively by barium meal and/or gastroscopy. 73 of the patients were male and 27 were female. Their ages ranged from 24-82 years with a mean age of 50. The operation carried out in all cases was truncal vagotomy and pyloroplasty. The operations were performed by consultants and by surgeons in training, namely registrars and senior registrars.

Two tests were used to investigate these patients:

(a) the Neutral Red Test carried out pre-operatively in 48 patients and in all 100 post-operative patients.

(b) the Hollander or Insulin Test carried out in all 100 post-operative patients only.

Watkin and Duthie in 1971 had shown that the Insulin Test performed less than one month post-operatively had given unreliable results but at two months, the results seemed to represent the final pattern of secretion. Therefore, both tests carried out in the present study were performed at some time, two to four months after operation.

Collection of Gastric Secretion

Pre-operatively and post-operatively, the patients were starved from midnight on the night preceding the test. An Andersen (H.W. Andersen Products, Colchester) double lumen tube (AN 10) was measured from the nose to a point 5cm above the umbilicus by applying the tube to the body contour and by appropriate marking. The tube was passed through the nose to this mark. The stomach was washed out with 100ml of warm water by means of a 20ml syringe until the aspirate was clear.

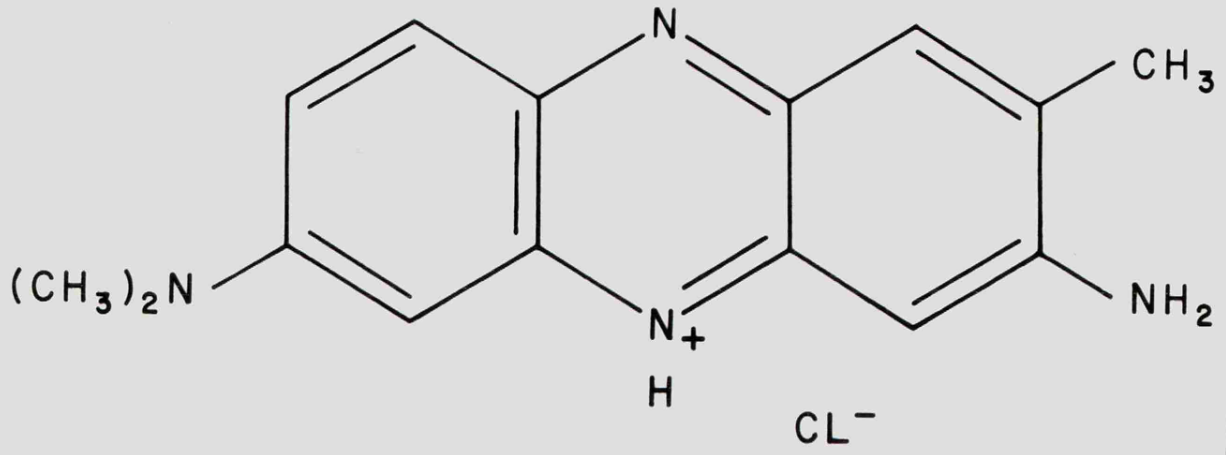
When the stomach was completely empty, the position of the naso-gastric tube was not checked radiologically but by the use of the water recovery test. The importance of checking the position of the tube by x-ray examination prior to performing gastric secretory studies has been stressed by previous workers (James and Pickering, 1949) but Hassan and Hobsley (1970) had found that a simple water recovery test was as reliable as fluroscopy for showing that the tip of the tube was within the stomach and that the exact position of the tube did not affect recovery. This work was confirmed by Findlay, Prescott and Sircus (1972). After emptying the stomach, the patient now drank 20ml of water and lay in a semi-recumbent position on the left side. If between 16-20ml of water could be recovered by using manual aspiration with a syringe, the position of the

tube was regarded as satisfactory. If not, the position of the patient was changed to **(a)** supine and then **(b)** the right lateral position. If adequate recovery was not achieved, the tube was withdrawn in 2.5cm stages. The position of the naso-gastric tube was considered to be satisfactory when 16-20ml of water was recovered. Findlay, Prescott and Sircus (1972) had shown that there was no significant differences between acid studies irrespective of the method used for positioning the naso-gastric tube, i.e. fluroscopy or water recovery.

With the naso-gastric tube in the correct position, it was then connected to suction. Continuous suction was maintained at a sub-atmospheric pressure of 3-8cm of Hg (Checketts 1966, Ross and Kay, 1964). Throughout the tests, care was taken to maintain patency of the tubes by injecting small quantities of air under pressure at frequent intervals into the side tube of the double lumen tube.

NEUTRAL RED

Neutral Red is a basic, azine dye with a molecular weight of 288.78. Its chemical structure is shown in Figure 9. The presence of a positively charged ion is to be especially noted. Ingraham and Visscher in 1935 showed that only dyes whose chromogen is constantly present in the cation and are, therefore, electropositive, are excreted in the gastric juice, while dyes whose chromogen is constantly present in the anion are, therefore, electronegative, are excreted in the pancreatic juice. The dye in its alkaline or neutral form has a yellowish brown colour and at pH 6.8 it changes into its red or acid form, Figure 9. The colour of the dye does not fade when exposed to light and I have kept samples which have remained unchanged for a period of 18 years.



MOL. WT. = 288·78.

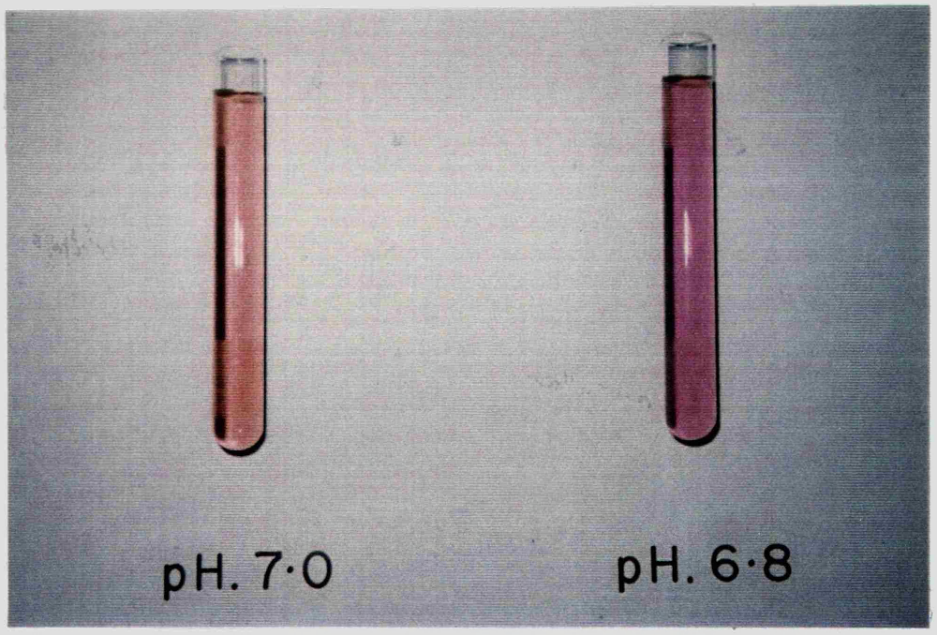


Fig. 9: Chemical structure of Neutral Red and colour change at pH 6.8.

PYLORIC LOSS AND DUODENAL REFLUX

In 1969 Hobsley & Silen proposed the use of an inert marker, phenol red, to improve the accuracy of gastric secretion studies. Since that time, the technique has been updated, Faber et al, 1975. This technique demands the use of phenol red, introduced into the stomach at the rate of 12ml per hour. With the use of a formula, the objective is to correct for pyloric loss and duodenal reflux. The phenol acid estimation is made by a spectrophotometric determination at 2 wavelengths, namely 550mm and 410mm. At 410mm correction is made in the optical density for the presence of any haemoglobin which almost invariably contaminates tube-aspirated secretions (Crawford & Hobsley, 1968). Because of the obvious difficulties of distinguishing between phenol red and neutral red spectrophotometrically no correction was made in this study for pyloric loss and duodenal reflux either in the Neutral Red or Insulin Test. Stature (Whitfield & Hobsley, 1979) has also been ignored in the interpretation of these tests.

Intravenous Injection of Neutral Red

The patient was allowed to rest for 10-15 minutes and the juice secreted during this period was discarded. In 25 patients, the basal half hour secretion was measured prior to the injection of the dye. 5ml of a 1% filtered, sterile and pyrogen free aqueous solution of

Neutral Red (50mg) was injected intravenously as rapidly as possible and a stop watch was started. The time taken for the dye to appear in the gastric juice was recorded. This was taken as the excretion time (E.T.) and samples were taken at 5 minute intervals for the next 30 minutes. The first 15 minutes and second 15 minute outputs were then calculated. During the test, the patients were asked not to swallow but to expectorate saliva.

Method of Measuring Neutral Red

Sevitt and Jepson (1948) estimated the concentration of the dye in each sample of gastric juice by direct vision in a comparator box using standard dilutions of the dye contained in identical test tubes. The standard tube was backed with a tube containing uncoloured juice and the unknown with a tube of water. They reported that with a little practice, the dilutions were easy to read. However, Komarov et al (1949) raised the possibility of absorption on the Neutral Red by proteins in gastric juice including cellular elements, mucus and food residues. They clearly showed that two major sources of error made the results of direct colorimetry unsatisfactory; **(a)** the opacity of the supernatant and, **(b)** the absorption of the dye by the solid phase. Their results amply prove that direct colorimetry is inadequate as a method of determining Neutral Red not

only in human gastric contents but also in cases of pure gastric juice as obtained in carefully controlled animal experiments. These authors were the first to introduce two methods to try and overcome the drawbacks of direct colorimetry; **(a)** the Acetone method and **(b)** the Benzoic Acid absorption method.

For the investigations presented in this thesis, the first method, the Acetone Method, was adapted. It is based on the ability of acetone in the presence of free hydrochloric acid to extract dye quantitatively from gastric contents and, at the same time, to precipitate the proteins.

The reagents required are **(a)** 0.1M hydrochloric acid and **(b)** acetone and 1ml of the gastric juice was placed in a graduated centrifuge tube. In addition, 1ml of water was placed in another tube. To each tube, 1ml of the 0.1M hydrochloric acid and 8ml of acetone were added. This solution in this last centrifuge tube became the blank. The tubes were stoppered, the solution mixed by inversion and stored overnight at 4 degrees C. Next day, the tubes are centrifuged and absorbances read in a Unicam SP 600 Spectrophotometer using 1cm light path cells at a wavelength of 520 millimicrons. The instrument is set at zero with the blank and the absorbances are read off against this blank. Initially, a full calibration curve was set up

with each batch of tests but linearity proved satisfactory through many batches and thereafter only one standard was used (1.0mg/100ml).

The optical densities obtained for each test solution were converted into dye concentrations by using a calibration curve. This had been previously constructed from optical densities of various concentrations of the dye ranging from 0.1mg to 1.0mg/100ml. As can be seen from Figure 9, Beer's law was obeyed in the above range.

In the first few patients subjected to the Neutral Red Test, blood was taken before and during the half hour test period and its electrolyte and blood sugar content estimated. No change occurred in electrolyte or sugar content. At the end of the test period, the patient and nursing staff were warned about the colouring of the urine and faeces which would ensue and not to be alarmed.

Previous studies had shown that the Neutral Red could be removed by simple filtration to give clear, gastric juice suitable for acid estimations. Gillman (1943) used cotton wool which he plugged into the barrel of a 20cc syringe; the gastric juice was then poured into the barrel above the cotton wool. Thus, the clear gastric juice could be expressed into a test tube. In the present study I separated the gastric juice from the

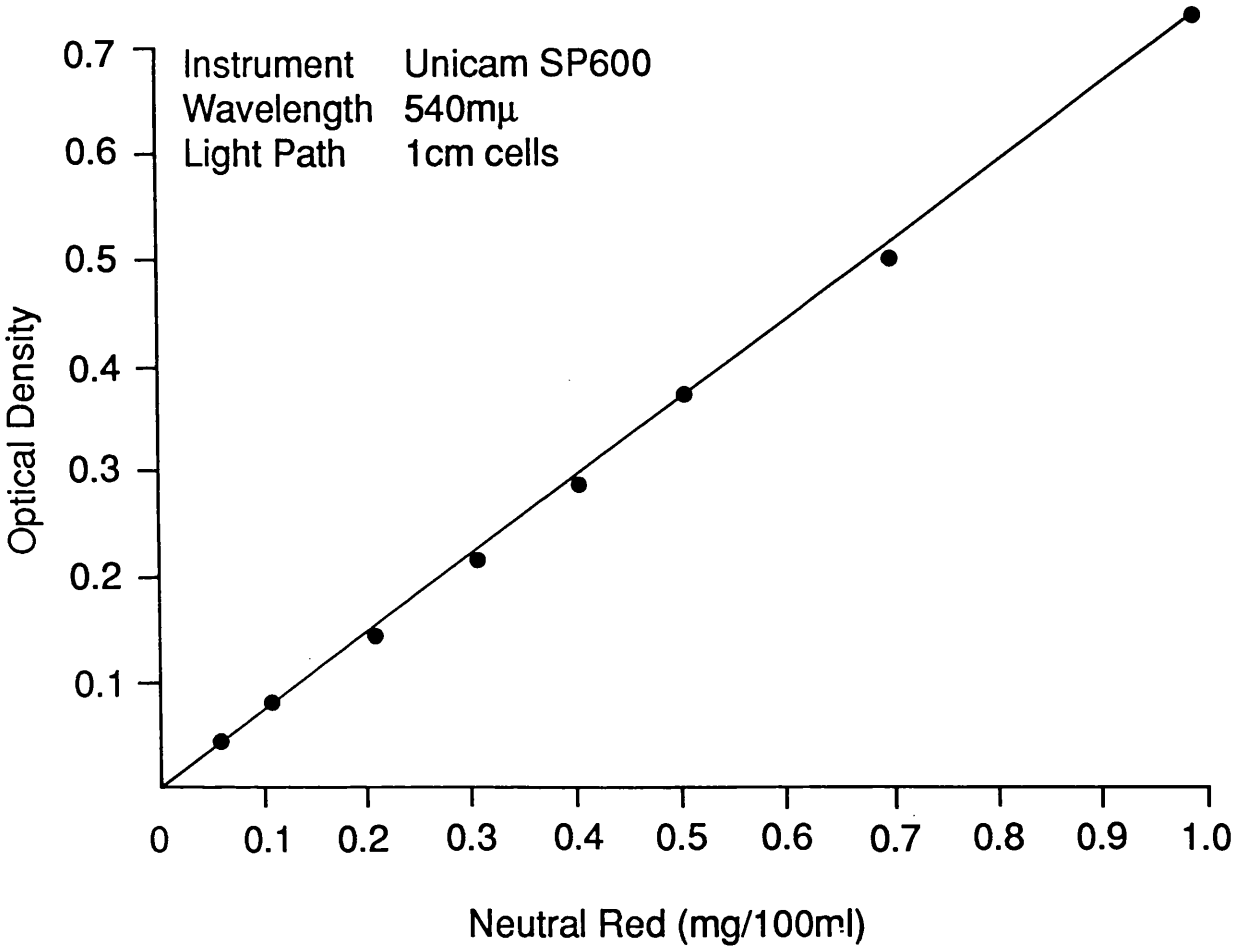


Fig.10: Calibration curve for Neutral Red.

Neutral Red by simple filtration through 2 or 3 thicknesses of filter paper as suggested by Kobayaashi 1926, Komarov et al, 1949, and Sevitt and Jepson, 1948. The technique offered an opportunity to assess the relationship between the secretion of Neutral Red and hydrochloric acid. The dye was removed by filtration and the acid content measured by titration to pH 8.4, the phenolphalein end point.

Three additional studies were carried out:

(a) The Gastroscopic Visualisation of Neutral Red

In this study, the gastric mucosa was visualised during routine pre-operative gastroscopy following an injection of 5cc's of a 1% Neutral Red solution.

(b) The Intra-Operative Use of Neutral Red

In this study the presence of Neutral Red was determined by swabbing the gastric mucosa with a sponge through a gastroduodenotomy performed as a part of pyloroplasty.

(c) The Effect of Atropinisation

The study only involved 5 patients as this was sufficient to show the dramatic effect Atropine had on Neutral Red excretion. Experimentally, this had been

confirmed in the dog by Weber et al (1975). The Neutral Red output was calculated pre-operatively and post-operatively following an injection of 600 micrograms of atrophine sulphate given intramuscularly half an hour prior to the injection of Neutral Red.

In all these studies there was no attempt made to administer a gastric secretory stimulant in the form of Histamine, Pentagastrin, Insulin or 2 D.G.

The Hollander or Insulin Test

This was performed in all the 100 post-operative patients. The collection of gastric juice was continuous suction at a negative pressure of 3-5cm of Hg with frequent air insufflation to maintain patency. After three 15 minute basal samples had been obtained crystaline insulin (0.2 units per Kg body weight) was given intravenously. Eight further 15 minute collections were then made. The volume of each sample was recorded and the acid concentration measured either by automatic titration to pH 7 using a glass electrode pH meter (radiometer) or by titration to the phenolphthalein end point, Ph 8.4 (30 Leicester patients).

In all tests, samples of venous blood were taken for estimation of blood glucose levels before and at 30 and

45 minutes after insulin injection.

The Insulin Test was interpreted by using the criteria propounded by Hollander (1948). A positive response was denoted by an increase in acidity of at least 20mmol/litre over the resting value within 2 hours of the insulin injection. When the resting juice was an acid, an increase of 10mmol/litre within 2 hours of the insulin injection also indicates a positive response. The positive response was further subdivided into "early" or "late" positive according to the criteria laid down by Johnston et al (1967). A response in the first hour was labelled as "early" and in the second hour as "late".

The Follow-Up Study

100 patients, 73 male and 27 female, were entered into the longterm study which was terminated on the 1st January, 1989. Most of the survivors were interviewed by me personally, either in Outpatients, in their homes or on the telephone. A few wrote to me after I had sent them a questionnaire and gave a full account of their state of health.

21 patients died during the course of the study. Within this group, I managed to get a detailed account of the health of the patient and a full clinical picture from:

(a) The Hospital notes

(b) The post-mortem findings, and

(c) A detailed history from surviving close relatives

An overall assessment of the clinical result was made by using a modified Visick grading (Table 1).

TABLE 1

VISICK CLASSIFICATION

(MODIFICATION OF DUTHIE & BRANSON, 1979)

Grade I	No gastric symptoms
Grade II	Mild symptoms easily controlled by slight adjustment to diet or way of life
Grade III	Moderate symptoms not controlled by simple manoevres and not interfering with social or economic life. Better than pre-operatively.
Grade IV	Symptoms as bad as or worse than before operation and patients having recurrent ulceration were assessed as Grade IV

RESULTS

I A description of the excretion of Neutral Red in patients with duodenal ulcer.

(a) Patterns of Excretion

(b) Effect of Atropine

(c) Effects of Bile

(d) Effect of Neutral Red on Acid Secretion

II Division of the Neutral Red Test into 'Early' and 'Late' Positive

III Parallelism between the excretion of Neutral Red and Acid Secretion

IV Result of the gastroscopic and intra-operative study

V Initial comparison between the Neutral Red Test and the Insulin Test

IV The Follow-Up Study

(a) Clinical Results

(b) Predictive value of both tests and the basal acid secretion

(c) The fate of the 'Late' Positive Response

THE NEUTRAL RED TEST

With the dosage of Neutral Red used in this study, 50mg (5ml of a 1%) in an aqueous solution, no adverse reaction was noted at the initial testing and at follow-up. The only feature noted in some patients was a cough and a short period of hyperpnoea during the injection of the dye. Some patients were monitored with an E.C.G. but I could find no change in heart rate as described in the rat and the dog (Jones, 1969, 1970(a), 1970(b), Kolm et al, 1945). The above effects must be due to a central vagal action.

No change occurred in the blood sugar or electrolyte content of the blood during the test. The excretion of the dye in the urine and in the faeces in the following 48 hours was physiological (Figure 16) and it was found advisable to warn nursing staff and patients of this occurrence so as to prevent undue anxiety and alarm.

PRE-OPERATIVE EXCRETION OF NEUTRAL RED

The pre-operative excretion of neutral red was performed in 48 patients, 39 male and 9 female. The mean excretion time (E.T.) was 3.1 mins., i.e. the time from the injection of the dye intravenously to its first appearance in the gastric aspirate. The age of the patient varied from 24 years to 76 years, the mean age for the males was 47 years and the mean age for the females was 43 years. The 5 min. output of neutral red was performed in 41 patients (Figure 11) and the 15 min. output in 48 patients (Figure 12). The larger excretion of neutral red occurred in the first 5 minutes and progressively falls off during the last 15 minutes (Figure 12). Similarly, the larger excretion of neutral red occurred in the first 15 minutes and was significantly larger than the second 15 minute output. 8 of the second 15 minute samples were heavily contaminated by bile, an incidence of 16.7% and were excluded from the study.

It can be seen from the results in the Appendix that there is a wide variation in individual outputs. The first 15 minute output varied from 16.8ug to 147.9ug (mean = 57.6ug) and the second 15 minute output varied from 4.7ug to 101.9ug (mean = 38.6ug). Therefore, there was only one patient (K.S.) in which the output was below 20ug in the first 15 minute period. Therefore,

15MIN OUTPUT OF NEUTRAL RED IN 41 PRE-OPERATIVE PATIENTS

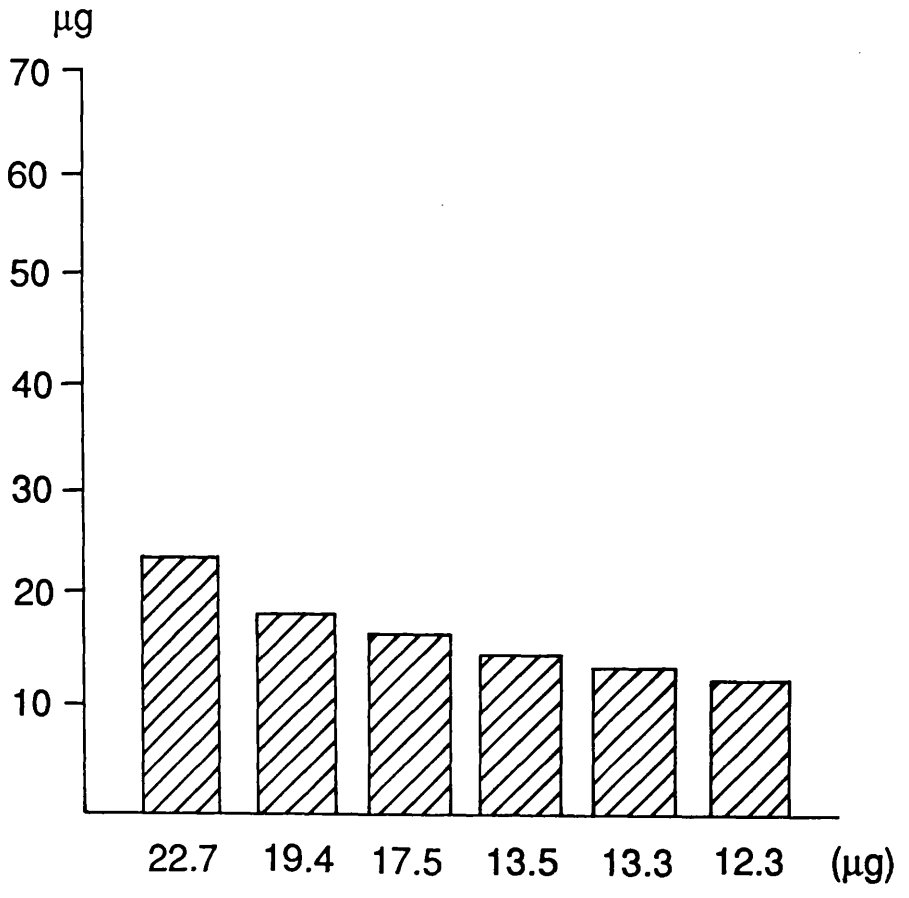


Fig. 11

15MIN OUTPUT OF NEUTRAL RED IN 48 PRE-OPERATIVE PATIENTS

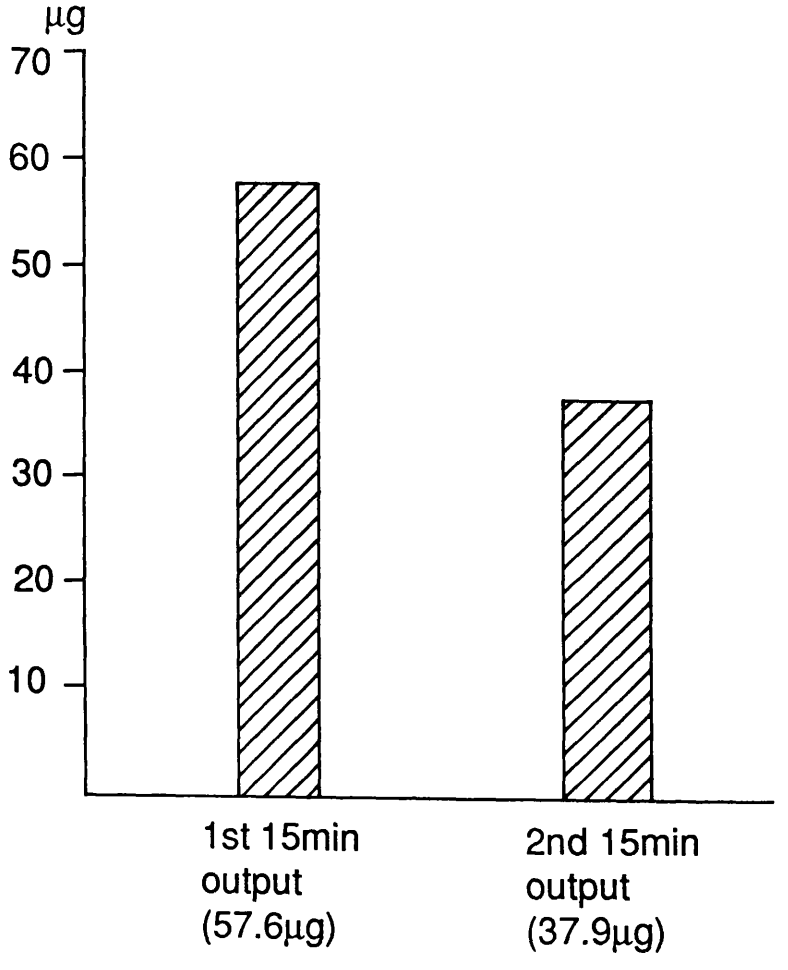


Fig. 12

EFFECT OF ATROPINE ON THE EXCRETION OF NEUTRAL RED

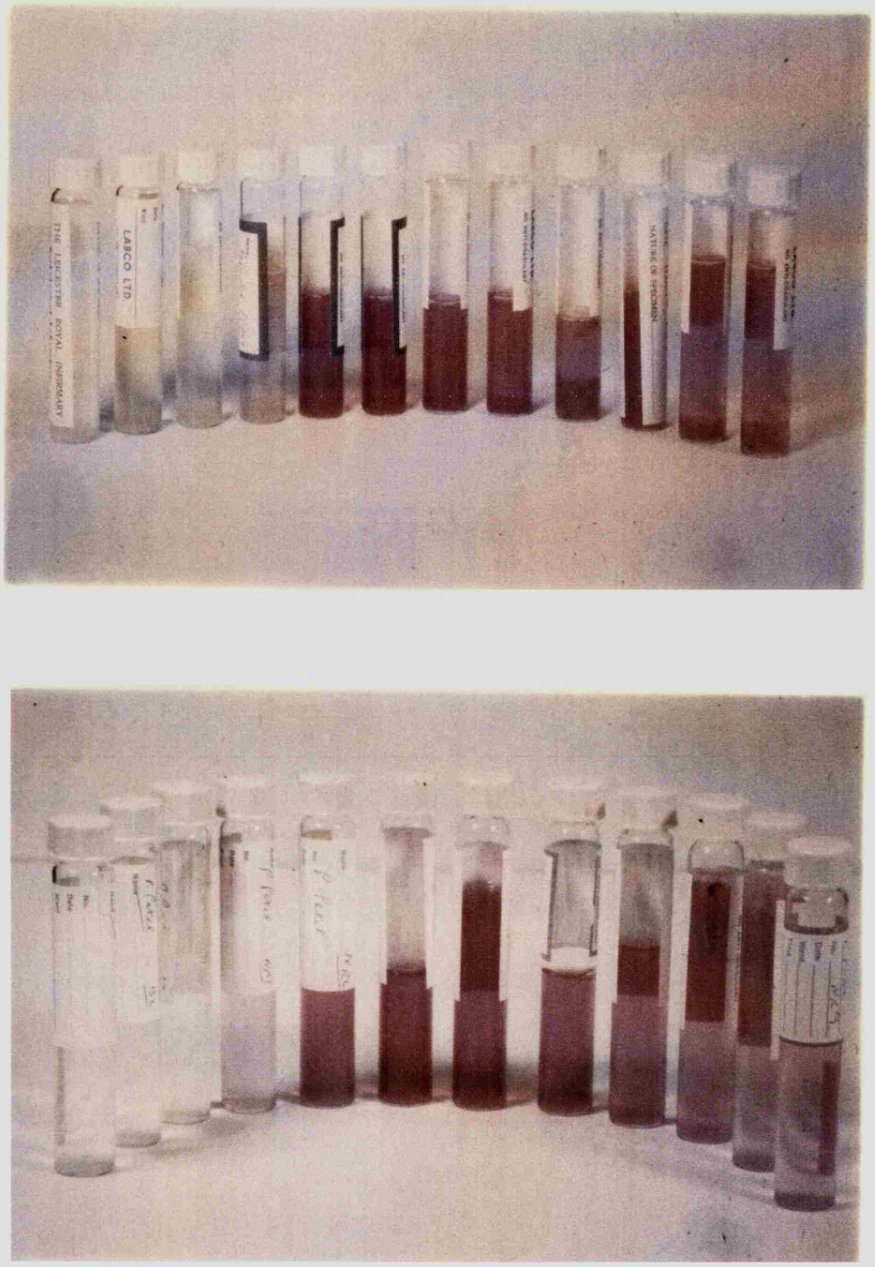


Fig. 13: Excretion of Neutral Red in a pre-operative case above and in an 'early' positive below.

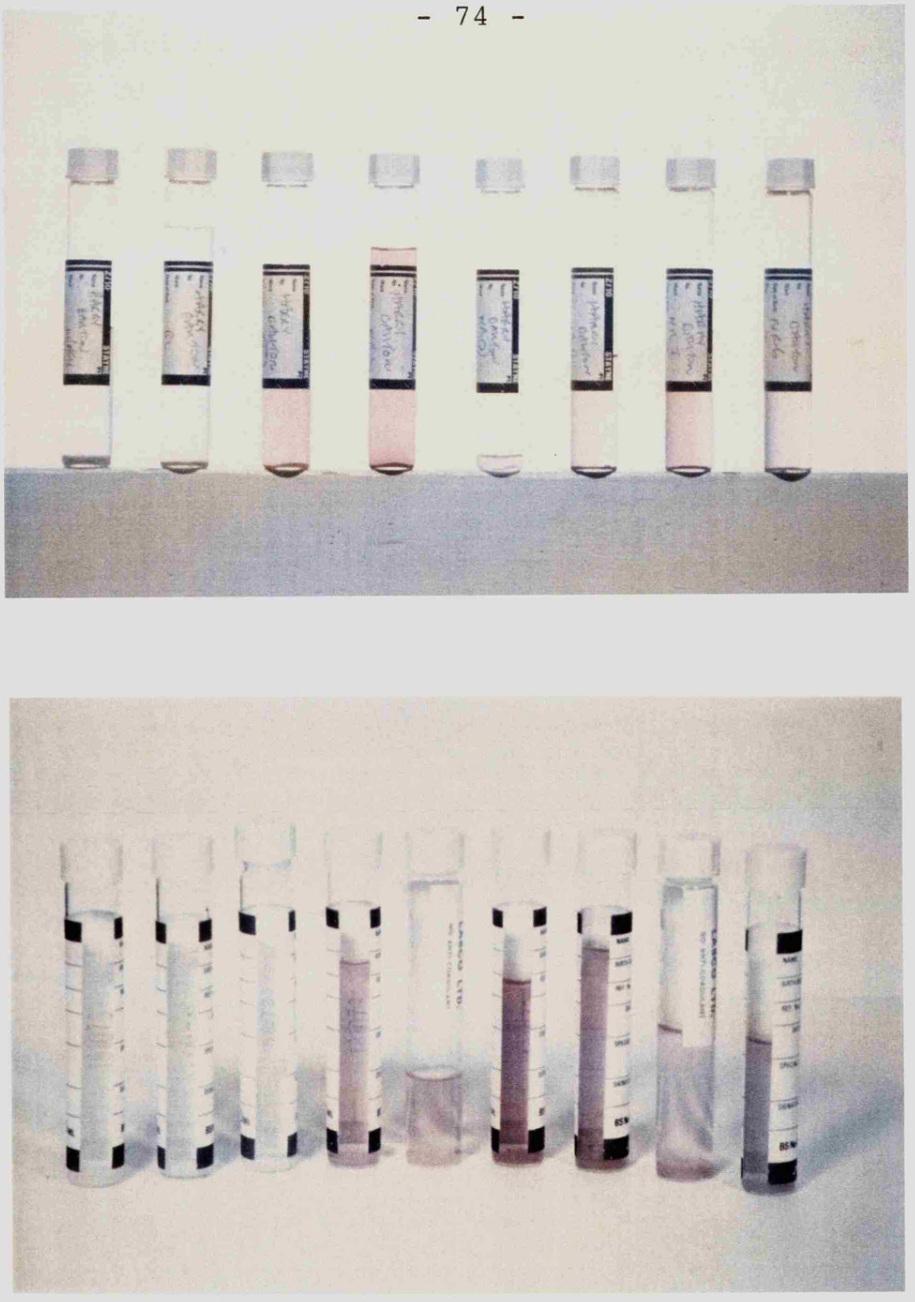


Fig. 14: Excretion of Neutral Red in two 'Late' Positive cases.

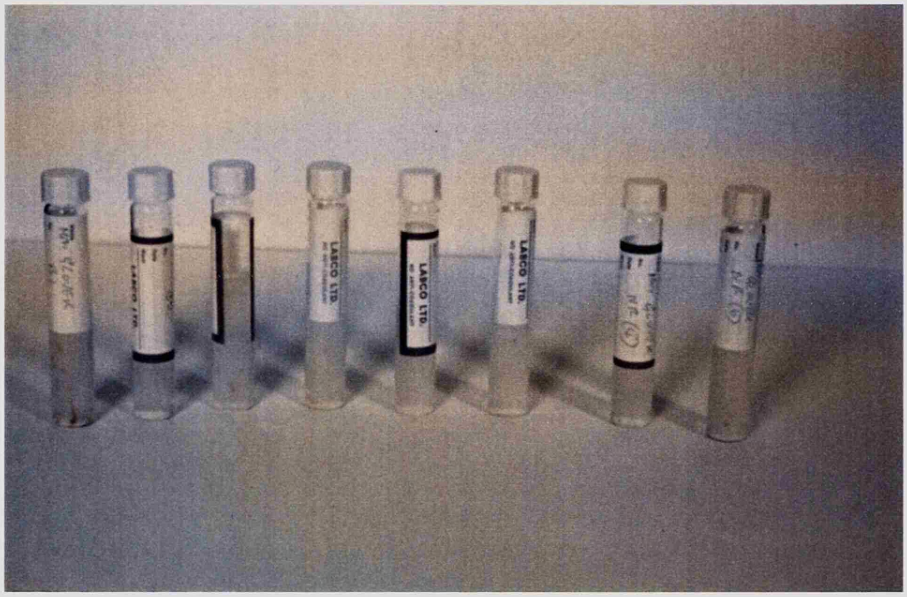
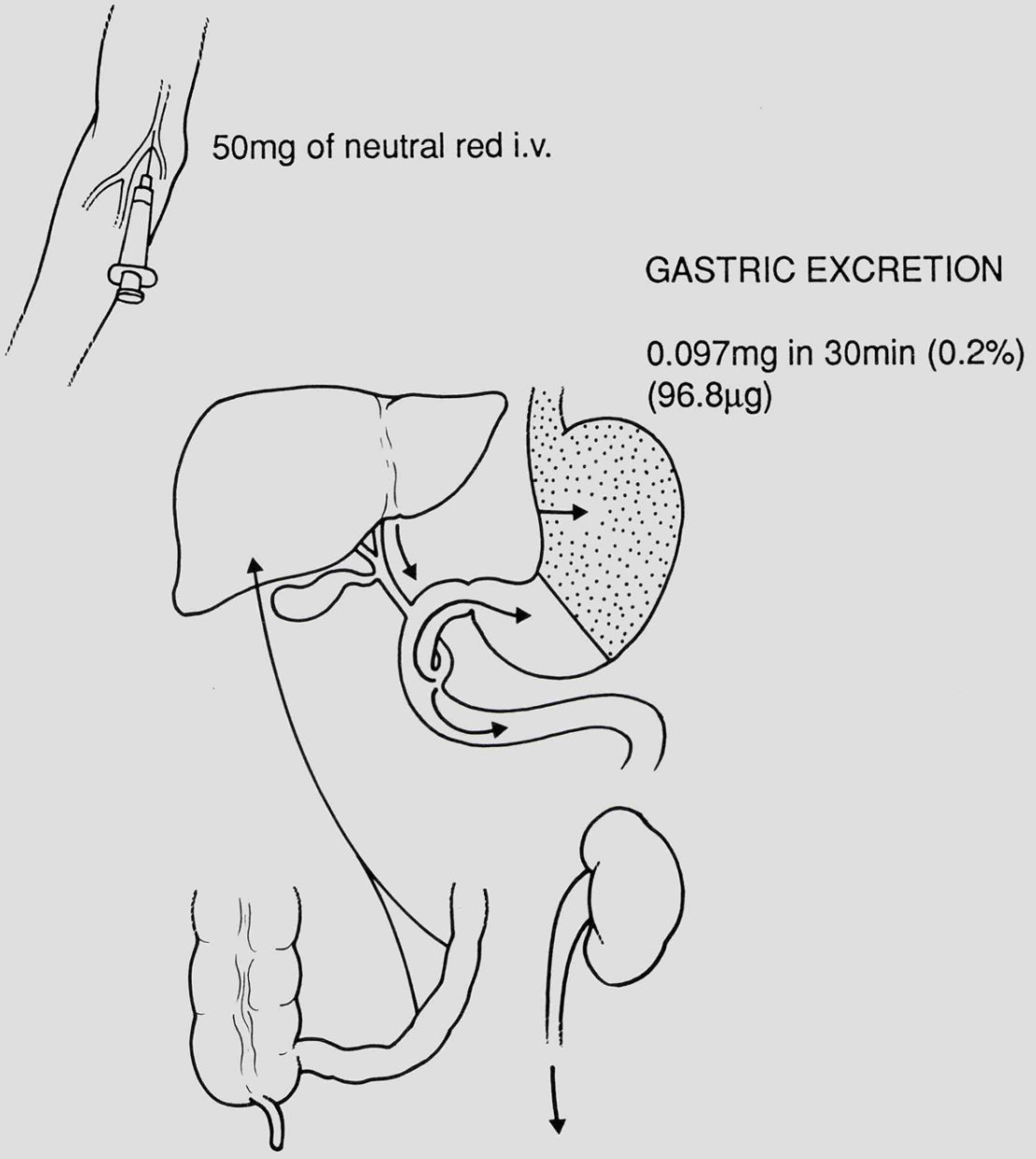


Fig. 15: Absent Neutral Red Excretion in a negative case.



PATHWAYS OF NEUTRAL RED ELIMINATION FROM THE BODY

Fig. 16

later in the study it was decided to use this cut off point to differentiate between 'early' and 'late' positive. Figures 13 to 15 show the actual specimens obtained in pre-operative patients and in post-operative patients that excreted more than 20ug/15 minutes in the 'early' positive, less than 20ug/15 minutes in the 'late' positive and the patients that failed to excrete neutral red in negative results.

Therefore, in pre-operative patients the excretion of the dye

(a) occurs quickly (mean 3.1 minutes)

(b) occurs mostly in the first 15 minute period when there is no obvious contamination by bile

(c) only a fraction of the dye is excreted by the stomach in the 30 minute test period, 0.2% (Figure 16)

(d) most of the dye is excreted by the liver, kidneys and intestine.

THE EFFECT OF ATROPINE ON THE EXCRETION OF NEUTRAL RED

The injection of subcutaneous atropine 20 minutes before the injection of neutral red has a profound effect on the excretion time (E.T.), increased from 4.4 minutes to 11.7 minutes and on the output of neutral red during the first and second 15 minute period (Table 2, Figures 17 and 18).

In two patients the excretion of neutral red was totally abolished.

This effect of atropine had been demonstrated previously. Kolm et al (1945) showed that atropinisation prior to the injection of neutral red in dogs had a significant effect on the amount of dye excreted. They came to the conclusion that the major part of the secretagogue effect of neutral red on the parietal cells is due to stimulation of the vagal mechanism. Weber et al (1975) had also shown in dogs that intramuscular atropine given preoperatively will give negative intraoperative and post operative 2DG-neutral red tests.

TABLE 2

EFFECT OF ATROPINE ON THE EXCRETION OF NEUTRAL RED

	Before Atropine			After Atropine		
Name	E.T. (min)	1st 15 min (µg)	2nd 15min (µg)	E.T. (min)	1st 15 min (µg)	2nd 15min (µg)
V.C.	6.0	116.5	167.8	15.0	47.9	18.0
W.Ch.	4.0	83.3	21.0	-	0	0
M.G.	5.0	34.5	26.1	-	0	0
P.G.	3.0	26.6	27.8	10.0	10.2	8.7
F.F.	4.0	94.9	87.0	10.0	30.4	18.8
Means	4.4	71.1	65.9	11.7	17.7	9.1

EFFECT OF ATROPINE ON THE EXCRETION OF NEUTRAL RED
(During the first 15 min)

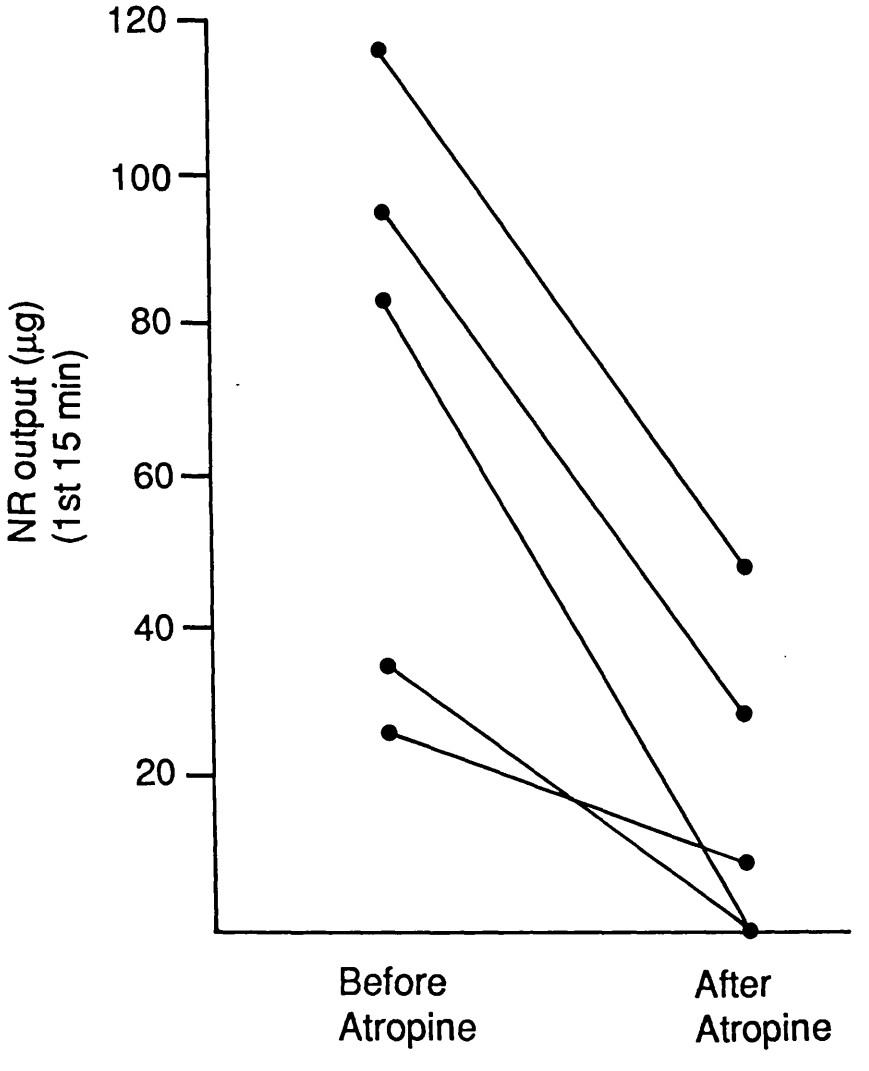


Fig. 17

EFFECT OF ATROPINE ON THE EXCRETION OF NEUTRAL RED
(During the second 15 min)

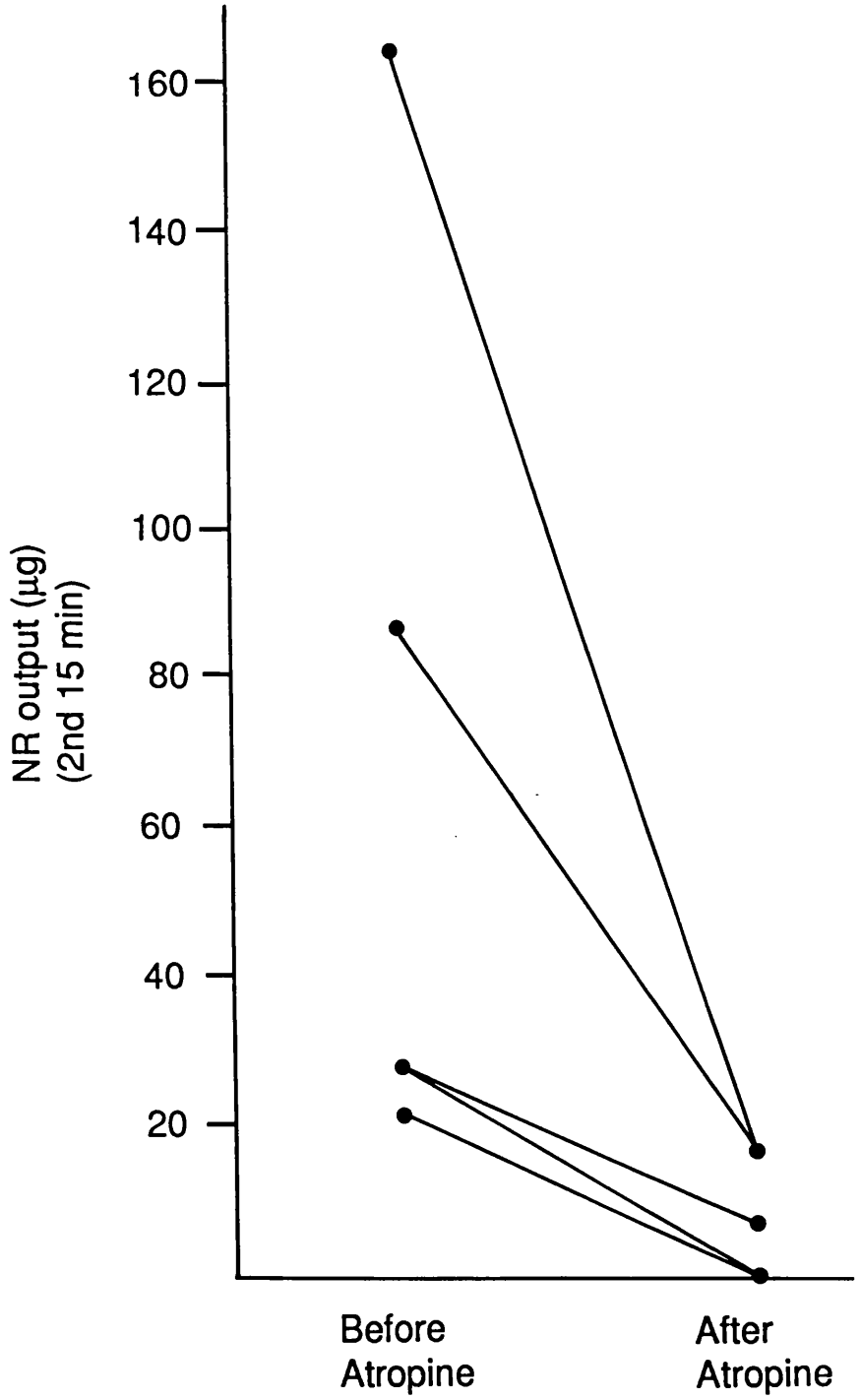


Fig. 18

EFFECT OF BILE ON THE ESTIMATION OF NEUTRAL RED IN GASTRIC JUICE

EFFECT OF BILE ON THE ESTIMATION OF NEUTRAL RED IN GASTRIC JUICE

Figure 19 shows the absorbance curves of neutral red and bile. The optimum measurement for neutral red is at wavelength 540m/u. At 520 m/u the interference from bile would have been significant. At this point it can be seen from the shape of the curves that bile is beginning to interfere significantly with the estimation of neutral red. An attempt was made to try and assess this effect experimentally and clinically.

An experiment was carried out using a 1 in 100,000 solution of neutral red, gastric juice and bile obtained from a cholecystectomy specimen. Percentage transmission was measured using the acetone method of the main study. The result is shown in Table 3 and it shows that increasing the amount of bile in the experiment did not significantly alter the percentage transmission.

Clinically, the early presence of bile, i.e. within 15 minutes, did not seem to alter the optical density of the specimens significantly. Three examples are taken from the particular study. Figures 20 and 21 show that the early excretion of bile, i.e. within the first 15

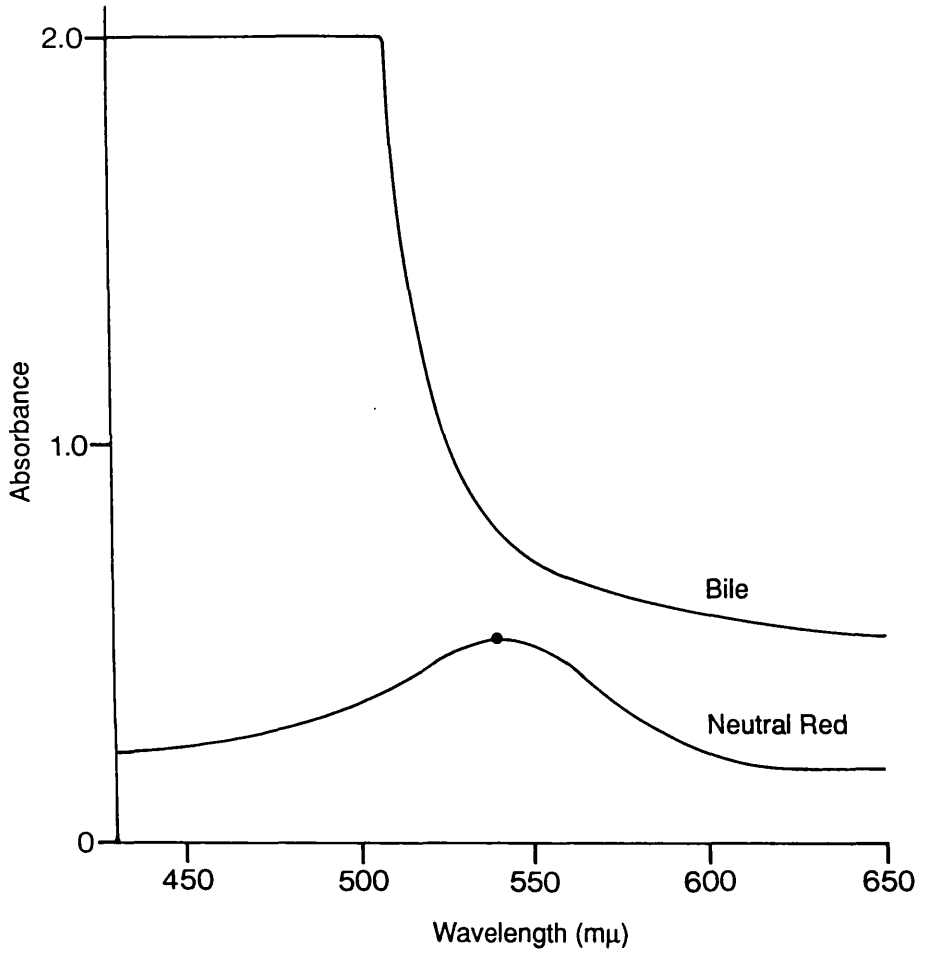


Fig. 19: Absorbance curves for Neutral Red and bile.

TABLE 3

EFFECT OF PURE BILE ON THE ESTIMATION OF NEUTRAL RED

	% transmission
Standard + Gastric Juice	6.0
Standard + Gastric Juice + 1 drop bile	5.5
Standard + Gastric Juice + 2 drops bile	5.5
Standard + Gastric Juice + 3 drops bile	5.5
Standard + Gastric Juice + 4 drops bile	6.0
Standard + Gastric Juice + 5 drops bile	6.5

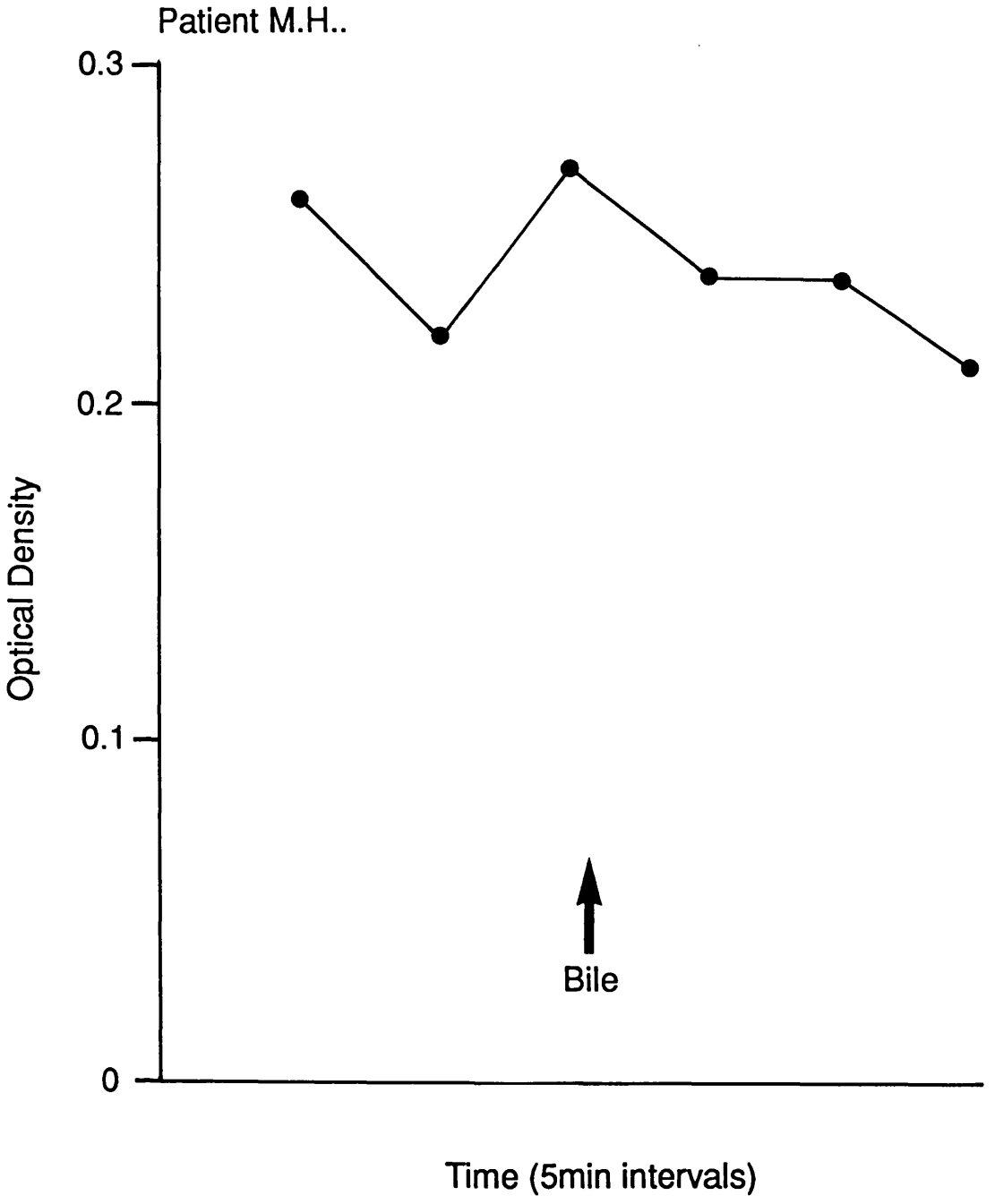
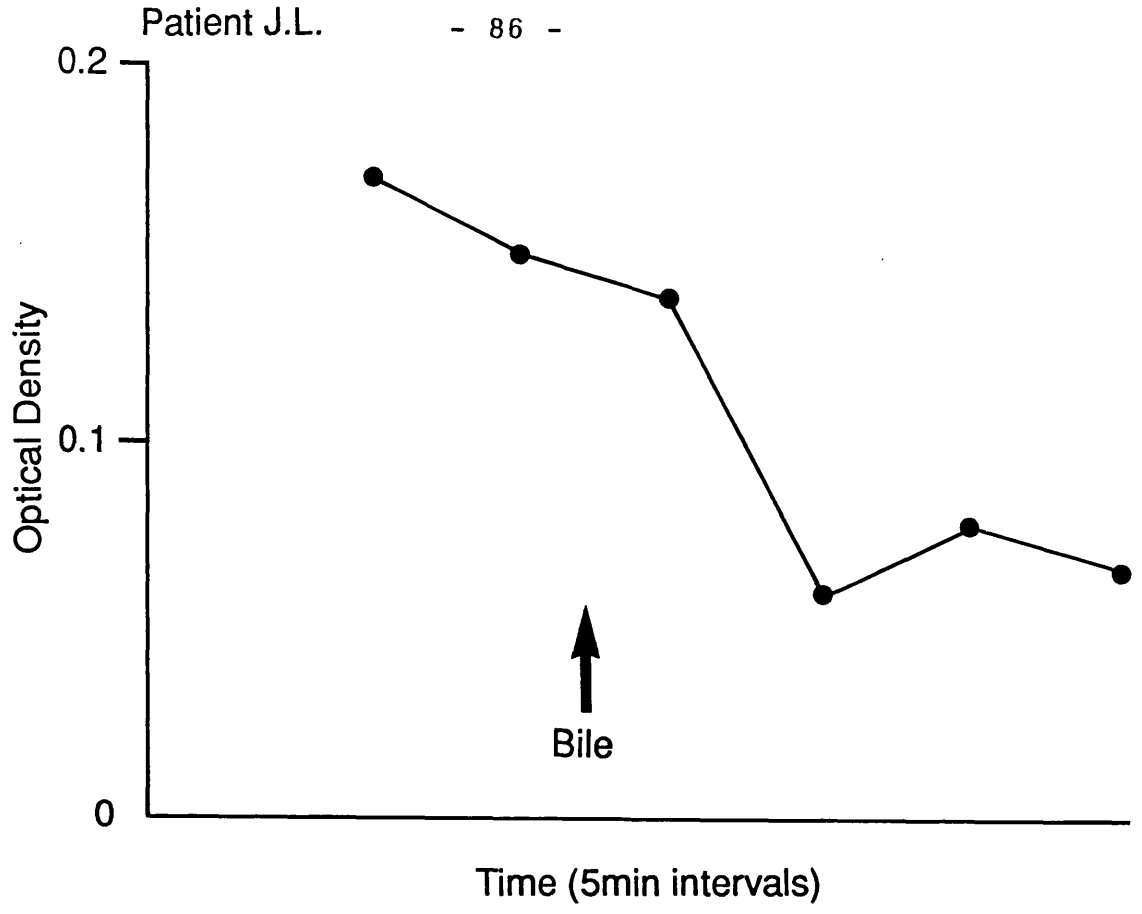

Patient M.H..
0.3
0.2
0.1
0
Optical Density
Bile
Time (5min intervals)

Fig. 20


Patient J.L.
0.2
0.1
0
Optical Density
Bile
Time (5min intervals)

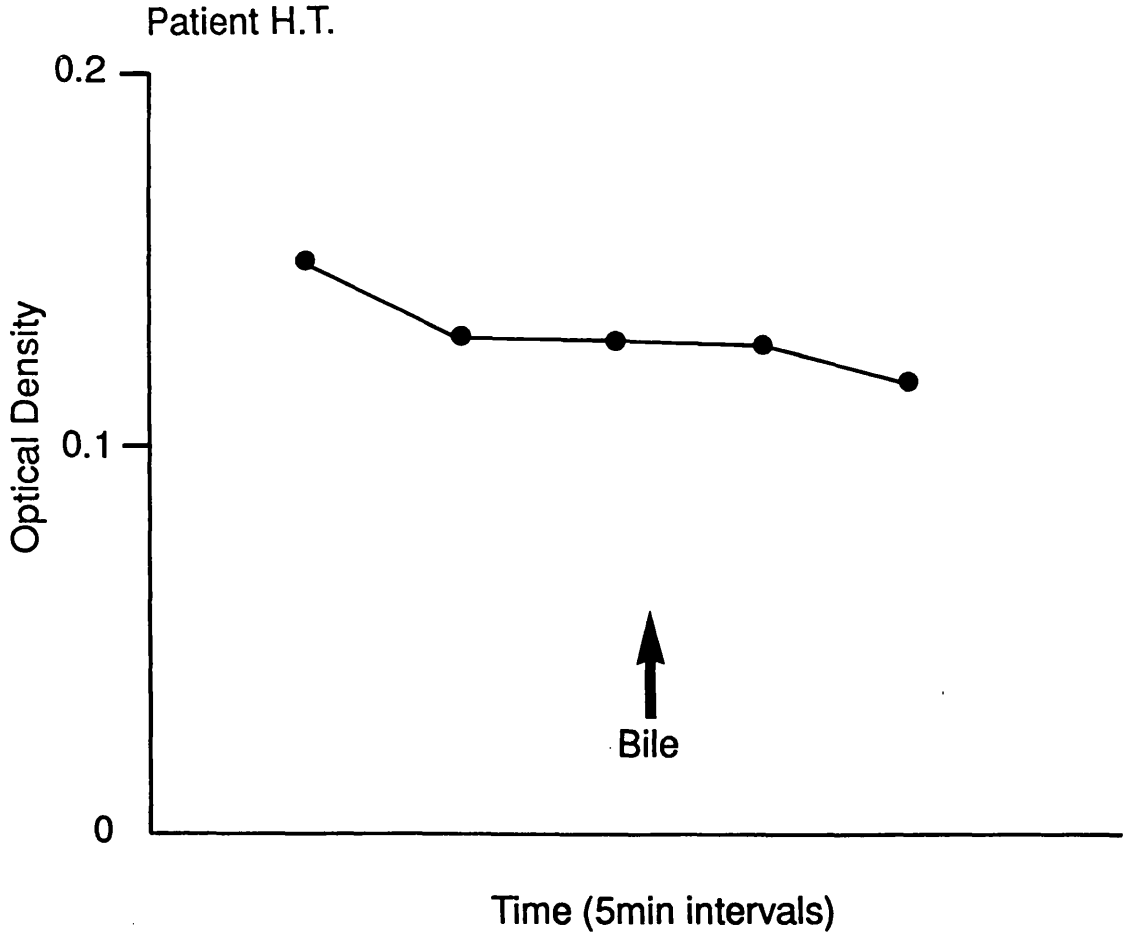

Patient H.T.
0.2
0.1
0
Optical Density
Bile
Time (5min intervals)

Fig. 21

minutes or so, did not significantly affect the optical densities and thus the estimation of neutral red.

However, the appearance of bile in the second 15 minute period can alter the estimation of neutral red. Piersol (1925) in man, and Komarov et al (1949) showed the main pathway for the excretion of neutral red is through the liver. In patient W.Ch. (Figure 22) we are witnessing the reflux of bile containing neutral red (Figure 22). Therefore, it is best to estimate the neutral red as early as possible (first 15 minutes) before this phenomenon occurs.

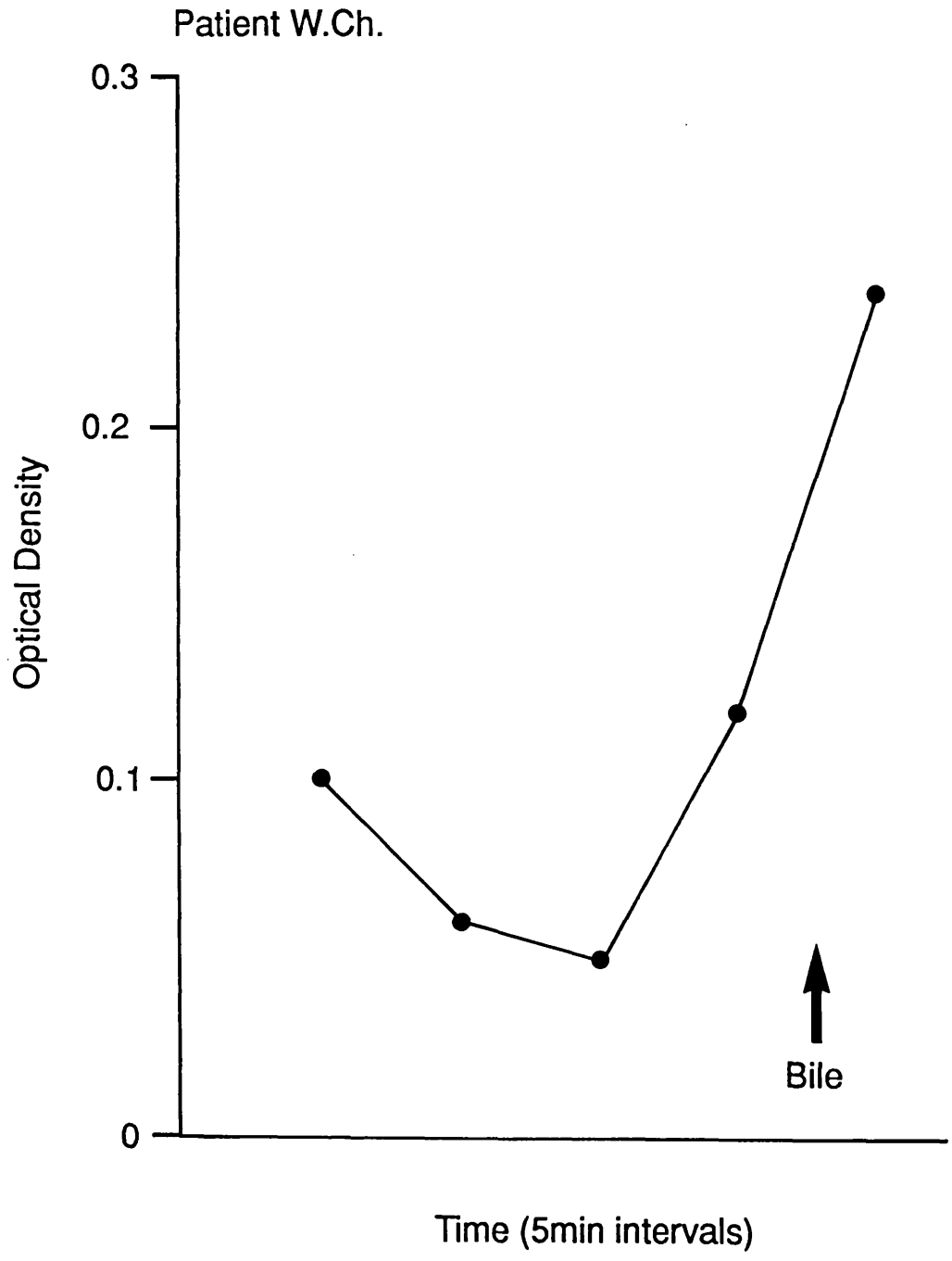

Patient W.Ch.
0.3
0.2
0.1
0
Optical Density
Bile
Time (5min intervals)

Fig. 22

EFFECT OF NEUTRAL RED ON ACID OUTPUT

A preliminary study was carried out to see whether the neutral red itself had a stimulatory effect on acid output. Because of the clinical and experimental evidence of its stimulatory effect (Jones, 1969, Kolm et al 1945), it was of interest to see whether this was appreciable and, therefore, could be measured clinically. 17 patients were studied.

The result is depicted in Tables 4 and 5 . The quantitative (acid output) and qualitative (acidity) effect was measured after an injection of 5cc's of an aqueous solution of neutral red. Table 4 shows the effect of injection of neutral red on the first and second 15 minute outputs of acid. In the first 15 minutes there is a rise to 1.94 mmol from the basal of 1.52 mmol which falls to 1.64 following the second 15 minutes. Using the Wilcoxen and Friedman tests this increase is not statistically significant ($p = 0.1$). As far as the results of acidity are concerned (Table 5), no statistically significant increase was found.

TABLE 4

No.	Patient	Basal Output (mmol) 15min	1st 15min Output (mmol)	2nd 15min Output (mmol)
8	M.P.	0.59	0.48	0.24
15	M.G.	1.12	1.13	0.80
18	D.H.	0.54	0.61	0.57
19	S.G.	0.30	2.22	1.31
20	G.Sh.	4.80	3.42	3.52
21	D.A.	4.09	2.86	2.15
25	R.P.	2.80	3.25	3.02
26	R.Th.	2.97	2.73	2.81
28	M.W.	0.73	3.42	2.05
29	G.M.	0.78	0.98	0.92
30	B.C.	1.02	2.49	2.14
31	B.S.	1.80	1.51	0.54
34	J.L.	1.28	1.63	2.29
36	Sh.P.	1.06	1.07	1.09
37	J.Th.	1.22	1.68	2.15
42	W.Ch.	0.41	2.35	0.75
45	A.R.	0.40	1.16	Bile
Mean		1.52	1.94	1.64

p = N.S.

Table 4: Effect of Neutral Red on acid output.

TABLE 5

No.	Patient	Highest Basal Acidity (mmol)	Highest Acidity in 1st 15min	Highest Acidity in 2nd 15min
8	M.P.	12	10	8
15	M.G.	56	54	42
18	D.H.	40	58	44
19	S.G.	20	30	46
20	G.Sh.	100	60	88
21	D.A.	66	66	60
25	R.P.	80	94	94
26	R.Th.	56	58	52
28	M.W.	82	90	1 00
29	G.M.	42	47	46
30	B.C.	25	66	76
31	B.S.	58	70	40
34	J.L.	64	50	96
36	Sh.P.	56	70	62
37	J.Th.	36	43	43
42	W.Ch.	18	36	34
45	A.R.	36	42	Bile
Mean		50mmol/L	56	58

p = N.S.

p = N.S.

Table 5: Effect of Neutral Red on acidity.

DIVISION OF THE NEUTRAL RED TEST INTO 'EARLY' AND 'LATE' POSITIVE

THE DIVISION OF THE NEUTRAL RED TEST INTO 'EARLY' AND 'LATE' POSITIVE

An attempt was made to divide the post-operative excretion of Neutral Red into two groups that would reflect the 'early' and 'late' responders of the Insulin Test. It can be seen that in the 48 patients studied pre-operatively, only one patient (K.S.) had a first 15 minute output of less than 20ug (see Appendix). Therefore, 20ug per 15 minute period was taken as the discriminatory point. All patients post-operatively with a first 15 minute output greater than 20ug were labelled as 'early' positive and all patients with a first 15 minute output less than 20ug were labelled as 'late' positive. (Figures 24 to 27)

In retrospect, and using the receiver operating characteristic curve (R.O.C.) of the 86 patients followed up it can be seen from the details in Table 6 and the graphic illustration in Figure 23 that 20ug is the best choice as a demarcation boundary giving a sensitivity of 0.69 and a specificity of 0.84 and a positive predictive value of 50% (see Appendix).

Table 7 summarises the dye outputs during the first and second 15 minute periods in pre-operative, 'early' positive and 'late' positive patients. There was no significant difference between the excretion time (E.T.)

TABLE 6

Post-operative Neutral Red Test	Visick I & II	Visick III & IV	Sensitivity	Specificity
A ≥ 1 µg	30	12	0.75	0.57
B ≥ 20 µg	11	11	0.69	0.84
C ≥ 40 µg	5	6	0.38	0.96
D ≥ 60 µg	3	6	0.38	0.96
E ≥ 80 µg	2	4	0.25	0.97

Table 6: Measurement of sensitivity and specificity at different cut off points of Neutral Red excretion in pre-operative patients.

USE OF RECEIVER OPERATING CHARACTERISTIC CURVE TO CHOOSE BOUNDARY

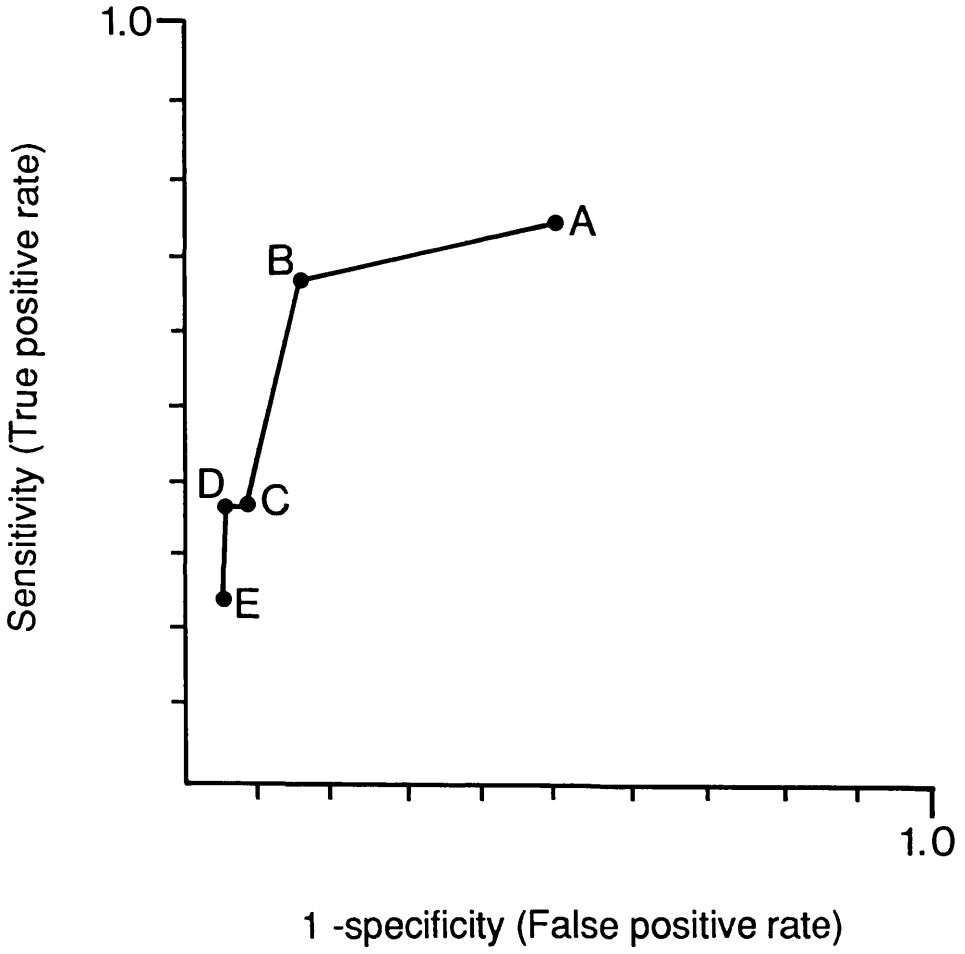


Fig. 23

5 MIN OUTPUT OF NEUTRAL RED IN 24 'EARLY' POSITIVE PATIENTS

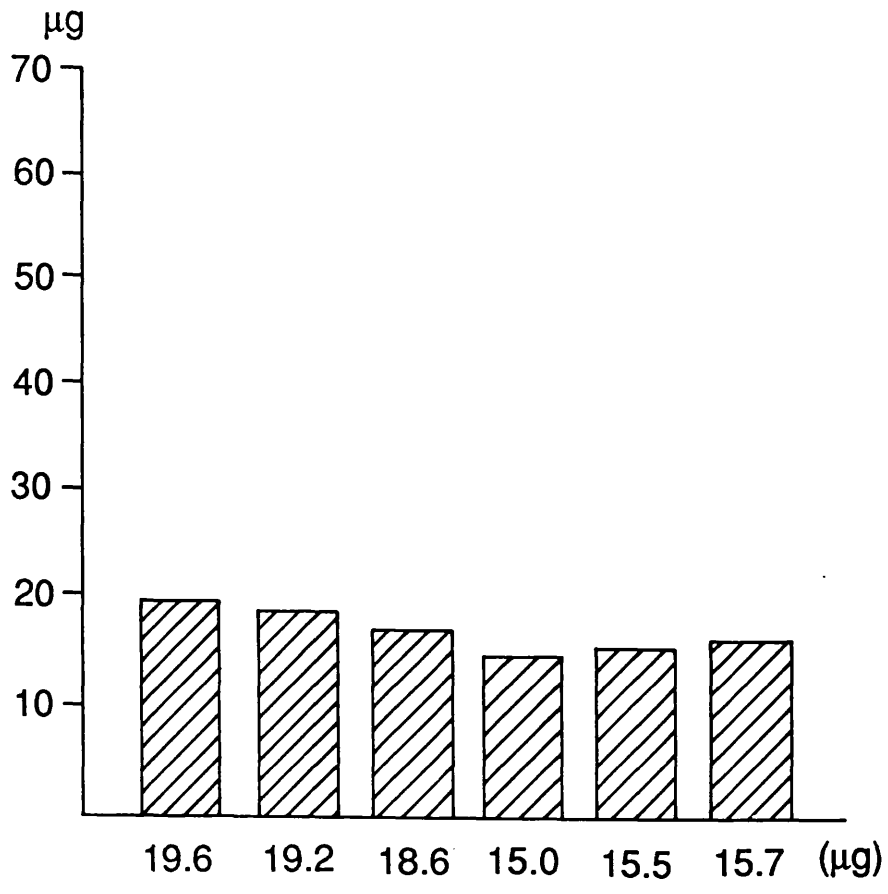


Fig. 24

15 MIN OUTPUT OF NEUTRAL RED IN 24 'EARLY' POSITIVE PATIENTS

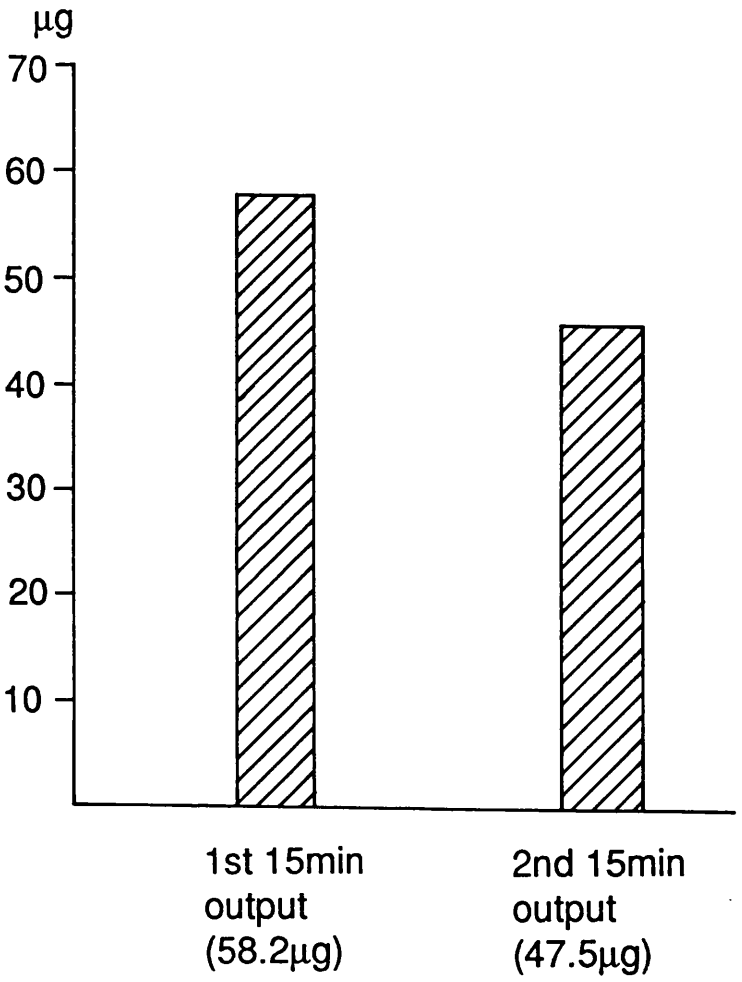


Fig. 25

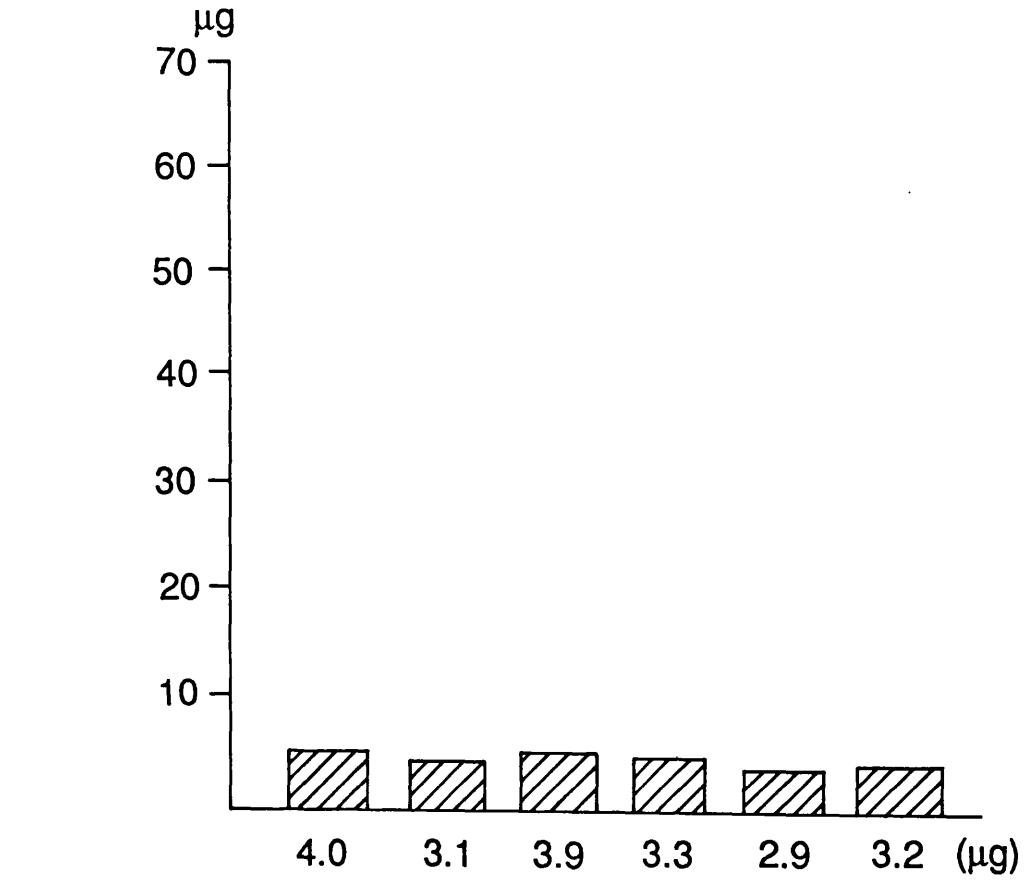

5 MIN OUTPUT OF NEUTRAL RED IN 26 'LATE' POSITIVE PATIENTS
µg
70
60
50
40
30
20
10
4.0
3.1
3.9
3.3
2.9
3.2
(µg)

Fig. 26

15 MIN OUTPUT OF NEUTRAL RED IN 26 'LATE' POSITIVE PATIENTS

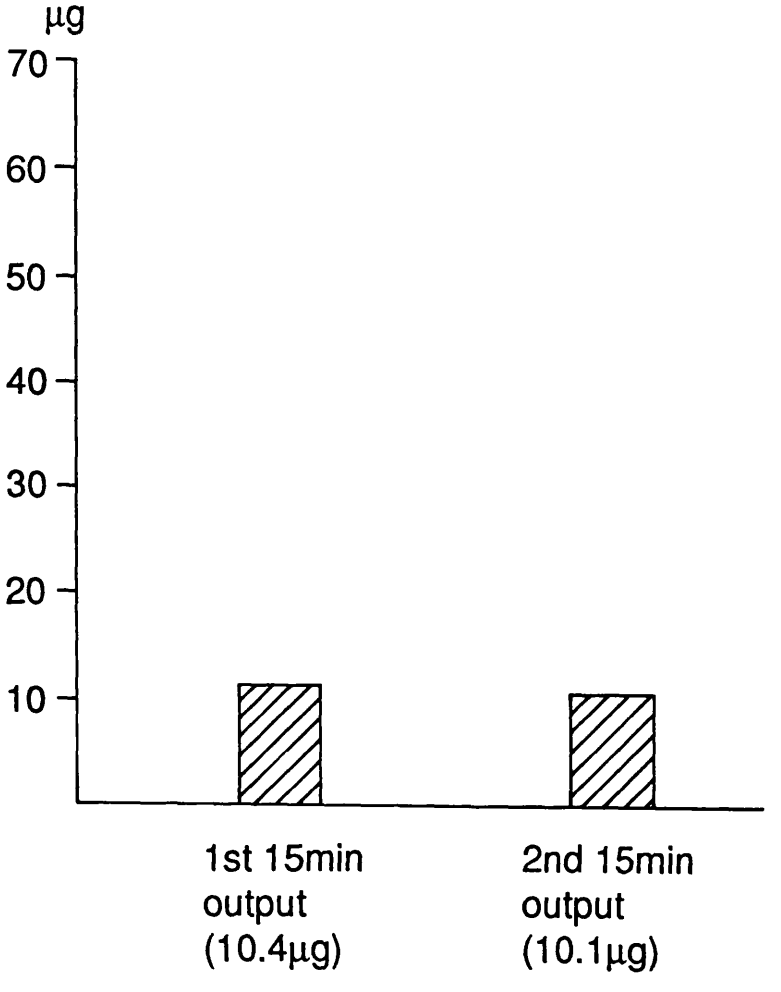


Fig. 27

TABLE 7

Type of patient	E.T. (min)	p	1st 15min (µg)	2nd 15min (µg)	p
Pre-operative	3.10	N.S.	57.6	37.9	N.S.
'Early' positive	4.3	p<0.01	58.2	47.5	p<0.01
'Late' positive	7.6		10.4	10.1	p<0.01

Table 7: A summary of the excretion of Neutral Red in pre-operative 'early' positive and 'late' positive patients.

in pre-operative (3.1 mins.) and 'early' positive (4.3 mins.) patients but a significant difference between these two and the excretion time in 'late' positive (7.6 mins.) patients ($p = 0.01$).

Again, there was no significant difference between the pre-operative and 'early' positive neutral red output during the two 15 minute periods but a significant difference between these outputs and the output in 'late' positive patients ($p = 0.01$).

Table 8 shows the difference between the responses in females and males. The difference is extremely marked and yet not statistically significant ($p > 0.10$).

TABLE 8

PERCENTAGE INCIDENCE OF 'EARLY', 'LATE' AND NEGATIVE TESTS IN MALES AND FEMALES

	NEUTRAL RED TEST			INSULIN TEST		
	'EARLY' POS	'LATE' POS	NEGATIVE	'EARLY' POS	'LATE' POS	NEGATIVE
FEMALE	11.1 *	29.6	59.3	11.1 *	22.2	66.7
MALE	28.8 *	24.6	46.6	21.9 *	23.3	54.8

* $p > 0.10$

PARELLELISM BETWEEN THE EXCRETION OF NEUTRAL RED AND THE SECRETION OF ACID

EXCRETION OF NEUTRAL RED AND THE SECRETION OF ACID

The basal acid output (B.A.O.) was measured in pre-operative, 'early' and 'late' positive and negative patients (Table 9, Figure 28). It can be seen that the ability of the stomach to excrete neutral red and to secrete hydrochloric acid are not necessarily allied. There is a certain parallelism but this is not always obvious. For example, the excretion of neutral red in the 'early' positive group is higher than the pre-operative group, yet the B.A.O. is significantly reduced in this group ($p < 0.01$). (There was a statistically significant fall in acid output between all four groups of patients.) At the other end of the scale it can be seen that the excretion of neutral red can be absent when the stomach is secreting basal acid at the level of 0.67 mmol/½ h.

I had previously shown this lack of parallelism experimentally in the rat (Jones, 1969, 1970(a), 1970(b)). In the group of rats subjected to total vagotomy and confirmed by the absence of neutral red excretion, significant amounts of hydrochloric acid were secreted by the stomach (Table 10), 0.052mmol per 7 hours compared to the control stomach of 0.479mmol.

A further lack of parallelism is seen when the excretion patterns of Neutral Red are examined more closely. In

the pre-operative patients and 'early' positive responders all patients secreted acid. However, in the 'late' positive responders there were two patients who excreted small amounts of dye but failed to secrete acid.

TABLE 9

EXCRETION (Neutral red)	B.A.O. (mmol / $^1/_2$h)	p
Pre-op	3.05	p<0.01
'Early' positive	1.62	p<0.01
'Late' positive	0.87	p<0.01
Negative	0.67	

Table 9: Basal acid output in pre-operative and post-operative patients in relation to Neutral Red excretion.

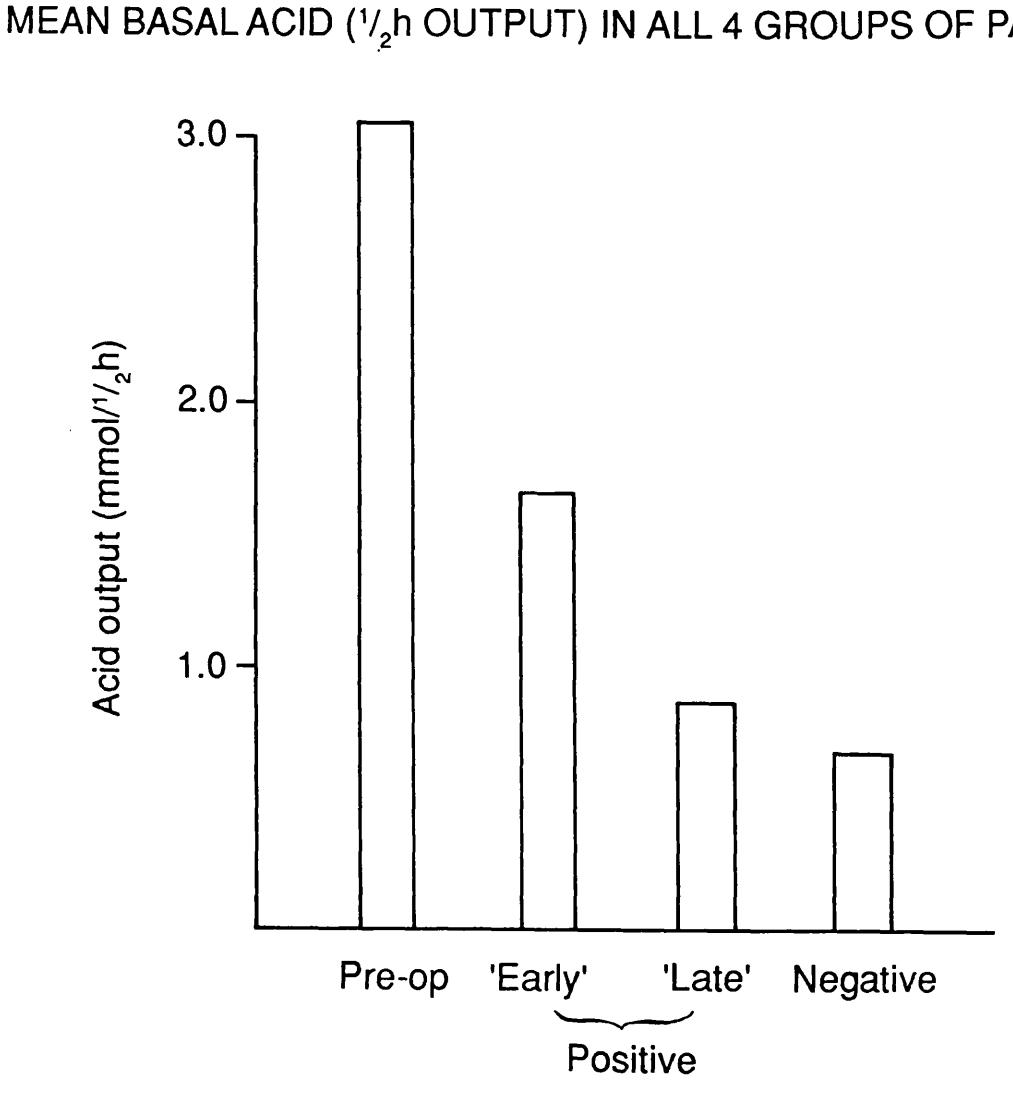


Fig. 28: Histogram to show the relationship between the excretion of Neutral Red and the basal acid output.

TABLE 10

THE ACID ANALYSIS IN CONTROL RATS WITH DIFFERENT TYPES OF VAGOTOMY

TYPE OF VAGOTOMY	WEIGHT MEANS ± S D	VOL GASTRIC JUICE MEANS ± S D	pH MEANS ± S D	mEq/L MEANS ± S D	mEq/7 hrs MEANS ± S D
NORMAL RATS	330.0 ± 36.4	6.8 ± 3.0	2.3 ± 0.2	69.7 ± 18.9	.479 ± .259
POSTERIOR TRUNK INTACT	366.5 ± 35.1	7.1 ± 3.0	2.7 ± 0.6	38.7 ± 14.7	.295 ± .201
FUNDIC BRANCH INTACT	327.5 ± 34.0	4.7 ± 2.7	3.6 ± 1.3	27.5 ± 18.1	.156 ± .156
TOTAL VAGOTOMY	310.5 ± 42.0	3.4 ± 2.4	4.6 ± 2.0	16.4 ± 13.1	.052 ± .062

COMPARISON BETWEEN THE NEUTRAL RED TEST AND THE INSULIN TEST AT THE INITIAL TESTING

COMPARISON BETWEEN THE NEUTRAL RED TEST AND THE INSULIN TEST AT THE INITIAL TESTING

Table 11 shows the results of both tests in the 100 patients that were entered into the study. The Neutral Red Test gives a slightly higher, though not a statistically significant, number of positive tests, 50% compared with 42%. In both tests, the number of 'early' and 'late' positive results are approximately the same.

There was total agreement between the two tests in 69% of patients (Table 12). When the 'early' and 'late' classification was ignored and the tests were recorded as positive and negative only, agreement was present in 74% of patients. Table 13 shows the number of patients where differences occurred between the two tests. A 'mild' disagreement is defined as one where one test showed a negative and the other a 'late' positive response and where one test reached a 'late' positive and the other an 'early' positive response. It must always be remembered that small positive responses or negative responses in the acid secretory test may be masked by excessive neutralisation (Weinstein et al, 1950).

There were 21 patients in this group (Table 14) and the

Insulin Test gave a more positive response in 66.6% of patients. A 'gross' disagreement is defined as one where one test showed an 'early' response and the other a negative response. There were 10 patients in the group (Table 14). All 10 patients gave a more positive response in the Neutral Red Test. When these 10 patients were analysed in the follow up study, 43% of patients had an "unsuccessful outcome" which is much higher than the 18.5% recorded for the whole series and 2 patients had recurrent ulcers. Thus it seems that the Neutral Red Test has a better ability to predict the clinical outcome than the Insulin Test.

TABLE 11

RESULTS OF THE NEUTRAL RED AND INSULIN TEST IN 100 PATIENTS

Neutral Red Test	No Patients	Insulin Test	No Patients
Negative	50	Negative	58
Positive	50	Positive	42
'Early' Positive	24	'Early' Positive	19
'Late' Positive	26	'Late' Positive	23

TABLE 12

COMPARISON BETWEEN THE NEUTRAL RED AND INSULIN TESTS IN 100 PATIENTS

Total Agreement (Ignoring the 'Early' & 'Late' classification)		Total Agreement (Using the 'Early & 'Late' classification)	
Negative	= 41	Negative	= 41
Positive	= 33	Positive	= 28
		'Early'	= 14
		'Late'	= 14
TOTAL	= 74	TOTAL	= 69

TABLE 13

COMPARISON BETWEEN THE NEUTRAL RED AND INSULIN TEST IN 100 PATIENTS

Total Agreement		= 69 Patients
'Mild' Disagreement		= 21 Patients
'Gross' Disagreement		= 10 Patients
	TOTAL	= 100 Patients

TABLE 14

COMPARISON BETWEEN THE NEUTRAL RED AND INSULIN TEST - A FURTHER BREAKDOWN

TOTAL AGREEMENT		69 PATIENTS
'MILD' DISAGREEMENT		
N R T	I T	
NEGATIVE	'LATE' POSITIVE	9 PATIENTS
'LATE' POSITIVE	NEGATIVE	7 PATIENTS
'LATE' POSITIVE	'EARLY' POSITIVE	5 PATIENTS
'GROSS' DISAGREEMENT		
N R T	I T	
'EARLY' POSITIVE	NEGATIVE	10 PATIENTS

THE FOLLOW-UP STUDY

CLINICAL RESULTS

The follow-up study came to an end on 18th January, 1989. Up to this point, of the 100 patients first studied 14 had been lost to follow up (14%) and of these 11 were male and 3 were female (Table 15). Of the remaining 86 patients, 21 (24.4%) died during the follow-up, 14 (66.7%) were male and 7 were female. The mean follow-up from operation to the time of death was 7 years 9 months (range 3 years 1 month to 17 years 3 months). The causes of death are listed in Table 16 . The main cause of death has been cancer with 9 patients dying from this. The main locations have been lung and breast with no evidence of stomach or colon playing a prominent part (Table 17).

The outcome in the 86 patients available initially for follow-up and assessed by the Visick Grading is shown in Table 20. Visick Grading I and II are grouped together and depict a "successful" outcome. Visick Grading III and IV are grouped together and depict an "unsuccessful" outcome. Recurrent ulcers are classified as Visick IV. As can be seen from Tables 18/19 there were 13 patients classified as Visick IV. 12 of these patients were proven gastroscopically to have recurrent ulcers and these are the ones described later. 1 patient (J.D.) had severe post-operative symptoms but at the time of gastroscopy no recurrent ulcer was found. However,

later when the predictive worth of the Neutral Red and Insulin Test is assessed, I have included him in the Visick IV group.

As can be seen from Table 18 and 19 , the proportion of patients in the "successful" and "unsuccessful" groups are similar. Therefore, the inclusion of patients who have died during the study have not biased the findings in any way. The clinical outcome when sex of the patients is taken into account is shown in Table 20. No significant difference in clinical outcome was found.

Of the 65 survivors, 48 were male (74%) and 17 were female, the same ratio as found in the original patients. The mean follow-up time was 14 years 6 months (range 10 years 10 months to 18 years 1 month).

12 patients developed recurrent ulceration, an incidence of 14% (9 were male and 3 were female). There was one death in this group, an incidence of 8.3%. The details of these 12 patients are depicted in Table 21 and Figure 29 . The average time to recurrence was 6.1 years. 2 patients required gastric resection but the remaining 9 patients were successfully treated by medical means.

Other complications from the operation are listed in

Table 22. Patients suffering from diarrhoea and dumping form the largest group.

TABLE 15

Patients	n	Male	Female
Entered study	100	73	27
Number of deaths	21	14	7
Lost to follow-up	14	11	3
Patients that were assessed by Visick grading	86	62	24

Table 15: The fate of the 100 patients who entered the study.

TABLE 16

CAUSE OF DEATH IN 21 PATIENTS

1	Recurrent Ulceration	1 (f) (5%)
2	Cancer	9 (3f/6m)
3	Myocardial Infarction	4 (1f/3m)
4	Cerebro-Vascular Accidents	2 (1f/1m)
5	Cholangitis	1 (f)
6	Motor Neurone Disease	1 (m)
7	Jejunal Haemorrhage	1 (m)
8	Unknown	2 (m)
		n = 21

TABLE 17

LOCATION OF CANCER IN 9 PATIENTS

	No. Patients
Lung	3 (m)
Breast	3 (2f/1m)
Prostate	1 (m)
Stomach	1 (m)
Brain	1 (f)
	9

TABLE 18

VISICK GRADING IN THE 21 PATIENTS WHO DIED DURING THE STUDY

VISICK I = 15 PATIENTS VISICK II = 2 PATIENTS	) = 81%	"SUCCESSFUL"
VISICK III= 0 PATIENTS VISICK IV = 4 PATIENTS	) = 19%	"UNSUCCESSFUL"

TABLE 19

VISICK GRADING IN THE 65 SURVIVORS

VISICK I = 46 PATIENTS VISICK II = 7 PATIENTS	) 81.5%	"SUCCESSFUL"
VISICK III= 3 PATIENTS VISICK IV = 9 PATIENTS	) 18.5%	"UNSUCCESSFUL"

TABLE 20

OUTCOME OF 86 PATIENTS AS ASSESSED BY THE VISICK GRADING IN MALES AND FEMALES

MALES

VISICK I VISICK II	)	51 PATIENTS = 82.3% "SUCCESSFUL"
VISICK III VISICK IV	)	11 PATIENTS = 17.7% "UNSUCCESSFUL"

FEMALES

VISICK I VISICK II	)	19 PATIENTS = 79.2% "SUCCESSFUL"
VISICK III VISICK IV	)	5 PATIENTS = 20.8% "UNSUCCESSFUL"

TABLE 21

Patient	Sex	Neutral Red Test	Hollander Test	Operation to recurrence (yrs)	Outcome
F.H.	F	+ late	+ late	4	Died from D.U.
P.B.	M	+ early	+ early	7	Medical treatment
J.D.	F	+ early	-ve	12	Medical treatment
H.B.	M	+ early	+ early	4	Medical treatment
I.Th.	F	-ve	-ve	8	Medical treatment
A.Th.	M	+ early	+ early	9	Medical treatment
R.B.	M	+ early	+ early	7	Partial gastrectomy
W.F.	M	+ early	+ early	8	Medical treatment
C.W.	M	+ early	-ve	5	Medical treatment
B.S.	M	-ve	-ve	6	Medical treatment
M.H.	M	+early	+ early	2	Partial gastrectomy
L.D.	M	+ late	+ late	1	Medical treatment
				Mean = 6.1	

Table 21: Listed are the patients with recurrent ulceration. Time in years from operation to onset of recurrence and subsequent treatment.

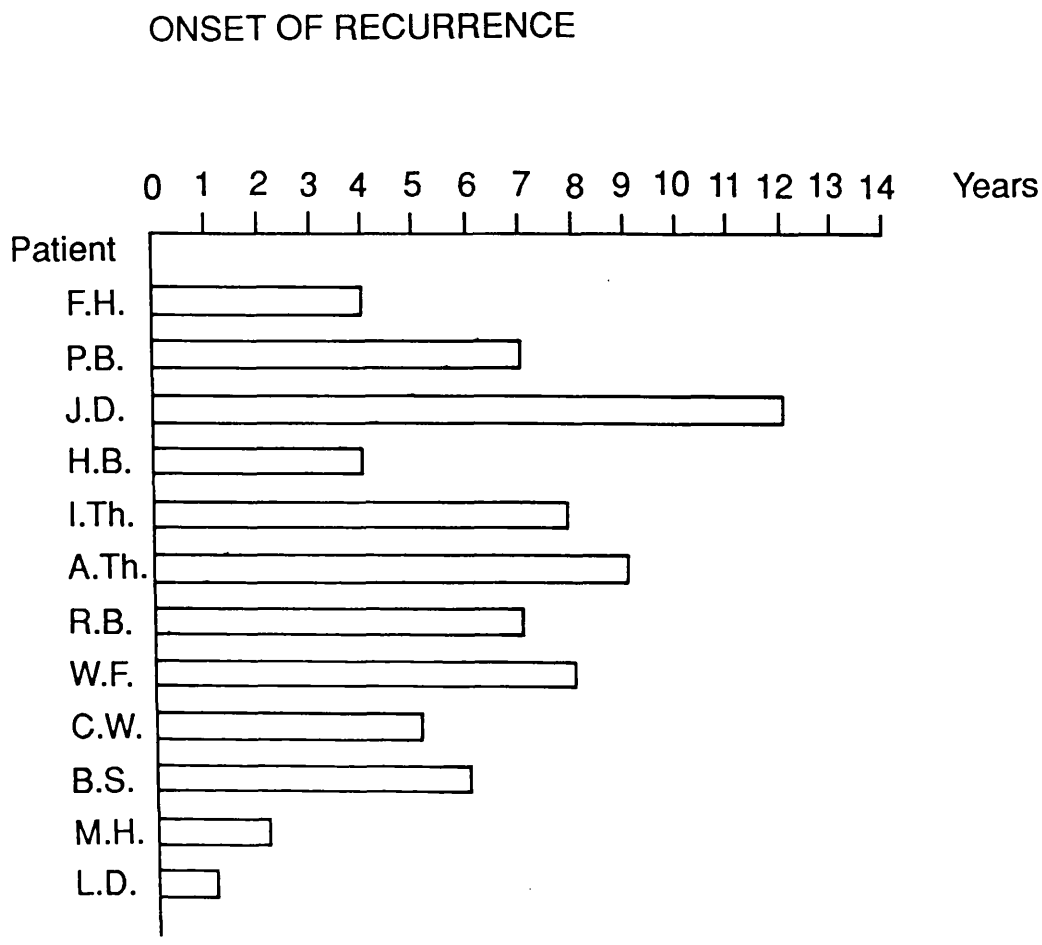


Fig. 29: Graphic representation of time of onset of recurrence.

TABLE 22

				%
1	Recurrent Ulcer		12	(14)
2	Diarrhoea:	Severe	4	(4.7)
		Mild	8	(9.3)
3	Dumping:	Severe	2	(2.3)
		Mild	3	(3.5)
4	Recurrent symptoms		6	(7)
5	Gastro-oesophageal reflux		3	(3.5)
6	Bilious vomiting		1	(1.1)
7	Biliary disease:			
		Gall stones	1	(3.5)
		Cholecystectomy	2	

Table 22: List of complications.

THE PREDICTIVE VALUE OF:

(1) Pre-operative Neutral Red Test

(2) Post-operative Neutral Red Test

(3) Post-operative Insulin Test

(4) Post-operative Basal Acid Output

The predictive value of the Neutral Red Test and Insulin Test was assessed by measuring the percentage incidence of poor results, namely "unsuccessful outcome" (Visick III and IV) and recurrent ulcer (Visick IV). Where appropriate, chi-square methods were used to analyse differences in the incidence of "unsuccessful outcome" and recurrent ulcer but in cases where expected frequences were less than five, Fischer exact test was used.

On the Neutral Red Test significant differences in the incidence of "unsuccessful outcome" were found between 'early' and 'late' positive (p 0.01) and 'early' and negative (p = 0.0006). These results can be seen in Table 23. Also, in the same table, the results of the Insulin Test show a significant difference in the incidence of "unsuccessful outcome" between 'early' and negative (p = 0.021) but no significant difference was found between 'early' and 'late' positive (p = 0.11). Also, no significant difference in the incidence of "unsuccessful outcome" was found between the Neutral Red Test and Insulin Test in 'early' positive results (p 0.10).

As far as recurrent ulcer is concerned (Table 24) in the Neutral Red Test significant differences in the

incidence of recurrent ulcer were found between 'early' and 'late' positive ($p = 0.007$) and between 'early' and negative ($p = 0.0002$). However, in the Insulin Test there is again a significant difference between 'early' positive and negative ($p = 0.018$) but no significant difference in the incidence of recurrent ulcer was found between the Neutral Red Test and Insulin Test in 'early' positive results ($p = 0.10$).

Table 25 shows the number of recurrent ulcers in the 'early', 'late' and negative responses for both tests. There was no statistical significant difference between the two tests as far as the 'early' positive response was concerned ($p > 0.05$). Therefore, even though the Insulin Test shows a marked difference between the fate of the 'early' and 'late' positive, it is more clearly statistically significant in the Neutral Red Test. However, the results from Tables 39, 40, 41,42 show that the 'late' positive and negative responses are similar as far as the predicting clinical outcome is concerned.

The predictive value of these tests was further tested by using 4 expressions as defined by Vecchio, 1966, when a significant difference in proportion of recurrences was found between the two sides of a critical level.

Sensitivity: percentage of patients with recurrence having a positive criterion.

Specificity: percentage of patients without recurrence having a negative criterion.

Negative Predictive Value (PV neg): percentage of patients with a negative criterion having recurrence.

Positive Predictive Value (PV pos): percentage of patients with a positive criterion having recurrence.

Tables 28, 29, 30 and 31 calculate these parameters for the two tests equating them with "unsuccessful outcome" and recurrent ulceration. Also, the pre- operative levels of neutral red excretion are assessed (Tables 26 and 27). It is seen that above average excretion of neutral red is associated with a statistically significant number of recurrences ($p = 0.05$).

The parameters of Vecchio have been used to calculate the criteria promoted by previous workers in the field and these are listed in Table 32. It can be seen that the predictive value for all these tests are low. The highest predictive value for "unsuccessful outcome" was achieved with the post-operative Neutral Red Test (50%)

and the Gillespie Criteria (42.9%). There was no significant difference between PV pos for Neutral Red Test and Insulin Test ($p = 0.49$).

The higher predictive value for recurrent ulceration was again achieved with the Neutral Red Test (40%) and with the Gillespie Criteria (40%). There was no significant difference between the PV pos for Neutral Red Test and Insulin Test ($p = 0.67$).

Finally, an R.O.C. curve was constructed for post-operative neutral red excretion and B.A.O. (basal acid output). It can be seen from the shape of the curve (see Appendix) hat the Neutral Red Test is superior (Table 33 and Figure 30).

TABLE 23

PERCENTAGE INCIDENCE OF "UNSUCCESSFUL OUTCOME" IN BOTH TESTS

	NEUTRAL RED TEST	INSULIN TEST
'EARLY' POSITIVE	50.0 *)	38.9 *)
'LATE' POSITIVE	9.1) P=<0.01	15.8) P=0.11
NEGATIVE	9.1) P=0.0006	12.2) P=0.021

* P = > 0.10

TABLE 24

PERCENTAGE INCIDENCE OF RECURRENT ULCER IN BOTH TESTS

	NEUTRAL RED TEST	INSULIN TEST
'EARLY' POSITIVE	40.0 *)	33.3 *)
'LATE' POSITIVE	4.5) P=0.007	10.5) P=0.10
NEGATIVE	6.8) P=0.002	8.2) P=0.018

* P = > 0.10

TABLE 25

RESULT OF NEUTRAL RED TEST AND INSULIN TEST IN PATIENTS WITH RECURRENT ULCER (N = 12)

	Neutral Red Test	Insulin Test	P
'Early' Positive	8 (66.6%)	6 (50.0%)	P> 0.05
'Late' Positive	1	2	
Negative	3	4	
	12	12	

TABLE 26

ASSOCIATION BETWEEN PRE-OPERATIVE OUTPUT OF NEUTRAL RED AND VISICK GRADING (III AND IV "UNSUCCESSFUL OUTCOME")

	VISICK I, II	VISICK III, IV	
EXCRETION ABOVE AVERAGE	9	5 *	14
EXCRETION BELOW AVERAGE	23	1 *	24
	32	6	38

* P = 0.025

SENSITIVITY = 83.3%

SPECIFICITY = 71.9%

POSITIVE PREDICTIVE VALUE PVpos = 35.7%

NEGATIVE PREDICTIVE VALUE PVneg = 95.8%

TABLE 27

ASSOCIATION BETWEEN PRE-OPERATIVE OUTPUT OF NEUTRAL RED AND VISICK GRADING (IV) (RECURRENT ULCERATION)

	VISICK I, II, III	VISICK IV	
EXCRETION ABOVE AVERAGE	10	4 *	14
EXCRETION BELOW AVERAGE	23	1 *	24
	33	5	38

* P = 0.05

SENSITIVITY = 80.0%

SPECIFICITY = 69.7%

POSITIVE PREDICTIVE VALUE PVpos = 28.6%

NEGATIVE PREDICTIVE VALUE PVneg = 69.7%

TABLE 28

ASSOCIATION BETWEEN THE POST-OPERATIVE NEUTRAL RED TEST AND VISICK GRADINGS III AND IV ("UNSUCCESSFUL OUTCOME")

	VISICK I, II	VISICK III, IV	
'EARLY' POSITIVE	10	10	20
'LATE' POSITIVE AND NEGATIVE	60	6	66
	70	16	86

SENSITIVITY = 62.5%

SPECIFICITY = 85.7%

POSITIVE PREDICTIVE VALUE PVpos = 50.0%

NEGATIVE PREDICTIVE VALUE PVneg = 90.9%

TABLE 29

ASSOCIATION BETWEEN THE POST-OPERATIVE INSULIN TEST AND THE VISICK GRADING III AND IV ("UNSUCCESSFUL OUTCOME")

	VISICK I, II	VISICK III, IV	
'EARLY' POSITIVE	11	7	18
'LATE' POSITIVE AND NEGATIVE	59	9	68
	70	16	86

SENSITIVITY = 43.8%

SPECIFICITY = 84.2%

POSITIVE PREDICTIVE VALUE PVpos = 38.8%

NEGATIVE PREDICTIVE VALUE PVneg = 86.8%

TABLE 30

ASSOCIATION BETWEEN THE POST-OPERATIVE NEUTRAL RED TEST AND THE VISICK GRADING IV (RECURRENT ULCERATION)

	VISICK I, II, III	VISICK IV	
'EARLY' POSITIVE	12	8	20
'LATE' POSITIVE AND NEGATIVE	62	4	66
	74	12	86

SENSITIVITY = 66.7%

SPECIFICITY = 83.8%

POSITIVE PREDICTIVE VALUE PVpos = 40.0%

NEGATIVE PREDICTIVE VALUE PVneg = 93.9%

TABLE 31

ASSOCIATION BETWEEN THE POST-OPERATIVE INSULIN TESTS AND THE VISICK GRADING IV (RECURRENT ULCERATION)

	VISICK I, II, III	VISICK IV	
'EARLY' POSITIVE	12	6	18
'LATE' POSITIVE AND NEGATIVE	62	6	68
	74	12	86

SENSITIVITY = 50.0%

SPECIFICITY = 83.8%

POSITIVE PREDICTIVE VALUE PVpos = 33.3%

NEGATIVE PREDICTIVE VALUE PVneg = 91.2%

TABLE 32

	"UNSUCCESSFUL OUTCOME"				RECURRENT ULCER			
	Ss	Sp	Pv NEG	Pv POS	Ss	Sp	Pv NEG	Pv POS
PRE-OP NEUTRAL	83.3	71.9	95.8	35.7	80.0	69.7	69.7	28.6
POST-OP NRT	62.5	85.7	90.9	50.0	66.7	83.8	93.9	40.0
POST-OP I T	43.8	84.2	86.8	38.8	50.0	83.8	91.2	33.3
BACHRACH 1962	53.3	72.7	87.2	30.8	58.3	72.5	90.9	26.9
BACHRACH 1962	64.2	73.1	90.7	33.3	58.3	71.0	90.7	25.9
BACHRACH 1967	80.0	48.5	91.4	26.1	83.3	47.8	94.3	21.7
BANK	53.3	77.3	87.9	34.8	58.3	76.8	91.3	30.4
STEMPIEN	74.0	57.6	90.4	28.2	69.2	55.9	90.4	23.0
BITSH	86.7	28.8	90.4	21.7	84.6	27.9	90.5	18.3
GILLESPIE	40.0	87.9	86.6	42.9	54.5	87.1	92.4	40.0

Ss = SENSITIVITY

Sp = SPECIFICITY

Pv POS = POSITIVE PREDICTIVE VALUE

Pv NEG = NEGATIVE PREDICTIVE VALUE

Table 32: Predictive Indices have been measured for all the tests carried out in the study and compared with other criteria from the world literature.

TABLE 33

Basal	Visick I & II	Visick III & IV	Sensitivity	Specificity
0.1 A	61	15	0.94	0.10
0.5 B	38	12	0.75	0.46
1.0 C	28	10	0.63	0.67
1.5 D	18	7	0.44	0.74
2.0 E	9	5	0.31	0.87
2.5 F	7	3	0.19	0.90

Table 33: Sensitivity and specificity at various cut off points in the basal acid output.

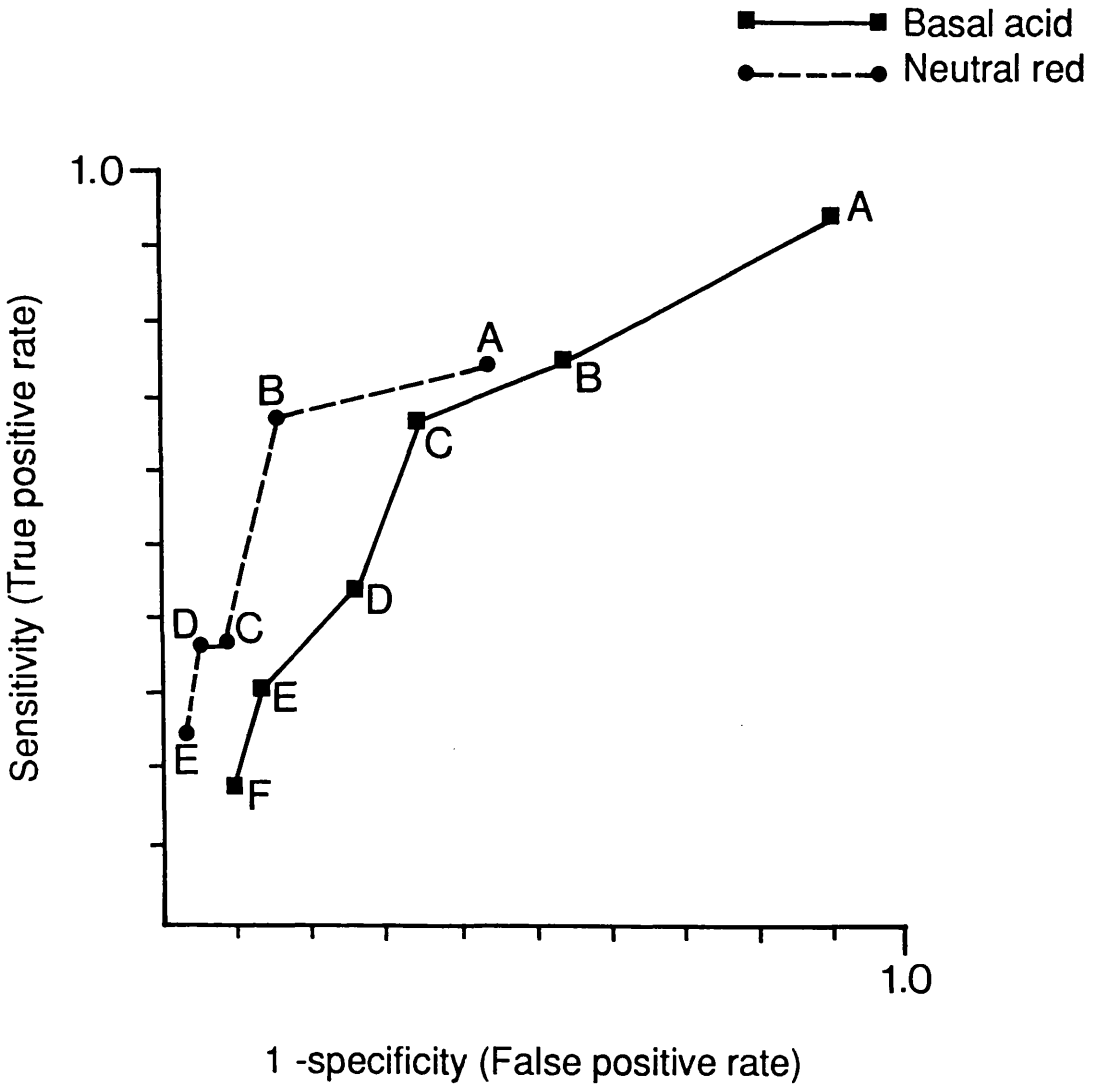


Fig. 30: Receiver operating curve for Neutral Red and basal acid output.

THE LONGTERM FATE OF THE 'LATE' POSITIVE RESPONDER

THE LONGTERM FATE OF THE 'LATE' POSITIVE RESULT AS FOUND IN THE NEUTRAL RED TEST AND IN THE INSULIN TEST

THE NEUTRAL RED TEST

Tables 34 ' shows the relationship between the results of the Neutral Red Test and Visick gradings III and IV ("unsuccessful" outcome) when the 'late' positive patients are included with the 'early' positive patients and with the negative patients. By grouping the 'late' positive patients with the negative patients, the positive predictive value for an "unsuccessful" outcome increases from 28.6% to 50.0%.

Table 36 shows the relationship between the results of the Neutral Red Test and Visick grading IV (recurrent ulceration) when the 'late' positive patients are included with the 'early' positive patients and with the negative patients. Bringing the 'late' positive patients in with the negative again increases the positive predictive value for recurrent ulceration from 21.4% to 40.0%.

THE INSULIN TEST

Table 35 shows the relationship between the results of the Insulin Test and Visick grading III and IV

("unsuccessful" outcome) when the 'late' positive patients are included with the 'early' positive patients and with the negative patients. By grouping the 'late' positive patients with the negative patients, the positive predictive value for an "unsuccessful" outcome increases from 27.0% to 38.8%.

Table 37 shows the relationship between the results of the Insulin Test and Visick grading IV (recurrent ulceration) when the 'late' positive patients are grouped with the 'early' positive patients and with the negative patients. By grouping the 'late' positive patients with the negative patients, the positive predictive value for recurrent ulceration increases from 21.6% to 33.3%.

Thus, the 'late' positive result obtained in both the Neutral Red Test and in the Insulin Test increases the positive predictive value for a poor result when it is grouped with the negative results. Thus, the 'late' positive patient behaves as a negative patient in the longterm and carries the good prognosis of the latter.

The results are summarised in Table 38. Further, in Tables 39, 40, 41 and 42 the positive predictive values of the 'early', 'late' and negative responses are calculated separately. It can be seen that the positive predictive value for the 'late' positive and negative

response is similar in both tests when "unsuccessful outcome" and recurrent ulcer are considered.

Therefore, the results of this study show that over the long term period of follow up, the 'late' positive response behaves as a negative response.

TABLE 34

ASSOCIATION BETWEEN NEUTRAL RED TEST AND VISICK GRADINGS III AND IV WHEN THE 'EARLY' AND 'LATE' POSITIVE RESULTS ARE GROUPED TOGETHER

	VISICK I, II	VISICK III, IV	
'EARLY' AND 'LATE' POSITIVE	30	12	42
NEGATIVE	40	4	44
	70	16	86

SENSITIVITY = 75.0%

SPECIFICITY = 57.1%

POSITIVE PREDICTIVE VALUE PVpos = 28.6%

NEGATIVE PREDICTIVE VALUE PVneg = 90.9%

TABLE 35

ASSOCIATION BETWEEN THE INSULIN TEST AND THE VISICK GRADINGS III AND IV WHEN 'EARLY' AND 'LATE' POSITIVE RESULTS ARE GROUPED TOGETHER

	VISICK I, II	VISICK III, IV	
'EARLY' AND 'LATE' POSITIVE	27	10	37
NEGATIVE	43	6	49
	70	16	86

SENSITIVITY = 62.5%

SPECIFICITY = 61.4%

POSITIVE PREDICTIVE VALUE PVpos = 27.0%

NEGATIVE PREDICTIVE VALUE PVneg = 87.8%

TABLE 36

ASSOCIATION BETWEEN THE RESULTS OF THE NEUTRAL RED TEST AND VISICK GRADING IV WHEN 'EARLY' AND 'LATE' POSITIVE RESULTS ARE GROUPED TOGETHER

	VISICK I, II, III	VISICK IV	
'EARLY' AND 'LATE' POSITIVE	33	9	42
NEGATIVE	41	3	44
	74	12	86

SENSITIVITY = 75.0%

SPECIFICITY = 55.4%

POSITIVE PREDICTIVE VALUE PVpos = 21.4%

NEGATIVE PREDICTIVE VALUE PVneg = 93.2%

TABLE 37

ASSOCIATION BETWEEN THE RESULTS OF THE INSULIN TEST AND THE VISICK GRADING IV, WHEN 'EARLY' AND 'LATE' POSITIVE RESULTS ARE GROUPED TOGETHER

	VISICK I, II, III	VISICK IV	
'EARLY' & 'LATE' POSITIVE	29	8	37
NEGATIVE	45	4	49
	74	12	86

SENSITIVITY = 66.7%

SPECIFICITY = 60.8%

POSITIVE PREDICTIVE VALUE PVpos = 21.6%

NEGATIVE PREDICTIVE VALUE PVneg = 91.8%

TABLE 38

SUMMARISES THE CHANGES IN POSITIVE PREDICTIVE VALUE (PVpos) WHEN THE 'LATE' POSITIVE IS GROUPED WITH THE 'EARLY' POSITIVE AND NEGATIVE RESULTS

	NEUTRAL RED TEST		INSULIN TEST	
	III, IV	IV	III, IV	IV
'LATE' POSITIVE WITH NEGATIVE	50.0%	40.0%	38.8%	33.3%
'EARLY' POSITIVE WITH 'LATE' POSITIVE	28.6%	21.4%	27.0%	21.6%

TABLE 39

POSITIVE PREDICTIVE VALUE (IN BRACKETS) FOR THE NEUTRAL RED TEST RESULTS WHEN "UNSUCCESSFUL" OUTCOME CONSIDERED

	VISICK I, II	VISICK III, IV	
'EARLY' POSITIVE	10	10 (50.0%)	20
'LATE' POSITIVE	20	2 (9.1%)	22
NEGATIVE	40	4 (9.1%)	44
	70	16	86

TABLE 40

POSITIVE PREDICTIVE VALUE (IN BRACKETS) FOR THE INSULIN TEST RESULTS WHEN "UNSUCCESSFUL" OUTCOME CONSIDERED

	VISICK I, II	VISICK III, IV	
'EARLY' POSITIVE	11	7 (38.9%)	18
'LATE' POSITIVE	16	3 (15.8%)	19
NEGATIVE	43	6 (12.2%)	49
	70	16	86

TABLE 41

POSITIVE PREDICTIVE VALUE (IN BRACKETS) FOR THE NEUTRAL RED TEST RESULTS WHEN RECURRENT ULCER IS CONSIDERED

	VISICK I, II, III	VISICK IV	
'EARLY' POSITIVE	12	8 (40.0%)	20
'LATE' POSITIVE	21	1 (4.5%)	22
NEGATIVE	41	3 (6.8%)	44
	74	12	86

TABLE 42

POSITIVE PREDICTIVE VALUE (IN BRACKETS) FOR THE INSULIN TEST RESULTS WHEN RECURRENT ULCER IS CONSIDERED

	VISICK I, II, III	VISICK IV	
'EARLY' POSITIVE	12	6 (33.3%)	18
'LATE' POSITIVE	17	2 (10.5%)	19
NEGATIVE	45	4 (8.2%)	49
	74	12	86

DISCUSSION

The Incidence of Duodenal Ulcer and Truncal Vagotomy

The incidence of duodenal ulcer disease escalated from the late nineteenth century to the 1950's, reaching an annual incidence of 3 per 1,000 inhabitants in the United States and Great Britain (Vogt & Johnson, 1980). Since that time, there has been a decline in the incidence of duodenal ulcer disease in the United States, Great Britain and Scandinavia which seems to have begun well before the introduction of the H_2 receptor antagonists in 1977 (Mendeloff, 1974, Gustavsson et al, 1988, Gustavsson, 1988, Wyllie et al, 1981). Walker (1988) reported on a decline of 75% in the number of patients undergoing elective duodenal ulcer operations in North Carolina from 1971 to 1985. However, emergency operations were becoming more frequent with bleeding being the commonest indication. Studies from Finland show a similar trend, a marked decline in the incidence of elective surgery, while the incidence of the main complications of ulcer disease, namely, perforation and haemorrhage, have remained unchanged, their occurrence having been unaffected by the introduction of H_2 receptor antagonists (Paimela et al, 1991).

Therefore, with the decline in the incidence of the disease and the introduction of H_2 receptor antagonists, there has been a trend away from elective operations to emergency surgery. In this situation the simpler operation of truncal vagotomy and pyloroplasty has regained its importance. Although Johnston et al (1973) reported on a series of bleeding duodenal ulcer successfully treated by highly selective vagotomy, there have been few reports of its use since. Truncal vagotomy and pyloroplasty with under-running of the bleeding vessel remains the operation of choice in the emergency situation (Venables, 1981). In a recent series from Birmingham, 60% of patients were treated by this method (Snyman & Keighley, 1989). In a study from Finland recently there had been a marked fall in the number of highly selective vagotomies performed and a concurrent rise in the number of truncal vagotomies and pyloroplasty since 1979 (Paimela et al, 1991).

With the decline in the incidence of elective surgery for duodenal ulcer the opportunity to train surgeons in the more meticulous and technically more demanding operation of highly selective vagotomy is fast declining. Nyhus (1984) wrote prophetically, "there is an interesting undercurrent of thought along with this universal acceptance of PGV, namely that the procedure is so technically challenging that only a special cadre of trained vagotomists should perform this operation.

This might be an acceptable approach in the controlled surgical clinics of the world but will not be accepted in the United States, at least during the next several decades".

Therefore, during the last few years there has been a re-birth and renewed interest in the technically simpler and, therefore, more universally acceptable operation of truncal vagotomy and pyloroplasty. The findings of the present study are consequently of great relevance in the present day surgical management of duodenal ulcer.

The Neutral Red Test

The excretion curves for the 30 minute test period whether assessed quantitatively or qualitatively showed a large individual variation in the 48 patients studied prior to vagotomy. Studies on gastric acid secretion in patients with duodenal ulcer have shown a similar wide variation with about a third to half of the patients in the hypersecretory range. Further, as far as acid secretion is concerned there appears to be a threshold of maximal acid output below which patients with duodenal ulcer are not found. This threshold is about 15mmol/h for peak acid output (Lawrie & Forrest, 1965). With neutral red excretion, only one patient in the pre-operative group had an output below 20ug/15 mins (see Appendix). An enlarged study to include a large number of control subjects could well show that this is the equivalent threshold for neutral red excretion. Both secretion of acid and excretion of neutral red are dependent on the number of parietal cells. It is known that the number of parietal cells in patients with duodenal ulcer is double normal (Cox, 1952) and it is possible to plot peak acid output and parietal cell mass to express a close relationship (Baron, 1972).

However, for the individual patient the excretion of dye

varied only slightly in the same subject on different occasions. Therefore, I was able to convince myself of the reproducibility of the test prior to embarking on this study. This had also been demonstrated many years previously by Gillman (Gillman, 1943, 1944). He had thought that the test could be used to diagnose pathological conditions of the stomach. In a large number of subjects he found the normal range of excretion and then divided the others into five patterns. He found the Neutral Red Test to be more reliable than acid secretion as an indicator of gastric dysfunction. However, Sevitt and Jepson (1948) found the normal excretion patterns to be insensitive to gastric disorders. For example, 3 of 10 patients with carcinoma of the stomach excreted normal amounts of neutral red and similarly 5 of 11 patients with chronic gastritis. However, they and earlier investigators, Davidson et al (1925) and Piersol et al (1925) were of the opinion that impaired excretion of neutral red indicated disease of the gastric mucosa.

The Neutral Red Test as carried out in this study was completely safe and no early or late complications were noted. It is particularly suited to patients with medical conditions such as heart disease and those with diabetes mellitus. The complex multi-organ elimination of the dye makes it imperative that the gastric sampling is done as soon as possible. Therefore, there is no

reason to extend the test beyond 15 minutes which makes it attractive as an out-patient investigation and several patients can be tested during one session. The gastric samples can be sent at leisure to the Biochemical Department for routine analysis. The contamination of the samples with bile deterred many of the early investigators (Fairley & Ive, 1925). A quantitative method was developed by Komarov et al (1949) for the determination of neutral red in bile but as the present study shows for the purpose of the Neutral Red Test bile does not interfere significantly with the estimation of neutral red.

Results from this study confirm the experimental work of Kolm, Komarov & Shay, 1945, that neutral red (or impurities in the dye) has a stimulatory effect on gastric secretion. They showed that this was of a triple nature, (1) central vagal, (2) peripheral vagal, and (3) direct cellular effect. The degree of stimulation in the present study did not reach statistical significance but it was sufficient to avoid the use of histamine, pentagastrin, insulin and 2DG. However, the use of 2DG combined with neutral red was reported from Ann Arbour by Weber et al (1975) who found it to be of value as a post-operative test for completeness of vagotomy. At that moment in time, I was four years into the study and did not want to change the protocol. Further, Thomas and Duthie (1968) had

reported some of the side effects of 2DG, namely, hypothermia, semi-coma and liver damage. Others had reported similar effects (Stalder, 1972, Duke et al, 1965). Therefore, the 2DG Neutral Red Test offered the same disadvantage as the Insulin Test and was not considered.

The parallelism with acid secretion has always intrigued investigators in this field. Piersol et al (1925) summarised their findings by stating that there was a rough relationship between the amount of dye excreted and the degree of acidity. In their studies they found that in stomachs producing low levels of acid, delayed excretion and diminished quantities of dye were found. Gillman (1943, 1944) thought that acid secretion and dye excretion did not necessarily parallel one another in either healthy or abnormal stomachs and he concluded that the dye excretion and the acid secretion were two independent functions. The results from the present study (Figure 28) agree with those of Sevitt & Jepson (1948) that a statistical relationship does exist between these two parameters but that the correlation has exceptions. For example, they found patients with normal acid production who did not excrete the dye. Evidence from the present study (Figure 28) and from experimental work in the rat (Figure 4 and Table), (Jones, 1969, 1970) show that the stomach can secrete acid in the absence of neutral red excretion. Neutral

red, therefore, is not merely an indicator of acid production. Its excretion is at times independent and probably more influenced by parasympathetic activity than acid secretion. As Sevitt and Jepson (1948) concluded, "the parasympathetic vagus nerves are probably the excitory nerves controlling the dye excretion and the sympathetic plays no part in the activity".

Comparison Between the Neutral Red Test and th Insulin Test

During the past few years the Insulin Test has suffered from severe criticism, despite the fact that in the best tradition of scientific investigation the patients act as their own control and the results are interpretated in terms of a rise in the secretion of acid during the insulin stimulated period compared with the basal period. Some investigators have questioned the validity of relating results to basal secretion which can often be variable (Baron, 1963). Grossman (1974) criticised the way the test was referred to as positive or negative and not in numerical terms. Despite the classical work of Sun and Shay (1960) who showed that the secretory response to insulin in the first 2 hours is vagally mediated, others have felt that much of the response to insulin could be as a result of extra vagal stinulation (Read et al, 1972).

Gillespie (1972) wrote, "much of the interest surrounding the Insulin Test lies in the discrepancy between the large number of positive tests after vagotomy and the relatively small number of patients who present with problems with further ulceration". The

present study is no exception with 42% of patients having a positive response to insulin. The discrepancy is even more marked for the Neutral Red Test when 50% showed a positive response with a recurrence rate of 14%. Grossman (1974) criticised the notion that stimulation of acid secretion by insulin is mediated solely by the vagus and goes on to say that, "until we have an independent test for completeness of vagotomy there is no way to determine whether the response to insulin after vagotomy is due to residual vagal innervation". He goes on to say that the discrepancy becomes less when only large responses, i.e. 'early' responders, are considered to be caused by failure to cut major branches, while the small responses, i.e. 'late' responders, may be due to non-vagal mediation. He classified the possible causes of persistence of responders to insulin after vagotomy as follows:

1. **Incomplete Vagotomy**
   - **(a)** Uncut and uninjured fibres
   - **(b)** Uncut, uninjured fibres that may later recur
   - **(c)** Cut fibres that regenerate:
     - **(i)** end to end
     - **(ii)** collateral nerve regeneration or sprouting
2. **Non-Vagal mechanisms**
   - **(a)** Neural, non-vagal mechanisms

(b) Non-neural, non-vagal mechanisms such as the release of adrenaline by hypoglycaemia which may release gastrin and thus stimulate secretion.

Hollander (1948) himself stated that a positive response to insulin does not imply that the surgeon has failed to interrupt the gastric vagi completely. Read et al (1972) showed that blocking beta-adrenergic activity with propanolol converted 50% of Insulin Tests from positive to negative. They postulated that the large number of positive Insulin Tests may be due in considerable measure to sympathetic over-activity, brought on by the hypoglycaemia rather than inadequate surgery (group 2 **(b)** above). When this sympathetic activity is blocked by propanolol (a) gastrin release is blocked, and (b) there is a decrease in mucosal blood flow, thus decreasing the acid secretion. Further, beta-agonists stimulate acid secretion and gastrin release (Brandsborg et al, 1975, Stadil and Rehfeld, 1973).

However, the results from the present study cast doubt on the above hypothesis. It has been shown that Neutral Red has:

(a) no hypoglycaemic effect

(b) a central stimulatory effect on the parasympathetic system

(c) excretion that is so prompt and rapid that it is unlikely to be induced by a gradual process such as the release of hormones. It is of great interest that acid output and gastrin release in response to modified sham feeding is not influenced by beta-adrenoreceptor blockade (Gaffner and Jarhult, 1984)

The present study also casts doubt on the reasons given in **1 (c)**. Watkin et al (1971) showed that delaying the test for two months after operation produced the final response pattern. It is unlikely that a significant amount of nerve regeneration occurred in this period either by conventional nerve regeneration or sprouting.

Another explanation for the high incidence of positive results following a complete abdominal vagotomy is that the parasympathetic system has not been completely abolished. Jefferson et al (1965) reported that the vagus does not provide the only cholinergic innervation to the stomach but that cholinergic fibres are found in the splanchnic nerves and in the anterior and posterior roots of the thoracic and lumbar spinal cord. Jordan and Condon (1970) were of a similar opinion. They

studied the Insulin Test in patients who had vagotomy and drainage and also in patients treated by vagotomy and antrectomy. The incidence of positivity was four times higher in the patients treated by vagotomy and drainage. They thought that the degree of incomplete vagotomy in the two groups would be similar as the patients were selected randomly and 50 surgeons were involved in the study. The difference in the response to the Insulin Test could best be explained by the existence of extra-vagal parasympathetic secretory fibres to the stomach that are abolished by the operation of antrectomy. The existence of such an extra-vagal innervation was supported by the high failure they achieved in changing the positive response in the Insulin Test by re-vagotomy. However, experimentally in the rat I was not able to show that the excretion of neutral red was affected by extra-vagal parasympathetic innervation (Figures 1 to 4). The excretion of neutral red was only affected by the degree of vagal innervation. Therefore, it is unlikely in man that the existence of an extra-vagal parasympathetic innervation contributes to the high positive rate in the Insulin Test. It must also be remembered that in the present series, as in many others, 58% of Insulin Tests are negative and it would be difficult to explain the presence of extra-vagal parasympathetic influences in these cases.

Therefore, the full explanation for the high positive rate for both tests remains to be elucidated. However, the close agreement between the Neutral Red Test and the Insulin Test and the Insulin Test and the Modified Sham Feeding Test (Athow et al, 1986) suggests that the results from these tests are perfectly valid but that the anatomical and physiological considerations are more complex than originally thought.

The present study shows that the number of women who have 'early' positive results are markedly less (though not statistically significant) in both tests. It confirms the work of Spencer et al, 1969, who showed a statistically significant higher incidence of incomplete vagotomies in males than in females, even after correcting for weight. Welbourn & Burns (1964) reported a difference in response to insulin between the sexes. Yet, despite this difference, the number of Visick I & II in both sexes is virtually the same (Table 20). The difference probably reflects the lower acid output in females which has been postulated to be due to the higher incidence of gastritis, Siurala et al (1968).

Recently, Kronberg (1981) has written that the Insulin Test should be replaced by the Sham Feeding Test. It is argued that sham feeding is a safer and purer vagal stimulant of acid secretion than insulin (Stenquist et al 1978) and that it does not activate the sympatho-adrenal

system (Brandsborg et al, 1975, Read et al, 1972). The acid response is lower than the response to insulin and is unaffected by Beta blockade (Graffner & Jarhult, 1983). It is claimed for the modified Sham Feeding Test that volume measurements alone are all that is required (Athow et al, 1984). Agreement with the Insulin Test as to the adequacy of vagotomy occurred in 84% of patients (Athow et al, 1984). However, recently Gilly et al 1989 , have criticised the test on the grounds that it is a cumbersome and time consuming method giving no more information than the post-operative basal or pentagastrin stimulated acid outputs. This "chew and spit" test could be abhorent and unpleasant to many patients and this factor alone could produce central vagal inhibition. Constant attention is also needed to prevent the patient from swallowing food particles. Therefore, despite the fact that this test may have some merit it is unlikely to gain widespread acceptance.

Criticism has also been levelled at the classification of Rose and Kay (1964) into 'early' and 'late' according to the timing of the response. These authors based their interpretation on the clinical course and on the results of the Augmented Histamine Test. Cowley et al (1973) found that 'early' and 'late' responders were about equal in each group, suggesting that the distribution has no validity and is completely random. Burns et al (1969) studied 100 patients with unoperated

duodenal ulcers and found that 37% had a 'late' positive response. They concluded that the division into 'early' and 'late' positive was artificial. The present study shows that the 'early' and 'late' responders in the Insulin Test are roughly equal, 19 'early' and 23 'late' responders and this is mirrored by a similar pattern in the Neutral Red Test, namely 24 'early' and 26 'late' responders. Therefore, an independent test of completeness of vagotomy confirms this pattern of response which many others have confirmed clinically (Bell et al, 1965). Furthermore, the present study shows that there is a marked difference in clinical outcome between the 'early' and 'late' responders in both tests. In the Neutral Red Test the difference between the two responders reached statistical significance when "unsuccessful outcome" and recurrent ulceration were considered ($p < 0.01$ and $p = 0.007$ respectively). In the Insulin Test the difference between the two responders was again very marked but did not quite reach statistical significance as far as "unsuccessful outcome" and recurrent ulceration were concerned ($p = 0.01$ and $p = 0.10$ respectively). Furthermore, when the fate of the 'late' positive responder is considered in the long-term study, it will be seen that it behaves as a negative responder.

GASTROSCOPIC AND INTRA-OPERATIVE NEUTRAL RED STUDIES

Both tests proved to be most disappointing. Pre-operatively, the dye appears as pin-point areas of red as shown many years ago by Lerner and Asher (1942). Pre-operatively the pattern of dye excretion is limited to the fundus and upper body of the stomach and no dye is seen in the antrum and pylorus. Post-operatively, I could not justify the use of gastroscopy because of:

(a) the post-operative Neutral Red Test seemed simple and successful, and

(b) I was afraid of losing patient compliance by over-investigation

Intra-operatively, the dye is excreted very badly and it is very difficult through a gastroduodenotomy performed as part of a pyloroplasty to decide on the area of excretion. This can be improved by performing a large gastrotomy but it is accompanied by added problems such as infection. However, the results of intra-operative testing could well be improved by using the technique described by Weber et al (1975) who combined neutral red with 2DG and produced a much more powerful excretion of the dye.

THE FOLLOW-UP STUDY

Meissner et al, 1988, in a recent review of truncal vagotomy and drainage, calculated 4,500 cases from 20 studies from the world literature. The Visick I & II grades showed a range of 62-96.4% with a mean of 81% which is exactly reported from this series. The recurrent ulcer rate ranged from 1.5% to 25.4% with a median rate of 9.0% at 6 years. From the same review, I calculated the recurrence rate in studies that had been prolonged over ten years and found a median recurrence rate of 15.7% which is very similar to the 14% found in the present study. Therefore, the recurrence rate increases with time of follow-up despite the fact that it is often taught that recurrences occur sooner rather than later. The average time to recurrence in this study was 6.1 years which is very similar to the study reported from the Mayo Clinic where they found the average time to recurrence to be 4.8 years (Pemberton and Heerden, 1980).

The relatively low recurrence rate after truncal vagotomy and drainage could be due to a reason other than inadequate vagotomy and could account for the higher recurrence rate after highly selective vagotomy. In 1984, Marshall & Warren successfully identified and cultured Campylobacter Pylori (C.P.). These S shaped spiral bacteria which are gram negative are found

predominantly in the gastric antrum and on islands of ectopic gastric epithelium in the duodenal cap. These organisms are found in 90% of patients with gastritis and duodenal ulcer. Even though the association is strong, the mode of action in the development of an ulcer is unknown. O'Connor et al, 1986, have studied the effect of duodenal ulcer surgery on Campylobacter Pyloris. Among the patients who had undergone highly selective vagotomy the proportion who were CP positive was similar to that in the unoperated group but among those who had undergone Billroth I and II partial gastrectomy or truncal vagotomy and drainage, it was significantly lower. Therefore, this could well be one of the factors contributing to the lower recurrence rates after truncal vagotomy.

The reasons for the unsatisfactory results after truncal vagotomy and drainage (Visick III and IV) are found in the higher incidence of side effects rather than recurrent ulceration (Stoddard et al, 1984). Stoddard et al (1984) from a study from Sheffield showed a statistically significant higher incidence of dumping and diarrhoea in truncal vagotomy and drainage compared to highly selective vagotomy. The incidence of diarrhoea in their series of truncal vagotomies is virtually the same as reported here (17.6% compared to 14% respectively). However, in the present series there were 4 cases of very severe diarrhoea (Table 22) and

compares badly with the very infrequent diarrhoea reported after highly selective vagotomy (Stoddard et al, 1984, Amdrup, 1988). The incidence of dumping was less in the present series when again compared to the Sheffield study (5.8% and 11.8%).

The present study also confirms the rather benign course of the recurrent disease, a lower mortality of 8.3% and a re-operation rate of only 16.7%. In other words the benign cause of the recurrent disease behaves like the original disease. Furthermore, there is circumstantial evidence that many asymptomatic ulcers remain asymptomatic and disappear without ever producing clinical symptoms and it would appear that these asymptomatic ulcers are more frequent in operated than in non-operated patients (Hess et al, 1980). This again explains the benign and self-limiting course of recurrent ulceration and its successful modern treatment with the H_2 receptor antagonists (Table 21). These findings from this study are similar to those reported by Clark et al, 1986. 22 patients with recurrent ulcers were treated with Cimetidine, 4 patients responded to a single therapeutic course while 10 patients needed long-term therapy to remain symptom free.

LONG TERM SEQUELAE

In 1958, Krause showed that patients tended to die prematurely in the years after surgical treatment with partial gastrectomy. The main causes of death were tuberculosis, carcinoma of the stomach remnant, suicide and alcoholism. It was, therefore, of interest to see whether truncal vagotomy and drainage predisposed to cancer of the stomach. There had been some experimental evidence to support this concept (Fujita et al, 1979, Morgenstern, 1968). However, this has not been borne out by the present study. The main reasons for the mortality after truncal vagotomy and drainage are lung cancer, myocardial infarction and cerebro-vascular accidents, diseases associated with cigarette smoking. This pattern is also seen in the Baltham post-gastectomy study where 323 patients died from lung cancer after 20 years and only 37 from gastric cancer (Caygill et al, 1987). In the Baltham series, 20 years had to lapse before a four to five fold increase in cancer of the stomach was observed.

Similarly, in the Edinburgh series (Ross et al, 1982) a follow-up period of 18.9 years showed no increased risk of gastric cancer after partial gastrectomy but they did document a relationship between gastric surgery and

colorectal carcinoma. Watt et al (1984) also showed that after vagotomy and drainage death from stomach and colorectal cancers were significantly more common than in the general population. However, they came to the conclusion that deaths from cancer were not as important as death from diseases related to smoking. In a recent study, Mullan et al (1990) suggested that abnormalities in bile acid metabolism may explain the increased risk of colorectal neoplasia after truncal vagotomy. However, in the present study I could find no evidence of an increased incidence of colorectal cancer. Most of the deaths were related to smoking (Table 16).

PREDICTIVE VALUE

The discrepancy between the high proportion of positive results in the Insulin Test and the much lower rates for recurrent ulcer has always worried investigators in this field. From Hollander's own department at Mount Sinai Hospital, New York came one of the first studies to attempt to correlate the Insulin Test with the clinical outcome (Weinstein et al 1950). Positive post-operative tests were obtained in 29% of cases and clinical results showed no correlation, thus coming to the conclusion that the Insulin Test cannot be used to prognosticate clinical outcome after vagotomy.

Many years later, Kronberg (1971, 1973, 1974) studied the subject extensively and again showed the low predictive value of basal, spontaneous, insulin and histamine activated secretion. He came to the conclusion that post-operative measurements have such a low predictive value for estimating risk of recurrent ulcer that they should not be used for that purpose. He was the first to use the four expressions as defined by Vecchio (1966) namely, sensitivity, specificity, predictive value of a positive criterion and predictive value of a negative criterion.

The low predictive value of the Neutral Red Test and Insulin Test is confirmed by the present study. As few

as 60% of patients with recurrent ulcer have a positive response (Jordan & Cowdon, 1970, Kenned et al 1973, Ross & Kay, 1964, Watkin & Duthie, 1971, Johnston et al, 1967, Eisenberg et al 1969). Yet the ability of the two tests to prognosticate a poor result is enhanced by dividing the positive responses into 'early' and 'late'. The difference is very marked in the Insulin Test and highly statistically significant in the Neutral Red Test when both "unsuccessful outcome" and recurrent ulcer are considered. Further, there is a statistically significant difference between the 'early' positive and negative in both tests.

The present study also shows the poor predictive value of basal acid output (BAO). It has always been an attractive option to avoid the use of any stimulatory agent such as histamine, pentagastrin and insulin and depend on a test that relies solely on the basal acid output. Good results were achieved by Holst-Christienson (1977) when using 5.2mmol/h as the discriminating point; below this level 10% recurrence rate was noted but above this a 54% was reported. However, the results from the present study confirm the work of others that BAO is a poor predictor (Cowely et al 1973). Primrose & Johnston (1986) came to the same conclusion and showed good sensitivity but poor specificity for the test. If BAO had any value as a discriminatory test then the criteria used by Bachrach (1962 and 1967) would have shown high

positive predictive values. Table 32 shows low positive predictive value and low specificity. It would be surprising if it was otherwise. It seems unreasonable to assume that basal hypersecretion after vagotomy must be due solely to incomplete vagotomy when it might be due to other factors such as hyperglycaemia from antral dominance.

Irving and Smith (1985) came to the conclusion that a test which does not have a 60% or greater predictive value is not worth performing. They were able to achieve this with a fall of less than 60% in maximal acid output (MAO) combined with a fall in maximal acidity of less than 40% between the pre-operative and post-operative tests. The positive value of all the tests carried out in this series did not reach that level (Table 32). However, it must always be remembered that the predictive value of a positive test (PV pos) increases with increasing disease prevalence (Vecchio, 1966) and for an operation that is over 80% successful and carries a low "unsuccessful outcome" and recurrence rate. The results presented in this thesis must be meaningful. Writing about the Insulin Test, Primrose & Johnston (1986) wrote that, "it would be premature to abandon it". The results from this study supports this and introduces a new method which is simpler, safer and quicker, namely the Neutral Red Test. Furthermore, it would be unusual if one could achieve a higher predictive value when only one parameter

is considered. Duodenal ulcers have many different causes and the approach in the past has been too symplistic. The patients continue to smoke despite medical advice. An increase in Pepsin 2 has recently been found in some duodenal ulcer patients. Prostaglandin deficiency is another factor and the recent work on Campylobactor Pylori has opened up a new avenue for investigation. It would be surprising, therefore, if Schwartz's famous dictum, "no acid, no ulcer" would apply to all patients with duodenal ulcer. It is perhaps worth ending this section by quoting from Hollander: "In brief, the basic premise underlying this procedure is that the primary aetiological factor in ulcer disease is a psycho-secretory process, operating along the vagi from the higher centres. If this premise is valid, complete interruption of the vagus pathways should abolish these neutral influences on the gastric secretory mechanisms and result invariably in ulcer cure. The failure of this to occur casts much doubt upon the validity of this hypothesis as the sole cause of ulcer in all cases". (Weinstein et al, 1950).

THE FATE OF THE 'LATE' POSITIVE RESPONSE

Serial Insulin Tests show a steady rise in positivity as the interval after operation increases. This has been reported following truncal vagotomy (Watkin and Duthie, 1971, Gillespie et al 1970 and Smith et al 1972) and also after highly selective vagotomy (Lyndon et al 1975, Johnston et al, 1973 and Jordan, 1979). This recovery of gastric function has been attributed to recovery from neurapraxia (Dragstedt et al 1950) and to nerve regeneration either from conventional nerve regeneration or from collateral nerve regeneration.

Jefferson et al 1967 showed experimentally in the dog that conventional nerve regeneration had occurred after one year and up to 21 months in 7 out of 8 dogs and regenerating fibres connecting both ends of the nerves were found. Motor responses were detected when the vagus nerve above the section was stimulated. The findings from the present study cast doubt on this phenomenon occurring to a significant degree. This is probably due to the fact that in all the patients the vagotomist had been trained to take large sections of nerves followed by ligation of both ends. The most likely cause for an 'early' positive result is failure to remove a vagal trunk, especially the posterior vagal trunk (Fawcett et al 1969, Taylor et al 1977). Taylor et al 1977 also showed that when nerve strands only were found at

revagotomy, there was less likely to be an 'early' positive response. Therefore, when vagal strands are left during the performance of truncal vagotomy, reinnervation of the gastric mucosa by collateral nerve regeneration or sprouting is theoretically possible.

During the performance of a highly selective vagotomy, vagal strands can be left not only at the hiatus but also along the lesser curve. These vagal fibres along the lesser curve have been studied experimentally in the rat (Joffe et al, 1982) and in the dog (Cuesta Valentin et al 1987) and both studies showed some evidence of collateral nerve regeneration. The capability of the ingrowth across the antral-corpus junction must also not be forgotten in highly selective vagotomy (Taylor and Pearson 1976).

Clark 1964, came to the conclusion in an experimental study in cats that 50% of the gastric vagal nerve-fibres must be divided if recurrent ulcer is to be minimised. My experimental work in the rat (Jones and Griffith 1970 (a) (b)) confirmed this and Figure 31 shows that after 1 year there was no change in the area of gastric mucosa innervated when a small fundic vagal branch was left intact and the acid output from such a stomach remained unchanged (Table 43). However, there was evidence of an increase in area of gastric mucosa innervated when an intact posterior trunk was left for one year (Table 44)

but no statistically significant increase in acid output occurred. Collateral nerve regeneration thus depended on the size of the remaining vagal fibre.(Figures 32 and 33)

Prior to the present work only two clinical studies had been carried out to assess the fate of the few vagal strands left at operation, Bell, 1964 and Bell et al, 1965. In the first study, (Bell, 1964) a group of 43 male patients were studied by the Augmented Histamine Test initially and at an interval of 3 years. The Insulin Test was also carried out initially and the response graded according to the classification of Ross & Kay (1964) into 'early' and 'late' positive and negative. The 'early' positive showed a 44% reduction in maximal acid response, a 'late' positive a 56% reduction and a negative response a 65% reduction. This study showed for the first time that:

(a) reduction in acid output achieved by complete vagotomy is maintained for at least 3 years after operation, and

(b) the 'late' positive response behaves as a negative response, the initial reduction being maintained for 3 years.

Bell came to the conclusion that any significant vagal re-innervation would have occurred during the period of study.

In the second study (Bell et al 1965) a series of 42 patients were studied to assess long term change after incomplete vagotomy. Over a period of 63 months, no significant change in acid output occurred in the 'early' or 'late' responders.

Therefore, the findings from the present study confirm the experimental results in the rat and the clinical results of Bell. Collateral nerve regeneration or sprouting cannot be a significant factor in the return of gastric secretory function after incomplete vagotomy when only a few small vagal fibres are left (incomplete but "adequate" vagotomy).

TABLE 43

THE ACID ANALYSIS IN RATS WITH INTACT FUNDIC BRANCH

TIME INTERVAL	WEIGHT MEANS ± S D	VOL GASTRIC JUICE MEANS ± S D	pH MEANS ± S D	mEq/L MEANS ± S D	mEq/7 hrs MEANS ± S D
INITIAL	327.5 ± 34.0	4.7 ± 2.7	3.6 ± 1.3	27.6 ± 18.1	.156 ± .156
6 MONTHS	527.0 ± 44.0	5.6 ± 3.3	3.2 ± 0.9	34.2 ± 12.7	.214 ± .179
1 YEAR	485.0 ± 55.8	6.4 ± 2.5	2.9 ± 0.8	32.3 ± 10.4	.207 ± .124

TABLE 44

THE ACID ANALYSIS IN RATS WITH INTACT POSTERIOR TRUNK

TIME INTERVAL	WEIGHT MEANS ± S D	VOL GASTRIC JUICE MEANS ± S D	pH MEANS ± S D	mEq/L MEANS ± S D	mEq/7 hrs MEANS ± S D
INITIAL	366.5 ± 35.1	7.1 ± 3.0	2.7 ± 0.6	38.7 ± 14.7	.295 ± .201
6 MONTHS	510.0 ± 52.3	8.7 ± 3.0	2.6 ± 0.3	41.2 ± 14.1	.374 ± .232
1 YEAR	511.5 ± 59.1	8.6 ± 3.6	2.5 ± 0.2	41.5 ± 11.4	.383 ± .217

CONCLUSION

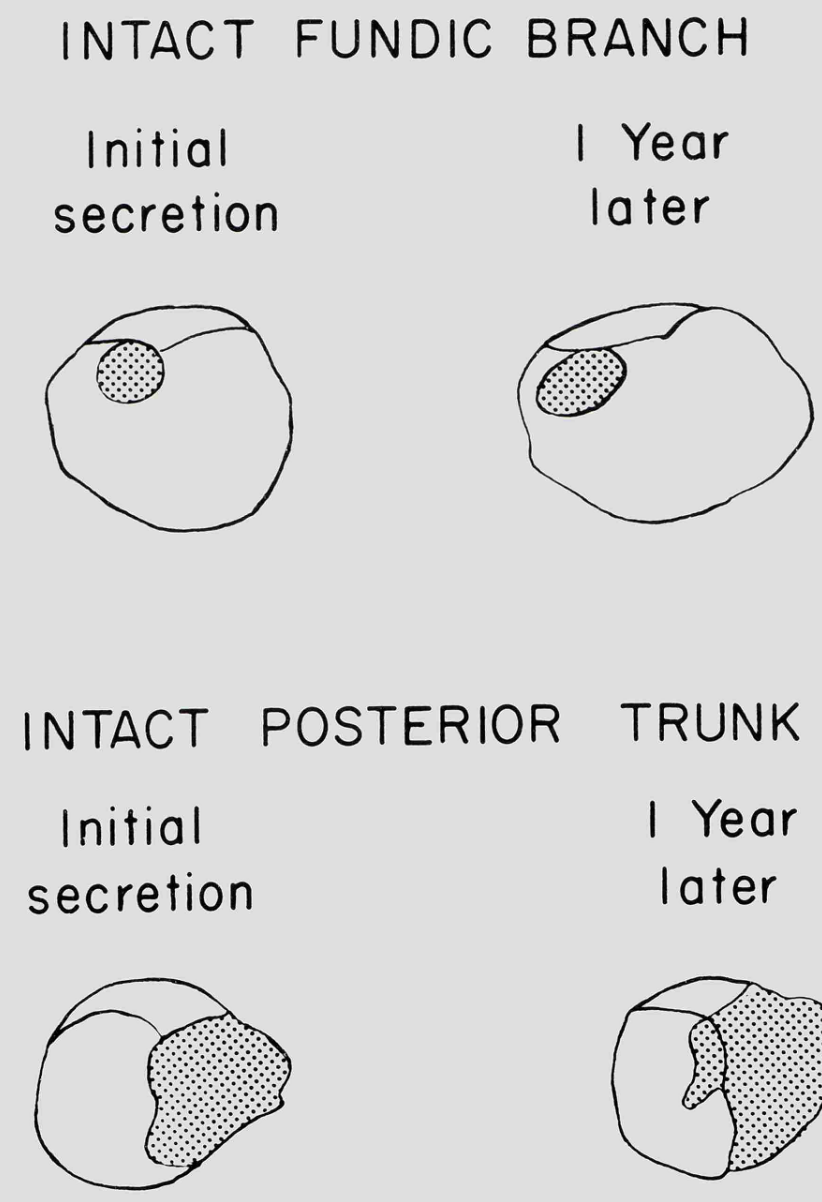
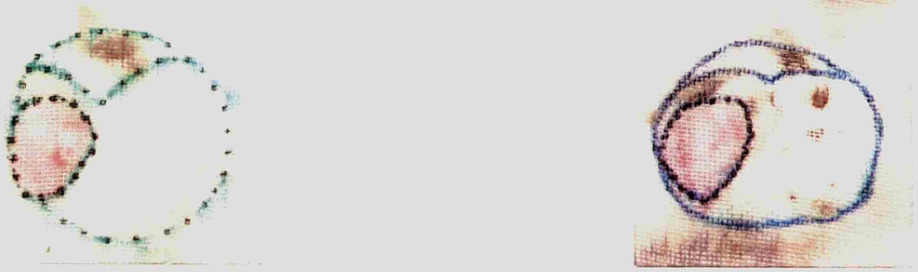

INTACT FUNDIC BRANCH
Initial secretion
1 Year later
INTACT POSTERIOR TRUNK
Initial secretion
1 Year later

Figure 31

INTACT FUNDIC BRANCH

Initial Secretion

3 Months later

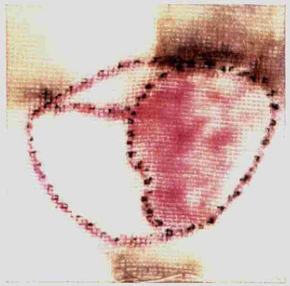


Rat no. 1

Figure 32

INTACT POSTERIOR TRUNK

Initial Secretion



3 Months later

Rat no. 141

Figure 33

CONCLUSION

(1) The study confirms that the Neutral Red Test is a simple and safe technique that can be used in all patients of whatever age or physical condition to assess the completeness of vagotomy. Gastric secretory stimulants such as insulin, 2-DG, histamine and pentagastrin can be avoided because the dye has a secretagogue action of its own acting through the vagal system.

(2) The test is a simple one which can be carried out in the Surgical Out-patient Department and the neutral red estimation requires no special equipment and can be carried out in any hospital biochemical department. The first 15 min. sample need only be used for measurement and the presence of bile in this early specimen can be ignored. However, later specimens can be affected by the entero-hepatic circulation of the neutral red. No adverse reaction occurred in many hundred tests and there was no disturbance of electrolyte or glucose metabolism.

(3) The Neutral Red Test confirms the validity on clinical grounds of the positive Insulin Test being divided into 'early' and 'late' according to the size of

the residual vagal fibres. The very high percentage of agreement between the two tests casts much doubt on the criticism levelled at the Insulin Test, in particular on the theory that positive results in the Insulin Test are due to stimulation of the adrenal sympathetic system.

(4) The predictive value of the Neutral Red and Insulin Test are similar. The highest positive predictive values are achieved by the post-operative Neutral Red Test and the Insulin Test using Gillespie's criteria. The basal acid output in this study had poor predictability. However, the predictive value of all tests are low, suggesting that other important factors are at play in producing a poor clinical outcome. However, there was a very marked difference in the clinical outcome when the responses are divided into 'early', 'late' and negative. Therefore, this study makes a strong plea for maintaining or re-introducing tests to assess the completeness of vagotomy, to prognosticate on clinical outcome and to assess the vagotomist.

(5) The long term results of truncal vagotomy are good with a relatively low recurrence rate and a low percentage of patients with diarrhoea and cumping. Illness is assessed in the patients during the study and

those which produced death were mainly associated with cigarette smoking, i.e. carcinoma of the lung and cardiovascular disease. This operation did not seem to be associated with an increase in carcinoma of the stomach and carcinoma of the colon.

Onset of recurrent ulcer occurred for many years after the operation (mean 6.1 years) which means that a long follow up period is required to get the full natural history of this complication.

(6) The study confirms the work of Bell that the 'late' positive response behaves as a negative response over a long period of time; in order words, in the human stomach a few residual vagal fibres are incapable of a significant degree of reinnervation due to collateral nerve regeneration or sprouting. This was the conclusion I made in my experimental work in the rat.

APPENDIX

EXCRETION OF NEUTRAL RED AT 5 MINUTE INTERVALS IN 41 PRE-OPERATIVE PATIENTS (OUTPUT IN MICRO GRAMMES)

	NAME	AGE	SEX	E.T.	5	10	15	20	25	30
1	G M	76	M	5	9.8	9.1	7.5	7.2	4.2	5.0
2	B H	37	M	4	10.5	13.3	12.5	10.7	3.5	5.8
3	G J	57	M	3	17.5	16.0	7.7	1.8	2.1	0.8
4	K W	47	M	3	37.1	47.2	63.6	BILE		
5	K S	35	M	2	7.2	2.4	7.2	3.2	20.8	2.5
6	M P	42	M	4	21.0	21.0	8.4	3.2	3.6	2.6
7	M B	33	M	5	11.7	8.3	9.6	8.9	BILE	
8	H B	36	M	2	39.0	29.4	28.0	25.2	21.6	5.5
9	H B	38	M	3	12.3	29.2	1.0	4.6	4.7	10.2
10	P G	33	M	3	11.0	4.0	11.6	4.8	13.5	9.5
11	A J	66	M	4	5.8	7.0	8.9	9.7	7.8	11.3
12	M G	36	M	5	12.2	13.0	9.0	8.5	12.5	5.7
13	J L	49	M	3	28.6	13.0	15.0	10.0	9.5	9.0
14	M G	51	F	3	37.6	12.8	16.7	8.3	9.8	5.6
15	D H	43	F	5	7.2	10.1	6.6	30.6		
16	S G	40	F	5	23.5	18.7	6.5	6.4	2.4	2.4
17	D A	54	F	4	19.6	48.5	45.9	16.8	40.3	9.9
18	H M	29	F	2	22.5	43.4	37.6	35.9	37.5	28.5
19	D C	56	M	3	48.8	49.0	27.0	34.1	BILE	
20	C W	37	M	2	36.9	40.0	37.1	21.5	14.0	19.3
21	R P	31	M	2	37.2	15.4	30.4	14.5	12.1	12.0
22	CH G	53	M	2	17.5	6.8	8.5	1.3	6.6	3.5
23	M W	42	M	3	52.2	4.7	8.3	2.0	4.5	5.0
24	G M	40	M	2	11.2	9.5	15.7	6.6	5.3	8.0
25	B C	37	M	3	30.0	39.6	5.3	14.7	11.2	8.4
26	B S	30	M	3	15.0	4.0	6.8	1.3	1.1	1.3
27	R B	38	F	4	42.3	37.6	26.7	27.0	25.2	19.8
28	F D	53	M	2	39.6	36.3	33.8	33.0	23.3	33.6
29	J L	50	M	3	28.5	33.0	BILE			
30	J C	59	M	3	7.5	8.9	6.9	3.6	4.9	4.7
31	SH P	40	F	3	22.5	13.2	11.0	3.2	2.8	7.7
32	H CH	63	M	2	9.2	7.5	3.6	BILE		
33	A H	55	M	3	27.8	25.3	30.4	29.4	17.5	12.0
34	M H	41	M	3	34.1	36.0	29.4	33.2	BILE	
35	R D	33	M	2	20.9	18.4	23.0	24.7	22.1	18.5
36	W CH	54	M	5	42.0	5.6	11.2	13.2	13.0	50.2
37	G G	33	M	2	23.0	12.5	8.4	8.4	13.5	17.2
38	J A	59	M	4	6.6	7.7	34.2	24.0	32.4	37.1
39	A R	55	M	3	9.8	13.6	16.5	BILE		
40	N W	24	M	3	26.5	13.3	17.6	21.6	30.5	30.0
41	V L	69	M	2	9.0	10.0	6.8	4.5	4.3	4.0

EXCRETION OF NEUTRAL RED AT 5 MINUTE INTERVALS IN 24 'EARLY' POSITIVE PATIENTS (OUTPUT IN MICRO GRAMMES)

	NAME	AGE	SEX	E.T.	5	10	15	20	25	30
1	J D	63	M	4	96.6			91.4		
2	G M	76	M	4	7.1	41.1	20.4	18.8	13.5	4.7
3	P B	45	M	3	22.4	20.6	20.9	15.3	18.1	10.8
4	J D	46	F	5	12.7	10.8	7.2	BILE		
5	H O	46	M	5	10.8	9.8	6.9	7.1	4.7	3.6
6	H B	36	M	2	30.6	21.0	22.8	16.8	8.3	22.5
7	A Th	37	M	3	16.6	16.5	BILE			
8	H D	62	M	4	5.5	9.5	7.5	BILE		
9	R B	40	M	4	8.9	8.5	5.7	4.4	2.8	6.3
10	G Sh	38	M	5	6.3	10.1	10.8	6.7	4.9	4.6
11	H T	53	M	5	10.5	12.6	9.0	7.2	8.8	BILE
12	W F	38	M	2	24.8	35.8	27.5	27.5	23.9	26.3
13	C W	37	M	6	1.7	9.8	12.8	12.5	BILE	
14	R P	31	M	3	16.6	13.7	20.8	15.9	20.4	22.8
15	M W	42	M	2	116.	22.0	8.5	6.2	4.8	3.3
16	A F	65	M	3	20.9	30.4	34.1	20.6	17.6	30.5
17	M H	41	M	3	54.0	58.9	71.3	49.5	62.7	60.9
18	W C	43	M	5	24.3	29.3	41.9	24.7	26.3	23.0
19	J A	59	M	5	2.5	8.1	11.8	12.3	9.1	6.0
20	D E	55	F	10	9.3	9.5	7.0	14.3	25.2	
21	A S	63	M	3	16.5	18.5	14.9	13.5	16.6	13.2
22	J B	41	M	5	9.0	13.2	13.3	6.3	9.4	10.0
23	G C	76	F	5	3.3	10.5	13.3	5.3	13.6	7.2
24	R D	33	M	6	21.2	21.6	20.4	14.0	14.0	11.9

EXCRETION OF NEUTRAL RED AT 5 MINUTE INTERVALS IN 26 'LATE' POSITIVE PATIENTS (OUTPUT IN MICRO GRAMMES)

	NAME	AGE	SEX	E.T.	5	10	15	20	25	30
1	G J	57	M	10	2.5	0	0	0	0	0
2	L K	54	F	5	4.4	4.4	9.4	8.8	10.6	3.7
3	F H	82	F	7	5.5	5.4	9.0	6.2	5.9	7.9
4	M P	42	F	4	6.0	6.0	6.5	6.3	2.6	
5	M B	33	M	6	3.3	2.5	2.5	6.5	2.3	2.1
6	J W	66	M	8	14.5			0	0	0
7	K H	42	M	7	4.0	BILE	BILE	BILE	BILE	BILE
8	H B	38	M	8	1.1		1.6	2.2	1.3	1.4
9	I W	54	F	10	1.2	1.3	3.5	0	0	0
10	G M	40	M	8	3.0	3.5	2.3	2.5	0.7	0.6
11	B C	37	M	5	3.3	2.8	3.6	3.2	3.3	2.0
12	G B	64	M	8	1.6	1.4	0.8	0.5	BILE	
13	R B	38	F	5	4.2	3.6	3.9	3.0	4.1	BILE
14	F D	53	M	5	7.5	3.8	6.5	3.6	1.5	2.5
15	J Sh	37	M	15	1.4	2.9	2.6	3.3	1.5	0.8
16	M B	63	F	6	0.5	1.2	2.3	1.6	2.0	1.0
17	J Th	47	M	6	1.2	1.9	1.2	0	0.1	0.1
18	C S	69	F	8	3.7	3.9	1.0	0	0	0
19	W Ch	54	M	9	14.3	2.6	0	9.1	2.6	0
20	G G	33	M	6	3.2	4.4	6.9	4.2	9.0	27.0
21	N W	24	M	15	2.7	4.4	6.0	2.8	2.4	1.6
22	E R	70	M	12	13.8	2.4	10.5		8.2	
23	F O	56	M	9	0.4	1.0	2.8	BILE	BILE	BILE
24	H B	75	M	5	3.6	5.6	5.8	6.8	6.3	8.4
25	C G	53	M	4	1.2	3.8	3.6	3.9	4.4	3.3
26	Sh P	40	F	7	2.3	2.1	8.1	2.3	1.9	1.4

TABLE : THE OUTPUT OF NEUTRAL RED EXCRETION DURING THE 1ST AND 2ND 15 MIN PERIODS IN 48 PRE-OPERATIVE PATIENTS 39 MALE AND 9 FEMALE (OUTPUT IN MICRO GRAMMES)

	NAME	AGE	SEX	ET MINS	FIRST 15 MIN	SECOND 15 MIN
1	J D	63	M	2	42.4	64.5
2	G M	76	M	5	26.4	16.4
3	B H	37	M	4	36.3	20.0
4	G J	57	M	3	41.5	4.7
5	K W	47	M	3	147.9	BILE
6	K S	35	M	2	16.8	26.5
7	L K	54	F	5	59.9	BILE
8	M P	42	F	4	50.4	9.4
9	M B	33	M	5	29.6	BILE
10	H B	36	M	2	96.4	52.3
11	M G	51	M	2	29.4	20.9
12	H B	38	M	3	42.3	19.4
13	P G	33	M	3	26.6	27.8
14	A J	66	M	4	21.6	28.7
15	M G	36	M	5	34.5	26.1
16	J L	49	M	4	56.6	28.5
17	M G	51	F	3	67.1	23.6
18	D H	43	F	5	23.9	30.6
19	S G	40	F	5	48.7	11.2
20	G SH	38	M	2	39.9	18.0
21	D A	54	F	4	113.9	70.0
22	H M	29	F	2	103.4	101.9
23	D C	56	M	3	124.8	BILE
24	C W	37	M	2	114.0	54.8
25	R P	31	M	2	83.0	38.6
26	R TH	60	M	3	30.6	21.7
27	CH G	53	M	3	32.7	11.4
28	M W	42	M	3	65.2	11.5
29	G M	40	M	2	36.4	19.9
30	B C	37	M	2	74.9	34.2
31	B S	30	M	3	25.7	3.7
32	R B	38	F	4	106.6	72.0
33	F D	53	M	2	109.7	89.9
34	J L	50	M	3	61.5	BILE
35	J C	59	M	3	23.3	13.1
36	SH P	40	F	4	46.7	13.7
37	J TH	47	M	3	39.0	30.0
38	H RH	63	M	2	20.4	BILE
39	A H	55	M	3	83.5	58.9
40	M H	41	M	3	99.5	BILE
41	R D	33	M	2	62.3	65.3
42	W CH	54	M	5	58.8	63.4
43	G G	33	M	2	43.9	39.1
44	J A	59	M	4	48.5	93.4
45	A R	55	M	2	39.9	BILE
46	N W	24	M	3	57.3	82.1
47	F F	50	M	2	94.9	87.0
48	V L	69	M	2	25.8	12.8

EXCRETION OF NEUTRAL RED IN 24 'EARLY' POSITIVE PATIENTS (OUTPUT IN MICRO GRAMMES)

	NAME	AGE	SEX	ET	FIRST 15 MINUTES	SECOND 15 MIN
1	J D	63	M	4	96.6	91.4
2	G M	76	M	4	68.7	36.9
3	P B	45	M	3	63.0	44.2
4	J D	46	F	5	30.7	BILE
5	H O	46	M	5	27.5	15.3
6	H B	36	M	2	74.4	47.6
7	A TH	37	M	3	33.1	BILE
8	H D	62	M	4	22.5	BILE
9	R B	40	M	4	23.1	13.5
10	G SH	38	M	5	27.2	16.1
11	H T	53	M	5	32.1	16.0
12	W F	38	M	2	88.0	77.6
13	C W	37	M	6	24.2	BILE
14	R P	31	M	3	51.1	59.1
15	M W	42	M	2	146.1	14.3
16	A F	65	M	3	85.4	68.7
17	M H	41	M	3	184.2	173.1
18	W C	43	M	5	95.5	73.9
19	J A	59	M	5	22.4	27.3
20	D E	55	F	10	25.8	39.5
21	A S	63	M	3	49.9	43.3
22	J B	41	M	5	35.5	25.6
23	G C	76	F	5	27.1	26.1
24	R D	33	M	6	63.2	39.9

EXCRETION OF NEUTRAL RED IN 26 'LATE' POSITIVE PATIENTS (OUTPUT MICRO GRAMMES)

	NAME	AGE	SEX	E.T.	FIRST 15 MIN	SECOND 15 MIN
1	G J	57	M	10	2.5	0
2	L K	54	F	5	18.2	23.1
3	F H	82	F	7	19.9	20.0
4	M P	42	F	4	18.4	8.9
5	M B	33	M	6	8.3	10.9
6	J W	66	M	8	14.5	0
7	K H	42	M	7	4.0	BILE
8	H B	38	M	8	2.7	4.9
9	I W	54	F	10	6.0	0
10	G M	40	M	8	8.8	3.8
11	B C	37	M	5	9.6	8.5
12	G B	64	M	8	3.8	BILE
13	R B	38	F	5	11.7	7.1
14	F D	53	M	5	17.8	7.6
15	J Sh	37	M	15	6.9	5.6
16	M B	63	F	6	4.0	4.6
17	J Th	47	M	6	4.3	1.7
18	C S	69	F	8	8.9	BILE
19	W Ch	54	M	9	16.9	11.7
20	G G	33	M	6	14.4	40.2
21	N W	24	M	15	13.1	6.8
22	E R	70	M	12	16.2	18.7
23	F O	56	M	9	4.2	BILE
24	H B	75	M	5	15.0	21.5
25	C G	53	M	4	8.6	11.6
26	Sh P	40	F	7	12.4	5.6

POST-OPERATIVE RESULTS

				NEUTRAL RED TEST output µg min.			INSULIN TEST acid output mmol					
	Age	*Name*	*Sex*	*E.T.*	*1st 15 min*	*2nd 15 min*	*Result*	*Basal 1/2h*	*1st hour*	*2nd hour*	*HBA/HSA*	*Result*	*Visick Grading*
1.	63	John Doman	M	4	96.6	91.4	+ early	1.48	0.36	1.61	17/12	- negative	IV
2.	65	Harry Lavender	M	0	0	0	- negative	3.70	2.12	2.07	37/48	- negative	I
3.	76	Gerald Matthews	M	4	68.7	36.9	+ early	0.88	0.72	0.83	40/32	- negative	I
4.	37	Brian Hancock	M	0	0	0	- negative	0	0	0.02	0/7	- negative	II
5.	70	Albert Kirby	M	0	0	0	- negative	0.20	0.27	0.01	11/15	- negative	I
6.	57	George Jackson	M	10	2.5	0	+ late	2.50	1.64	7.00	46/93	+ late	I
7.	47	Kenneth Williams	M	0	0	0	- negative	1.55	2.44	5.93	61/103	+ late	III
8.	35	Keith Smith	M	0	0	0	- negative	0.04	0.38	0.53	27/18	- negative	I
9.	54	Lucy Kay	F	5	18.2	23.1	+ late	1.42	0.43	1.48	26/49	+ late	I
10.	82	Florence Hodkin	F	7	19.9	20.0	+ late	0.34	1.56	10.89	42/89	+ late	IV R.U.
11.	45	Patrick Buxton	M	3	63.0	44.2	+ early	0.11	0.46	2.84	5/51	+ early	IV R.U.
12.	42	Mary Putman	F	4	18.4	8.9	+ late	0.62	5.58	6.93	30/62	+ early	I
13.	33	Martin Bernes	M	6	8.3	10.9	+ late	1.74	0.64	2.59	28/65	+ late	II
14.	74	Evelyn Daniels	F	0	0	0	- negative	0.14	0.03	0.66	8/28	+ late	I
15.	46	Jean Damms	F	5	30.7	Bile	+ early	0.88	2.31	0.57	35/26	- negative	IV R.U.
16.	46	Herbert Ogden	M	5	27.5	15.3	+ early	0.52	0.28	0.60	27/23	- negative	I
17.	36	Harry Bower	M	2	74.4	47.6	+ early	3.54	8.58	10.19	32/86	+ early	IV R.U.
18.	29	Francis Johnson	M	0	0	0	- negative	0.44	0.34	0.43	10/10	- negative	I
19.	75	Fred Fantham	M	0	0	0	- negative	1.27	1.37	1.31	48/37	- negative	I
20.	66	Jo Waterfall	M	8	14.5	0	+ late	0.84	0.64	1.91	26/40	- negative	I
21.	42	Kenneth Homer	M	7	40	Bile	+ late	----------no details----------			6/7	- negative	II
22.	35	Edwin Ogden	M	0	0	0	- negative	0	0	0.00	0/0	- negative	I
23.	29	Jeffrey Wilson	M	0	0	0	- negative	0.20	0	0.19	8/15	- negative	I
24.	51	Joan Williams	F	0	0	0	- negative	0	0	0	0	- negative	I
25.	66	Sydney Thompson	M	0	0	0	- negative	0.79	0.56	1/58	48/48	- negative	II

				NEUTRAL RED TEST output µg min.				INSULIN TEST acid output mmol						
	Age	*Name*	*Sex*	*E.T.*	*1st 15 min*	*2nd 15 min*	*Result*	*Basal $^1/_2$h*	*1st hour*	*2nd hour*	*HBA/HSA*	*Result*	*Visick Grading*	
26.	70	Irene Thacker	F	0	0	0	- negative	1.27	0.18	0	10/4	- negative	IV	R.U.
27.	65	Elsie Rodgers	F	0	0	0	- negative	0	0	0	0	- negative	I	
28.	61	Mary Outram	F	0	0	0	- negative	0	0	0	0	- negative	I	
29.	53	Phyllis Garner	F	0	0	0	- negative	0.18	0	0	6/0	- negative	I	
30.	48	Joyce Smith	F	0	0	0	- negative	1.77	2.40	4.28	41/58	- negative	I	
31.	51	Martin Grzyb	M	0	0	0	- negative	0.52	1.16	0.45	26/36	- negative	I	
32.	68	Edith Bloodworth	F	0	0	0	- negative	0.88	0.25	3.04	37/46	- negative	I	
33.	38	Harry Barton	M	8	2.7	4.9	+ late	0.20	0	0.05	4/0	- negative	I	
34.	45	George Blackman	M	0	0	0	- negative	0	0	0	0	- negative	I	
35.	33	Peter Gabbitas	M	0	0	0	- negative	----------no details----------				- negative	I	
36.	66	Arthur Johnson	M	0	0	0	- negative	1.30	0.15	0.03	31/6	- negative	I	
37.	69	Fred Boote	M	0	0	0	- negative	0.73	1.28	1.42	57/61	- negative	I	
38.	54	Irene Webb	F	10	6.0	0	+ late	0.58	2.52	3.65	22/77	+ early	I	
39.	37	Allan Thacker	M	3	33.1	Bile	+ early	1.73	5.72	9.57	57/121	+ early	IV	R.U.
40.	62	Harry Daughty	M	4	22.5	Bile	+ early	1.4	2.11	19.82	52/109	+ early	I	
41.	36	Malcolm Gabbitas	M	0	0	0	- negative	0	0	0	0	- negative	I	
42.	40	Reginal Bush	M	4	23.1	13.5	+ early	0.51	1.86	4.37	19/84	+ early	IV	R.U.
43.	49	John Latham	M	0	0	0	- negative	0.21	0.56	0.28	14/24	- negative	I	
44.	51	Mini Glover	F	0	0	0	- negative	0.29	1.21	0.79	16/24	- negative	I	
45.	43	Dorothy Hibbert	F	0	0	0	- negative	0.16	0.59	0.82	18/32	- negative	I	
46.	40	Susan Gallagher	F	0	0	0	- negative	0.19	0.49	0.95	10/28	- negative	I	
47.	38	Gordon Shawley	M	5	27.2	16.1	+ early	1.93	2.90	2.21	36/68	+ early	I	
48.	54	Dorothy Allan	F	0	0	0	- negative	0.72	1.05	0.43	20/16	- negative	I	
49.	53	Herbert Turner	M	5	32.1	16.0	+ early	0.72	3.0	16.43	60/110	+ early	I	
50.	38	William Foster	M	2	88.0	77.6	+ early	2.20	11.0	27.31	57/131	+ early	IV	R.U.

				NEUTRAL RED TEST output µg min.				INSULIN TEST acid output mmol						
	Age	Name	Sex	E.T.	1st 15 min	2nd 15 min	Result	Basal $^1/_2$h	1st hour	2nd hour	HBA/HSA	Result	Visick Grading	
51.	56	Douglas Coupe	M	0	0	0	- negative	0.72	0.60	5.70	42/85	+ late	I	
52.	37	Clifford West	M	6	24.2	Bile	+ early	2.10	2.09	4.33	59/77	- negative	IV	R.U.
53.	31	Reginald Peaks	M	3	51.1	59.1	+ early	1.88	5.32	7.18	66/120	+ early	I	
54.	42	Maurice Ward	M	2	146.1	14.3	+ early	0.54	2.26	4.95	36/76	+ early	I	
55.	40	Graham Monk	M	8	8.8	3.8	+ late	0.75	1.36	7.45	22/96	+ early	I	
56.	37	Bernard Calow	M	5	9.6	8.5	+ late	0.10	0.42	0.96	14/34	+ late	I	
57.	30	Barry Smith	M	0	0	0	- negative	0.03	0.25	0.20	8/16	- negative	IV	R.U.
58.	65	Arthur Ford	M	3	85.4	68.7	+ early	1.99	19.75	23.45	67/135	+ early	I	
59.	64	George Bird	M	8	3.8	Bile	+ late	1.68	5.25	10.30	68/107	+ late	I	
60.	38	Rita Bullimore	F	5	11.7	7.1	+ late	1.64	0.23	0.36	20/20	- negative	I	
61.	53	Father Dowd	M	5	17.8	7.6	+ late	2.23	2.16	6.58	69/90	+ late	I	
62.	37	Jack Shirley	M	15	6.9	5.6	+ late	3.29	2.30	4.31	47/83	+ late	I	
63.	63	Mary Bell	F	6	4.0	4.6	+ late	0.39	1.58	2.76	28/103	+ late	I	
64.	68	Mary Wormsley	F	0	0	0	- negative	0.37	0.29	0.83	38/45	- negative	I	
65.	50	Harry Evans	M	0	0	0	- negative	1.50	1.76	2.46	46/69	+ late	I	
66.	50	James Logan	M	0	0	0	- negative	2.36	0.64	0.55	43/36	- negative	I	
67.	59	John Clark	M	0	0	0	- negative	0.32	0.79	0.90	35/37	- negative	I	
68.	47	James Thornborrow	M	6	4.3	1.7	+ late	0.22	0.82	1.39	8/34	+ late	I	
69.	63	Harold Rhodes	M	0	0	0	- negative	0	0	0	0	- negative	I	
70.	41	Maurice Henderson	M	3	184.2	173.1	+ early	1.40	9.91	36.64	28/127	+ early	IV	R.U.
71.	43	William Cristlo	M	5	95.5	73.9	+ early	4.57	2.03	5.93	55/86	+ early	III	
72.	69	Connie Shaw	F	8	8.9	Bile	+ late	0	0	0	0	- negative	III	
73.	54	William Channing	M	9	16.9	11.7	+ late	0.29	0.18	0.54	12/30	- negative	I	
74.	33	Graham Grant	M	6	14.4	40.2	+ late	0	2.30	4.54	0/54	+ early	I	
75.	66	George Crookes	M	0	0	0	- negative	0.55	2.02	3.97	40/110	+ late	I	

				NEUTRAL RED TEST output μg min.				INSULIN TEST acid output mmol					
	Age	Name	Sex	E.T.	1st 15 min	2nd 15 min	Result	Basal $^1/_2$h	1st hour	2nd hour	HBA/HSA	Result	Visick Grading
76.	59	James Armitage	M	5	22.4	27.3	+ early	0.24	0.39	1.10	29/41	- negative	I
77.	24	Neil Wakeham	M	15	13.1	6.8	+ late	0.20	0.21	0.94	5/41	+ late	I
78.	54	Arthur Mansell	M	0	0	0	- negative	1.57	1.54	1.10	47/69	+ late	I
79.	47	Leslie Damms	F	0	0	0	- negative	----------	no details	----------	11/109	+ late	IV R.U.
80.	55	Colin Darrington	M	0	0	0	- negative	----------	no details	----------	33/67	+ late	II
81.	45	Douglas Hopewell	M	0	0	0	- negative	----------	no details	----------	48/42	- negative	I
82.	69	William Pinder	M	0	0	0	- negative	0.32	0.22	0.58	34/20	- negative	I
83.	31	Robert Gillatt	M	0	0	0	- negative	0.07	0	0.07	12/18	- negative	I
84.	70	Edward Ringrose	M	12	16.2	18.7	+ late	1.11	0.54	1.11	46/90	+ early	I
85.	55	Dorothy East	F	10	25.8	39.5	+ early	0.24	0.51	0.83	13/28	- negative	I
86.	48	Kathleen Colgrave	F	0	0	0	- negative	0.15	0.23	0.27	7/15	- negative	I
These 14 patients have been lost to follow up:													
87.	63	Austin Stokes	M	3	49.9	43.3	+ early	1.58	1.21	1.81	42/50	- negative	
88.	41	James Bambridge	M	5	35.5	25.6	+ early	0.47	0	0.21	7/10	- negative	
89.	56	Frank Oldfield	M	9	4.2	Bile	+ late	0	0	0.38	0/19	+ late	
90.	75	Harland Baxter	M	5	15.0	21.5	+ late	0.89	0.87	2.20	45/67	+ late	
91.	76	Gladys Clayton	F	5	27.1	26.1	+ early	1.54	2.07	7.72	42/102	+ early	
92.	48	John Elliot	M	0	0	0	- negative	0.80	0.97	1.20	26/31	- negative	
93.	29	Hazel Mullins	F	0	0	0	- negative	2.60	3.70	3.76	48/35	- negative	
94.	60	Ronald Thompson	M	0	0	0	- negative	0	0.05	0.96	0/86	+ late	
95.	53	Charles Granger	M	4	8.6	11.6	+ late	0.61	0.01	0.99	41/48	- negative	
96.	40	Sheila Potter	F	7	12.4	5.6	+ late	1.17	0.47	1.34	33/56	+ late	
97.	55	Arthur Hedley	M	0	0	0	- negative	1.02	0.04	0	30/8	- negative	
98.	33	Raymond Dawes	M	6	63.2	39.9	+ early	6.20	2.06	5.93	55/66	- negative	
99.	55	Albert Redfern	M	0	0	0	- negative	0.67	0.91	0.60	8/17	- negative	
100.	69	Victor Lester	M	0	0	0	- negative	2.10	----------	no details	53/49	- negative	

FOLLOW UP TO DEATH / JANUARY 1989

	Age	Name	Sex	Date of Operation	N.R.T.	I.T.	Visick Grading	Follow up							
1.	63	John Doman	M	November 1975	+ early	- negative	IV	12	years	-	1	month			Died
2.	65	Harry Lavender	M	August 1975	- negative	- negative	I	3	years	-	3	months			Died
3.	76	Gerald Matthews	M	August 1975	+ early	- negative	I	13	years	-	4	months			
4.	37	Brian Hancock	M	March 1975	- negative	- negative	II	13	years	-	9	months			
5.	70	Albert Kirby	M	April 1972	- negative	- negative	I	3	years	-	1	month			Died
6.	57	George Jackson	M	May 1975	+ late	+ late	I	13	years	-	7	months			
7.	47	Kenneth Williams	M	September 1975	- negative	+ late	III	13	years	-	3	months			
8.	35	Keith Smith	M	July 1975	- negative	- negative	I	13	years	-	5	months			
9.	54	Lucy Kay	F	November 1974	+ late	+ late	I	8	years	-	0	months			Died
10.	82	Florence Hodkin	F	February 1975	+ late	+ late	IV	4	years	-	2	months	R.U.		Died
11.	45	Patrick Buxton	M	December 1967	+ early	+ early	IV	7	years	-	0	months	R.U.		
12.	42	Mary Putman	F	April 1973	+ late	+ early	I	15	years	-	8	months			
13.	33	Martin Bernes	M	May 1975	+ late	+ late	II	13	years	-	7	months			
14.	74	Evelyn Daniels	F	April 1974	-	+ late	I	2	years	-	4	months			
15.	46	Jean Damms	F	April 1974	+ early	-	IV	14	years	-	8	months	R.U.		
16.	46	Herbert Ogden	M	April 1974	+ early	-	I	3	years	-	5	months			Died
17.	36	Harry Bower	M	July 1974	+ early	+ early	IV	14	years	-	5	months	R.U.		
18.	29	Francis Johnson	M	January 1975	- negative	- negative	I	13	years	-	11	months			
19.	75	Fred Fantham	M	April 1975	- negative	- negative	I	8	years	-	1	month			Died
20.	66	Jo Waterfall	M	April 1975	+ late	- negative	I	4	years	-	0	months			Died
21.	42	Kenneth Homer	M	October 1975	+ late	- negative	II	13	years	-	2	months			
22.	35	Edwin Ogden	M	November 1970	- negative	- negative	I	18	years	-	1	month			
23.	29	Jeffrey Wilson	M	May 1972	- negative	- negative	I	16	years	-	2	months			Died
24.	51	Joan Williams	F	January 1971	- negative	- negative	I	17	years	-	3	months			Died
25.	66	Sydney Thompson	M	June 1974	- negative	- negative	II	14	years	-	6	months			
26.	70	Irene Thacker	F	October 1973	- negative	- negative	IV	7	years	-	10	months	R.U.		Died
27.	65	Elsie Rodgers	F	November 1972	- negative	- negative	I	7	years	-	0	months			Died
28.	61	Mary Outram	F	October 1972	- negative	- negative	I	16	years	-	2	months			
29.	53	Phyllis Garner	F	December 1974	- negative	- negative	I	14	years	-	0	months			
30.	48	Joyce Smith	F	October 1973	- negative	- negative	I	15	years	-	2	months			

	Age	Name	Sex	Date of Operation	N.R.T.	I.T.	Visick Grading	Follow up		
31.	51	Martin Grzyb	M	June 1973	- negative	- negative	I	15 years - 6 months		
32.	68	Edith Bloodworth	F	November 1972	- negative	- negative	I	9 years - 2 months		Died
33.	38	Harry Barton	M	September 1972	+ late	- negative	I	16 years - 3 months		
34.	45	George Blackman	M	October 1971	- negative	- negative	I	5 years - 0 months		Died
35.	33	Peter Gabbitas	M	January 1973	- negative	- negative	I	16 years - 0 months		
36.	66	Arthur Johnson	M	August 1974	- negative	- negative	I	14 years - 4 months		
37.	69	Fred Boote	M	March 1972	- negative	- negative	I	3 years - 5 months		Died
38.	54	Irene Webb	F	September 1973	+ late	+ early	I	15 years - 3 months		
39.	37	Allan Thacker	M	February 1975	+ early	+ early	IV	9 years - 0 months	R.U.	Died
40.	62	Harry Daughty	M	November 1973	+ early	+ early	I	15 years - 1 month		
41.	36	Malcolm Gabbitas	M	October 1972	- negative	- negative	I	16 years - 2 months		
42.	40	Reginal Bush	M	August 1974	+ early	+ early	IV	14 years - 4 months	R.U.	
43.	49	John Latham	M	March 1973	- negative	- negative	I	15 years - 9 months		
44.	51	Mini Glover	F	August 1973	- negative	- negative	I	15 years - 4 months		
45.	43	Dorothy Hibbert	F	March 1973	- negative	- negative	I	15 years - 9 months		
46.	40	Susan Gallagher	F	May 1973	- negative	- negative	I	15 years - 7 months		
47.	38	Gordon Shawley	M	June 1973	+ early	+ early	I	15 years - 6 months		
48.	54	Dorothy Allan	F	April 1973	- negative	- negative	I	15 years - 8 months		
49.	53	Herbert Turner	M	March 1974	+ early	+ early	I	14 years - 9 months		
50.	38	William Foster	M	October 1973	+ early	+ early	IV	15 years - 2 months	R.U.	
51.	56	Douglas Coupe	M	May 1975	- negative	+ late	I	13 years - 7 months		
52.	37	Clifford West	M	November 1974	+ early	- negative	IV	14 years - 0 months	R.U.	
53.	31	Reginald Peaks	M	May 1973	+ early	+ early	I	15 years - 9 months		
54.	42	Maurice Ward	M	August 1973	+ early	+ early	I	15 years - 4 months		
55.	40	Graham Monk	M	June 1973	+ late	+ early	I	15 years - 6 months		
56.	37	Bernard Calow	M	March 1973	+ late	+ late	I	15 years - 9 months		
57.	30	Barry Smith	M	August 1973	- negative	- negative	IV	15 years - 4 months	R.U.	
58.	65	Arthur Ford	M	August 1973	+ early	+ early	I	15 years - 4 months		
59.	64	George Bird	M	January 1974	+ late	+ late	I	6 years - 0 months		Died
60.	38	Rita Bullimore	F	April 1975	+ late	- negative	I	13 years - 8 months		

	Age	Name	Sex	Date of Operation	N.R.T.	I.T.	Visick Grading	Follow up	
61.	53	Father Dowd	M	October 1974	+ late	+ late	I	14 years - 2 months	
62.	37	Jack Shirley	M	July 1973	+ late	+ late	I	15 years - 5 months	
63.	63	Mary Bell	F	April 1975	+ late	+ late	I	13 years - 8 months	
64.	68	Mary Wormsley	F	February 1975	- negative	- negative	I	12 years - 0 months	Died
65.	50	Harry Evans	M	December 1973	- negative	+ late	I	15 years - 1 month	
66.	50	James Logan	M	January 1975	- negative	- negative	I	13 years - 11 months	
67.	59	John Clark	M	November 1974	- negative	- negative	I	14 years - 1 month	
68.	47	James Thornborrow	M	June 1973	+ late	+ late	I	10 years - 9 months	Died
69.	63	Harold Rhodes	M	November 1974	- negative	- negative	I	2 years - 9 months	Died
70.	41	Maurice Henderson	M	December 1974	+ early	+ early	IV	14 years - 1 month	R.U.
71.	43	William Cristlo	M	February 1972	+ early	+ early	III	16 years - 10 months	
72.	69	Connie Shaw	F	May 1973	+ late	- negative	III	15 years - 7 months	
73.	54	William Channing	M	June 1973	+ late	- negative	I	15 years - 6 months	
74.	33	Graham Grant	M	October 1972	+ late	+ early	I	16 years - 2 months	
75.	66	George Crookes	M	September 1973	- negative	+ late	I	15 years - 3 months	
76.	59	James Armitage	M	October 1974	+ early	- negative	I	14 years - 2 months	
77.	24	Neil Wakeham	M	February 1975	+ late	+ late	I	13 years - 10 months	
78.	54	Arthur Mansell	M	November 1971	- negative	+ late	I	17 years - 1 month	
79.	47	Leslie Damms	F	September 1977	- negative	+ late	IV	11 years - 2 months	R.U.
80.	55	Colin Darrington	M	February 1978	- negative	+ late	II	10 years - 10 months	
81.	45	Douglas Hopewell	M	August 1977	- negative	- negative	I	11 years - 4 months	
82.	69	William Pinder	M	May 1977	- negative	- negative	I	11 years - 7 months	
83.	31	Robert Gillatt	M	June 1976	- negative	- negative	I	12 years - 6 months	
84.	70	Edward Ringrose	M	February 1976	+ late	+ early	I	12 years - 10 months	Died
85.	55	Dorothy East	F	January 1977	+ early	- negative	I	11 years - 11 months	
86.	48	Kathleen Colgrave	F	November 1973	- negative	- negative	I	15 years - 1 month	

14 patients who I failed to follow up:

	Age	*Name*	*Sex*	*Date of Operation*		*N.R.T.*	*I.T.*
87.	63	Austin Stokes	M	November	1974	+ early	- negative
88.	41	James Bambridge	M	December	1974	+ early	- negative
89.	56	Frank Oldfield	M	February	1975	+ late	+ late
90.	75	Harland Baxter	M	November	1973	+ late	+ late
91.	76	Gladys Clayton	F		1972	+ early	+ early
92.	48	John Elliot	M	August	1975	- negative	- negative
93.	29	Hazel Mullins	F	March	1975	- negative	- negative
94.	60	Ronald Thompson	M	June	1973	- negative	+ late
95.	53	Charles Granger	M	December	1972	+ late	- negative
96.	40	Sheila Potter	F	May	1973	+ late	+ late
97.	55	Arthur Hedley	M	November	1974	- negative	- negative
98.	33	Raymond Dawes	M	November	1974	+ early	- negative
99.	55	Albert Redfern	M	May	1973	- negative	- negative
100.	69	Victor Lester	M	September	1977	- negative	- negative

APPENDIX

Receiver Operator Characteristic Curve

The concept of receiver operator characteristic (R.O.C.) curves has been described in the clinical evaluation of obstetric testing (Richardson et al, 1985) as well as in the evaluation of other laboratory tests (Robertson and Zwelg, 1981, Schwartz, 1987).

The term is cumbersome and derives from radar technology. Where a true signal has to be distinguished from background noise, then an operator who identifies a high proportion of these signals also experiences a high rate of false positive signals with a given instrument (receiver). Another operator using the same receiver may identify fewer true and fewer false positive signals. For any given operator and receiver, a relationship can be drawn between the proportion of true signals identified (the sensitivity) and the number of false positives (specificity). This relationship can be represented graphically - the receiver operator characteristic curve. This plots a test's true-positive (i.e. sensitivity) versus its false-positive (i.e. specificity). Therefore, by plotting R.O.C. curves of each several alternate tests one can determine which test is best at discriminating patients with disease from those without disease. When two or more laboratory

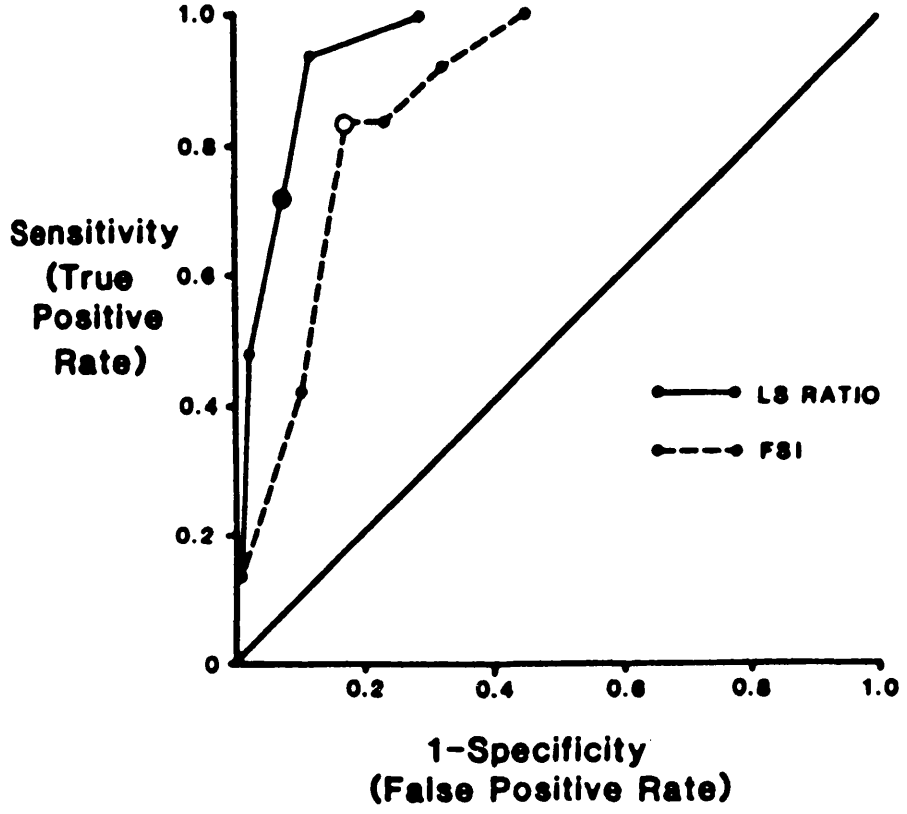


Figure 34: The ROC curve furthest to the left is best at discriminating patients with disease, at 45^{o} the tests ability is no better than chance.

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