

MASSIVE NON-VARICEAL BLEEDING IN PATIENTS WITH CIRRHOSIS

Analysis of treatment with emergency surgery
and selective intra-arterial vasopressin infusion

PROEFSCHRIFT

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To Margriet, our children and our parents.

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A physician need not always declare his prognosis, but he should always try to make one for himself - it decides the treatment.

James Jackson, 1831

Introduction

The coexistence of peptic ulcer disease and cirrhosis of the liver is extensively documented by many authors. The association of the two diseases was recognized as a serious problem because of its major complication: massive upper gastro-intestinal bleeding. Massive "non-variceal" bleeding was also considered to be one of the complications after operations for decompression of portal hypertension. However no causal relationship has been demonstrated for peptic ulcer disease, either with liver cirrhosis, or with portal decompression.

Peptic ulcer disease includes gastric and duodenal ulcers and hemorrhagic gastritis. There are three different therapeutic possibilities when either of these sources starts bleeding. Surgical treatment is generally preferred; medical treatment for massive bleeding is largely abandoned. Both are usually accused of a very high mortality, but no mortality figures have been published so far. A new possibility has been added to the therapeutic armament by the applications of selective angiography and intra-arterial infusion with vasoconstrictive agents.

Selective infusion of vasopressin has resulted in pharmacologic control of gastro-intestinal bleeding, especially in patients with cirrhosis of the liver.

The purpose of this thesis is to answer three main questions:

1. How high is the postoperative mortality in patients with cirrhosis of the liver, who have had massive upper gastrointestinal bleeding from sources other than esophageal varices, and who underwent an emergency operation for this bleeding?
2. Does preoperative clinical information and/or biochemical data bear any relationship to postoperative mortality?
3. What are the results of selective angiography and intra-arterial infusion of vasopressin in the treatment of massive non-variceal bleeding in patients with cirrhosis?

The answer to the first question would provide a better understanding of the extent and gravity of the problem of non-variceal bleeding in patients with cirrhosis.

If the second question can be answered affirmatively the information could possibly provide directives for the decision how to treat these patients, with an emergency operation or not.

The third question, finally, engages in the search for alternative ways of treatment for these patients, either in selected cases when surgical treatment is contraindicated, or as a substitute for surgical treatment.

To answer these questions two series of patients from the Massachusetts General Hospital in Boston were studied. The results of emergency surgery were analysed in 64 patients from the 10 year period 1962-1972. The results of selective vasopressin infusion were analysed in 32 patients from the period 1971-1974

It should be stressed that this study concentrates on short term results of treatment only - chiefly expressed as *mortality*. Neither long term survival nor quality of life after treatment will be discussed in detail.

Although the data of the two patient series will sometimes be compared, it is *not* the intention to compare and weigh the merits of vasopressin therapy against those of a surgical intervention.

During the analysis of preoperative factors that are possibly related to post-operative mortality, it gradually became clear that any positive relationship which might be found, could only be used and tested in a (prospective) clinical situation when it is moulded into a workable formula. Therefore we combined the parameters with a positive relation and formed a new point score system for the prediction of surgical mortality of massive non-variceal gastroduodenal bleeding in patients with cirrhosis of the liver.

CHAPTER I

Peptic ulcer disease in patients with cirrhosis of the liver

Coexistence of peptic ulcer and cirrhosis.

Massive bleeding from esophageal varices is so well known that this diagnosis is born in mind every time a clinician is confronted with an upper gastrointestinal bleeding in a patient who is known to have cirrhosis of the liver. However, a substantial number of cirrhotic patients with gastro-intestinal bleeding, even if they are known to have esophageal varices, do not bleed from these varices but from peptic ulcers or hemorrhagic gastritis.

Much has been written about the association of liver cirrhosis and peptic ulcer disease. No causal relationship has been demonstrated so far.

In 1900 Preble drew attention to a possible clinical importance. He reported 6 patients with cirrhosis who died of uncontrollable upper gastro-intestinal bleeding, in whom the cause of bleeding at autopsy could not be attributed to ruptured esophageal or gastric varices. The bleeding was most likely caused by hemorrhagic gastritis.

Some authors have considered the combination of ulcers and cirrhosis so rare as to justify publication as a case report (Krauss, 1865; Mathieu, 1897; Paolazzi, 1936; Firman, 1941; Mallory, 1947; Dole, 1947; Carpenter and Mac Carthy, 1947; Deutsch, 1949; Bogardus, 1956).

Lipp and Lipsitz (1951, 1952) reviewed the literature and gained the impression that, although the coexistence of cirrhosis and ulcer was occasionally alluded to, the prevailing medical opinion was, that this association was regarded as "unusual, probably coincidental and therefore of little practical significance".

They stressed the point that because of the extreme variability in the natural history of both diseases, neither was susceptible to satisfactory statistical analysis. The published data were conflicting and inconclusive. The dif-

ficulty in proving or disproving a direct of causal relationship between liver disease and the development of ulcers being that the material used in studies of the association of the two diseases was likely to be selected and not chosen at random.

Some studies have been based on clinical observations, others are the result of examination of autopsy material (see table 1). The importance of this distinction was clearly shown in their own studies (Lipp and Lipsitz, 1951 and 1952). Based on clinical criteria they found a coexistence of the two diagnoses in 3.2 per cent. In routine autopsies the combination was seen in 11.5 per cent. Alarmed by this figure, and with a greater clinical awareness of the possibility, they found in a later clinical study of 302 patients with cirrhosis an incidence of peptic ulcer of 5 per cent. Despite the limited series of patients, they felt justified in concluding that portal cirrhosis and peptic ulcer occur in association in a "clinically significant" number of cases; the chief clinical situation where the association of the diseases was of importance being massive hemorrhage, as the outcome here was usually fatal.

Following this publication a constant stream of articles on this subject was written (see table 1). Initially only gastric or duodenal ulcers were cited, but later hemorrhagic gastritis was mentioned more frequently. The incidence varies widely. The highest was cited by Merigan in 1960. He found peptic ulcer or gastritis in 66 out of 158 patients with cirrhosis, an incidence of 41.7 per cent.

None of these publications (table 1), however, can be mutually compared. All studies are retrospective and there is no consensus regarding criteria of "cirrhosis" or "peptic ulcer disease". It is not always specified whether the ulcers are active, acute or chronic or whether bleeding has occurred. The extent of bleeding is not always specified and criteria for massive or moderate hemorrhage are lacking. The same holds for criteria of hemorrhagic gastritis.

Gastritis is a rather common condition in many situations other than cirrhosis, particularly uremia, acute alcoholism and severe generalized infection. Because gastritis is transient, usually becoming evident only when it leads to bleeding, and because it leaves no recognizable residuals upon healing, its incidence is unpredictable and very difficult to determine. Gastritis as a cause for hemorrhage may go unrecognized unless the patient is examined gastroscopically during or shortly after the hemorrhage (Palmer, 1957). Massive exsanguinating bleeding is frequently mentioned as being the most common and serious complication of ulcers in cirrhosis (Rudnicki, 1960);

Table 1: Incidence of peptic ulcer disease in patients with cirrhosis

| | <i>author</i> | <i>total patients</i> | <i>ulcers</i> | <i>%</i> | <i>clinical/autopsy</i> |
|------|-----------------------|-----------------------|---------------|----------|-------------------------|
| 1922 | Appel | 151 | 3 | 1.9 | aut. |
| 1931 | Askanazy | 64 | 5 | 7.8 | aut. |
| 1934 | Schnitker and Hass | 72 | 14 | 19.4 | clin. |
| 1934 | Suzuki | 21 | 3 | 14 | aut. |
| 1935 | Di Stefano | 11.900 | 347 | 2.9 | aut. |
| 1940 | Ask - Upmark | 38 | 9 | 24 | aut. |
| 1942 | Ratnoff and Patek | 386 | 14 | 3.6 | aut. |
| 1949 | Lipp | 1.418 | 46 | 3.2 | clin. |
| 1950 | De la Cruz | — | — | 11.7 | clin.(radiol.) |
| 1951 | Lipp and Lippsitz | 130 | 15 | 11.5 | aut. |
| 1952 | Lipp and Lippsitz | 302 | 15 | 5.0 | clin. |
| 1952 | Puccini | 550 | 22 | 3.9 | aut. |
| 1952 | Chalmers and Zamcheck | 101 | 44 | 18 | aut. |
| 1952 | Järvinen | 19 | 3 | 15.7 | clin. + aut. |
| 1953 | Caroli and Paraf | 88 | 8 | 9.1 | aut. |
| 1953 | Palmer and Brick | 150 | 22 | 14.6 | clin (rad.) |
| 1953 | Antonini and Marinoni | 175 | 7 | 4 | aut. |
| 1954 | Sullivan | 94 | 4 | 4.2 | clin. (radiol.) |
| 1955 | Swisher | 417 | 58 | 13.9 | clin. (radiol.) |
| 1955 | Dagradi | 92 | 12 | 13.1 | clin. |
| 1955 | Fainer and Halsted | 94 | 16 | 17.0 | aut. |
| 1958 | Koide | 252 | 13 | 5.6 | clin (radiol.) |
| 1958 | Enquist | 476 | 91 | 19.1 | aut. |
| 1958 | Davis | 100 | 14 | 14 | aut. |
| 1959 | Ask - Upmark | 50 | 6 | 12 | aut. |
| 1959 | Belkin and Conn | 36 | 7 | 19 | clin. + aut. |
| 1960 | Palmer | 518 | 71 | 15.8 | clin. |
| 1960 | Oetting | 100 | 19 | 19 | clin. + aut. |
| 1960 | Merigan | 158 | 66 | 41.7 | clin. |
| 1960 | Cachin and Pergola | 94 | 9 | 10.0 | clin. (radiol.) |
| 1960 | Rudnicki | 148 | 16 | 10.8 | clin. (radiol.) |
| 1960 | Rudnicki | 94 | 9 | 9.5 | aut. |
| 1961 | Wantz and Payne | 101 | 9 | 6.9 | clin. |
| 1961 | Potet | 282 | 35 | 12.4 | |
| 1962 | Mikkelsen | 230 | 6 | 2.6 | clin. |
| 1964 | Brick and Palmer | 1.000 | 150 | 15 | clin. |
| 1964 | Tabaqchali and Dawson | 290 | 33 | 11.3 | clin. |
| 1964 | Conn | 64 | 21 | 32.8 | clin. |
| 1964 | Schreiberq | 173 | 24 | 13.9 | clin. + aut. |
| 1965 | Justin and Besancon | 318 | 5 | 1.5 | aut. |
| 1966 | Wolgemut and Schille | 305 | 56 | 18.0 | |
| 1966 | Mogena and Campos | 80 | 11 | 13.7 | clin. (radiol.) |
| 1968 | Fraisse | 250 | 26 | 10.4 | clin. |
| 1968 | Lataste | 139 | 17 | 12.2 | clin. |
| 1969 | Orloff | 32 | 4 | 12 | clin. |
| 1971 | Jackson | 155 | 17 | 11 | clin. |

perforation is hardly mentioned as a complication and is apparently very rare. Until 1958 only four cases were reported in the literature (Koide, 1958; Bogardus, 1968).

Bleeding ulcers in patients with cirrhosis.

From 1950-1970 abundant literature was published on the management of massively bleeding ulcers. Several proposals were made about medical or surgical treatment, the timing, and the kind of operation. Most authors agreed that medical treatment was no longer warranted, but there was no general agreement about the type of surgical procedure that should be used. Figures about mortality rates are difficult to interpret. After reviewing these articles our main conclusion is: *There are no exact and reliable figures about mortality after surgical treatment of bleeding ulcers in patients with cirrhosis.*

In series of cirrhotic patients with ulcers (see table 1) treatment is usually not specified, nor is mortality. In series about surgical treatment of massive upper gastrointestinal bleeding, patients with cirrhosis are sometimes excluded, as it is felt that this group confuses mortality figures too much. However, Palmer (1964) showed that the risks of *elective* surgery in cirrhotic patients are almost equal to the risks in non-cirrhotic patients (mortality 4 per cent). In the few *emergency* operations that he reported, mortality was increased (25 per cent). From the figures of Thorne (1965) on the surgical treatment of massive upper gastrointestinal hemorrhage, a mortality rate of 33 per cent can be calculated for patients with a history or physical signs of cirrhosis. In Darin's (1961) series of 128 patients with massive hemorrhage from peptic ulcer, cirrhotic patients contributed to 20 per cent of the total surgical mortality.

Several authors have postulated a possible causal relationship between the existence of cirrhosis and the formation of peptic ulcers. This search has been hampered by the observation that both in experimentally induced cirrhosis in animals (mostly dogs) and in cirrhotic patients gastric acid secretion is significantly lower than in controls (Yakhontova, 1974). The stimulating action of alcohol on gastric secretion is well known, but in a recent study of 36.656 "white male and female subjects" no positive relationship could be demonstrated between alcohol consumption and a prevalence of peptic ulcer (Friedman, 1974).

Peptic ulcer after portacaval decompression.

Increased attention was paid to the problem of complicating peptic ulcers when more and more follow-up studies were published about surgical treatment for portal hypertension.

Though initially denied (Blakemore, 1952; Child, 1954 and 1958; Linton, 1958; Wantz and Payne, 1961), it was gradually understood that both acute ulcers in the immediate postoperative period, and chronic ulcers after some time represented a frequent complication in patients with a portacaval or splenorenal shunt. A fairly complete review of the literature on this subject was given by Poliak in 1970 - unfortunately in Russian (table 2).

Later studies (Dubuque, 1957; McDermott, 1961; Tabaqcheli, 1964) gave incidences of up to 24 per cent. Nevertheless, the question remains unanswered whether the incidence is higher compared to non-operative treated cirrhotic patients and also compared to non-cirrhotic patients. There is one point on which all authors agree - even those who do not accept an increased inci-

Table 2: Peptic ulcer after portacaval shunt

| <i>author</i> | <i>total patients</i> | <i>ulcers</i> | <i>incidence in %</i> |
|----------------------------|-----------------------|---------------|-----------------------|
| 1952 Blakemore | 130 | 2 | 1.5 |
| 1954 Child | 31 | 1 | 3 |
| 1957 Hallenbeck | 40 | 2 | 5 |
| 1958 Ludington | 8 | 3 | 38 |
| 1958 Clarke | 62 | 5 | 8 |
| 1958 Dubuque | 60 | 9 | 15 |
| 1958 Hanlon | 43 | 8 | 18.6 |
| 1958 Child | 100 | 5 | 5.0 |
| 1958 Linton | 200 | 4 | 2.0 |
| 1961 Linton | 137 | 10 | 7 |
| 1961 Wantz and Payne | 101 | 3 | 3 |
| 1961 Mc. Dermott | 237 | 35 | 15.0 |
| 1962 Mikkelsen | 230 | 16 | 6.9 |
| 1963 Rousselot | 104 | 6 | 5.7 |
| 1963 Bendett | 11 | 1 | 9.1 |
| 1963 Schriefers | 125 | 2 | 1.6 |
| 1964 Tabaqchali and Dawson | 35 | 5 | 14.3 |
| 1964 Liebowitz | 50 | 8 | 16 |
| 1965 Wilkinson and Riddell | 65 | 5 | 7.7 |
| 1966 Sedgwick | - | - | 5.0 |
| 1969 Orloff | 58 | 14 | 24 |
| 1970 Voorhees | - | - | 12.0 |
| 1971 Foster | - | - | 4.0 |
| 1971 Hermann and Taylor | 75 | 1 | 1.3 |

dence of ulceration – and that is the *virulent behaviour* of postshunt peptic ulcers.

Several animal experiments were undertaken in search for a causal factor. Dubuque e.a. (1958) found a threefold increase in 24-hour acid output from Heidenhain pouches in dogs after side-to-side portacaval shunt and ligation of the portal vein close to the liver. Daily histamine stimulation actually caused death from duodenal ulcer much sooner than in normal controls.

They suggested that an agent produced by the liver, or one whose metabolism is decreased in the liver, might be responsible.

Clarke e.a. (1958) also showed a substantial increase of acid secretion from a Heidenhain pouch after portacaval transposition. This increase was markedly reduced by fasting and persisted after resection of the gastric antrum. They suggested a humoral secretagogue originating in the abdominal viscera and normally inactivated by the liver.

Castaneda (1961) found that postshunt gastric acid hypersecretion persisted in dogs, in which either the proximal or distal half of the small bowel had been resected, and suggested that the secretagogue originated from the entire small intestine.

Kohatsu (1959) observed that shunting resulted in hypersecretion in dogs in which the cephalic and antral phases were inoperative, and concluded that secretion was due to a gastric secretory hormone or secretagogue produced by the intestine on contact with food. The nature of this humoral agent is unknown, but it may well be an intestinal form of gastrin, easily inactivated on passage through the liver (Thompson, 1969). Gastrin itself does not seem to play an important role.

It is difficult to interpret these experimental data, mostly derived from dog-experiments, against the background of clinical information.

There is general agreement that acid output is diminished in cirrhotic patients (Clarke, 1958; Ostrow, 1960; Bendett, 1963; Scobie, 1964).

Cirrhotic patients with a symptomatic ulcer have a significantly higher level of gastric acid secretion than those without such lesion, but the acid levels are still within normal limits (Ostrow, 1960; Liebowitz, 1964).

The reports of gastric secretory studies on shunted patients are *not* in general agreement. In those studies that were performed before and after shunting on the same patient, there was great variability in the responses of both basal and histamin-stimulated acid secretion (Ostrow, 1960; Bendett, 1963; Schriefers, 1963; Tabaqchali, 1964; Wilkinson, 1965).

Thus, the mechanism for postshunt hypersecretion in dogs has not yet

been completely unravelled, whereas hypersecretion in shunted patients has not been documented satisfactorily.

Even if gastric secretion is changed after portacaval anastomosis, it must be kept in mind that the incidence of peptic ulcer after shunt surgery might not be different from the incidence in cirrhotic patients who have not had this operation. Therefore it is extremely difficult to understand whether these changes in gastric acid secretion are of any importance in the genesis of peptic ulcers. (Irvine, 1962; Tabaqchali, 1964).

Peptic ulcer in the general population.

Estimates of the incidence of peptic ulcer in the population at large are open to criticism on many grounds. No two reports on this subject are comparable because no generally accepted criteria and statistical principles exist concerning pathological types and sites of ulcer, standards of examination, age groups or population at risk.

Since no widely accepted method of classification of subjects as "ulcer" or "non-ulcer" patients exists, major errors of interpretation must be expected and admitted as the diagnostic tests for ascertaining the presence and location of an ulcer each will have its own false negatives and false positives. The magnitude of these errors in classification are not known or at least not agreed upon.

As Watkinson (1960) pointed out in his excellent comparison of two major surveys, "necropsy statistics can be likened to corsets, as undesirable, uncomfortable, frequently giving a fallacious impression of truth, yet in special selected circumstances forming a basis for deduction, and at all times much sought after".

Between 1930 and 1950 duodenal ulcer was recognized as a frequent disorder, especially in males.

Ivy (1946) thought that one male in 10 would harbour a duodenal ulcer by age 65, a figure cited over and over again. The Leeds survey of 20,000 autopsies between 1930 and 1949 showed an overall incidence of duodenal and gastric ulcer, both active and inactive, in the male population over 35 year of age, of 17 to 23 per cent. A multicentered study in England and Scotland in 1956 showed a much lower incidence with 8 to 12 per cent.

The decrease however, is almost entirely due to the difference in chronic ulcers; the totals for acute and subacute ulcers are nearly identical in the two studies with 2.5 and 2.6 per cent respectively.

In this study (Watkinson, 1960) it was concluded that the best estimate of the incidence of ulcer in the population as a whole could be made from the frequency of ulcers found in patients dying from causes other than peptic ulcer.

Sturdevant (1976) reported the conclusions reached on a conference on the epidemiology of peptic ulcer (California, 1975). The incidence of duodenal and gastric ulcer in the United States and the United Kingdom, seems to have reached a peak some 20 years ago and is now declining. Mendeloff (1974) demonstrated the remarkable rapidity of this decline, amounting to almost 8 per cent per year for 1967 to 1971.

Table 3: Incidence of peptic ulcer in non-cirrhotic patients

| | <i>author</i> | <i>Incidence in %</i> | <i>population</i> |
|------|--------------------|-----------------------|--|
| 1932 | Alvarez | 3.3 | Mayo Clinics |
| | Steigman | 0.88 | Cook County Hospital |
| | Jamison | 1.38 | Metropolitan Life Insurance Co. |
| | Drammen | 2.45 | 21,918 adults >15 years |
| 1949 | Lipp | 3.9 | Veterans Adm. Hosp. 112,670 pat. 4429 ulcer |
| 1952 | Lipp and Lippsitz | 6.6 | 1000 autopsies >35 years |
| 1952 | Puccini | 2.41 | 29,909 autopsies |
| 1953 | Antonini | 1.77 | 6859 autopsies >19 years |
| 1955 | Fainer and Halsted | 10.6 | 1184 autopsies |
| 1958 | Enquist | 4.6 | 1000 autopsies |
| 1968 | Blumenthal | 1.9 | |
| 1971 | Jackson | 4 | General Veteran Population in the U.S. between 20 - 64 years |

Summary and conclusions chapter I

The coexistence of peptic ulcer disease and portal cirrhosis is sometimes referred to as being 'classical'. The literature about this association however, is very conflicting and inconclusive. Reported incidences vary from 2 to 42 per cent, but in retrospect these figures cannot be compared because of the difference in criteria for the definition of "ulcer" and "cirrhosis". The major difference in incidence is seen between studies based on autopsies and those on clinical assessment. On the other hand the data about the incidence of peptic ulcer in the population at large are not unanimous.

For the very same reasons it is difficult to discern whether an increased incidence of peptic ulcer exists after portacaval decompression operations. The single most important fact on which all authors agree is the ominous character of these ulcers when they start bleeding, a complication which is encountered far more than perforation.

Massive upper gastrointestinal bleeding in a patient with cirrhosis therefore has specific acute problems, both in diagnosis and treatment. Reports on mortality after medical or surgical treatment of these ulcers are only incidental.

Experimental evidence that portacaval anastomosis results in an increased acid output in dogs could not be confirmed in the clinical situation. The hypothesis of a humoral agent arising from the small intestines and causing hypersecretion is challenging.

CHAPTER II

Angiography in the diagnosis and treatment of massive upper gastrointestinal bleeding

Percutaneous selective angiography

Percutaneous selective celiac and superior mesenteric arteriography was first described in detail by Ödman in 1956 and 1958. Using this technique, Nusbaum and Baum (1963) were able to demonstrate bleeding points of 0.5 ml per minute in dogs. Two years later they reported on 5 patients in which gastrointestinal bleeding was diagnosed by this method, which appeared to be more advantageous than the segmental mesenteric angiography during operation suggested by Margulis (1960). As an outgrowth of the interest of this surgical-radiological team Nusbaum and Baum did further experimental work on dogs in the field of liver cirrhosis and portal hypertension. They tried to control intestinal bleeding with vasoconstrictive drugs. Since the experimental work of Kehne (1956) and Davis (1957), and their early experience with reducing portal pressure by *intravenous* injection of vasopressin in patients with esophageal varix bleeding, "surgical Pituitrin" had been utilized universally for many years. However, the rather large doses of vasopressin, 40 to 80 U in 250 ml of saline, which had to be given over a relatively short period of time were found to have side effects as coronary constriction (Slotnik, 1951; Beller, 1971), decrease in cardiac output (Drapanas, 1961), and bowel spasms causing abdominal discomfort (Shaldon, 1961). In addition to this, repeated dosages of vasopressin could cause a tachyphylactic reaction so that increasing or repeating the doses produced less peripheral vascular response (Kehne, 1956). For these reasons many clinicians had abandoned the use of vasopressin or reserved it for desperate situations only.

In 1967 Nusbaum and Baum published their conclusions of experiments with dogs using various vasoactive drugs. They continuously infused

various dosages of pharmacologic agents through a catheter, directly into the superior mesenteric artery by means of an infusion pump. Epinephrine, norepinephrine and angiotensin were found to produce constriction of splanchnic vessels and a decrease of portal flow, but they also produced an increase of portal outflow resistance. Therefore no sustained hypotensive action was seen from these drugs (Steckel, 1968; Rösch, 1970; Swan and Reynolds, 1971).

Vasopressin (pituitrin) and vasopressin derivatives, like phenylalanine-lysine-vasopressin (Tsakiris, 1964), were found to produce splanchnic vasospasm without causing a portal outflow block. It produced a decrease to an average of 58 per cent of superior mesenteric arterial flow; a decrease of portal inflow; and – most important – a decrease of portal pressure. When continuously infused, vasopressin showed a prompt and sustained portal hypotensive action in normal dogs, averaging a decrease of 20 per cent of preinfusion pressure. In dogs with induced portal hypertension the decrease even averaged 50 per cent.

In the dosages that were used, 0.1-0.2 U per ml per minute, no side effects were seen: no change in cardiac output, no ischemic changes of the bowel, no change in pH, pCO₂, or oxygen saturation of both portal and superior mesenteric arterial blood.

Clinical experience with intra-arterial vasopressin infusion

Clearly these experimental data had to be followed by clinical experience. In 1968 Nusbaum and Baum reported on the first two patients with massive hemorrhage from esophageal varices, successfully managed utilizing selective mesenteric arterial drug infusion. Two years later they reported on 13 patients with variceal bleeding, that had been controlled in 12 of them. More over, 3 patients with *arterial* bleeding had been treated successfully with intra-arterial vasopressin infusion of 0.2 pressor units per ml per minute for five to seven days. (Baum and Nusbaum, 1970). In addition to controlling the bleeding, continuation of the same infusion during the actual portacaval shunt operation permitted an easier operation, with relatively low portal venous pressure and with less than anticipated bloodloss (Marubbio, 1973). The advantage over hypotension induced by anesthetics is the avoidance of decreasing hepatic arterial flow, which – especially in cases of cirrhosis – could be harmful. Fortunately, a decrease of portal venous

flow has been shown to result in an increase of hepatic arterial flow thus protecting total liver bloodflow (Heimbürger, 1960; Ternberg and Butcher, 1965; Brant, 1972).

In 1973 Baum, Athanasoulis and Waltman described their experiences with 160 patients suffering from gastrointestinal bleeding, diagnosed with angiography and treated with direct arterial infusion of vasopressin. The majority of their patients had bleeding esophageal varices, but a variety of other bleeding conditions were also treated this way: Mallory-Weiss tears at the cardio-esophageal junction; bleeding esophagitis associated with hiatus hernias and iatrogenic tears of the distal esophagus, due to trauma associated with inflating a Blakemore-Sengstaken tube; gastric, duodenal and anastomotic ulcers; hemorrhagic gastritis and stress ulcers; tumors and hemorrhagic telangiectasis; postoperative bleeding; bleeding of colonic inflammatory disease and colonic diverticula.

By this time several other authors had reported their experiences, mostly on bleeding varices (Rösch, 1970; Steckel, 1971; Rösch and Dotter, 1971 and 1972; Conn, 1972; Brant, 1972; Marubio, 1973). Successful treatment, defined as complete cessation of bleeding during the infusion, was stated to be as high as 80-90 per cent. Poor results (success rate only 22 per cent) were reported by Murray-Lyon (1973). There is less experience and probably less success in treating patients with hemorrhagic gastritis and bleeding peptic ulcers by this method (Morello, 1972; Athanasoulis, 1973; Rau, 1974). Athanasoulis (1974) reported on 50 patients with acute gastric mucosal hemorrhage. Vasopressin was infused selectively into the artery supplying the bleeding in 37 of these patients, resulting in control of the bleeding in 31 of them, or 84 per cent (62 per cent of the total group).

"Control of the bleeding" was now defined as: "no clinical evidence of bleeding for at least five days after discontinuation of the vasopressin infusion". The clinical criteria were: nasogastric aspirate clear; no blood transfusion requirements; and stable hematocrit, blood pressure and pulse rate. In 8 patients vasopressin infusion could not be instituted because it was technically not possible to catheterize the appropriate artery selectively.

In 46 patients it was attempted to catheterize the left gastric artery, which in the majority of patients proves to be the bleeding artery. Catheterization was successful in 33, giving a technical failure rate of 28 per cent. This emphasizes the relative difficulty of this technique that was described in detail by Waltman (1973). With increasing experience however, the success rate will increase too.

The next step in the application of angiography and vasopressin infusion was

in the diagnosis and treatment of *nonvariceal* bleeding in patients with cirrhosis and portal hypertension. Selective arteriography had gained increasing acceptance as a safe and reliable procedure for localizing acute arterial bleeding as well as demonstrating hepatofugal flow with esophageal or gastric varices. It was known from experience with vasopressin infusion for variceal bleeding that this type of treatment could be used in cirrhotic patients, including those that were poor operative risks. Ring (1974) reported on 13 cirrhotic patients with angiographic evidence of portal hypertension, who had major upper gastrointestinal hemorrhage and in whom an arterial bleeding point could be demonstrated in the distal part of the esophagus, in the stomach, or in the duodenum. In 11 of the 13 patients vasopressin infusion into the bleeding artery resulted in immediate cessation of the bleeding. The two patients in whom the bleeding did not respond to vasopressin infusion both underwent emergency operations and died. Four of the 11 patients in whom the bleeding was controlled, died within one month after the infusion, one of these after operation for recurrent bleeding. Only seven of the 13 patients survived the bleeding episode without further surgical therapy and were discharged from the hospital.

At this point it is probably worthwhile to make a few comments and raise some questions. Most important is to realize that whenever in these quoted series is spoken of "success rate" or "control of bleeding" this refers to *selected patient material*. All these studies were retrospective and few data about prospective randomized series are as yet available (Conn, 1975). Secondly, in most series about cirrhotic patients no specifications are given about the degree of cirrhosis, whether expressed in Child's classification or otherwise. Therefore it is impossible to compare, or calculate what the possible risk or success would have been after surgical treatment. The same is true for the degree of bleeding. Lastly, no follow up on the long term is available up to now. Thus controlled data about long term survival and rebleeding will have to follow before definite conclusions in this respect can be drawn. In the only prospective controlled clinical trial up to now, Conn (1975) concluded that although vasopressin was more effective in controlling variceal bleeding than conventional therapy, it did not affect patient survival.

Complications of vasopressin infusion

There are two sorts of potential problems: those related to the catheter,

and those related to the action of vasopressin. There have been remarkably few reports about complications of either sort (Athanasoulis, 1976).

Complications related to the catheter

Oozing from the catheter insertion in the groin, during infusion or after withdrawal of the catheter, is often seen in patients after multiple blood-transfusions resulting in low platelet counts, or in patients with abnormal clotting mechanisms. Mild pressure to the groin is usually sufficient to control the oozing and very rarely infusion has to be stopped for this reason. *Arterial thrombosis* at the site of the catheter insertion had never occurred in over 160 cases reported by Baum (1973), but Murray-Lyon (1973) found a non-occlusive thrombus at autopsy in two patients, one in the aorta and one in the femoral artery at the site of the catheter. Conn (1972) described a patient in whom arterial emboli had resulted in absent pulses in the lower extremity. Athanasoulis (1976) states that the frequency of arterial thrombosis is not higher than in patients undergoing visceral angiography for diagnostic purposes, reported to be 0.02 per cent by Meaney (1973). Marubbio (1973) reported a *laceration of the femoral artery* which necessitated subsequent surgical repair. Arterial surgery was necessary in 3 out of 19 patients reported by Murray-Lyon (1973). Nusbaum (1972) reported on a false aneurysm at the site of catheter insertion, the catheter having been in place for two weeks.

Dislodgement of the catheter is reported now and then, most frequently by Murray-Lyon: six times in 18 patients.

In general, it can be stated that the complications related to the catheter are essentially the same as those that will be encountered when catheterization is done for diagnostic purposes only. Nevertheless it is difficult to avoid bias. Complications occurring during angiography are not necessarily due to the catheterisation. In a very elegant study Baum (1966) reviewed patients in whom a scheduled angiographic examination was cancelled for some reason. The reasons frequently turned out to be the very same complications (like myocardial infarction) which sometimes occurred *following* angiography, and which now apparently had happened just *before* angiography.

Complications related to vasopressin

The side effect most frequently encountered, in spite of the low doses given intra-arterially, is a decrease in urinary output caused by the *antidiuretic*

action of vasopressin. This action will accentuate the well documented reduction in free water clearance in cirrhosis (Chaimovitz, 1972). Monitoring of fluid input and output, hematocrit values, central venous pressure, and electrolytes is mandatory. Marubbio (1972) reported a patient with severe hyponatremia mimicking hepatic encephalopathy. A much more serious complication is small bowel *necrosis*, secondary to thrombosis of the superior mesenteric artery or vein. This fatal complication was described by Conn (1972), Renert (1972) and Berardi (1974). Although ischemic changes were never seen in the original dog-experiments in which relatively high doses of vasopressin were used, differences in individual response to vasopressin may lead to more extensive vasoconstriction than anticipated. Therefore, a control angiogram after 10-20 min. of infusion is mandatory. A control angiogram was not mentioned in the case report of Berardi, who infused a high dose (0.3 U/min.). These precautions are even more pressing when dealing with a patient who is in shock at the beginning of the infusion. Intermittent infusion, as recommended by Rösch (1970), is not proven to be safer, and the effect is unpredictable.

Spontaneous mesenteric venous thrombosis had been reported to occur rather frequently in patients with cirrhosis (Johnson, 1949; Van Way, 1971). In the majority of such cases the portal vein was occluded as well, which should be readily identified with angiography.

Infusions into the left gastric artery theoretically carry a low risk of ischemia, considering the extensive intra-arterial anastomotic system of the stomach as demonstrated by Barlow (1951) and Reid Brown (1952). Here, the major risk is catheter dislodgement into the hepatic artery, with the possibility of endangering arterial bloodsupply to an already compromised liver. The great variety in hepatic bloodsupply adds to this problem (Athanasoulis, 1976). Whereas in experimental animals and non-cirrhotic subjects infusion into the hepatic artery does not evoke changes in liverfunction tests (Barr, 1975; Athanasoulis, 1976), in patients with cirrhosis it is thought to jeopardize hepatic function and has been shown to cause infarction of the liver as reported by Marubbio (1973).

Cardio-respiratory complications were reported by Conn (1972): 5 patients with bradycardia, 1 patient with a non fatal cardiac arrest and 1 patient with respiratory arrest. The same author reported on the problem of *infectious disease* in cirrhotic patients, by describing one patient with spontaneous peritonitis and 4 patients with bacteremia and positive cultures from the cathetertips.

Summary and conclusions chapter II

Percutaneous selective celiac and superior mesenteric arteriography has become a widely used and accepted method for demonstrating gastrointestinal bleeding.

Experimental evidence that intra-arterial infusion of vasoconstrictive drugs, like vasopressin, is followed by a sustained portal venous hypotensive action, as a result of a decreased mesenteric arterial inflow, has resulted in therapeutical applications in the clinical situation.

Both bleeding esophageal varices and other bleeding conditions, like hemorrhagic gastritis and bleeding peptic ulcers, have been treated with selective arterial vasopressin infusion.

Reported success rates and complication rates vary, but there is general consensus that the method is relatively safe, and has less side effects when compared with single injections of vasopressin intravenously.

Continuous arterial vasopressin infusion can be used as an adjunct to surgical therapy, but also as an equivalent of surgical intervention.

Patients with cirrhosis of the liver and portal hypertension constitute a special diagnostic and therapeutical problem when they are admitted to the hospital with massive upper gastrointestinal bleeding. Selective catheterisation may accurately identify whether the bleeding is caused by ruptured esophageal varices, or by hemorrhagic gastritis or peptic ulcers. Vasopressin infusion through the same catheter may lead to cessation of the bleeding, especially in patients who are considered "high risks" for portal decompression operations or any other kind of emergency surgical intervention.

However, no sufficient data from controlled studies are available at present; prospective randomized studies will have to follow in order to evaluate the merits of selective intra-arterial vasopressin infusion, with respect to control of the bleeding and survival of the patient.

CHAPTER III

Classification methods in portal hypertension

Classifications based on liver function tests

Emergency surgical procedures for bleeding esophageal varices carry a high mortality rate, averaging between 30 and 70 per cent.

It is not surprising therefore that whenever possible, emergency shunt operations are avoided. Because the major cause of death after emergency surgery consists of hepatic insufficiency, it was a logical step to try to assess hepatic function preoperatively, in order to measure the extent of liver damage caused by the cirrhosis and to appraise the chances of survival.

A second set-back after portacaval decompression is the development of encephalopathy, occurring in 10-20 per cent of those patients who survive the operation. This problem had prompted a search for preoperative criteria which could predict the probability of developing encephalopathy.

The third factor which has influenced the demand for preoperative assessment of cirrhotic patients was the early recognition that shunting procedures did prevent recurrent bleeding, but did not prolong life expectancy.

Of the different methods that have been devised for assessing "hepatic function" or "functional hepatic reserve", the classification of Child (1964) is the best known and generally accepted method.

Child (1954) tried to identify the variables of liverfunction which are decisive for the capacity of a patient and his liver to withstand the stress which is inherent to massive blood loss and a major operation, as well as the resulting factors like altered hepatic bloodflow.

He divided patients into three different groups:

A - with good liver function, B - with moderately impaired hepatic function and C - with advanced hepatic dysfunction.

Assignment of patients to one of these three groups is done on clinical and laboratory criteria as outlined in table 4.

This classification was advocated as being "useful, logical and generally understood by all physicians and surgeons". We do agree that his classification is useful or at least widely accepted and used. Whether it is generally understood and therefore interpreted in the same way as Child intended we do not know, but there is reason to doubt this (see later). In his own patient material this classification identified three groups with a clearly significant difference in post-operative mortality after end-to-side portal decompression. In a total of 128 patients the mortality rate for groups A, B and C was 0.0, 9.0 and 53.0 per cent respectively. He did not mention however, how many patients were operated electively and how many as an emergency procedure, nor did he mention whether the indication for operation was bleeding or - for instance - intractable ascites.

Wantz and Payne (1961), using the same criteria, reported mortality rates of 4.4, 10.4 and 47.4 per cent for groups A, B and C. The high mortality in group C is mainly caused by the patients in this group who underwent an *emergency* portacaval shunt; this group carried a mortality of 62.0 per cent. Patients in group C who underwent a elective shunt operation did much better.

Turcotte (1973) used Child's criteria on 247 patients and found essentially the same differences in mortality, again with a 60 per cent mortality after emergency operations in group C.

Table 4: Clinical and laboratory classification of patients with cirrhosis in terms of hepatic functional reserve. (C.G. Child, III, 1954)

| group designation | A minimal dysfunction | B moderate dysfunction | C advanced dysfunction |
|-------------------|--------------------------|---------------------------|---------------------------|
| serum bilirubin | < 2.0 | 2.0-3.0 | > 3.0 mg % |
| serum albumin | > 3.5 | 3.0-3.5 | < 3.0 gm % |
| ascites | none | easily controlled | poorly controlled |
| encephalopathy | none | minimal | advanced, coma |
| nutritional state | excellent | good | poor, wasting |

Several other methods were devised as experience with portacaval shunting grew, simultaneous to the discontent with existing methods. None of these methods have become widely accepted, but some are mentioned here for review purposes. Linton (1951) was one of the first to discriminate between "serious" and "good" operative risk, basing his definitions on the same parameters as Child, with inclusion of cephalin flocculation test, BSP-retention test and prothrombin time. The problem with this kind of classification is that Linton depicts a "standard ideal" and a "standard high risk" patient, overlooking the fact that most patients do not fit in either group.

McDermott (1960) tried to solve this problem by calculating a "liver index" (see table 5), thus creating a wide range in the degree of operative risk.

A liver index between 0 and 2 is comparable to group A as defined by Child.

Originally this classification was described for the treatment of ascites, but later it was applicated to patients with bleeding esophageal varices without rendering an account of the considerations leading to this step. (McDermott, 1974).

Mikkelsen (1962) considered a patient arbitrarily a "poor risk" if two or more of the following features were present: serum bilirubin >4.0 mg/100 ml; serum albumin < 3.0 gm/100 ml; presence of ascites; presence of encephalopathy. Mortality rates were 68 per cent in the "poor risk" group against no death in the "good risk" group (0 or 1 of the above features).

Lindenmuth and Eisenberg (1963) tried to focus not only on postoperative

Table 5: Liver index (W.V. McDermott, Jr., 1974)

| rating for liver index | 0 | 1 | 2 | 3 | 4 | |
|---------------------------------|------|------|------|------|------|---------|
| BSP-retention | < 4 | <10 | <20 | <30 | >30 | % |
| albumine | >3.9 | <4.0 | <3.5 | <3.0 | <2.5 | gm % |
| bilirubine | <1.0 | <1.5 | <3.0 | <6.0 | >5.9 | mg % |
| alk. fosfatase | <4.0 | <6.0 | <15 | <30 | >29 | Bod. U |
| cephalin floccu- lation test | 0 | 1 | 2 | 3 | 4 | 48 hrs. |
| prothrombine time | > 80 | <80 | <60 | <40 | <20 | % of N |

mortality, but also on postoperative complications of woundhealing and hemorrhage. Three groups of *mild*, *moderate* and *severe* cirrhotics were formed, based primarily on BSP-retention test and serum albumin. These three groups had a complication rate of 17, 21 and 35 per cent respectively after a variety of surgical procedures.

Hermann e.a. (1966) also classified patients as "good" or "poor" hepatic risks, based on essentially the same clinical and laboratory criteria and reported mortality rates of 9 and 28.5 per cent. (Hermann and Taylor, 1971). Leger (1967) from Paris calculated a "clinical coefficient" and stated that patients with a score up to 20 were operable; those with a score of 21-24 were doubtful; and those with a score of 25 or more were inoperable. He does not give a logical explanation for this system and it is doubtful whether such logic does exist. There is certainly no reason to assign 2, 4 or 6 points to a single feature instead of 1, 2 or 3 points.

Galambos and Warren (1976) reported on a selection system based on a quantitative estimate of what they called one of the real liverfunctions: the maximum rate of urea synthesis. Although they could empirically define a critical value for the likelihood of developing encephalopathy after shunt-operations, the test had no predicting value for the risk of postoperative mortality.

Nevertheless, this type of test is attractive because one actually deals with measuring the functional activity of the remaining liver cells. This

Table 6: Clinical and biological calculation of operability (L. Leger, 1967)

| | |
|--------------------------------------|---|
| age > 60 yr. | 4 |
| hemorrhage recurrent or longstanding | 4 |
| ascites not responding to therapy | 4 |
| edema of the legs | 2 |
| jaundice | 4 |
| coma or pre-coma | 6 |
| persistent anemia | 2 |
| low prothrombin, not improving | 4 |
| pro-accelerlin decreased | 2 |
| thrombocytopenia < 100.000 | 2 |
| impaired liver functions | 2 |
| severely impaired liver functions | 4 |
| azotemia > 1 γ /ml | 2 |
| albumin < 30 g/100 ml | 4 |

activity, in turn, depends on the capability of circulation and respiration to supply these liver cells sufficiently with oxygenized blood (Stahl, 1971). The general circulatory and respiratory status of a patient is therefore closely related to the functional capacity of the hepatocytes. Cardiac insufficiency, even when it is not clinically recognized, may cause terminal liver insufficiency which is so much more easily diagnosed as a cause of death.

Classifications based on hemodynamic studies

Del Guercio (1964) based his studies on the assumption that the patho-physiologic changes in systemic- and pulmonary circulation which are seen in patients with cirrhosis, are comparable to circulatory changes as seen in septic shock. Spider angiomas, warm red palmar skin, bouncing pulse, widened pulse pressure and decreased circulation time, are all manifestations of a decreased peripheral resistance with arteriovenous shunting, leading to increased cardiac output. This arteriovenous shunting is supposedly caused by a humoral vasodilating factor, comparable to endotoxines in septic shock. By analyzing a multitude of hemodynamic and respiratory parameters he defined the "hyperdynamic cardiovascular state", as originally described by Gorling (1962). A patient with this hyperdynamic cardiovascular state is more likely to develop cardiac insufficiency, resulting in hepatic insufficiency and death.

Although this explanation is purely hypothetical, Siegel, Greenspan and Del Guercio (1968) were able to differentiate between patients with a high (70%) probability of mortality and those with a low (5%) probability. Their conclusions were drawn on analysis of cirrhotic patients who underwent an *elective* operation for portal decompression. Whether this method, based on advanced measurement techniques, will also be valid and applicable in the acute situation of a massively bleeding patient is open to discussion, but deserves to be tested. Siegel (1969 and 1974) even introduced a computer based "survival index" for the prediction of operative survival. This survival index enabled preoperative separation of cirrhotic patients into three groups with a probability of survival of > 90%, 50% and < 20% respectively.

The method is also claimed to discriminate in patients who show no significant differences when conventional liver function tests are applied. The major advantage of this computer evaluation is the *dynamic* information that can be obtained, indicative of a positive or negative trend.

Parameters of liver function

With the evidence at hand that classification methods, like the one Child advised, do work and are able to predict surgical mortality rates, it is important to realize that most of the "liverfunction-tests" that are currently in use do not measure the essential metabolic functions of the liver, such as deamination of amino acids or the maintenance of blood sugar levels (Snell, 1957). Little if any correlation should be expected of these tests with the histologic appearance of liver cells as shown by needle biopsy.

The best of these tests are relatively crude; most of them are affected to some extent by extraneous factors and all are subjected to laboratory error. The range of biologic activity of the liver parenchyma is far too great to permit any simple or easy approach. However, the same liverfunction tests can contribute a great deal to the clinical appraisal of a patient with liver disease, especially when used in combination with a number of tests. In order to appraise the relative value of these conventional liverfunction-tests a short discussion on some of these tests is given.

Serum bilirubin

The determination of bilirubin in blood serum as first described by Hijmans van den Bergh and his associates, identifies two main types of Ehrlich reaction, a direct and an indirect. In the literature on cirrhosis serum bilirubin values are almost without exception given as *total bilirubin values*.

Total bilirubin is not a sensitive indicator of hepatic dysfunction and may not accurately reflect the degree of liver damage. Moderate hepatic parenchymal damage does not necessarily lead to hyperbilirubinemia. The capacity of the human liver to remove bilirubin from serum before hyperbilirubinemia ensues is at least twofold greater than the daily pigment load of 250 to 300 mg normally presented to this organ (Combes and Schenker, 1975). The pigment load will be increased in cases of multiple blood transfusions, the bilirubin concentration of transfused blood being $< 2 \text{ mg}\%$ ($< 34 \mu\text{mol/l}$) and free serum hemoglobin in banked blood usually being $< 10 \text{ mg}\%$. Gilligan and his co-workers (1941) observed that a single injection of hemoglobin was cleared in six hours with little change in serum bilirubin concentration. Thus an elevation of serum bilirubin resulting from transfusions could be an indication of abnormal hepatic function.

Under normal circumstances and in a steady state the height of serum bilirubin will accurately reflect the intensity of jaundice and the increase in total blood pigment. Presence in the serum of substances like salicylates, sulfonamides and free fatty acids can transiently lower the serum bilirubin concentrations by displacing bilirubin from its attachment to plasma albumin and enhancing the transfer of the pigment into tissues. On the other hand increased serum albumin concentrations may induce a temporary shift of bilirubin from tissue sites into the circulation, thus increasing the serum bilirubin level.

Whether such a shift will play a role in patients who receive multiple albumin infusions daily is not known.

Protein metabolism

Serum albumin is one of the most accurate indicators of parenchymal liver disease. It should be realized however that serum albumin alone is not a parameter for albumin production. Serum protein levels in liver disease are usually the product of a depressed albumin fraction and a raised globulin fraction, primarily due to an increase in gamma-globulin.

In alcoholic patients with cirrhosis a low serum albumin level may in part be due to other causes, like protein malabsorption and nutritional deficiencies. Serum albumin levels below 3.0 - 2.6 gm % are usually considered to carry a poor prognosis for patients undergoing operation, although some doubt has been raised on this conception (Lindemuth, 1963; Orloff, 1967; Turner, 1974). The extent of the protein alterations appears to depend on both the severity and the duration of the hepatic disease. Well-compensated cirrhotics of the alcoholic-nutritional and postnecrotic types may show a persistent hyperglobulinemia with normal serum albumin. Progression of the disease is frequently indicated by a progressive fall in albumin and rise in globulins.

Bromsulphalein retention test (B.S.P.)

The determination of residual dye in blood 45 minutes after a test dose of Bromsulphalein is the oldest test for determining functioning hepatic cell mass.

The metabolic clearance rate for B.S.P. in the liver is high, and therefore depends on hepatic bloodflow. It is evident that changes in hepatic bloodflow will significantly affect the results of the Bromsulphalein test.

Hepatic bloodflow is changed in patients with cirrhosis, due to spontaneous

hepatofugal shunting of portal bloodflow. Arterial hepatic bloodflow is decreased in patients with hypovolemic shock; this is particularly true in cases of massive bleeding from the gastroduodenal artery.

Other clinical situations like fever, heart failure, massive ascites and high bilirubin levels will render the test inaccurate (Enquist, 1958).

On these grounds we would consider this test useless in the situation of a massively bleeding cirrhotic patient, who is likely to be in shock, have elevated bilirubin levels and who may very well have ascites.

Laboratory tests of hemostasis

Although it was generally believed that the abnormalities of hemostasis, well known to occur in liver disease, predispose to hemorrhage, this fact was never clearly established until fairly recently.

Spector and Milton (1967) demonstrated that some of the clotting factor deficiencies are more common, or more severe, in those patients with cirrhosis who actually *do bleed* than in those who do *not bleed*.

The liver is a site of synthesis of the factors: I (fibrinogen), II (prothrombin), V (proaccelerin), VII (serum prothrombin conversion accelerator), IX (Christmas factor, plasma thromboplastin component or PTC) and X (Stuart-Prower factor).

It was previously considered that hypofibrinogenemia was a significant factor in the production of hemorrhage in liver disease. Subsequently this has been shown to be not true, probably because fibrinogen is also produced by the extrahepatic reticulo endothelial system (Spector, 1967).

The *one-stage prothrombin time* as first described by Quick e.a. (1935) not only reflects the level of prothrombin (factor II) in the plasma, but also the levels of factors V, VII and X. Any of these factors may be deficient in patients with liver disease and each affects the prothrombin time.

As the factors II, VII and X are so-called vitamin K-dependent factors, the one-stage prothrombin time is frequently prolonged as a result of vitamin K deficiency. Walls (1971) suggested that all bleeding patients with liver disease should be given 10 mg of vitamin K parenterally daily, irrespective of the one-stage prothrombin time as this may be normal despite a gross deficiency of protrombin (Mindrum, 1959). On the other hand, when 10 mg vitamin K is given parenterally to a cirrhotic patient having a prolonged prothrombin time, it is generally considered to carry a poor prognosis if prothrombin time does not return to normal within 24 hours (Schiff, 1975; Linton, 1974). Factor V is independent of vitamin K. This factor may be

diminished more frequently and to a greater extent in patients with clinically more severe cirrhosis (Marchal, 1960).

The fourth vitamin-K dependent factor is factor IX. Low levels of factor IX appear to be more closely related to the occurrence of hemorrhage than do subnormal levels of factors V, VII and X. The *thrombotest* seems to be a good indicator of factor IX levels in patients with chronic liver disease.

Spector (1966) showed that transfusions with fresh frozen plasma could reduce abnormal prothrombin times to within three seconds of control values. Large volumes (600-1800 ml daily) however, were necessary to produce and maintain this effect. From this observation, it would follow that the prothrombin times recorded preoperatively are not likely to be influenced by multiple bloodtransfusions, unless large amounts of *fresh* blood are given.

Summary and conclusions chapter III

The high postoperative mortality, the development of encephalopathy and the problem of recurrent bleeding, have stimulated the search for classification methods for the selection of patients with cirrhosis and bleeding esophageal varices.

Of the various systems that have been proposed, the classification of Child, based on clinical and laboratory parameters of functional hepatic reserve, is widely known and universally accepted.

The parameters of liverfunction consist of conventional liverfunction tests. An important disadvantage of Child's classification, as well as of many other systems, is the wide range of overlap between the different groups. Other selection systems have been described, based on hemodynamic and respiratory parameters, but none of these have gained general acceptance. Whereas advanced technical equipment is necessary for assessment of hemodynamic functions, conventional liverfunction tests and clotting parameters are easily determined.

A short discussion is given on some of these tests, with special reference to sources of misinterpretation.

CHAPTER IV

Materials and method

Selection of patients

By employing the computer system used in the Massachusetts General Hospital for coding diagnoses, we reviewed all records since 1962 bearing a possible combination of the diagnosis of cirrhosis or portal hypertension and the diagnosis of peptic ulcer disease or surgical treatment thereof. At the time of this study patient records were coded only up till 1968. Records from 1969 till 1971 were compiled by examining the operation reports in the Operating Room files. All patients who underwent a gastrectomy or analogous operation were traced for a diagnosis of liver cirrhosis or portal hypertension.

All patient charts obtained by either method were checked whether they met the criteria for liver cirrhosis, massive non-variceal bleeding and emergency operation.

The charts of patients who received selective vasopressin infusion for the treatment of upper gastrointestinal bleeding, were collected by reviewing the angio-report files of the Department of Angiography in the Massachusetts General Hospital. Angio reports were examined over the 3 year period October 1971 to 1974. Patient charts were then checked and selected for the same criteria for cirrhosis and massive non-variceal bleeding. These criteria will be outlined in the following paragraphs.

Criteria and definitions

Diagnosis of cirrhosis

In the emergency surgery group the diagnosis of cirrhosis was based on histo-

logical examination in 48 patients, either by biopsy or at autopsy.

"Fatty livers" were not included. The diagnosis was accepted only when a written report of the pathologist was found in the records; the criteria used by the pathologist were accepted as such and not open to question, as this was not the purpose of the study.

In 6 patients the diagnosis was made in hospitals elsewhere, either by biopsy, or based on findings at laparotomy for other purposes. In 16 patients the diagnosis was based on clinical evidence only. A prerequisite in these cases was an unequivocal description of the macroscopic aspects of the liver, supplemented with symptoms or signs of portal hypertension. A long history of excessive alcohol intake without any clinical or histological evidence was not accepted as proof of liver cirrhosis.

In the vasopressin group the diagnosis of cirrhosis was based on histology in 21 patients, 16 x by biopsy, 5 x by autopsy. In 9 patients there was a clear description of the liver and portal system in earlier or following operations. In 2 patients the clinical picture together with the angiographic findings substantiated this diagnosis.

Non-variceal bleeding

A non-variceal bleeding was considered any bleeding in the upper gastrointestinal tract from a source other than esophageal or gastric varices.

Thus the bleeding source could be a duodenal or gastric ulcer*, hemorrhagic gastritis, a Mallory-Weiss tear, or a combination of any of these sources. In 6 cases of the emergency surgery group bleeding varices were present in addition to a non-variceal bleeding source. Usually these were localized in the gastric fundus. In all 6 cases it was stipulated that either on preoperative examination (endoscopy or angiography) or at operation these varices were established *not* to be the *major* cause of bloodloss. A number of patients were found to have some degree of gastritis in addition to bleeding varices: these patients were not included in this study.

On the other hand, when a patient was thought to bleed from esophageal varices, but on subsequent laparotomy was found to have a bleeding ulcer or hemorrhagic gastritis, this patient was included. Thus, all surgical interventions were aimed to stop or excise an arterial or capillary bleeding source. Nevertheless it is possible that during the same operation steps were taken to stop or prevent further variceal bleeding, either by ligation of varices or by a portacaval decompression procedure. When the source of bleeding could not be established either preoperatively or at operation, the patient was not included in the study.

*malignant gastric ulcers were excluded.

Massive bleeding

Until fairly recently no criteria were accepted to define the clinical description of "massive hemorrhage". As a result the many studies on this subject are not comparable and the conclusions are sometimes contradictory. Clinical manifestations like hematemesis and melena are usually associated with major bleeding, but they need not be present, nor is their absence a reason to justify exclusion of this diagnosis (Koomen, 1971).

Stewart (1948) restricted the qualification "massive" for those bleedings in which at least 40 per cent of the total amount of free circulating erythrocytes had been lost. Welch (1949) and Gott (1952) reversed this rule and called any blood loss that left 2,5 - 3 million erythrocytes a massive bleeding. Similar values were described for hemoglobin and hematocrit, the critical values being 8 gm% hemoglobin and 30 % hematocrit. Nowadays the ready availability of banked blood generally does not allow these values to drop to such critical values.

The clinical picture of hypovolemic shock, with the aid of objective measurements as bloodpressure, pulsefrequency, pulsepressure, central venous pressure, pulmonary artery wedge pressure, etc. is important information in the diagnosis of massive bleeding. There are however many different descriptions and definitions of "manifest clinical shock".

A probably more reliable method that is widely used now is the determination of how much blood or plasma is needed to restore these values to normal or to keep them stable over a given period of time (Andersen, 1968). This represents the most important factor in massive bleeding: the *rate of bleeding*. Clearly this cannot be determined by measuring only one parameter: repeated determinations of several clinical and laboratory parameters are necessary to describe in unequivocal terms the clinical picture of "massive bleeding". Fortunately these parameters need no special or expensive equipment: they can be determined in every hospital at any time. Foster (1971) combined these criteria in a clinically useful definition:

"massive hemorrhage is any hemorrhage requiring a minimum of 3 transfusions to stabilize vital signs, plus at least one of the following:

- a syncopal episode
- a hemoglobin < 10 gm% or hematocrit < 25%
- gross hematemesis which occurred *in* the hospital.

This definition was used in our study.

Emergency operation

The decision to operate a patient as an *emergency* is mostly mentioned by the surgeon in his preoperative evaluation of the problem and noted in the patient charts or operative reports. The notation "emergency" usually suggests that patients be taken to the operating room immediately upon admission to the hospital. This is not necessarily so.

From 12 to 48 hours can be consumed in arresting hemorrhage by non-surgical means and in restoring deficits in electrolytes, water and blood before operation is even considered. Foster (1971) defined emergency operation as "any operation taking priority over regular scheduled work in which the surgeon was forced to operate at a time earlier than he would ordinarily elect". We adopted this definition. The amenity consists of the possibility to include such common situations as shortage of banked blood for rare bloodgroups.

Patients who were admitted with evidence of massive bleeding, but in whom the bleeding had stopped spontaneously, and who were subsequently operated on following a regularly scheduled program, were classified as *elective* and not included.

Postoperative death

A death was considered postoperative mortality if it occurred within 6 weeks of the operation from any cause, or at any time during the same hospitalization if the cause could be related to the operation in any manner. A period of 6 weeks was arbitrarily chosen in view of the severity of the disease.

Control of bleeding with vasopressin infusion

Treatment with vasopressin infusion was considered successful when the bleeding had stopped during the infusion and no rebleeding occurred within at least five days after discontinuation of the infusion. When a patient was subsequently operated on an elective basis within five days, the bleeding was also considered to be completely controlled.

Criteria for *no rebleeding* consisted of clinical considerations: stable vital signs (bloodpressure and pulse) and stable hematocrit without blood transfusions. Blood transfusions that were given in this period to correct the previous bloodloss were excluded from these criteria. Rebleeding that occurred

six or more days after discontinuation of vasopressin infusion was considered to be *rebleeding after treatment*.

Statistical analysis

Non-Gaussian distribution of most data precluded useful interpretation of standard errors; for this reason standard errors will not be mentioned. Statistical significance was assessed by the χ^2 method, by the Mann-Whitney test, and by computing Goodman-Kruskal's \mathcal{V} , which is a method of correlation analysis for grouped data, described in detail by Blalock (1972). Compared with χ^2 , \mathcal{V} is more sensitive to directional trends.

CHAPTER V

Treatment with emergency surgery

Objectives

Over the 10-year period from 1962 to 1972 patient records were reviewed of patients with cirrhosis who underwent an emergency operation for massive non-variceal bleeding, and the outcome was recorded.

The following factors were analysed in search for a positive relation with postoperative mortality:

- *general factors*

age

sex

ward/private

- *clinical factors in history or physical examination*

indication for admission

peptic ulcer disease in patient-history

varices and portal decompression

encephalopathy

- *biochemical factors*

serum bilirubin

serum albumin and globulin

prothrombin time

- *factors related to the operation*

indication for operation

interval admission-operation

number of preoperative blood transfusions

bleeding source

type and duration of operation

Results

Composition of patientgroup and mortality

In the Massachusetts General Hospital the frequency of non-variceal bleeding in cirrhotics - an average of 6 or 7 patients per year - is apparently not high. The ensuing mortality however, is disturbingly high: 36 of 64 patients died postoperatively, amounting to a mortality of 56 per cent. (table 7)

Table 7: Mortality following emergency surgery

| year | male | female | total | death | mortality % |
|-------|------|--------|-------|-------|-------------|
| 1962 | 3 | 2 | 5 | 3 | } 61% |
| 1963 | 5 | 2 | 7 | 4 | |
| 1964 | 3 | 3 | 6 | 4 | |
| 1965 | 3 | - | 3 | 1 | |
| 1966 | 1 | 1 | 2 | 2 | |
| 1967 | 6 | 1 | 7 | 4 | } 54% |
| 1968 | 4 | - | 4 | 2 | |
| 1969 | 8 | 4 | 12 | 7 | |
| 1970 | 3 | 3 | 6 | 3 | |
| 1971 | 10 | 2 | 12 | 6 | |
| total | 46 | 18 | 64 | 36 | 56% |

An account of the analysis of factors, which could possibly contribute to this high mortality, is now given.

Age and sex

Age varied from 35 to 80 years, with a peak in the age group of 50 - 59 years (fig. 1). Mortality shows only a slight increase with age, as shown in fig. 2.

There were 46 males and 18 females, giving a male predominance of 2.5 : 1. No significant difference in mortality is seen between males and females: 25 out of 46 males died (54 per cent) and 11 out of 18 females (61 per cent).

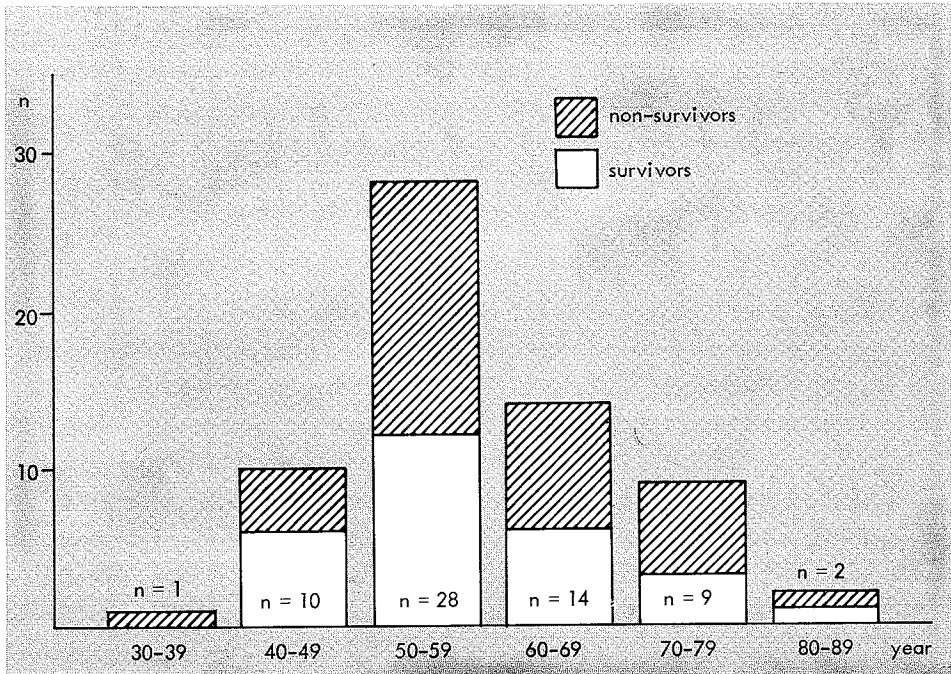


Fig. 1.: Age distribution in decades

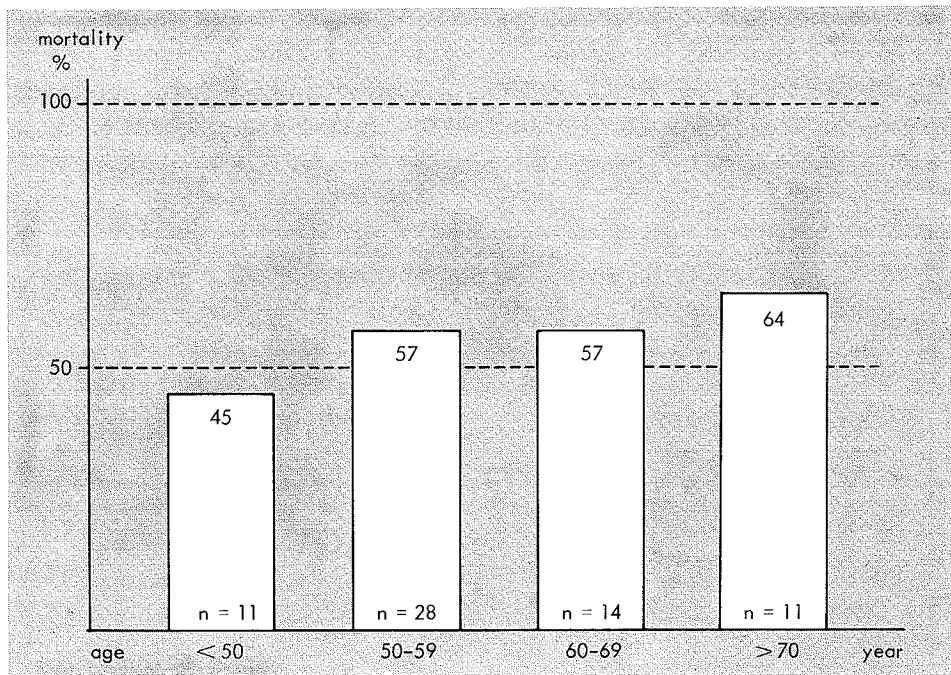


Fig. 2.: Mortality in relation to age

Private versus ward patients

In the Massachusetts General Hospital surgical treatment of patients with cirrhosis or portal hypertension is not confined to a few surgeons. Therefore, the patients pertaining to this study have been operated on by a variety of consultants and houseofficers, the latter group being shifted by nature over a period of 10 year. Considering the usual procedure in this hospital one can assume that all private patients were operated on by the Visiting Staff and most ward patients by the Resident Staff. There were 42 ward patients and 22 private patients. Mortality was the same in both groups.

Indication for admission

Most patients were admitted with massive bleeding. In 10 patients the bleeding started when they were hospitalized for various other reasons, generally in connection with cirrhosis and hepatic dysfunction. Two patients were admitted with gastrointestinal bleeding, diagnosed as variceal bleeding, and treated as such. After portal decompression bloodloss continued. In one patient the bleeding was due to a gastric ulcer, in the other it was due to gastritis with ulcers in stomach and duodenum. Mortality in this group of patients, usually referred to in literature as "in-hospital bleeders", is considerably higher than average, being 92 per cent.

Peptic ulcer in history

More than half of the patients mentioned a previous history of peptic ulcer disease and a surprisingly large proportion of these, 26 patients, also had experienced previous bleeding. Medical treatment had been sufficient in most, including the use of blood transfusions. 11 Patients underwent one or more surgical interventions for treatment of bleeding or perforated peptic ulcers. Though this information might have been interesting, it was not possible to determine whether these patients were already cirrhotic at the time the operations were performed, nor could it be ascertained whether the operations were done electively or as emergencies.

No difference in mortality was found between patients with or without an ulcer history, neither was mortality influenced by previous bleeding. Even patients who had a previous operation for peptic ulcer in history were not faced with a higher mortality.

Varices and portal decompression

As might be expected, esophageal and/or gastric varices were present in many, but not all patients. In 19 patients varices were established preoperatively by endoscopy or during operation. In 5 patients varices were documented in earlier admissions. Eight patients had had previous portal decompression, 4 x a portacaval and 4 x a splenorenal shunt.

Varices were reported to be bleeding at operation in 6 patients; in all of these cases the major source of bleeding was clearly stated not to be the varices, and all patients were treated accordingly.

Mortality in the total group of patients in whom varices were found – either in history or at the present admission – as evidence of portal hypertension, was 83 per cent. Mortality among patients with a previous portosystemic shunt operation was equally high: seven of the eight patients did not survive.

Encephalopathy

Encephalopathy, either in the patient-history, at admission on physical examination, or a combination of both, was found in one-third of the

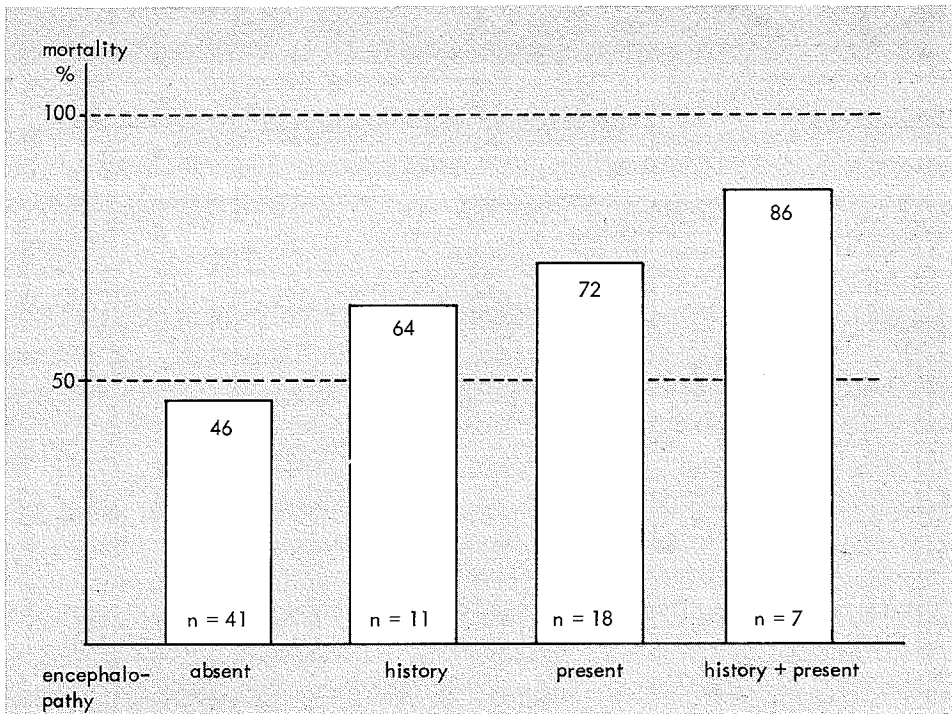


Fig. 3.: Mortality in relation to encephalopathy

patients. The combination, present and in history, appeared to be very ominous: six out of seven patients died (figure 3). The determining factor however, is encephalopathy in the immediate preoperative period, as this finding alone carried a mortality of 72 per cent. The same high mortality (7 out of 8) was found in those patients, that were admitted to the hospital for treatment of cirrhosis with manifest encephalopathy. These patients belong to the afore-mentioned notorious group of "in-hospital bleeders".

Serum bilirubin

Serum total bilirubin, expressed in mg per 100 ml or mg %, was routinely determined in most patients. In only two patients no data from the immediate preoperative period were available. The bilirubin values that were used in this study were determined on the day of operation or, at the most, two days preoperatively. Distribution of the serum bilirubin values is shown in fig. 5.

Mean values were: 3.5 mg % * for the total group; 1.5 mg % for the survi-

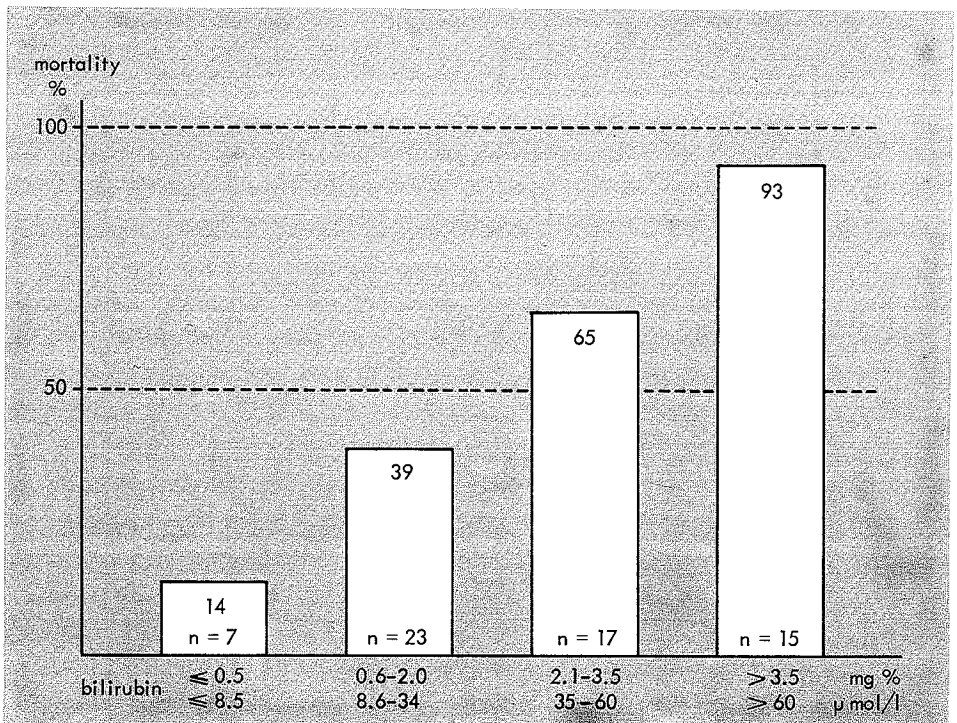


Fig. 4.: Mortality in relation to serum bilirubin values

*converted into μmol/l these values are 59.8, 26.8 and 85.1 μmol/l respectively.

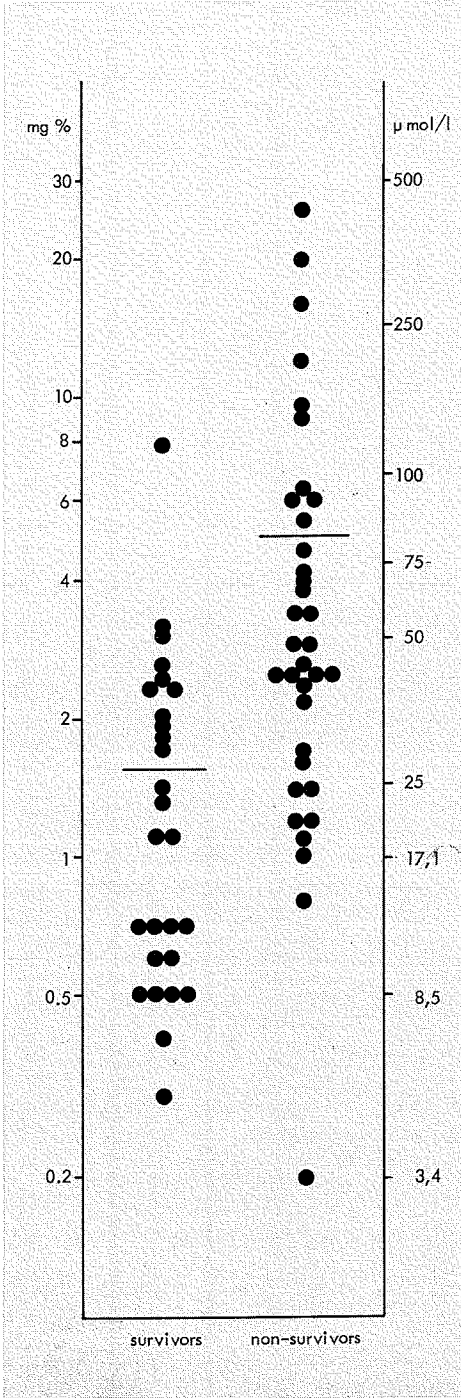


Fig. 5.: Distribution of serum bilirubin values*

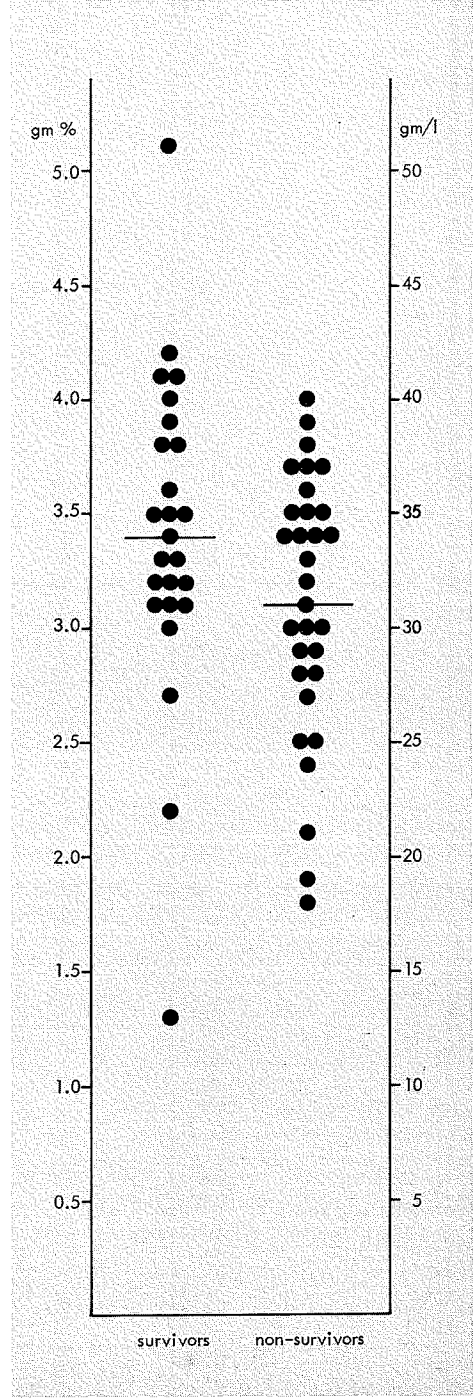


Fig. 6.: Distribution of serum albumin values

* = semi logarithmic scale

vors; and 4.9 mg% for the deaths. The difference between survivors and deaths is statistically significant ($p < 0,001$).

Mortality appeared to be directly proportionate to the level of serum bilirubin. This is shown in fig. 4. A bilirubin of over 3.5 mg% was associated with more than a 6-fold increase of mortality compared to levels of 0.5 mg% or lower.

Serum albumin

Serum albumin levels were obtained in 56 patients. Missing data were in those patients that were operated on in a very acute situation; determination of protein fractions is time consuming.

Mean values were: 3.24 gm% for the total group; 3.41 gm% for the survivors; and 3.11 gm% for the deaths. The difference between survivors and deaths is statistically significant ($p < 0,05$).

Distribution of values is shown in fig. 6.

Mortality was markedly increased at values of 3.0 gm% or lower and was inversely proportionate to the level of serum albumin, as shown in fig. 7.

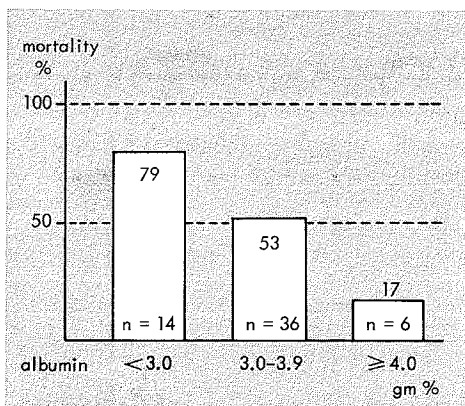


Fig. 7.: Mortality in relation to serum albumin values

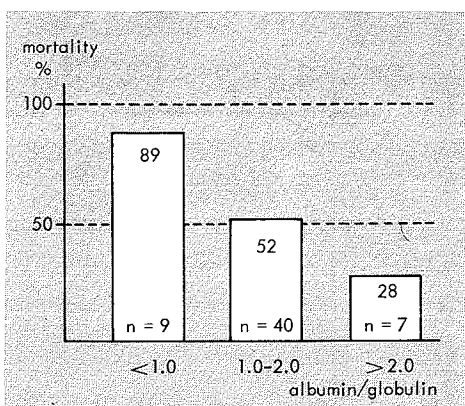


Fig. 8.: Mortality in relation to albumin/globulin ratio

Albumin/globulin ratio's were calculated and related to mortality. This provided essentially the same information as from serum albumin alone; it did not show any greater discriminatory effect.

Prothrombin time (P.T)

Prothrombin times were given in percentages until 1967. Thereafter they were given in seconds, in combination with a control value. When given in percentages they indicate *the remaining* part of prothrombin activity.

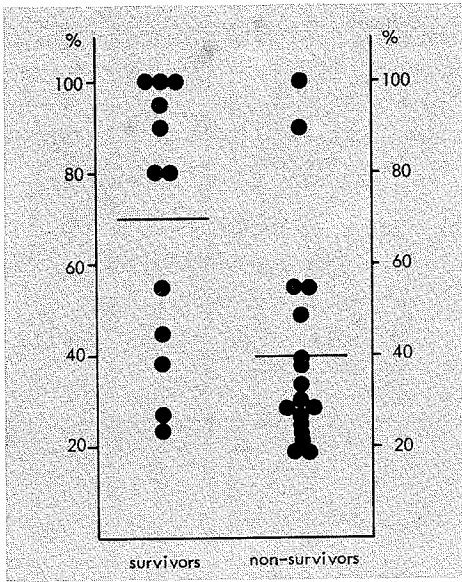


Fig. 9.: Distribution of prothrombin times in%.

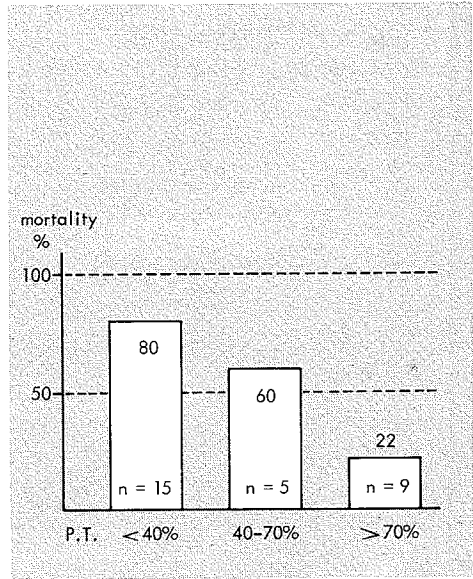


Fig. 10.: Mortality in relation to prothrombin times in % .

Fig. 9 shows the distribution of P.T. values in percentages. The mean value of the survivors was 70 per cent, of the deaths 40 per cent.

Mortality was inversely proportionate to the height of P.T. values in percentages, as shown in fig. 10.

Fig. 13 shows the distribution of P.T. values in seconds. The mean value of the survivals was 13,5 seconds, and of the deaths 16,2 seconds. The difference is statistically significant ($p < 0,008$).

Mortality was directly proportionate to the length of prothrombine time, as shown in fig. 11.

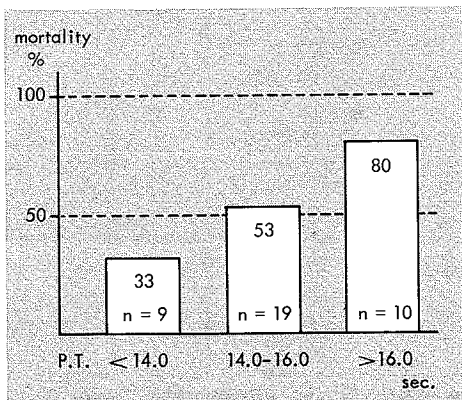


Fig. 11.: Mortality in relation to prothrombin times in sec.

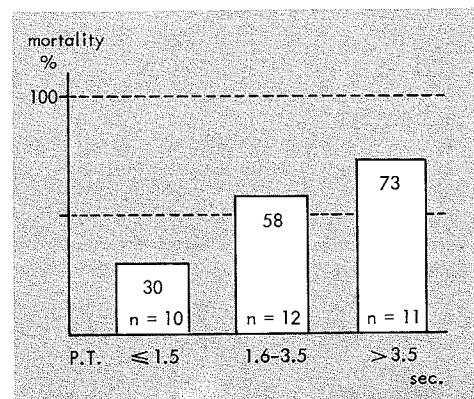


Fig. 12.: Mortality in relation to prolongation of prothrombin times in sec.

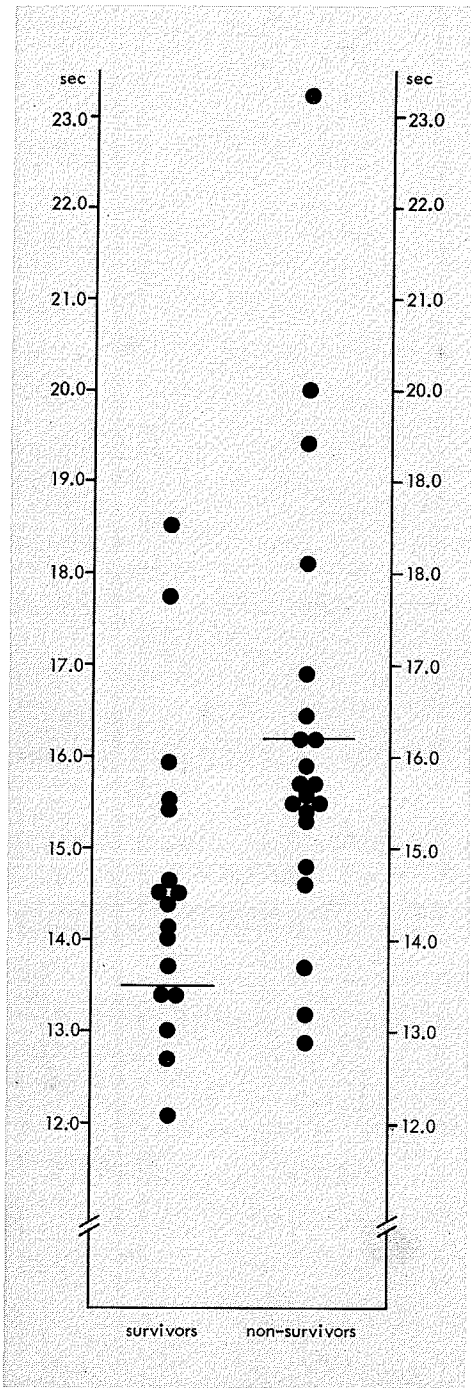


Fig. 13.: Distribution of prothrombin times in sec.

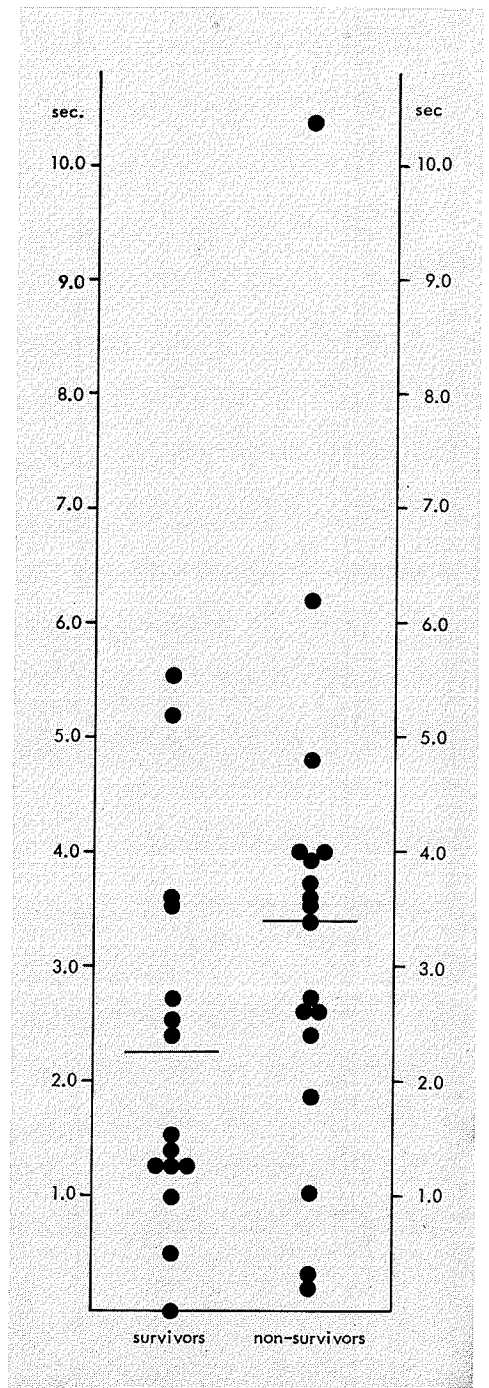


Fig. 14.: Distribution of prolongation of prothrombin times in sec.

The use of the absolute values of prothrombin time is debatable, because in that way the individual values are not related to their control value. Therefore a more accurate method might be the measurement of the actual prolongation of the prothrombin time, i.e. calculation of the difference between P.T. and control value. These differences varied from 0 to 10,4 seconds: the distribution is shown in fig. 14. Mean prolongation in the survivors was 2,3 seconds, in the deaths 3,4 seconds. The difference is statistically significant.

Mortality was directly proportionate to the length of prolongation, as shown in fig. 12. When P.T. was prolonged more than 2.5 seconds, mortality was raised to 87 percent, compared to only 33 per cent at or below this value.

Interval between admission and operation

The majority of patients were operated on within 48 hours after admission; half of the patients were operated within 24 hours and half of these within 12 hours. Five patients had recurrent bleeding after control of the initial bleeding with medical treatment, or continued bloodloss at a rate necessitating several bloodtransfusions daily despite medical treatment. These patients were operated on one week or longer after admission or the start of the bleeding. There is no significant difference in mortality after operations performed within, or after, 24 hours. Also, there is no essential difference in the group "delayed forced operations", i.e. those patients in whom a continued or recurrent bloodloss eventually results in an emergency operation.

Bloodtransfusions

The number of preoperatively given bloodtransfusions varied from 2 to 17 units (\pm 500 ml.), averaging 8.7 units per patient. The maximum amount given during operation was 40 units, the average amount of preoperatively given transfusions was 8.2 units. Postoperative bloodtransfusions were not evaluated, but the need for banked blood is excessively high, as evidenced by a patient who received a total of 56 units of whole blood.

Mortality was not related to the number of preoperative bloodtransfusions, the average amount given to survivors being 8.1 units and to the non-survivors 9.2 units. The difference is not statistically significant.

Bleeding sources

The different causes of bleeding are summarized in table 8, in order of frequency. Because several patients had more than one bleeding source it is difficult to determine mortality in relation to all bleeding sources. For this reason mortality was only calculated for the major bleeding sources: duodenal and gastric ulcer, and gastritis. The result is summarized in table 9.

Table 8: Sources of bleeding

| | |
|----------------------|------|
| gastritis | 29 x |
| gastric ulcer | 26 x |
| duodenal ulcer | 19 x |
| Mallory - Weiss tear | 3 x |
| stomal ulcer | 2 x |
| varices ** | 6 x |

Table 9: Mortality related to bleeding source*

| <i>source</i> | <i>n</i> | <i>mortality</i> |
|----------------|----------|------------------|
| duodenal ulcer | 19 | 68% |
| gastric ulcer | 26 | 50% |
| gastritis | 29 | 62% |

In 51 patients the bleeding source was diagnosed correctly and could be confirmed at operation. In 8 patients the preoperative diagnosis was not confirmed by the operative findings; in only one patients an erroneous preoperative diagnosis of bleeding esophageal varices was made. In 5 patients an exploratory laparotomy was performed without a presumptive diagnosis.

Type of operation

A variety of different surgical techniques were used in the treatment of our patients. All operations were divided into three groups arbitrarily:

1. - partial or total gastrectomy
2. - hemigastrectomy with vagotomy
3. - vagotomy and pyloroplasty

Group 1 included 3 total gastrectomies and 38 partial gastrectomies.

"Partial" gastrectomies included customary "standard" resections (23 x) and more extensive "subtotal" resections (15 x). In group 3 one patient was included in whom a gastrojejunostomy was performed without vagotomy,

* = combination of different sources included

** = bleeding varices found at operation, but explicitly stated to be not the major bleeding source.

as this had been done on an earlier occasion. All vagotomies were "truncal" vagotomies; no selective or highly selective vagotomies were performed. Bleeding ulcers were suture ligated when not resected. In the 10-year period of this study all types of surgical treatment were used, without any particular preference for one type in some period, as shown in table 10.

Table 10: Distribution of operations

| | <i>partial/total gastrectomy</i> | <i>hemigastrectomy + vagotomy</i> | <i>vagotomy + pyloroplasty</i> |
|------|--------------------------------------|---------------------------------------|------------------------------------|
| 1962 | 5 | - | - |
| 1963 | 5 | 1 | 1 |
| 1964 | 3 | 1 | 2 |
| 1965 | 2 | 1 | - |
| 1966 | 1 | 1 | 1 |
| 1967 | 5 | 1 | 1 |
| 1968 | 2 | 1 | 1 |
| 1969 | 6 | 5 | 1 |
| 1970 | 5 | - | 1 |
| 1971 | 7 | 4 | 1 |

Duration of operation

The duration of an operation was usually mentioned in the operation report, or could be deduced from the anesthesia report. The average duration of all surgical procedures was rather long: 5 hours 40 minutes. This was caused, in part, by incidental surgical interventions, as listed in table 11.

Table 11: Incidental operations

| | |
|-----------------------------|-----|
| accidental splenectomy | 4 x |
| repair Mallory-Weiss tear | 2 x |
| repair hiatus hernia (Hill) | 2 x |
| cholecystectomy | 1 x |
| repair perforated colon | 1 x |
| portacaval shunt | 1 x |

When incidental operations are excluded, the following duration could be calculated for each type of surgery (see table 12).

Table 12: Mean duration of operation

| | |
|----------------------------|---------------|
| total gastrectomy | 6 hr. 30 min. |
| hemigastrectomy + vagotomy | 6 hr. |
| partial gastrectomy | 6 hr. |
| vagotomy + pyloroplasty | 3 hr. 50 min. |

The possible advantage of a short duration of an operation like vagotomy and pyloroplasty, was nullified in most patients of this group because of several incidental operations.

The additional interventions made the mean operation time in this group to be 5 hr. 35 min. This may in part explain the high mortality rate (62 per cent) in this group.

Discussion

In view of undeniable improvements in postoperative intensive care facilities, which were accomplished during the years of this study, it is somewhat surprising and disappointing that no substantial decrease in mortality can be seen over this period.

Postoperative care is only one example of the various factors which apparently have little or no influence on the outcome of emergency operations for massive non-variceal bleeding in patients with cirrhosis.

Other factors, of which no relation with the postoperative mortality could be demonstrated, will be discussed now:

Age

The minimal increase of mortality with age of the patients is in contrast with the majority of conclusions found in literature. Darin (1961), Thorne (1965) and Byrne (1970) all found a three- to four fold increase of mortality in elderly patients after surgery for massive gastrointestinal bleeding.

Sex

The 2.5 : 1 ratio for males to females is in accordance with the review of literature given by Sturdevant (1976). The almost equal mortality rate is not commented on in literature.

Private versus ward patients

In discussions about operative results, postoperative mortality and complication rates, the technical qualities and experience of the performing surgeon were implicated. Qualified surgeons are usually credited with better results than surgical residents, and best results are obtained by someone who specializes in the matter in question.

In this study no difference in results was demonstrated between ward and private patients, which is in accordance with the findings of McDermott (1961), but in contradiction with many others (Jensen, 1970).

Coexisting disease

Although a very high mortality (92 per cent) was found in the 10 so-called "in-hospital-bleaders" (Hamilton, 1965), the fact that these patients were hospitalized already when they started bleeding does not seem to be that important. The crucial factor appears to be the degree of hepatic dysfunction, as evidenced by serum bilirubin levels.

The mean serum bilirubin value in our "in-hospital-bleaders" was 9.2 mg%, which is almost twice the mean value of *all* patients who died (4.9 mg%). This finding can be even better appreciated when other "debilitating factors" are considered, like diabetes mellitus.

Diabetes mellitus

Diabetes mellitus (treated with insulin or oral antidiabetics) was present in 9 patients, in the majority of adult onset type. This high incidence of 14 per cent is surprising, though in accordance with Wantz and Payne (1961) who found diabetes in 14.5 per cent of their patients. They did not attempt to specify mortality among these diabetic patients, but in general diabetes is assumed to infer a greater risk. This was not confirmed by our study, as only 3 of the 9 patients died. Here again, the determining factor seems to be the degree of hepatic dysfunction: mean serum bilirubin of the surviving diabetic patients was 1.8 mg% against 10.0 mg% in the non-survivors.

The incidence of peptic ulcer disease in patients with diabetes is as controversial as its incidence in patients with cirrhosis. Considering the regular life style of diabetic patients one would expect a very low incidence (Wood, 1974), in contrast with alcoholic patients with cirrhosis (Hall, 1953).

Ellison (1959) found twice as many diabetics among patients with peptic ulcer disease as might be expected, based on a total series of 20,000 autopsies. Our incidence of diabetes may be the same as Wantz and Payne found,

but it is three times as high as quoted in the classical study of Ratnof and Patek (1942), who named their incidence of 5 per cent as "unexpectedly high". Monson (1970) could not demonstrate a relation between diabetes and peptic ulcer disease in a study among 974 Massachusetts physicians, thus answering the rhetorical question: "does anyone ever see a report concerning the coincidence of duodenal ulcer and some other condition, with the conclusion that the two disorders are *not* related?" It would not be surprising if "Berkson's Fallacy" plays an important role in many of these discussions (Grosse, 1965).

Peptic ulcer disease

It is noteworthy that no difference in mortality existed between patients with or without an ulcer history. Neither was mortality influenced by previous bleeding. Most remarkable was the finding that even a previous operation for peptic ulcer did not adversely affect mortality, considering the increased technical difficulty usually associated with "second" operations.

Mortality in relation to bleeding source and type of operation

Mortality associated with the different surgical techniques is shown in table 13. The low mortality following hemigastrectomy and vagotomy is evident, but no conclusions can be drawn from these data, because the study was in retrospect. Operations were not randomized and selection must have occurred to some degree. Several (unknown) factors play a role in such a selection process. Thus one may expect that the most simple and fastest operation, i.e. pyloroplasty and vagotomy, will be selected for the most critically ill patients. This is reflected in the mean serum bilirubin values when calculated for each group*: in group 1 - 4.2 mg%; group 2 - 1,5 mg % ; and in group 3 - 6,9 mg % .

Table 13: Mortality related to type of operation

| <i>operation</i> | <i>n</i> | <i>mortality</i> | <i>mean bilirubin</i> |
|----------------------------|----------|------------------|-----------------------|
| partial/total gastrectomy | 41 | 63 % | 4.2 mg % |
| hemigastrectomy + vagotomy | 15 | 33 % | 1,5 mg % |
| vagotomy + pyloroplasty | 8 | 62 % | 6,9 mg % |
| total | 64 | 56 % | 3,5 mg % |

*see page 54

With these considerations in mind it is very obvious that one can not conclude that the low mortality after hemigastrectomy with vagotomy makes this operation the "treatment of choice".

As shown in table 9 duodenal ulcers are associated with a higher mortality than gastric ulcers or gastritis. It may be wondered whether a different treatment for the same bleeding source is followed by a difference in mortality. To evaluate this, we divided all patients into two groups: group A - all patients treated with a partial gastrectomy *without vagotomy*, and group B - all patients treated with a hemigastrectomy or pyloroplasty *with vagotomy*. Thus group A is the same as group 1* without the total gastrectomies; group B is the combination of group 2* and 3*. Mortality in patients of group A who had a duodenal ulcer was 82 per cent; mortality in duodenal ulcer patients in group B was only 37 per cent.

The most obvious conclusion is recommendation of a surgical procedure that includes vagotomy, as mortality in gastrectomies without vagotomy is doubled.

The fallacy of such conclusions becomes clearly evident when mean serum bilirubin values are plotted against mortality rates: mean serum bilirubin in group A is 4,6 mg%, in group B 2,1 mg%. Thus, mortality is only doubled when serum bilirubin is doubled!

A technical factor may also have played a role in the decision of the surgeon to do a vagotomy or not. In the operation reports the liver is frequently mentioned as being "exceedingly firm" or "huge and hard". In 4 patients the condition of the liver made a vagotomy technically impossible and this was stated explicitly.

Summary and conclusions chapter V

The purpose of this study was to answer two main questions:

- 1 - how high is the postoperative mortality rate after emergency surgical treatment of massive non-variceal upper gastrointestinal bleeding in patients with cirrhosis
- 2 - is *postoperative* mortality related to clinical and/or laboratory data which can be obtained *preoperatively*.

In order to clarify these two problems we analysed the charts of 64 patients with cirrhosis, who were massively bleeding from sources that were proven to be non-variceal, and who were treated with an emergency operation. For the selection of these patients, who were admitted to the Massachusetts General Hospital over a 10-year period from 1962 to 1972, criteria were used as outlined in chapter IV.

*see page 54

Overall surgical mortality appeared to be 56 per cent, not improving over a decade.

Of the clinical and laboratory factors that were evaluated, several turned out to have an unequivocal relationship to post-operative mortality, whereas several other factors, that are usually granted to exert considerable influence on surgical mortality, appeared to have little or no relationship.

Among the last category were – in arbitrary order – the following factors:

- age of the patient: patients over 70 years of age have a slightly increased mortality, but not comparable to other diseases as stated in literature.
- coexistent disease like diabetes mellitus does not increase mortality; a previous history of peptic ulcer disease, although it may contribute to the occurrence of bleeding as a complication, does not influence mortality once this complication becomes evident.
- time-lapse between onset of bleeding and operation, or between admission and operation, does not influence the outcome of an operation; however, when bleeding starts in patients that are already hospitalized for liver cirrhosis, the outcome is dire.
- type of operation, i.e. extent of resection, with or without vagotomy, is not related to result, nor is the duration of an operation.
- no significant difference in mortality is seen in relation to the different sources of the bleeding: duodenal ulcer, gastric ulcer and gastritis.
- the amount of blood given preoperatively bears no relation with postoperative mortality.
- finally, no possible difference in quality could be detected between the treatment given to ward patients and of that given to private patients.

Among the laboratory factors which showed a good relation to postoperative mortality, serum bilirubin levels most clearly correlated, with near linearity, to postoperative results. Other laboratory data which showed good correlation, were prothrombintime and serum albumin, the latter being inversely proportionate to mortality.

The presence of encephalopathy, and presence or history of varices, were the only two clinical entities positively correlated with death rate.

CHAPTER VI

Treatment with vasopressin infusion

Objectives

A second group of patients with cirrhosis and non-variceal bleeding was treated in the Massachusetts General Hospital with selective vasopressin infusion, in a different time period. In the analysis of this group three different aspects were evaluated.

In the first place the group as a whole was assessed for the same criteria of hepatic function as were used in the emergency surgery group. This was done in order to appreciate whether the two groups were comparable with respect to severity of the disease. For the same purpose general factors like age distribution, sex, severity of the bleeding etc., were analysed. The second objective of this study was to assess the validity of angiography and vasopressin infusion in the treatment of non-variceal bleeding. In other words: to answer the question whether intra-arterial vasopressin infusion is able to stop the bleeding.

The third objective was to evaluate mortality after vasopressin treatment. From the start of this study it was clearly understood that "control of the bleeding" is far from identical with "survival of the patient". For this reason mortality was evaluated in relation to the same parameters as mentioned above.

Results

Composition of patient group

The first patient with cirrhosis and massive upper gastrointestinal bleeding from a non-variceal source who was treated with vasopressin infusion, was admitted in October 1971. In the three year period till the end of 1974 a

total of 32 patients, 26 males and 6 females, who fulfilled the criteria for cirrhosis and massive non-variceal bleeding were treated.

Vasopressin infusion was the *initial* treatment, but in many cases *not* the *only* treatment. Patients who did not respond to vasopressin infusion usually subsequently underwent an emergency operation in an effort to stop the bleeding. Therefore, the figures about mortality, as given in table 13, refer to the multidisciplinary treatment in which vasopressin infusion was instituted primarily.

Mortality

Overall mortality was 56 per cent, which is equal to mortality after emergency surgery (56 per cent).

Table 14: Mortality following vasopressin infusion

| year | male | female | total | death | mortality |
|-------|------|--------|-------|-------|-----------|
| 1971 | 1 | - | 1 | 0 | - |
| 1972 | 12 | 2 | 14 | 8 | 57 % |
| 1973 | 4 | 1 | 5 | 1 | 20 % |
| 1974 | 9 | 3 | 12 | 9 | 75 % |
| total | 26 | 6 | 32 | 18 | 56 % |

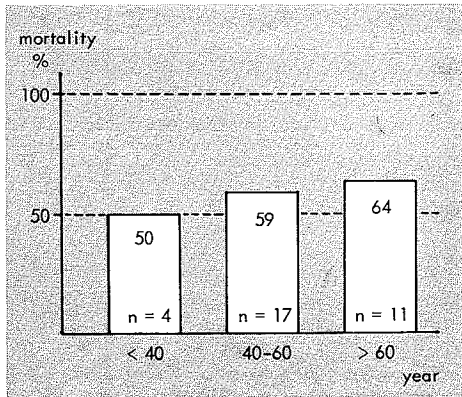


Fig. 15.: Mortality in relation to age.

Age

Age varied from 26 to 75 years with an average of 54,2 year. Splitting the group into 3 age groups shows a tendency of mortality to increase very slightly with age, almost identical to the emergency surgery group (fig. 15).

Indication for admission

23 Patients were admitted for massive upper gastro-intestinal bleeding. The remaining 9 patients were admitted for other reasons (see table 14) and started bleeding *in* the hospital. Mortality in this group of "in-hospital bleeders" is expectedly high: 78 per cent.

Table 15: Indication for admission and mortality of "in-hospital bleeders"

| <i>indication</i> | <i>patients</i> | <i>deaths</i> |
|--------------------------------|-----------------|---------------|
| congestive heart failure | 2 | 2 |
| hepatic dysfunction, cirrhosis | 2 | 1 |
| ileus, vomiting, fever | 2 | 2 |
| retroperitoneal bleeding | 1 | 1 |
| sepsis, abdominal distension | 1 | 1 |
| aneurysm abd. aorta, diabetes | 1 | 0 |
| total | 9 | 7 |

Varices and portal decompression

Presence of esophageal or gastric varices, with or without a history of varices, was demonstrated in 23 patients. Ten patients had a portosystemic shunt, either performed during a previous admission or during the same admission, but prior to vasopressin infusion (5 x portacaval, 4 x splenorenal and 1 x mesocaval). No apparent influence of varices on mortality was seen, but 7 of the 10 shunted patients died.

Encephalopathy

Six patients had a history of encephalopathy, 9 patients had encephalopathy in various degrees on admission. Three of those had hepatic coma or impending coma, the remaining 6 patients showed confusion, disorientation and drawsiness.

Encephalopathy on admission was associated with an increased mortality (78 per cent). The combination of a positive history and the presence of encephalopathy was lethal, as shown in fig. 16.

Serum bilirubin

Serum bilirubin values were distributed as shown in fig. 18.

The mean value of the survivor group was 1.6 mg%(27.4 μ mol/l), and 10.9 mg%(186 μ mol/l) in the non-survivors. When excessive values in the latter group are excluded the mean value is 4.0 mg%(68 μ mol/l).

Mortality is clearly related to serum bilirubin levels, as shown in fig. 17.

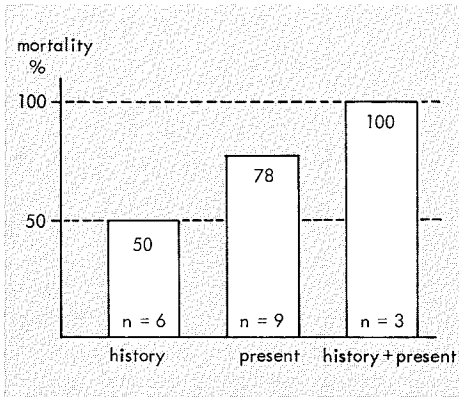


Fig. 16.: Mortality in relation to encephalopathy

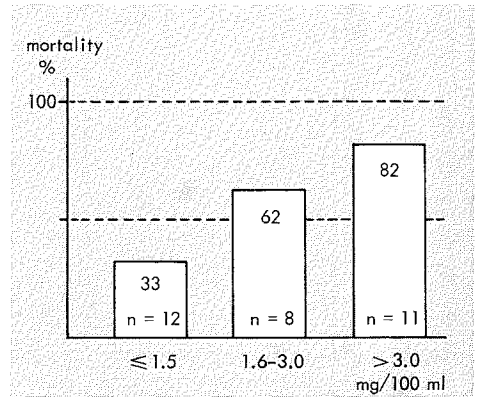


Fig. 17.: Mortality in relation to serum bilirubin values

Serum albumin

As shown in fig. 19, serum albumin values were equally distributed in the survivors and non-survivors; mean values were 3.03 gm% and 3.01 gm% respectively. Therefore, no correlation at all could be demonstrated between serum albumin values and mortality. Albumin-globulin ratios even showed an inverted relation, caused by the very low ratios in the survivors (mean value 1.01).

Prothrombin time and partial thromboplastin time

In the period of this investigation prothrombin time (P.T.) was always given in seconds and no longer in percentages. In all patients of this series prothrombin time was repeatedly determined. In addition to prothrombin time a partial thromboplastin time (P.T.T.) was determined in most patients. The mean prolongation of P.T. in the survival group was 2.5 sec., in the non-survivors 3.5 sec. The mean values of P.T.T. were 34.5 sec. for the survivors, against 41.1 sec. for the deaths.

Mortality was increased when prothrombin time was more than 3 sec. prolonged, as shown in fig. 20. Partial thromboplastin time showed a better discriminatory effect on mortality. Fig. 21 shows that mortality was doubled when P.T.T. values were over 38 sec.

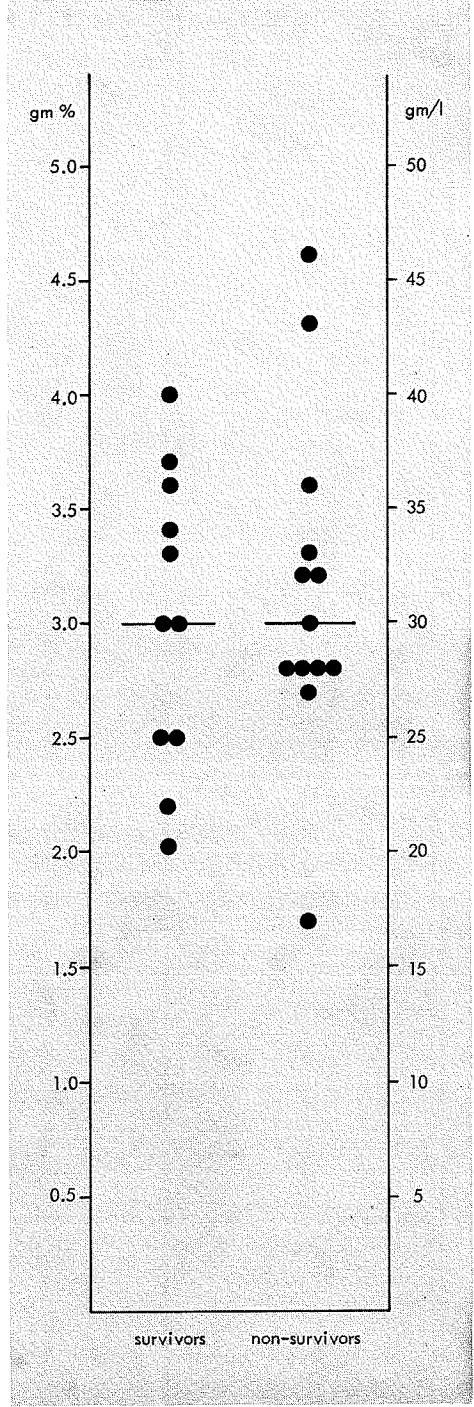
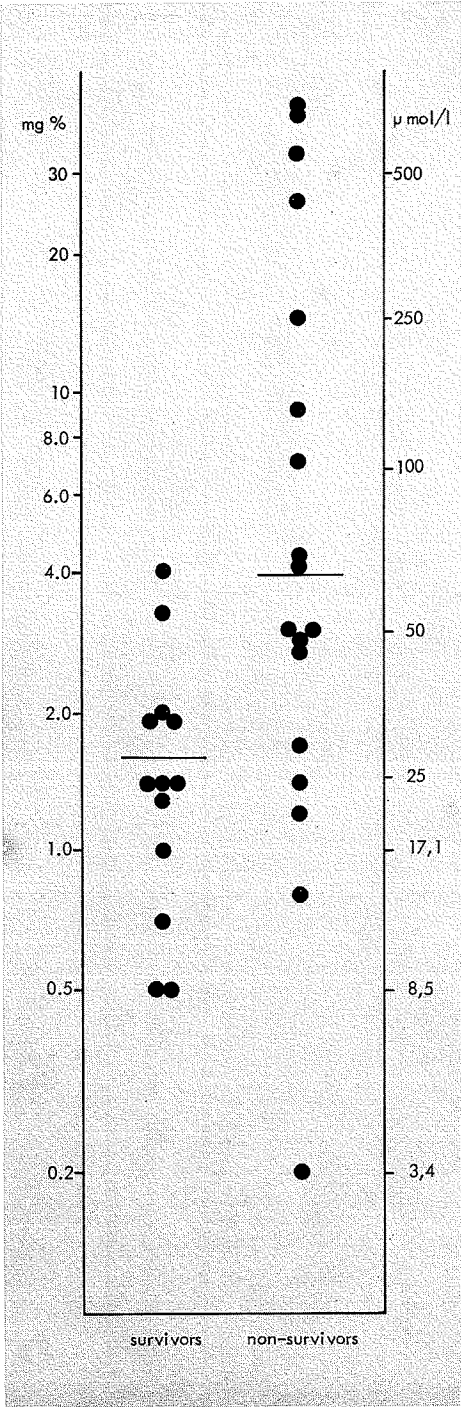


Fig. 18.: Distribution of serum bilirubin values

Fig. 19: Distribution of serum albumin values

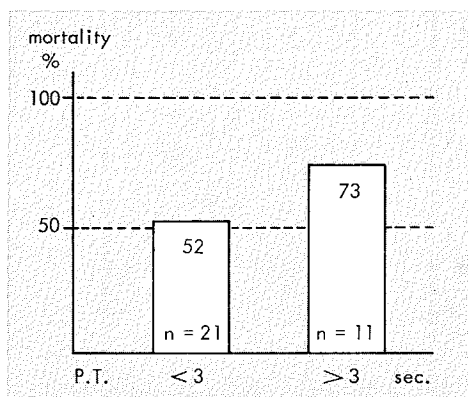


Fig. 20.: Mortality in relation to prolongation of prothrombin time in sec.

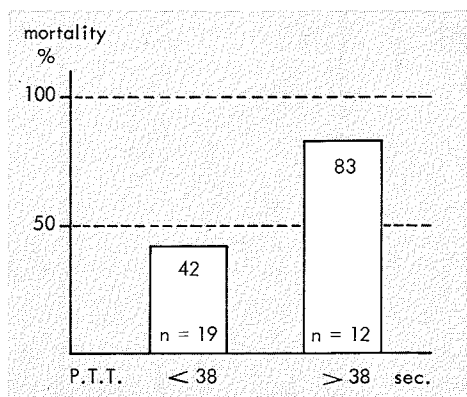


Fig. 21.: Mortality in relation to partial thromboplastin time.

Blood transfusions

The number of blood transfusions given before, during and after vasopressin infusion is summarized in table 16.

Table 16: Average number of blood transfusions*

| | <i>survivors</i> | <i>non-survivors</i> | <i>total group</i> |
|---------------|------------------|----------------------|--------------------|
| pre-infusion | 8,8 | 9,3 | 9,1 |
| per-infusion | 2,2 | 1,3 | 1,7 |
| post-infusion | 1,1 | 7,9 | 4,9 |
| total | 12,1 | 18,5 | 15,7 |

The average number of blood transfusions given before vasopressin infusion was started does not differ significantly for survivors or non-survivors. As a result no relationship between number of transfusions - i.e. severity of the bleeding - and mortality could be demonstrated.

Bleeding sources

The majority of patients was presented to the radiologist with a clinical diagnosis of the bleeding source - either confirmed by endoscopy or only tentatively, based on clinical information. Barium swallow studies were never used in these patients. As esophago-gastroscopy was not routinely

*blood transfusion = 1 unit = \pm 500 ml.

performed in all patients prior to angiography, most patients were referred for confirmation of the clinical diagnosis; in only 3 patients no tentative diagnosis was made.

The diagnosis was confirmed by angiography in 16 out of 29 patients; in 3 patients no bleeding source could be identified with angiography, but here the bleeding was seen on endoscopy, performed just prior to angiography.

Bleeding sources are summarized in table 17.

Table 17: Sources of bleeding

| <i>diagnosis</i> | <i>clinical</i> | <i>angiographical</i> |
|---------------------------|-----------------|-----------------------|
| gastritis | 11 | 19 |
| gastritis + ulcer | - | 1 |
| esophageal varices | 10 | - |
| duodenal ulcer | 3 | 7 |
| gastric ulcer | 1 | 2 |
| duodenal or gastric ulcer | 3 | - |
| esophagitis | 1 | - |
| no diagnosis | 3 | 3 |

Infusion sites

In the majority of cases (22 x) selective infusion was into the left gastric artery, in 6 cases in combination with a second catheter in a different artery. In 5 cases it was not possible to catheterise the artery supplying the bleeding source selectively.

Table 18: Infusion sites

| | |
|--|----|
| left gastric artery | 16 |
| left gastric artery + gastroduodenal artery | 1 |
| left gastric artery + superior mesenteric artery | 4 |
| left gastric artery + celiac artery | 1 |
| gastroduodenal artery | 3 |
| gastroduodenal artery + superior mesenteric artery | 1 |
| hepatic artery | 3 |
| celiac artery | 1 |
| splenic artery | 1 |
| superior mesenteric artery | 1 |

In these cases the catheter was placed as peripheral and selective as possible, in the hepatic artery, celiac axis and superior mesenteric artery respectively. The splenic artery was infused in a case of fundal gastritis, supplied by the short gastric arteries. Infusion sites are summarized in table 18.

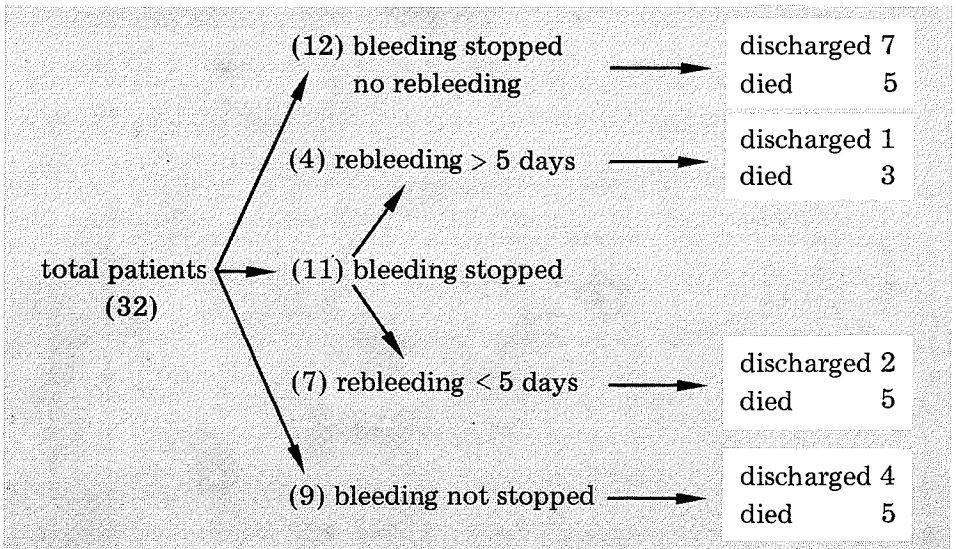
Duration and dosage of vasopressin infusion

The duration of vasopressin infusion varied from 30 minutes to 83 hours. The average duration was 28 hour 20 min. for the total group; 23 hour 25 min. for the survivors, and 31 hour 40 min. for the non-survivors. In the majority of patients infusion was started with 0.2 U/ml / min. In some patients this dose had to be increased to demonstrate sufficient vasoconstriction on control angiograms. The maximal dose never exceeded 0.4 U/ml / min (the equivalent of 24 U/hour), but in all 4 patients requiring this dose the bleeding could not be controlled. Further increase of the dosage was not tried out of fear for side effects and all these patients underwent a subsequent emergency operation.

Control of bleeding and survival

Complete control of bleeding was achieved in 16 patients, i.e. 50 per cent. Overall mortality was 56 per cent. Control of bleeding however, is far from identical with "survival". As shown in table 19 there is no clear relation of survival to control of bleeding.

Table 19: Control of bleeding and survival of the patient



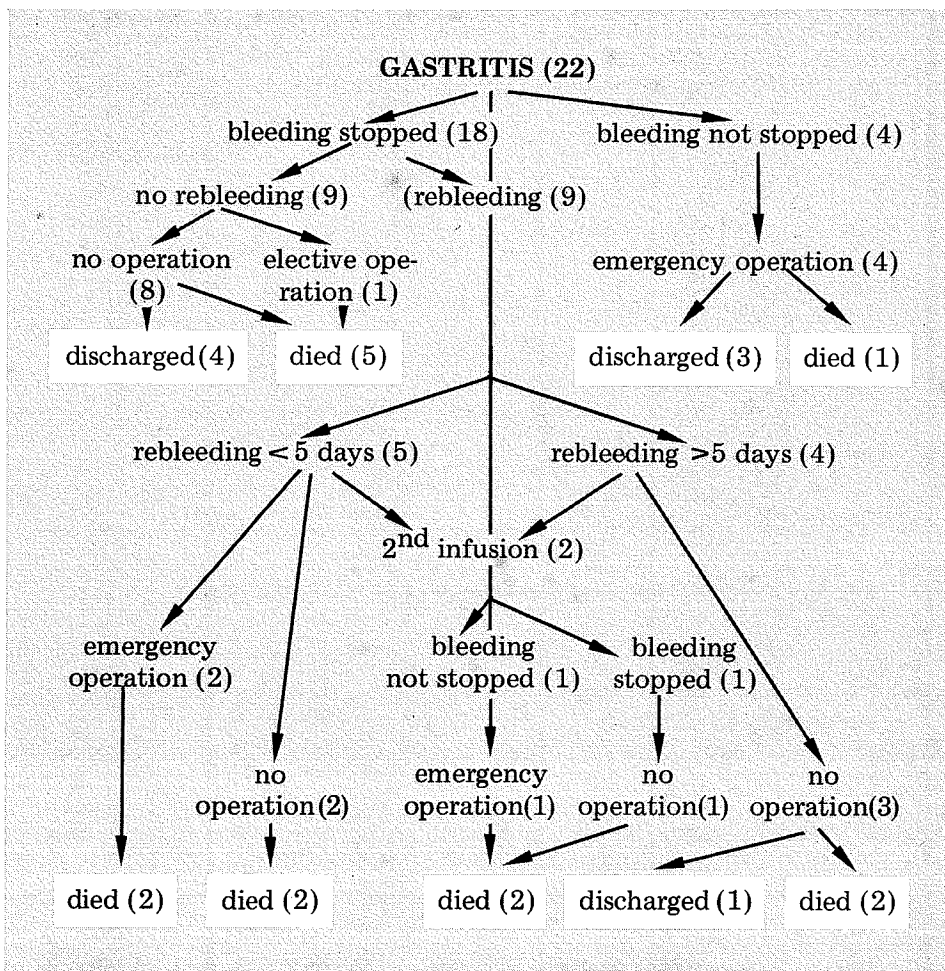


Table 20: results of angiographic treatment for hemorrhagic gastritis

Mortality in the group of 16 patients in whom the bleeding was stopped for more than 5 days was 50 per cent.

Mortality in the 16 patients in whom the bleeding could not, or only temporarily, be controlled with vasopressin was only slightly higher with 62 per cent.

In tables 20, 21 and 22 a review is given of the various ways of treatment, results of treatment, and mortality after treatment for bleeding from 3 different sources.

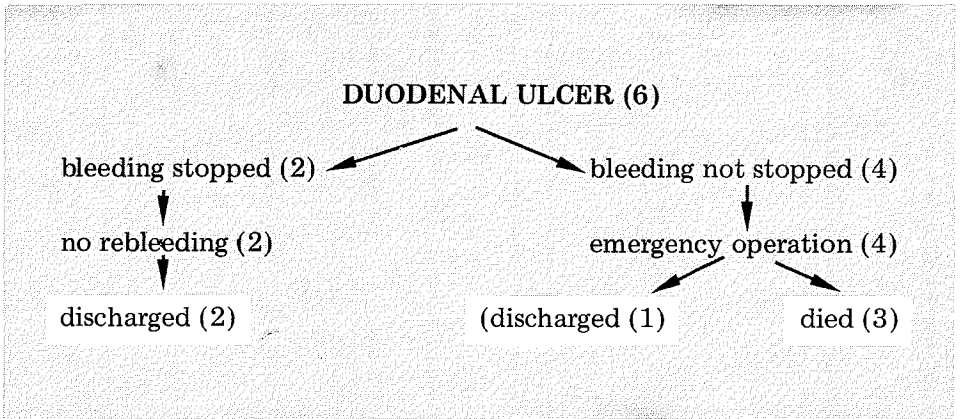


Table 21: results of angiographic treatment for duodenal ulcer

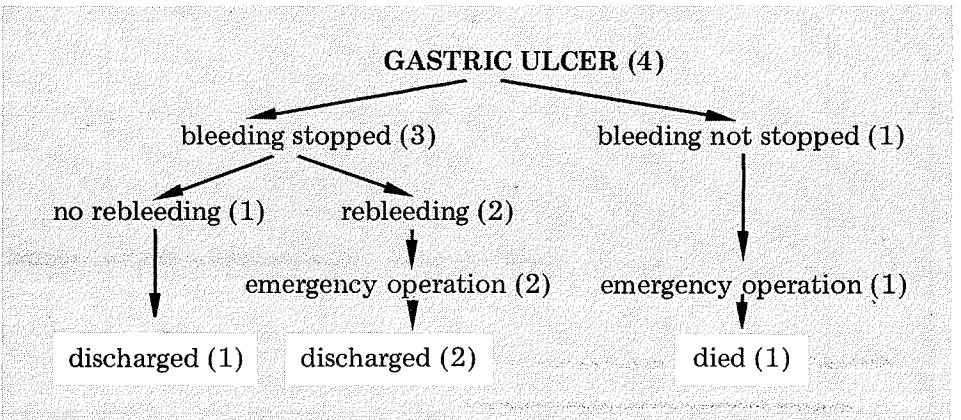


Table 22: results of angiographic treatment for gastric ulcer

Discussion

The major advantage of the use of angiography in gastrointestinal bleeding lies in its dual application – for diagnostic and therapeutical purpose. For diagnostic purposes selective angiography appears to be a reliable and accurate means to diagnose arterial bleeding, both in literature and in our study. The bleeding source was identified in 91 per cent of the cases. The importance of an exact diagnosis in cirrhotic patients with massive bleeding is illustrated by the 10 patients who were presented to the radiologist with a tentative diagnosis of bleeding esophageal varices. In all of these patients selective angiography demonstrated other bleeding sources, that were felt to be responsible for the major bloodloss. It needs no argument that the treatment for these bleeding sources is totally different from the treatment for bleeding esophageal varices. On angiographic evidence

alone, however, bleeding varices cannot be ruled out. This is reflected in the 5 patients in whom a second catheter was placed in the superior mesenteric artery, in order to diminish total mesenteric bloodflow and to decrease portal pressure. (table 17).

Of the clinical and laboratory parameters of hepatic function which were analysed in the vasopressin group, varices, encephalopathy, serum bilirubin and clotting parameters showed the same relation to mortality as in the emergency surgery group. No such relationship could be demonstrated for serum albumin.

We have no explanation for this finding. In retrospect one might speculate about a possible influence of transfusions with "fresh frozen plasma" and other albumin containing fluids. These were given more frequently in the years after 1970 than before. We did not acknowledge a possible interaction of these transfusions and therefore did not record the amounts of plasma and albumin that were given prior to the determination of the serum protein fractions. As this kind of treatment was sometimes started even before bloodtransfusions could be given it is not impossible that serum albumin determinations, done in the latter period, are no reflection of albumin production in the liver.

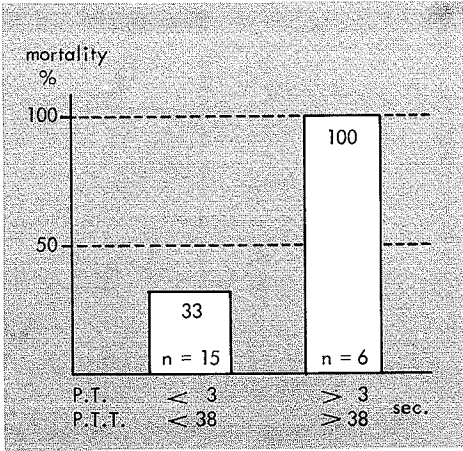


Fig. 22.: Mortality in relation to the combination of prothrombin time and partial thromboplastin time

Analysis of the clotting parameters "Prothrombin time" (P.T.) and "partial thromboplastin time" (P.T.T.) resulted in a better relationship of mortality with P.T.T. than with P.T. Beyond the critical value of 38 sec. for P.T.T., mortality is twofold increased.

As both determinations were done at the same time in all patients but one,

it is possible to combine the critical values for P.T.-prolongation and P.T.T. This results in an enhanced discriminatory effect, as fig. 22 shows. Mortality is threefold increased with P.T. and P.T.T. values above the critical values of 3 sec. prolongation and 38 sec. respectively.

The clinical picture of *jaundice* is used in many authors in relation to the severity of liverdisease, i.c. livercirrhosis.

This clinical picture however is not very precise and usually it is not given in relation to the actual serum bilirubin values. Jaundice may be detected by the skilled observer when the concentration of serum bilirubin reaches 2 mg%, and "is obvious to the most unobservant" (Schiff, 1975), when the concentration exceeds 7 of 8 mg%. Thus a false impression can arise, as the term "jaundiced" is dependant on personal, subjective judgement and it may be overlooked in poor or artificial light. The following observation will illustrate this.

Fourteen patients were described on physical examination as being jaundiced; only 8 had serum bilirubin values of over 2.5 mg%. Six out of 16 patients in whom jaundice was not mentioned had serum bilirubin values above this level. The fallacy becomes apparent when mortality figures are calculated. Mortality in the *jaundiced* group is 86 per cent against 35 per cent in the *non-jaundiced* group. These figures are almost identical to the figures for serum bilirubin over and under 2.5 mg%. This statistical relation cannot be but false considering the above mentioned factors.

Selective vasopressin infusion resulted in control of the bleeding in half of the patients (16), and was temporarily successfull in another 7 patients. Rebleeding appears to be a serious problem, both after initial control and after longer periods of control. Arrest of the bleeding was thus achieved in 72 per cent.

Although this success rate is not impressive one might conclude that vasopressin infusion allows the surgeon to buy time - time to evaluate the risks of a surgical intervention and time to await the natural history of this complex disease.

In our series emergency surgery was necessary as yet in 14 patients, and 1 patient was operated on electively. The resulting mortality (60 per cent) is not different from the total series, but these mortality figures might improve since the introduction of acid secretion blocking agents like cimethidin. If the incidence of rebleeding after initial arrest of the bleeding can be decreased, more operations could be done electively.

Theoretically these elective operations would carry a significantly lower mortality (Palmer, 1964; Wirthlin, 1974).

Long term survival was not included in this study, but it seems worthwhile to mention the follow-up data that were available at the time of this study. Of the 14 patients (44 per cent) that could be discharged from the hospital, 3 patients died within half a year and 1 patient died after 8 months, all with hepatic failure. Of 4 patients no data were available; 2 patients had encephalopathy after 6 and 12 months respectively. The remaining 4 patients had been followed for periods varying from 2 to 12 months, one patient doing "remarkably well". Thus, the tragedy of these patients does not stop at their leaving of the hospital: 70 per cent (and probably more) of the total group died within 6 months from the start of their bleeding. This finding is in concordance with the prospective study of Conn (1975).

An advantage of vasopressin treatment may be the lower total number of bloodtransfusions that were needed for this group of patients, compared to the group of surgically treated patients.

The figure of more than 345 units given to 32 patients, before and during infusion, seems extremely high. The average number of 10.9 units per patient, however, is much lower than the average of 16,9 units given to the 64 patients treated with an emergency operation. Therefore, treatment with vasopressin infusion reduced the need for banked blood significantly, while the severeness of the bleeding before treatment was equal in both groups (average given pre-operatively 8.7 units, average given pre-infusion 9.1 units).

Summary and conclusions chapter VI

Selective intra-arterial Vasopressin infusion was used during 1971-1974 as initial treatment for 32 cirrhotic patients with massive non-variceal bleeding. Treatment was successful in arresting the bleeding *initially* in 7 patients and *lasting* (i.e. more than 5 days) in 16 patients. Hepatic insufficiency - with or without rebleeding - is the major cause of death, which was the ultimate result in 56 per cent of the total group.

Whether the bleeding was arrested or not, is not reflected in the mortality rate after treatment with infusion. Mortality in patients in whom the bleeding was not, or only initially, controlled was 62 per cent, whereas in patients in whom the bleeding was controlled for more than 5 days mortality still reached as high as 50 per cent.

The severity of liver dysfunction expressed in clinical and laboratory parameters of liver function, appears to be the most prominent and determining factor for survival and mortality. Other factors, like age of the patient, severity of the bleeding, and source of the bleeding appeared to be less im-

portant or were overshadowed. No correlation with mortality could be demonstrated for serum albumin values; this may in part be due to the early administration of plasma and plasma components.

Whereas the severity of bleeding, expressed in number of blood transfusions given before vasopressin infusion was started, was in average equal to the severity of bleeding in the surgically treated group, the total amount of banked blood which was necessary for this group of patients was significantly lower than for the surgically treated group.

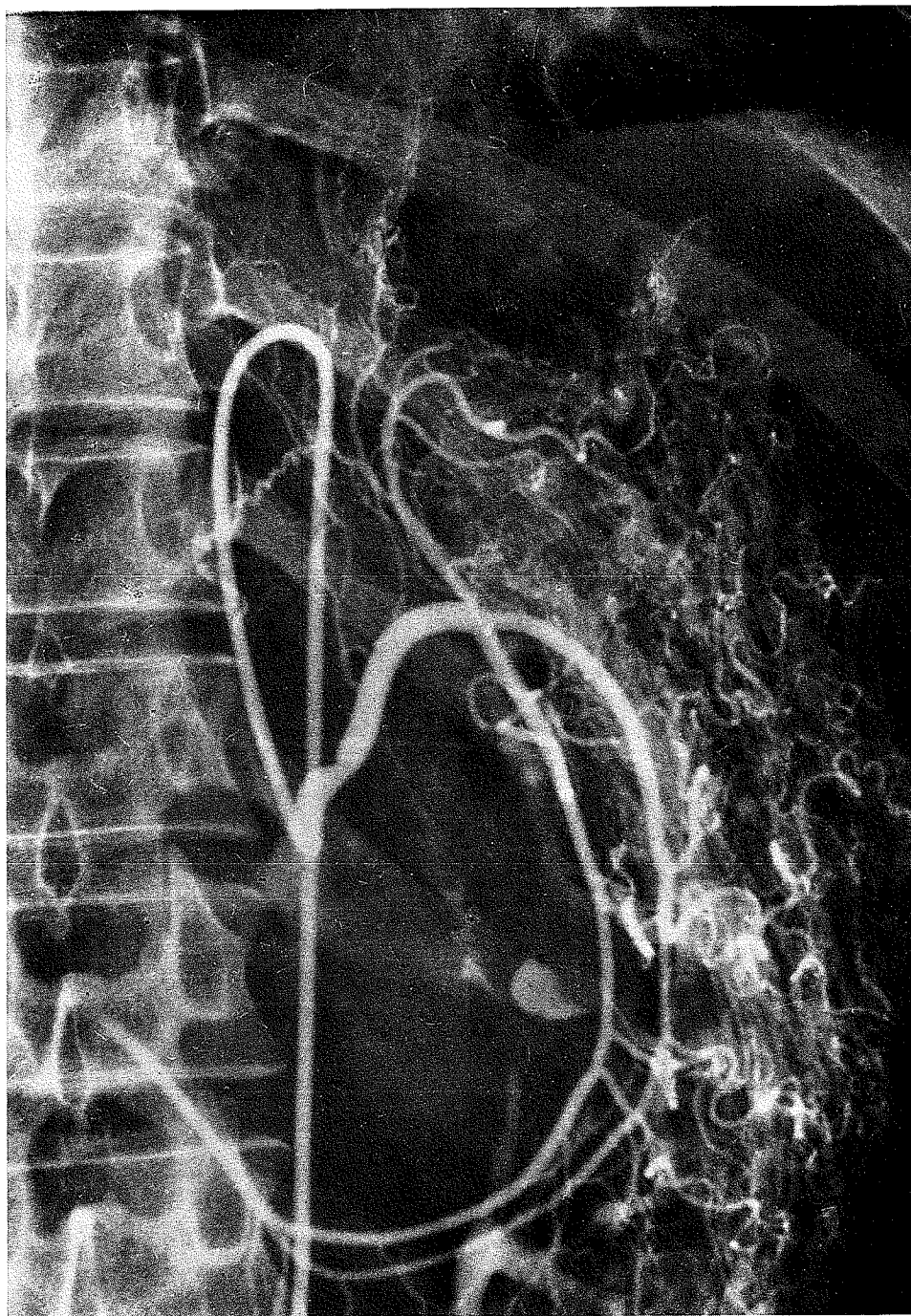


Plate 1: selective arteriography of left gastric artery showing gastritis. Arterial phase with hyperemic and tortuous intramural arterial branches.

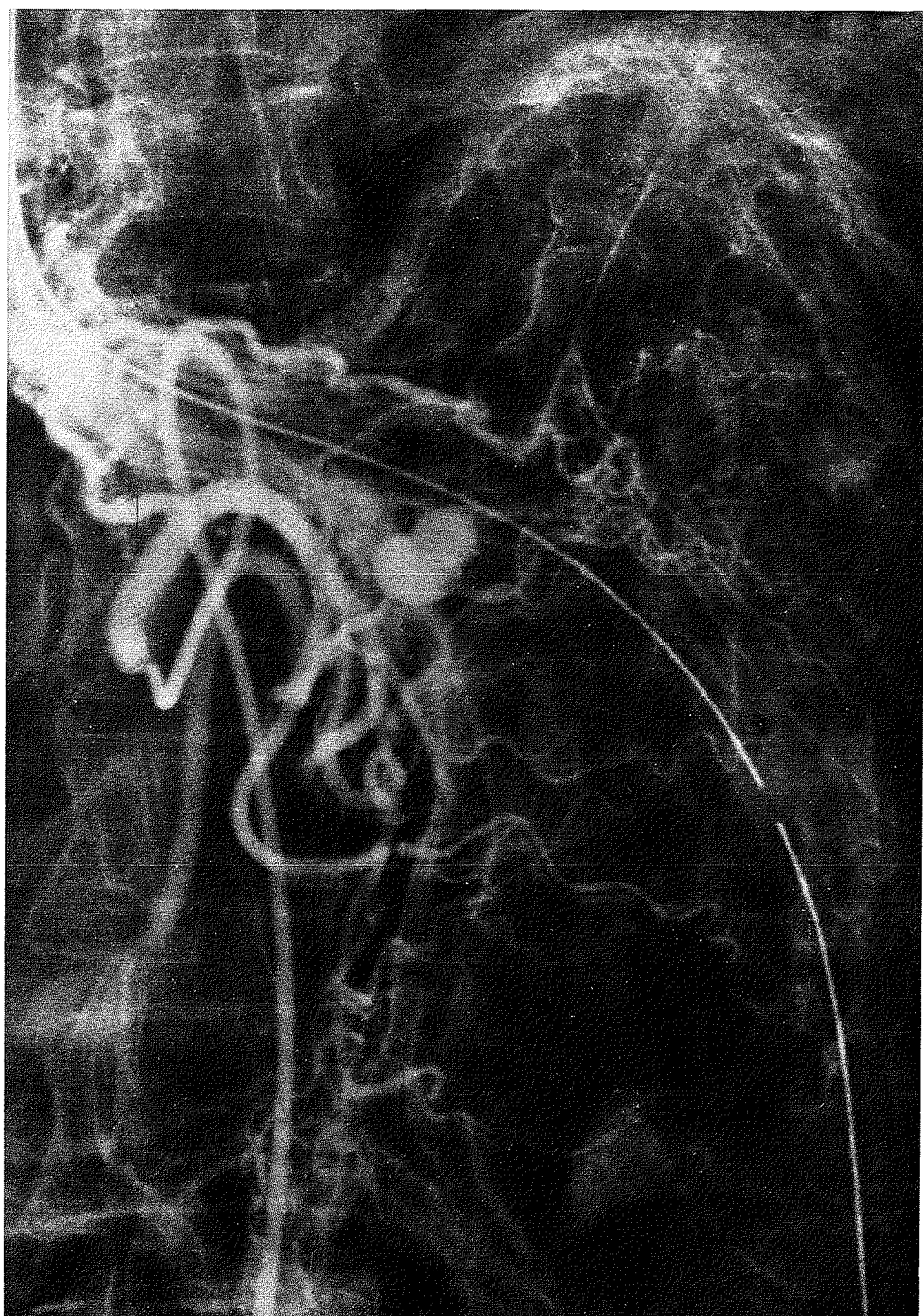


Plate 2: selective arteriography of left gastric artery, showing gastritis with extravasation in gastric erosion.
A. late arterial phase with contrast extravasation.

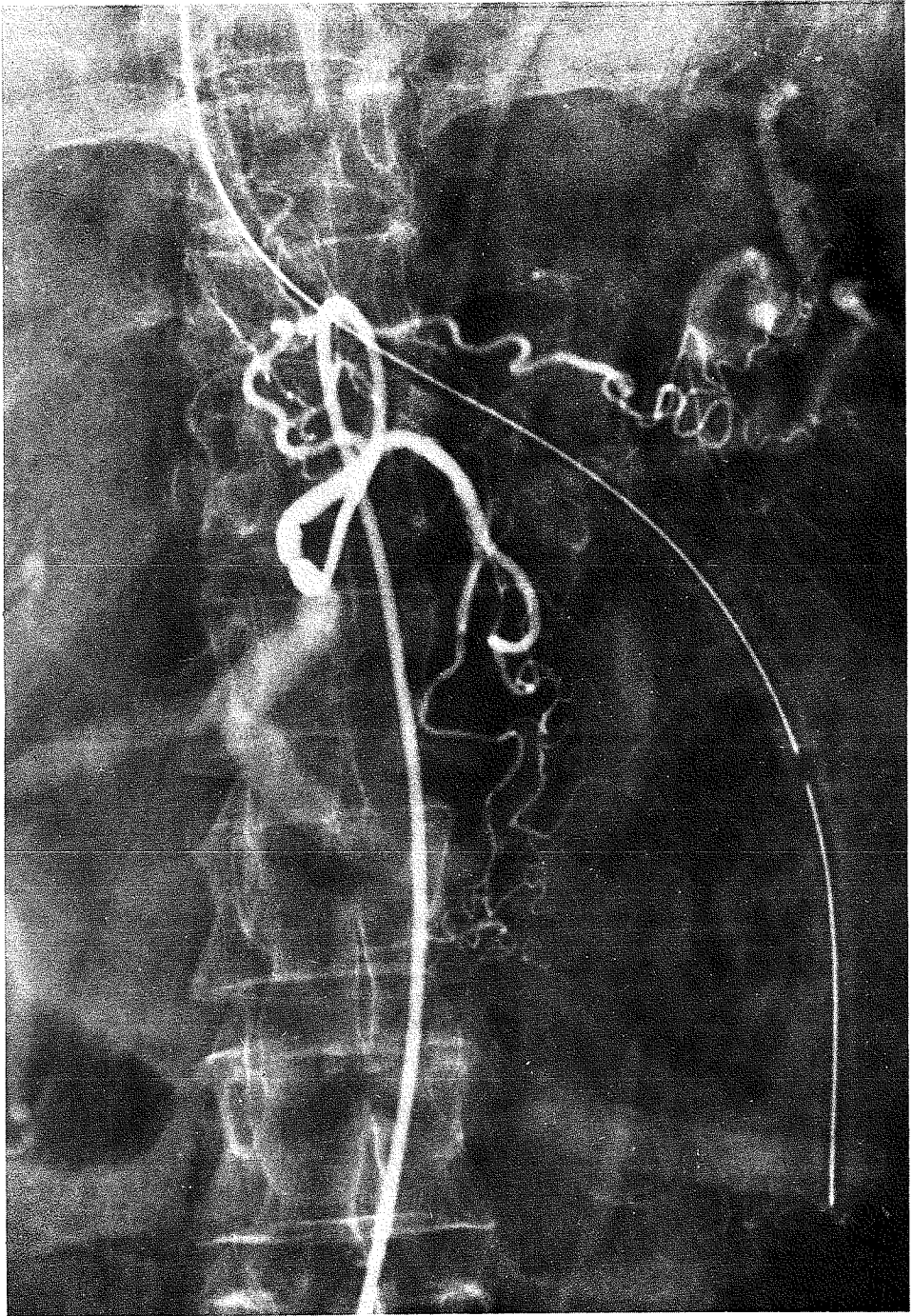


Plate 2: B. after vasopressin infusion; note tapering of artery and reflux of contrast into celiac trunc as result of increased resistance in left gastric artery.

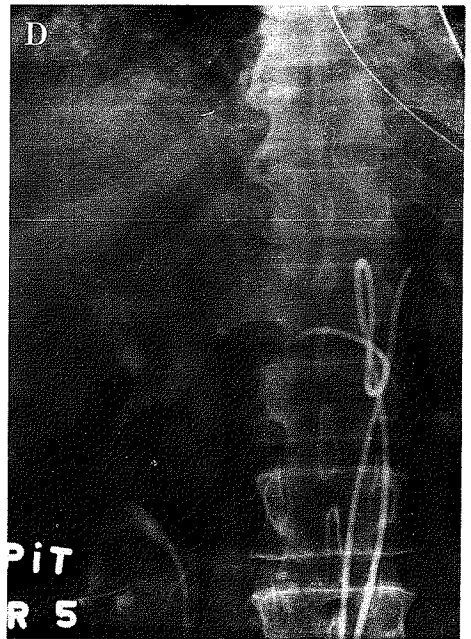
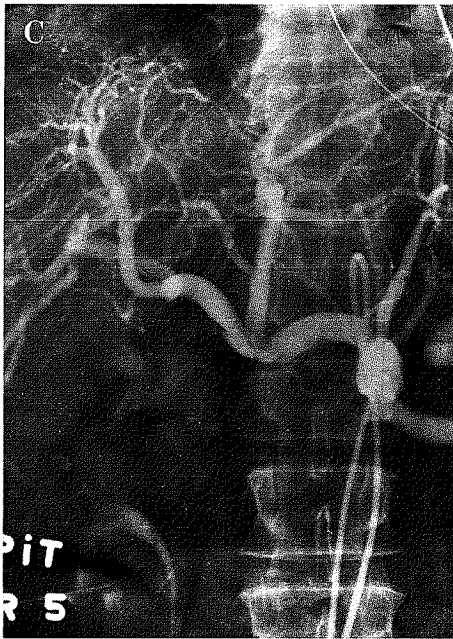
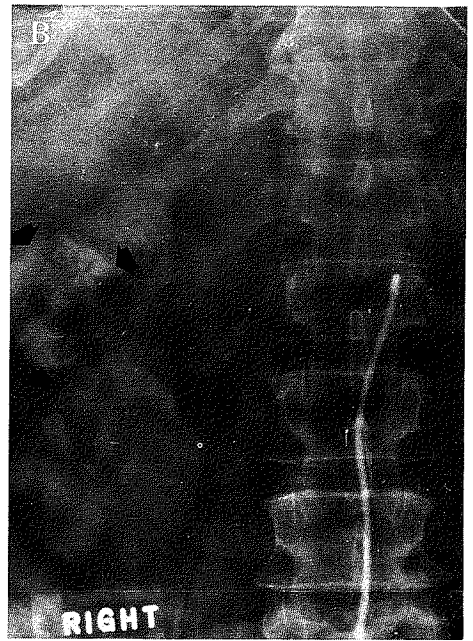
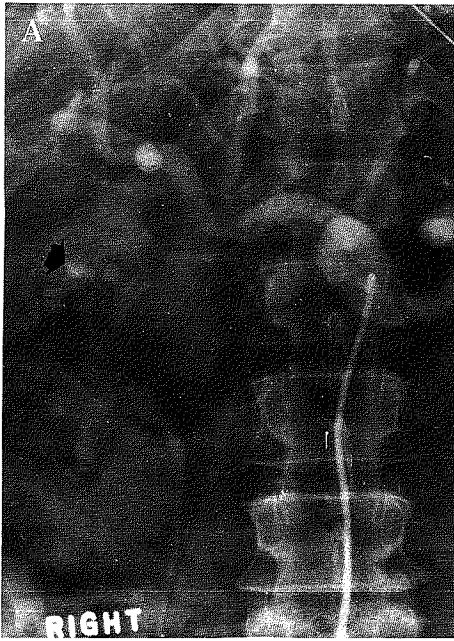


Plate 3: selective arteriography of celiac artery showing bleeding duodenal ulcer.
 A. late arterial phase; extravasation from gastroduodenal branch
 B. venous phase; contrast remaining in duodenal lumen
 C. arterial phase after vasopressin infusion: control of bleeding
 D. venous phase after vasopressin infusion.

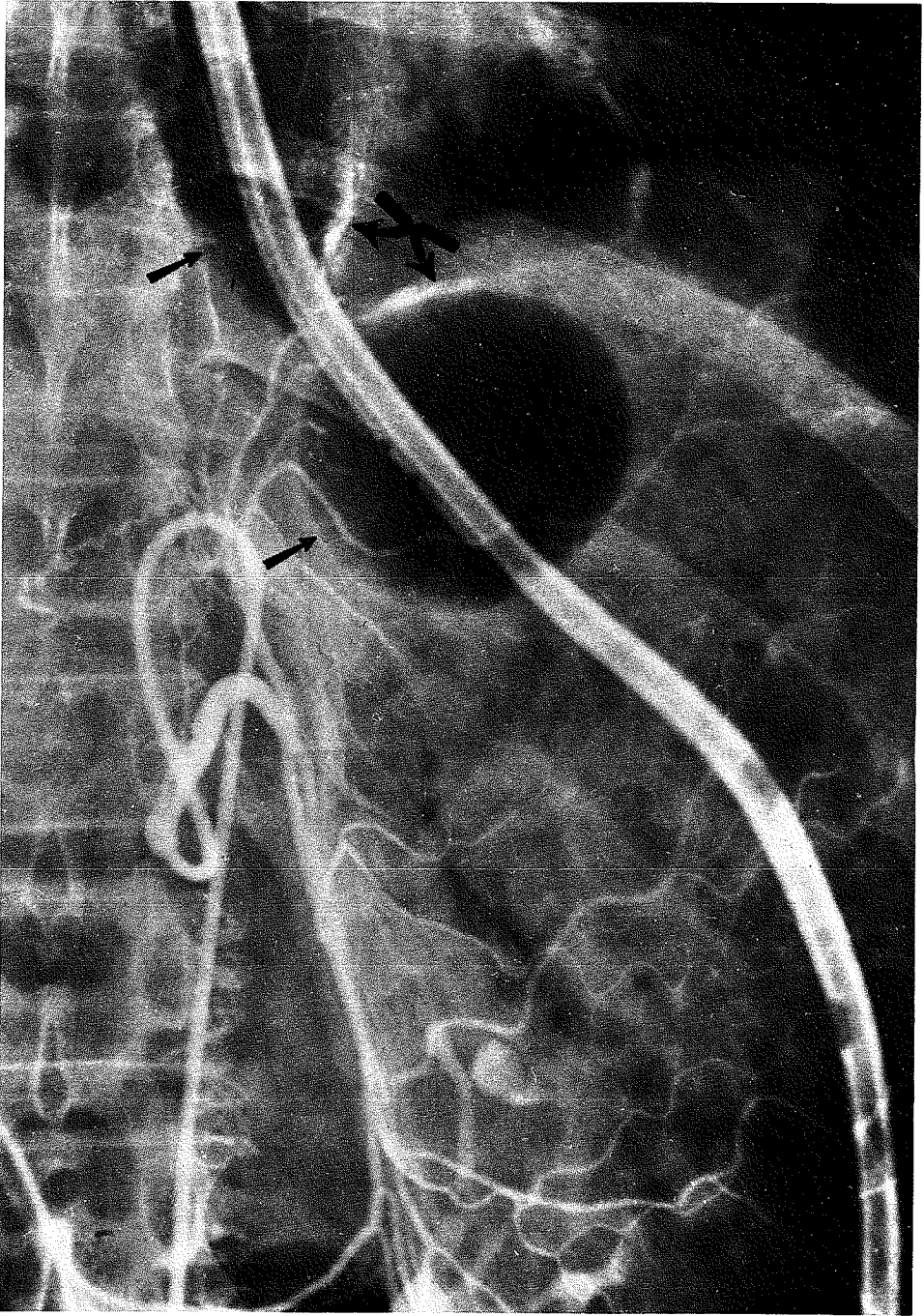


Plate 4: selective catheterization of the left gastric artery showing extra-vasation in gastro-esophageal junction. Bent arrows: contrast extravasation; straight arrows: esophageal and gastric balloon of Sengstaken-Blakemore tube.

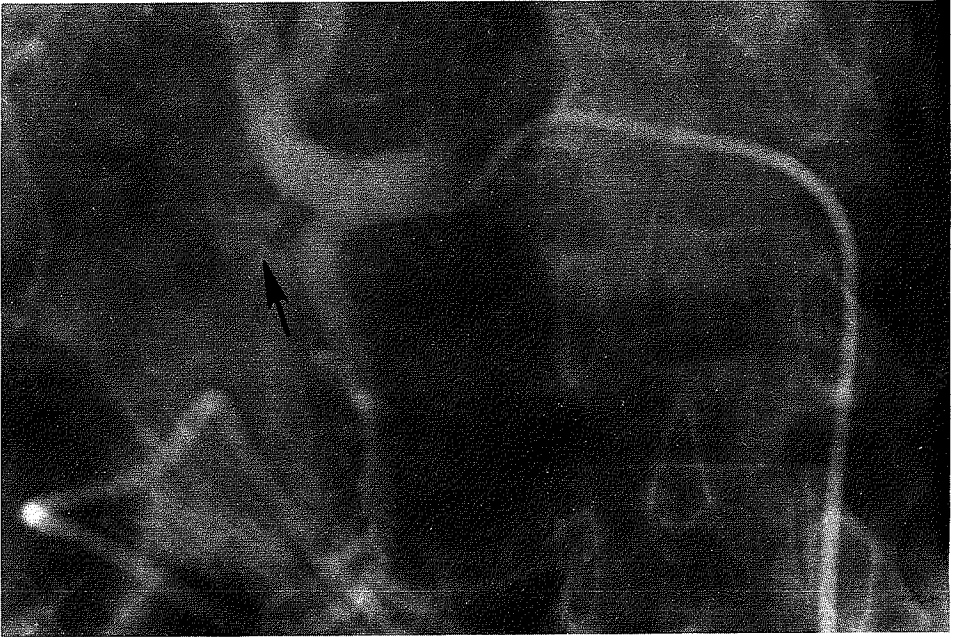


Plate 5: selective arteriography of gastroduodenal artery showing bleeding duodenal ulcer.
A. arterial phase: contrast material collecting from small branch arising from gastro-duodenal artery.

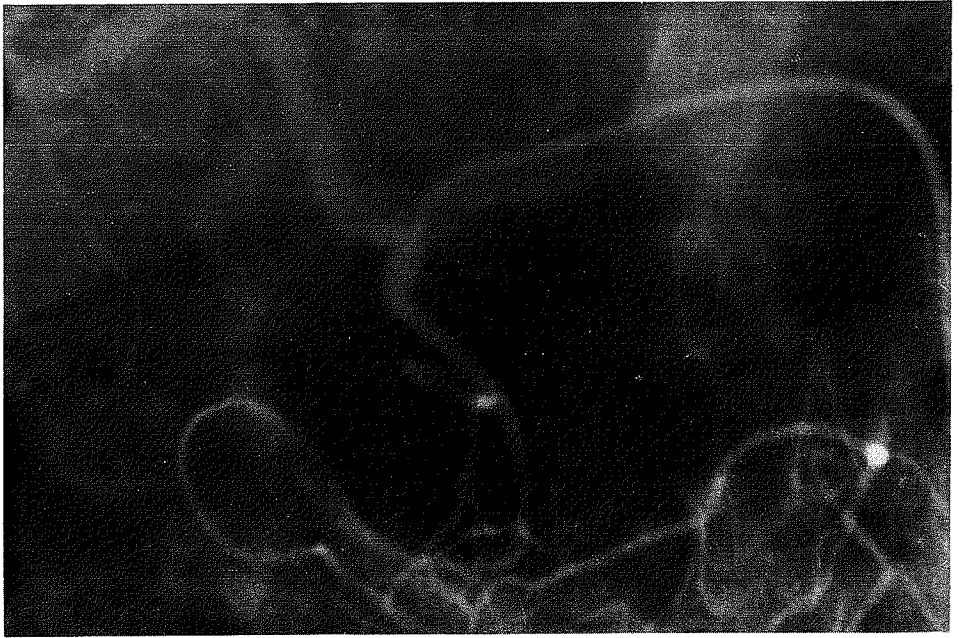


Plate 5: B. after vasopressin infusion; constriction of gastro-duodenal artery, no contrast extravasation.

CHAPTER VII

Prediction of mortality after emergency surgery

Introduction

The high mortality associated with massive non-variceal bleeding which is found in this study (56 per cent), is not surprising but merely confirms the impression - and fear - of many a surgeon dealing with these patients. The few figures given in literature all indicate the same high mortality. Of all patients who died from massive gastroduodenal bleeding in the Boston City Hospital from 1960 to 1969 (Byrne, 1970), more than half had cirrhosis. Though not explicitly stated in his report, a mortality rate for patients with cirrhosis can be calculated as high as 44 per cent (21 out of 46 patients). Merigan (1960) described 172 bleeding episodes in 158 patients with cirrhosis. In 42 per cent the lesion was a gastric or duodenal ulcer, or gastritis; no mortality figures are given for the total group, but 5 out of 7 patients who underwent a subtotal gastrectomy, died.

Considering these high mortality rates, it becomes debatable whether surgical treatment should be given at all to severely cirrhotic patients, who represent a very poor surgical risk. The ever returning problem - as in other forms of surgical treatment for patients with cirrhosis - is how to identify the patients likely to die after emergency operations, despite modern postoperative care (Jackson, 1968).

As reviewed in chapter III, no system is known to predict surgical mortality in patients with cirrhosis, meeting the requirements of reliability one would wish to have in dealing with both the patient and his family. We did not really expect to find such a system in the analysis of factors of our study. We did, however, bear in mind the intention to check whether parameters, generally used in patients with portal hypertension and variceal bleeding, ac-

tually would show the same good correlation in patients with portal hypertension, who were **not** bleeding from varices.

This hypothetical possibility was corroborated by our findings as summarized in chapter V. It would seem only natural than, to see whether these same parameters can predict mortality, by applying them to our patients in the same way as Child advised.

Here, however, a serious problem arises, which we have not encountered in literature. When we tried to classify our patients in group A, B or C, according to Child's criteria*, only 13 out of 64 could be assigned without any problem. In the remaining 51 patients considerable "overlap" existed, the data of one patient falling into two or three different groups. What to do with these patients? Child did not indicate which factor should prevail over the others.

In fact - and this is the key-problem - he described three different "standard" patients with neatly separated "standard values", thus avoiding the problem of overlap.

The logical consequence is the introduction of subjective judgment in a system that is based on objective parameters. As Turcotte (1973) pointed out: "the decision to recommend decompression of the portal system in patients with hepatic cirrhosis and bleeding varices is still based largely on **opinion** rather than objectively defined indications".

When we consider the two biochemical criteria, serum bilirubin and serum albumin, they belong to the *same* category of Child's classification in only 25 patients; 22 x there is a difference of one category (A and B, or B and C); 7 x a difference of two categories (A and C). In 10 patients one of the two determinations is missing, which sets forth another problem: the missing data. In the acute situation of a massive bleeding this problem will be frequently encountered.

"Point score system"

As has been previously stated it was **not** our purpose to add yet another classification system to the many that are in existence already. Nevertheless, the above considerations have led us to ponder the individual merits of each parameter.

Serum bilirubin level taken just before operation was the best single predictor of death ($p < 0,001$, $\chi^2 = 0,68$).

* from our data it was not possible to assess the state of nutrition, but this does not interfere with the problem.

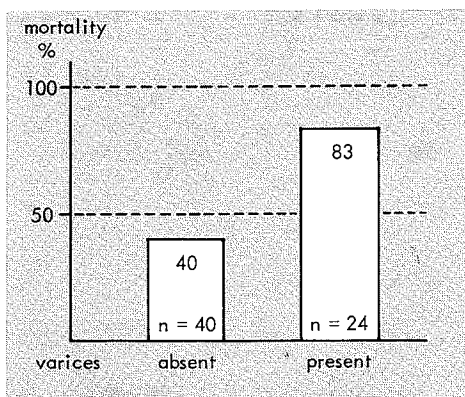


Fig. 23.: Mortality in relation to presence or absence of varices.

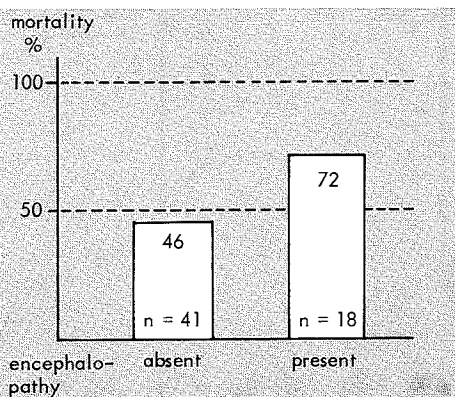


Fig. 24.: Mortality in relation to presence or absence of encephalopathy

The two clinical criteria, presence of *encephalopathy* and history or presence of *varices*, each seem to indicate a different, but important, aspect of cirrhosis, in contrast to ascites. Encephalopathy and varices were found in combination in only 8 patients and as single features in 25 patients. From this it would follow that it is important to use each as a separate entity, and not let one prevail over the other (fig. 23 and 24).

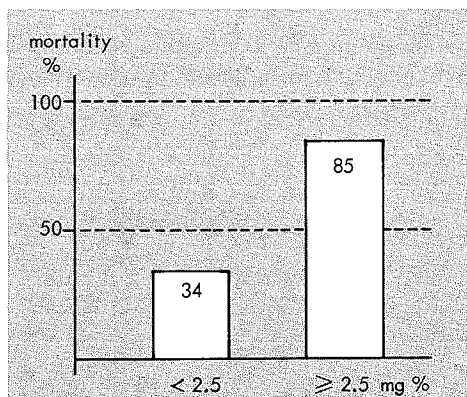


Fig. 25.: Critical value of serum bilirubin

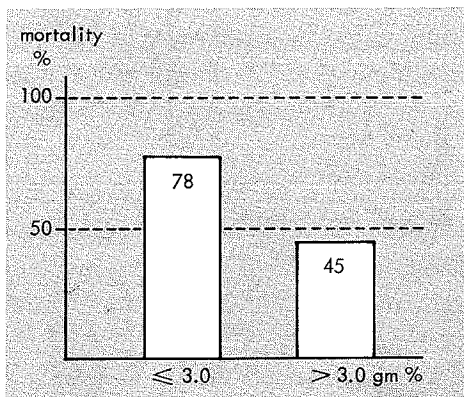


Fig. 26.: Critical value of serum albumin

In serum bilirubin, as well as in the other laboratory criteria serum albumen and prothrombin time, it is possible to determine a "critical" value, discriminating between relatively high and low mortality rates. (fig. 25, 26, 27 and 28). These critical values indicate the largest difference in mortality rate for the two groups of patients with values below or beyond this critical value.

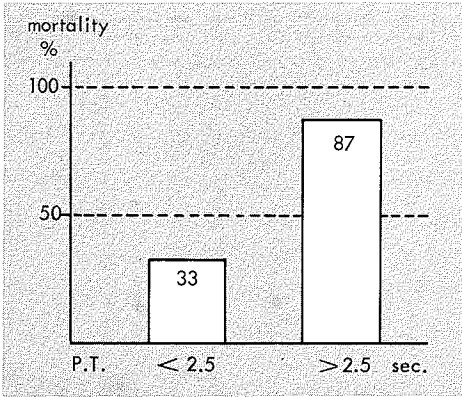


Fig. 27.: Critical value of prothrombin time in sec.

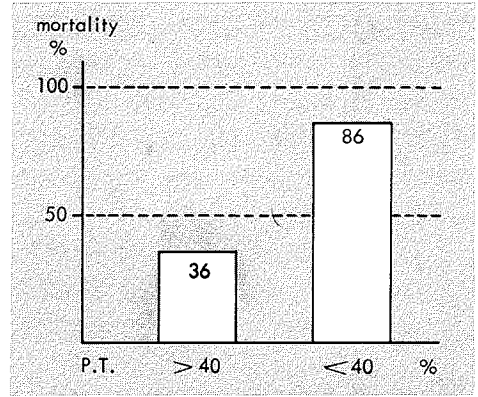


Fig. 28.: Critical value of prothrombin time in %.

Based on the critical values and clinical features outlined above, we constructed an empirical point-score system in order to predict mortality for any individual patient.

One point is assigned for each of the following signs or tests;

- serum bilirubin ≥ 2.5 mg
- serum albumin ≤ 3.0 gm
- prothrombin time ≤ 40
 > 2.5 sec. prolonged
- presence of encephalopathy
- presence of varices

As shown in fig. 29 a score of 0 points is associated with a low mortality rate of 7 per cent. A score of 3 points is associated with an 83 per cent mortality rate, and a score of 4 points with invariable death.

This system is based solely on the data of the patients treated with an emergency operation and therefore applies only to the preoperative assessment of the chances of postoperative mortality and survival.

After completing the data of the patients treated primarily with vasopressin infusion, we wondered whether the same point score system would be able to predict mortality in this group of patients. Naturally, it should be realized that the number of patients in this group (32) is very limited. However, a striking similarity in mortality rates is found, resulting in the same almost linear relationship between the total point score and mortality. Here too, a score of 1 point is associated with a 45 per cent chance of mortality and a score of 4 points leaves no survivors (fig. 30).

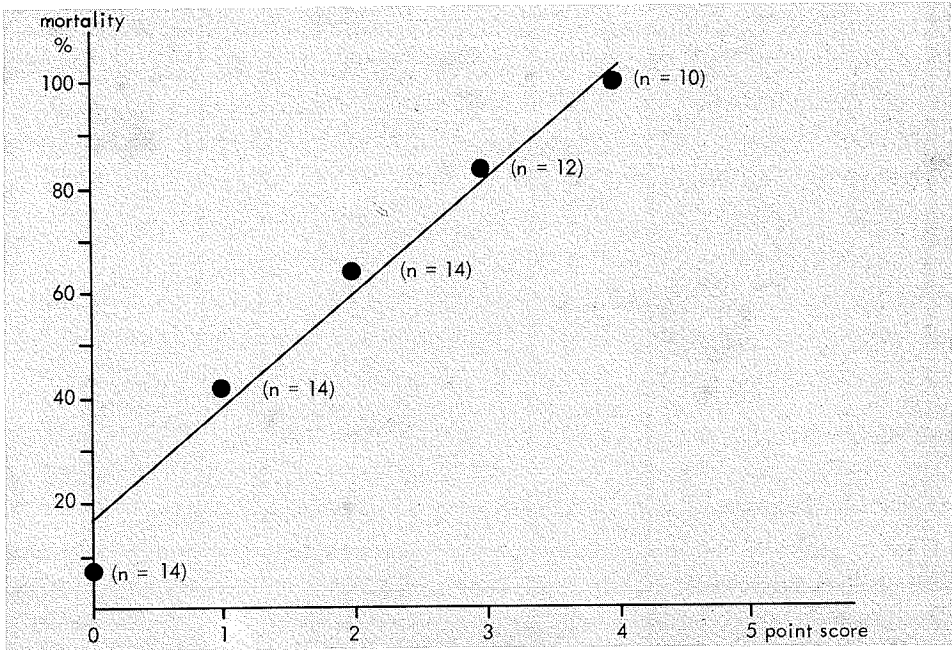


Fig. 29.: Postoperative mortality in relation to pointscore

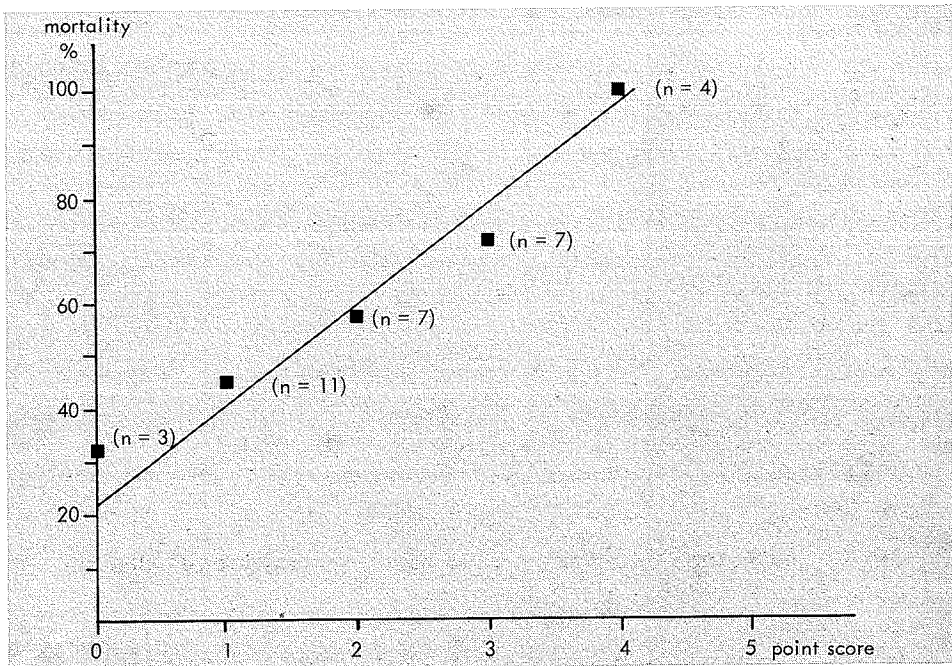


Fig. 30.: Postinfusion mortality in relation to pointscore.

Discussion

The advantage of this system over other classification methods is the fact that *all* patients – and not only "standard" patients – can be classified, even when some data are not (yet) available. Thus, a patient with known varices, encephalopathy found on admission, and a serum bilirubin of more than 2,5 mg% is already faced with an over 80 per cent chance of mortality without doing any clotting studies or the more difficult and time-consuming determination of serum protein fractions.

Whether classification systems are justified in weighing the pro's and con's of surgical treatment in these desperately ill patients, remains a question that cannot be answered here. Without exception *all* classification systems will have a certain margin of false positive and false negative predictions. Our point score system is based on the patient population of the Massachusetts General Hospital only. It may have no predicting value in other populations. There may be better parameters or better systems. The main purpose of using any classification method should be the advantage of a wider and more objective scope of means in the process of "decision-making" in the treatment of these very difficult patients.

Obviously the most difficult decision is whether a given patient should be treated or not, when "treatment" means a difficult operation, large amounts of blood and plasma, and a major effort of all people involved with "intensive care".

It is not difficult to improve postoperative mortality by selecting only the good risk patients for operation.

Likewise it is not difficult to neglect all mortality figures and operate on all patients, good risks or not. The difficulty arises only when one is aware of a responsibility towards a single patient against the background of medical, ethical and economical responsibilities towards the patient population as a whole.

We would not imply that objective parameters should replace subjective feelings or impressions. We do believe however, that subjective criteria alone no longer meet the requirements of accountable treatment. Subjective appraisal with the use of objective criteria may be a reasonable approach to this problem.

We feel that our point-score system may help in solving the problem.

Summary and conclusions

When patients with cirrhosis of the liver are admitted to the hospital with massive upper gastrointestinal bleeding, a major diagnostic and therapeutic problem is inevitable. A correct diagnosis of the bleeding source is mandatory, because a substantial number of patients do bleed from sources other than esophageal varices. In the majority of these cases the bleeding is from peptic ulcers or hemorrhagic gastritis. The association of peptic ulcer disease and cirrhosis of the liver is extensively reported in literature, incidence varying from 2-42 per cent. Several conducive factors have been proposed, but no causal relationship has been corroborated, neither in the clinical situation nor in animal experiments. The pertaining literature is discussed in chapter I.

Treatment for massive bleeding usually consists of an emergency surgical procedure, with an allegedly high mortality rate. The introduction of selective angiography and the use of intraarterially infused vasoconstrictive agents like vasopressin, have widened the therapeutical range of treatment for patients with cirrhosis, who are considered operative "high risks". Reported success and failure rates, as well as complications, are discussed in chapter II. Selective angiography with vasopressin infusion appears to be a relatively safe procedure, capable of controlling massive gastro-intestinal hemorrhage in selected cases.

In the surgical treatment of patients with cirrhosis and portal hypertension who are massively bleeding from esophageal varices, much emphasis is laid on the degree of liver insufficiency or functional hepatic reserve, as this was shown to be of prognostic significance.

One of the aims of this study was to analyse whether clinical and/or biochemical data, obtained prior to surgery, would show any relation to postope-

rative mortality following surgical treatment for *nonvariceal* bleeding, analogous to the situation in *variceal* bleeding. In chapter III a discussion is given on factors assessing liver function, and on classification systems for the prediction of surgical mortality based on these factors. A common disadvantage of selection methods which are currently in use is the inability to classify all patients in confined groups without considerable overlap.

Chapters IV, V and VI relate to the analysis of two series of cirrhotic patients treated for massive non-variceal bleeding in the Massachusetts General Hospital in Boston. Chapter IV describes the criteria used in the selection of patients and the definitions used for the various clinical characteristics pertaining to the subject.

Chapter V presents and discusses the analysis of 64 patients from a 10-year period, 1962-1972, all treated surgically. Overall mortality appeared to be very high with 56 per cent, not improving over the 10-year period. Of the various clinical and biochemical factors that were examined for a positive relation to postoperative mortality, only those expressing the severity of liver dysfunction showed a statistical relationship. No influence could be attributed to a variety of factors which are usually granted to affect mortality, like age, sex, coexistent disease, duration and amount of bloodloss, source of bleeding, and type or duration of the surgical intervention. A good relation to postoperative mortality was demonstrated for serum bilirubin, serum albumin and prothrombin time. Of these laboratory data serum bilirubin levels correlated most clearly to postoperative results. Presence of encephalopathy and varices were the only two clinical entities positively correlated with death rate.

In chapter VI the results are described and discussed in 32 patients, who fulfilled the same criteria as the surgically treated group, but who were treated with selective infusion of vasopressin as initial treatment. Mortality (56 per cent) in this group is equal to mortality in the surgical group.

Survival is far from equivalent with *control of bleeding*, but shows the same relation with functional hepatic reserve, with an exception for serum albumin.

The clearly demonstrated relationship between preoperative clinical and laboratory parameters and postoperative mortality, as outlined in chapter V, lead us to combine the single features into a clinically useful formula for the prediction of postoperative mortality.

If one point is assigned for each of the following signs or tests - serum bilirubin level over 2.5 mg%, serum albumin level less than 2.0 gm%, prothrombin time more than 2.5 sec. prolonged (or less than 40%), presence of encephalopathy, and presence or history of esophageal varices - the total predicts mortality with near linearity. Thus detection of undeniable jaundice, with evidence of portal hypertension and signs of encephalopathy can predict a dire outcome (mortality over 80 per cent) without laboratory tests. This point score system is described and discussed in chapter VII. A major advantage of this system is the possibility to obtain a point score on any given patient, without overlap, even when not all clinical or laboratory data are available.

No judgement is given on the benefits of either surgical or angiographical treatment, *not* because mortality rates after either way of treatment are equal, but because both series of patients were studied in retrospect, thus precluding any conclusions in this respect beforehand. This thesis merely aims at a better understanding of the pathological pathways one is confronted with in dealing with patients with cirrhosis of the liver and massive non-variceal bleeding.

Samenvatting en conclusies

Patiënten met levercirrhose en een massale bloeding in de tractus digestivus vormen een groot probleem, zowel wat betreft de diagnostiek als wat betreft de behandeling. Een juiste diagnose van de oorzaak van de bloeding is noodzakelijk, omdat het bekend is dat bij een niet onaanzienlijk aantal van de patiënten met levercirrhose bloedingen worden veroorzaakt door peptische ulcera of haemorrhagische gastritis en *niet* door bloedende oesophagus-varices.

Het gelijktijdig voorkomen van peptische ulcera en levercirrhose is in de literatuur uitgebreid beschreven, hoewel de opgegeven percentages vrij sterk uiteenlopen. Verschillende factoren zijn in de loop der tijden als oorzaak aangewezen, maar nooit is een causaal verband werkelijk aangetoond. Dit geldt zowel voor klinische onderzoeken als voor dierexperimenten. De betreffende literatuur wordt beschreven in hoofdstuk I.

De behandeling van een massale bloeding hoog in de tractus digestivus bestaat meestal uit een spoedoperatie, die in het algemeen gepaard gaat met een hoge mortaliteit. De conservatieve behandeling van massale bloedingen is grotendeels verlaten.

De introductie van selectieve angiografie gevolgd door intra-arteriële infusie van stoffen met een constrictieve werking heeft het therapeutisch arsenaal voor o.a. patiënten met levercirrhose vergroot, met name voor de groep van patiënten die een groot operatie risico vormen. De in de literatuur vermelde resultaten en complicaties worden besproken in hoofdstuk II. Selective angiografie en intra-arteriële infusie met vasopressine wordt in het algemeen beschreven als een betrekkelijk veilige methode, waarmee ook massale bloedingen in de tractus digestivus tot staan gebracht kunnen worden. Meestal is er echter sprake van geselecteerde patiëntengroepen, waardoor vergelijking met andere methoden niet mogelijk is.

In de literatuur over de chirurgische behandeling van patiënten met levercirrhose, portale hypertensie en massaal bloedende oesophagusvarices, speelt de mate van leverinsufficiëntie een belangrijke rol bij het bepalen van de prognose. Analoog aan de situatie bij varicesbloedingen werd in onze studie gezocht naar klinische en biochemische factoren, die een positieve relatie vertonen met de postoperative mortaliteit van operaties voor niet-variceuze bloedingen. In hoofdstuk III worden de verschillende factoren besproken die een maatstaf zijn voor de leverfunctie. Tevens worden verschillende selectie methoden beschreven die gebaseerd zijn op de mate van leverreserve en die gebruikt worden voor het bepalen van de te verwachten chirurgische mortaliteit. De meeste van deze methoden hebben één nadeel gemeen, nl. een belangrijke mate van overlap tussen de verschillende risico-groepen waarin de patiënten verdeeld moeten worden.

Hoofdstuk IV t/m VI betreffen de analyse van twee series patiënten met levercirrhose, die in het Massachusetts General Hospital te Boston, U.S.A., werden behandeld voor massale niet-variceuze bloedingen in de tractus digestivus. De criteria die werden gebruikt bij het uitzoeken van de patiënten en de definities van de verschillende klinische begrippen worden beschreven in hoofdstuk IV.

In hoofdstuk V worden de gegevens besproken van 64 patienten uit de periode 1962-1972, die allen een spoedoperatie ondergingen. De mortaliteit in de totale groep blijkt zeer hoog te zijn, nl. 56 procent. Van de verschillende factoren die werden onderzocht op een mogelijk verband met de postoperatieve mortaliteit, kon dit alleen worden aangetoond voor die factoren, die een uitdrukking zijn van de gestoorde leverfunctie. Van andere factoren, zoals leeftijd, sexe, bijkomende ziekten als diabetes mellitus, duur van de bloeding en de mate van bloedverlies, aard van de operatie en duur van de ingreep, kon géén invloed op de mortaliteit worden aangetoond.

Een goede statische relatie werd aangetoond voor de serum bilirubine en albumine waarden en de prothrombine tijd. De aanwezigheid van encephalopathie en oesophagus-varices vormden de klinische verschijnselen die van invloed zijn op de mortaliteit.

In hoofdstuk VI worden de resultaten besproken van 32 patienten die in de periode 1971 t/m 1974 in eerste instantie werden behandeld met selectieve infusie van vasopressine. Deze patienten voldeden aan dezelfde criteria voor cirrhose, massale bloeding e.d. als de groep operatief behandelde pa-

tienten. De mortaliteit (56 procent) in deze groep is gelijk aan de mortaliteit in de chirurgische groep.

Er is echter in het geheel geen verband tussen het *tot staan brengen* van de bloeding met behulp van vasopressine en het *overleven* van de bloeding. Ook hier blijkt de mortaliteit een duidelijk verband te vertonen met de factoren die de mate van leverfunctiestoornis bepalen, met uitzondering van het serum albumine.

Hoewel dit niet direct de opzet van de studie was, bleek het mogelijk de in hoofdstuk V beschreven relatie tussen preoperative klinische en biochemische parameters enerzijds en postoperatieve mortaliteit anderzijds, te combineren tot een klinisch bruikbare eenvoudige formule waarmee de te verwachten postoperatieve mortaliteit berekend kan worden. In hoofdstuk VII wordt dit puntensysteem beschreven.

Een punt wordt toegekend voor de aanwezigheid van elk van de hierna volgende biochemische waarden of symptomen: serum bilirubine gehalte $\geq 2.5 \text{ mg \%}$ ($43 \text{ } \mu\text{mol/l}$); serum albumine gehalte $\leq 3.0 \text{ gm \%}$; prothrombine tijd $> 2.5 \text{ sec.}$ verlengd of $\leq 40\%$; de aanwezigheid van encephalopathie; de aanwezigheid van oesophagusvarices. De postoperatieve mortaliteit is vrijwel lineair afhankelijk van de som van de aldus toegekende punten.

Een belangrijk voordeel van dit puntensysteem is het feit dat elke willekeurige patiënt kan worden ingedeeld - zonder overlapping - zelfs wanneer (nog) niet alle gegevens bekend zijn.

In dit proefschrift wordt geen oordeel uitgesproken over de waarde van chirurgische therapie ten opzichte van vasopressine infusie. Dit is niet het geval omdat de mortaliteit na beide behandelings methoden gelijk is, maar omdat het hier een retrospectief onderzoek betreft, waardoor dergelijke conclusies bij voorbaat uitgesloten zijn. Het onderzoek heeft uitsluitend tot doel gehad een bijdrage te leveren tot een beter begrip van het pathologisch gebeuren waarmee men geconfronteerd wordt bij de behandeling van patiënten met levercirrhose en massale bloedingen in de tractus digestivus van niet-variëuze oorsprong.

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AFDELING HEELKUNDE
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”..... after reviewing many of these discussions we have concluded that they are composed variably of emotionalism, wishful thinking and verifiable knowledge. All suffer from common handicaps – basic ignorance of the true nature of cirrhosis, incomplete knowledge of portal hemodynamics, sketchy information on the regulation of splanchnic bloodflow, and transposition of facts from animals with normal livers to men and women with cirrhotic livers.....”

Charles G. Child, III., 1964.

STELLINGEN

I

Patienten met levercirrhose, bij wie zich een gastro-intestinale bloeding voordoet, dienen met spoed endoscopisch onderzocht te worden.

II

Bij patienten met levercirrhose, portale hypertensie en gastro-intestinaal bloedverlies, dient arteriografisch onderzoek verricht te worden alvorens chirurgische therapie wordt ingesteld.

III

Een ulcus pepticum bij een patient met levercirrhose is een indicatie voor langdurige behandeling met cimetidine, ook na genezing van het ulcus.

IV

Het verrichten van een zogenaamde "blinde resectie" bij patiënten met een bloeding in de tractus digestivus is een kunstfout.

V

De mogelijkheid van het transplanteren van nieren van verwante levende donoren dient een grotere bekendheid te krijgen.

VI

Voor de behandeling van tracheo-oesophageale fistels ten gevolge van een maligne tumor verdient het plaatsen van een prothetische plastic buis onder endoscopische geleide de voorkeur.

VII

Elke praktiserende arts die een kind met verwondingen onder behandeling krijgt dient het "kindermishandelings-syndroom" bij zijn diagnose te betrekken.

VIII

Het enige zekere argument voor de diagnose bijschildklier carcinoom is het vinden van metastasen.

IX

De hoge target/non-target ratio van Adosterol®-I¹³¹ rechtvaardigt het gebruik van dit radio-pharmacon voor de localisatie van bijniertumoren tegenover de hoge kosten.

X

Het gebruik van per-operatieve autotransfusie verdient een ruimer toepassingsgebied dan alleen in de open-hartchirurgie.

XI

De veronderstelde causale relatie tussen het gebruik van corticosteroiden en het ontstaan of reactiveren van peptische ulcera is niet bewezen.

XII

Het "Intensive Care - syndroom" bestaat niet.

XIII

Voor de functie van directeur van een ziekenhuis zijn management capaciteiten belangrijker dan een medische opleiding.

XIV

Ziek zijn kent óók geen baaldagen.

H. van Urk.

11 november 1977.