B I L I A R Y & P A N C R E A T I C

O B S T R U C T I O N S

A Thesis submitted for the Degree of

Master of Surgery

by

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INTRODUCTION

Frank H. Lahey, who has left his name indelibly printed in most branches of general surgery, described the surgical treatment of gallstones as having passed through three phases beginning with the era of drainage of the gallbladder, followed by the period when cholecystectomy became de rigueur and finally a growing readiness to explore the ducts as well. Lahey has, of course, advocated the third approach even in the absence of any history of jaundice. Nevertheless, we have the paradox that the difficulties encountered in this field of surgery, and in the complications which arise, are only too often the result of the timid and cautious methods of older practitioners. Thus it has come about that the Lahey Clinic and the like have built up a world-wide reputation on this system of thoroughness and enterprise.

As the title implies, this thesis is divisible into two main parts. The first is a clinical study of the surgery of the extrahepatic biliary system apart from the gallbladder. This opens on an embryological theme. Annular pancreas is /

is possibly much commoner than a reading of the medical literature leads us to suppose, but the case recorded is the only one which I have come across in the course of 20 years' experience. The case is interesting because it did not present itself as a duodenal but as a biliary obstruction. This anomaly was the subject of a paper written in conjunction with Dr. John R. Anderson.*

It is a truism that the diagnosis of the cause of jaundice requires that sense of clinical judgement which can match the age, history and physical findings against the findings of the liver function tests. In the consideration of this problem one is reminded of the saw oft repeated by Sir David Wilkie in another regard, - "Better a living mistake than a dead diagnosis". Yet even the facilities afforded by laparotomy may not supply the complete answer. There remains the more direct method of study, namely contrast radiography which is applicable both to jaundice and to other types of cases. Retrograde cholangiography serves as a means of locating the size and number of stones and the site of organic strictures; it also affords the opportunity for /

for observing functional disorders of, and the effects of drugs on, the sphincter mechanism that controls the flow of bile into the duodenum. The radiological studies, which are recorded in the second chapter, cover a series of 48 biliary cases. I wish to express my indebtedness to Dr. S.D. Scott Park and his staff for their co-operation. The other chapters in the first part of the thesis are concerned with the problems of traumatic and neoplastic strictures respectively. Arising out of the former study two papers were published.*

In so far as it touches on so many fields of differing activity, the aetiology of the acute affections of the pancreas is a problem of immense complexity. The limitations of clinical studies are generally admitted and we still have to turn to experiments on animals in the hope of achieving a more direct attack on the problem. My work in this connection is confined to experimental observations on the effects of acute obstruction of the secretory pathways of the pancreas on this organ. Both normal humans and normal dogs were used as subjects for the investigations. One should /

should explain that in the human studies, which were carried out during the years 1940-43 at the Western Infirmary, Glasgow, and at Killearn Hospital, the obstructive agent employed was morphine. The results have been published.* The functional effects of pinching the pancreas were investigated in the course of my association with the Broadstone Jubilee Hospital, Port Glasgow, in 1948-50. The animal studies cover a wider field of more direct investigation on the causes of acute pancreatitis. These were conducted during the years 1940-42 in the Surgery Department, University of Glasgow. The expenses were defrayed by the Rankin Trust Fund.

PUBLICATIONS

ANNULAR PANCREAS Brit. J. Surg. 39 p. 43. 1951

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THE PANCREATIC SIDE-EFFECTS OF MORPHINE. Brit. Med. J. Feb.14. p.373. 1953.

ACQUIRED BENIGN STRICTURES OF THE BILE DUCTS: A Critical Review Based on Some Personal Experiences. Glas. Med. J. 34 p.141. 1953

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ANNULAR PANCREAS.

The encirclement of the second part of the duodenum by an annular extension of the pancreas is a rare abnormality. The first case was reported by Tiedemann in 1818. McNaught published a review of the literature relating to this anomaly up to 1933, in which he summarized the findings in 40 cases. Swynnerton and Tanner (1953) reckoned that up till June 1952, the total number of cases recorded was at least 75. Its incidence in males is much higher than in females; and other congenital abnormalities have been associated in roughly 25 per cent.

Most of the cases have been incidental post-mortem findings, though the condition appears to be accompanied not infrequently by some degree of duodenal constriction and dilatation of the proximal part of the duodenum and sometimes the stomach. Anderson and Wapshaw (1951) estimated that up till 1950 there were 18 reported cases in which this constriction gave rise to severe symptoms necessitating surgical relief. It is worthy of note that acute pancreatitis affecting the main gland was a fatal complication in two of these cases. The /

The following case is almost unique in that the condition was associated with jaundice due, it would seem, to recurrent pancreatitis affecting the annulus.

Case Report

Mrs. E.R. 32 years, was admitted under my care on the 26th November, 1949, to the Broadstone Jubilee Hospital, Port-Glasgow. Three days previously she was suddenly seized with a pain of overwhelming severity in the lower epigastrium, radiating to the right hypochondriac and right infra-scapular areas; frequent bouts of vomiting and retching added to her distress. Jaundice appeared on the third day of illness.

Earlier in the same year, in April and again in June, she had had similar attacks of pain but of less severity, each lasting about five days. She first became jaundiced during the second episode. In between these illnesses she was relatively well and in August she was delivered of a full term child.

Physical Examination. On admission the temperature was 102°F., pulse rate 72, and respiratory rate normal. The patient was moderately jaundiced but appeared to be otherwise healthy. She was not in /

in severe pain and the abdomen moved freely with each respiration. Deep tenderness without muscle guarding was elicited in the region of the gall-bladder, which was not palpable. There were no other noteworthy findings.

The stools were at first acholic; the urine on admission was acid, specific gravity 1010, and contained albumin and bile.

Course of Illness. During the next 5 days the jaundice disappeared and the temperature settled; the abdominal pain and nausea subsided, and the patient's condition steadily improved. Cholecystography, performed fifteen days after admission to hospital, failed to demonstrate the gall-bladder and showed no abnormal opacities. The serum amylase during the third week of illness was within normal limits.

A presumptive diagnosis of intermittent biliary obstruction due to gall-stones was made, and laparotomy was carried out 18 days after admission to hospital.

Operation (H. Wapshaw). The gall-bladder had a slightly thickened wall but was flaccid and did not show any sign of recent inflammation. It did not contain any stones. Both the cystic and common bile-ducts were very considerably dilated and also appeared to be free of/

of stones. In searching for further cause of the jaundice, the ring pancreas was discovered. Once the mesocolon had been detached by gauze dissection a good exposure of the second part of the duodenum was obtained.

The annulus resembled somewhat a signet ring, measuring in width 1.5 cm. anteriorly, and 2.5 cm. posteriorly, and approximately 1 cm. in thickness. The aberrant tissue had a nodular surface and felt unduly firm; it completely encircled the second part of the duodenum but did not cause obvious constriction. The stomach, intestines, appendix, and spleen all appeared to be normal.

The patency of the common bile-duct was tested in the usual manner through a supraduodenal approach; no stones were found therein and a medium-sized urethral sound was passed without hindrance into the duodenum. The bile was amber-coloured and quite clear; drainage was provided by an indwelling T-tube.

In view of the absence of any demonstrable blockage or stenosis of the common bile-duct, it was considered that the symptoms might be causally related to the ring pancreas, the firmness and rigidity of which pointed to the presence of chronic inflammatory change. Resection of a segment of the ring seemed to offer a good/

good chance of permanently relieving any pressure on, or distortion of, the common bile-duct. This was carried out without difficulty, although adherence to bowel wall was so intimate that most of the outer muscle coat had to be sacrificed. The cut surfaces of the ring presented a yellowish fibrous appearance. Marginal oozing was easily controlled. A piece was taken from the body of the pancreas for microscopical examination.

Post-operative Course. The patient vomited once or twice each day for the first week, after which convalescence was uninterrupted.

Post-operative Investigations.

(1) Bacteriology of Bile from Common Duct. No organisms were seen on direct examination and no growth obtained on culture.

(2) Pathological Report of Pancreatic Tissue.

A. The excised portion of the annulus was of firm consistency and retained the shape of a segment of a ring. In transverse section (fig. 1), it measured 2 by 0.7 cms; one surface was coated with smooth muscle of the duodenal wall while the other was lined by peritoneum.

Microscopically a cross-section of the annulus consisted of dense fibrous tissue in which were embedded groups of normal and atrophic pancreatic acini, and occasional islets (figs. 2). A single duct of / ‘

of 1 millimetre diameter was seen to be cut in transverse section with smaller tributaries cut obliquely (fig. 3). There was patchy aggregation of lymphocytes and mononuclear cells throughout the fibrous tissue, related particularly to groups of atrophic acini.

B. The piece taken for biopsy from the body of the pancreas consisted microscopically of normal tissue.

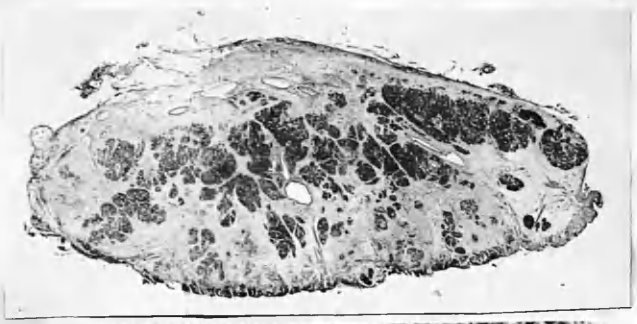


Fig.1. A transverse section of the excised portion of the annulus. The longitudinal muscle coat of the duodenum is seen along the lower margin while the upper surface is lined by peritoneum. The main annular duct is seen in cross-section in the middle of the section. (Haemalum and eosin.) (x 3.3)

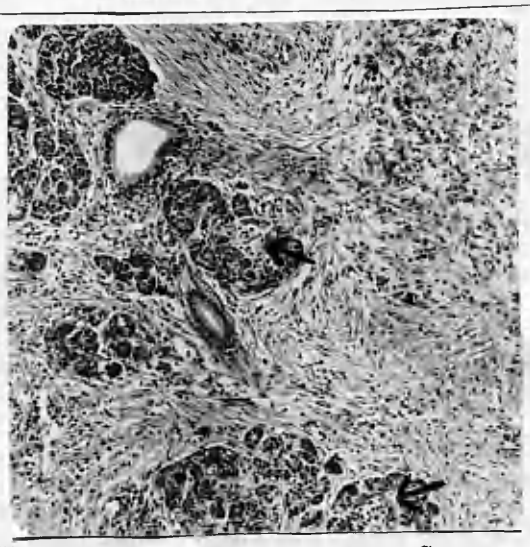


Fig. 2. Annulus. Groups of acini ducts and islet tissue (arrows) are embedded in dense fibrous tissue. In the upper right corner of the field are the remains of atrophic acini. Lymphocytes and mononuclear cells are scattered throughout the fibrous stroma. (Haemalum and eosin.) (x 125)

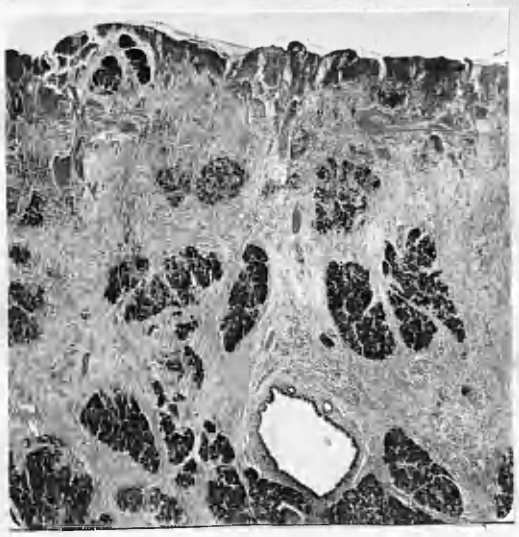


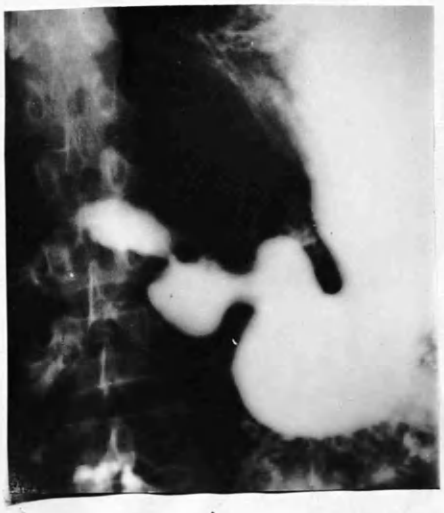
Fig. 3. A higher magnification of part of Fig. showing the main duct, and occasional tributaries cut obliquely. The outer part of the muscle coat of the duodenum bounds the surface.

(3) Cholangiography carried out 14 days after operation by injection of lipiodol via the T-tube in the common bile duct showed an incomplete obstruction at the distal end of the common duct. Further cholangiograms taken three days later also showed some delay in the passage of the lipiodol. It should be stated that no opiates or other drugs were administered prior to these examinations. An interesting feature was the visualization of the duct of the annulus (fig. 4.).

Fig.4. Cholangiogram of the case reported showing dilatation of the biliary passages. An arrow (A) indicates the small duct opening into the common bile-duct and considered to be that draining the annulus. (B) marks the narrow track of contrast medium passing into the duodenum.

(4) Barium meal examination was carried out two weeks after operation, and showed an obstruction of smooth rounded outlines in the second part of the duodenum, through which the barium trickled along the pancreatic border. The stomach was not /

not abnormally dilated although gastric emptying was slow. A second barium meal examination was performed six weeks later with similar findings, but with a slightly less degree of duodenal constriction. A third examination, after a further period of six months, showed neither obstruction nor deformity of the duodenum. (fig. 5).



A

B

C

Fig. 5. Radiographs taken two weeks (A), six weeks (B), and three months (C), after operation. A and B illustrate the hold-up of barium at the second part of the duodenum. C shows a normal duodenal cap and normal flow of barium into the jejunum.

D I S C U S S I O N.

I. Clinico-pathological Considerations.

The clinical complex in this case is unusual, and apart from a case reported by Reitano (1932), of a five month old infant and one by Burger and Alrich (1949) 4 days old, there is no other known record of an annular pancreas having given rise to obstructive jaundice. The pre-operative course suggested that the patient was suffering from repeated attacks of acute cholecystitis associated with gall-stones, but no stones were found at operation, nor was there any obvious sign of recent inflammatory change, while the sample of bile taken from the common bile-duct was sterile. A bougie was passed along the common duct into the duodenum without difficulty, yet the dilatation of the common and hepatic ducts was such as not to be ignored. The cholangiograms taken after operation proved conclusively that there was partial obstruction of the common bile-duct near its termination. Indeed the appearance suggested that the duct had become permanently kinked at the part of its course lying within the ring.

The histopathology of the excised piece of the ring threw further light on the problem. The/

The picture of acinar loss with replacement by fibrous tissue encouraged the belief that the annular portion of the pancreas had been the seat of repeated attacks of subacute pancreatitis and the history of the case is not inconsistent with this interpretation. The serum amylase test, performed after disappearance of the acute symptoms gave, not unexpectedly, a normal result. Accordingly it is suggested that the jaundice which appeared during the second and third episodes was due to the common duct being subjected to compression during more acute phases of the pancreatitis.

That the annular pancreas is prone to chronic inflammatory change is evident from Lehman's observations(1942)that in all five operation cases in which a portion of the ring was examined histologically, chronic pancreatitis was observed. Lehman considers that this may be due to increased pressure in the abnormal tortuous annular duct caused by peristalsis and ballooning of the duodenum. Acute pancreatitis has been noted in two instances (Benedetti, 1920 and Brines, 1930). The observation that in some cases (McNaught and Cox, 1935; Goldyne and Carlson, 1946) the annulus has been composed of normal pancreatic tissue suggests the possibility that when fibrosis does occur it is due to inflammatory/

inflammatory changes, and not merely a feature of the ectopic tissue.

Roentgenological studies offer the best, if not the only, means of arriving at a definite diagnosis, that is to say provided the possible existence of this rare abnormality is borne in mind. The appearances after an opaque meal have been variously reported as a "partial obstruction", "constricting ulcer", "polyp", and "diverticulum" of the second part of the duodenum. Only in Lehman's case was the correct presumptive diagnosis made before laparotomy. In the case herewith reported radiological studies were carried out only post-operatively. Barium meal examination was performed on three occasions over a period of seven months: the first and second revealed a narrowing and partial hold-up at the site of the ring. The patency of the duodenum at that level having been established at operation, the appearances were interpreted as being due to segmental atony or perhaps spasm of the gut wall following interference with the myenteric nerve plexus. The final examination showed a complete return to normal form and function. It is difficult to be certain whether or not the biliary obstruction has been permanently relieved, although the patient's /

patient's progress to date has been encouraging.

Surgical Relief has been conferred in some cases by a direct attack on the annulus and in others by a short-circuiting procedure. Until 1950 (Anderson and Wapshaw, 1951) division or partial resection had been performed on 7 of the reported cases with 2 deaths. This method carries with it the risk of cutting a sizeable duct which might lead to a pancreatic fistula. Some leakage occurred in Zeck's case (1931) and Howard (1930) found that he had to deal with a pancreatic pseudo-cyst by drainage before the patient became symptom-free. It is for this reason that the body of opinion seems to favour measures that side-track the site of obstruction. There were seven records of gastro-enterostomy having been performed. Three of the patients died, all from respiratory infection. The surgical treatment carried out on these cases can scarcely be described as elective because the real character of the obstructive lesion became apparent only at necropsy. So far as is known, duodeno-jejunostomy has been performed only once, the result being satisfactory (Gross and Chisholm, 1944). The patient was a three days' old infant, whose colon was mal-rotated, so that the existing conditions were highly suitable for the performance of what would otherwise/

otherwise have been a rather difficult procedure.

In the present case the choice lay between resection of the annulus and cholecysto-jejunostomy. Considering the dilated state of the common duct at the time of operation, it seemed unwise to expose the liver to the threat of an ascending infection. Partial resection of the annulus proved to be technically easy and was followed by no untoward complications. Perhaps one was fortunate in this respect, but if, as is the experience of those versed in the surgery of the pancreas, due regard is paid to haemostasis and an attempt made to occlude any visible duct by ligation or, if none is visible, a stitch of non-absorbable material is run along the exposed surface of the annulus, little harm should result.

It may happen that the exposed segment of duodenum fails to expand, in which case the bowel may be incised in its longitudinal axis and the wound sutured in the transverse - the so-called Heineke-Mikulicz pyloroplasty - as reported by Zeck (1931). Swynnerton and Tanner (1953) cured their patient with this procedure combined with a subphrenic vagotomy. On the other hand, gastroenterostomy may be safer, especially where the gut wall is somewhat thinned, e.g. owing to the stripping of the outer layer of the muscle coat, as in my case. If this /

this operation were decided upon, section of the vagal nerves is perhaps advisable in order to diminish the risk of the occurrence of an anastomatic ulcer.

The co-existence of a peptic ulcer will also be a matter for consideration in deciding the line of treatment. A gastric ulcer was noted in four of the 13 cases that required surgical attention in the series reported up to 1950. In one of these (Custer and Waugh, 1944) cure was effected by subtotal gastrectomy. It is possible that in these cases there is some interference with the reflux of the alkaline contents of the duodenum. One may add that partial gastrectomy has been performed in a case not complicated by gastric ulcer, and with a good result (Ohlmacher and Marshall, 1950).

II. Embryological Considerations.

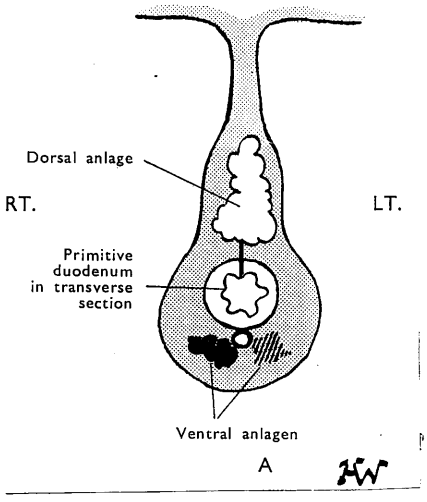
To understand fully the mode of development of an annular pancreas, it is necessary to consider the normal development of the organ, excellent accounts of which are available (Baldwin,1910., Lecco,1910., Keibal and Mall,1912., McNaught, 1933).

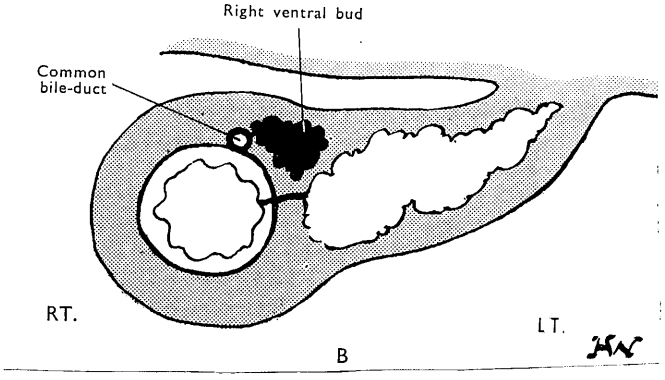
Normal Development.

The pancreas is derived from two primordia, or rudiments, which grow from that part of the gut which is destined to become the second part of the duodenum.

The dorsal rudiment, the first to appear, begins as an endodermal thickening in the dorsal mesogastrium. It enlarges until it meets the spleen and is represented in the adult by the tail, body, neck, and all but the lower right quadrant of the composite organ. The ventral rudiment arises from the inferior angle between the intestine and the hepatic rudiment when the embryo is 4 millimetres. It lies more caudally than the other. As the intestine expands and rotates to the right, the ventral pancreatic bud, in common with the bile-duct, goes with it and at the same time migrates dorsally until the two rudiments make contact with each other on the left side of the gut. Fusion takes place at the 12 millimetre stage. In the adult, the part surrounding the terminal 2 - 3 centimetres of the bile and main pancreatic ducts is roughly speaking the derivative of the ventral primordium.

Each of the two primary outgrowths has a single duct and these also unite. That of the ventral bud taps, as it were, that of the dorsal in the region of the neck of the adult gland and thus the main duct is formed. This is the explanation for the peculiar S-shaped course taken by the main duct in its way through the pancreas. The part of the dorsal duct which extends from the point of anastomosis to the duodenum persists as the accessory duct (fig. 6).





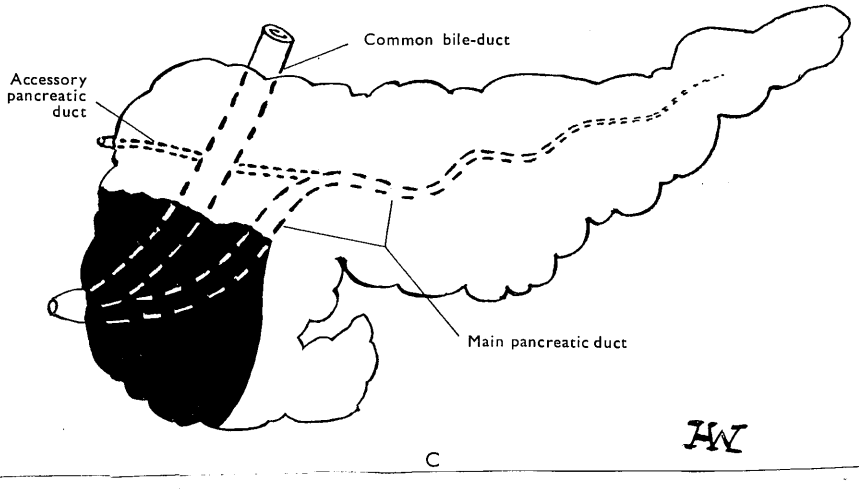


Fig. 6.- Normal pancreatic development. A, showing the dorsal rudiment (white) growing into the mesoduodenum, and the two primordia of the ventral rudiment lying on either side of the bile duct; the right (black) persists, the left (shaded) atrophies or fuses with the right bud. B, Later stage. Duodenum swinging to the right, while the bile-duct and the right ventral pancreatic bud migrate dorsally and approach the dorsal pancreatic outgrowth. C, Adult form, showing the parts of the pancreas formed by the ventral (black) and dorsal (white) rudiments and the usual arrangement of the ducts. When an annulus is present, its duct usually enters the main pancreatic duct close to its termination.

The ventral pancreas is worthy of closer consideration for reasons that will become apparent when discussing the congenital abnormalities of the gland. It has long been known that in the earliest stages of development the ventral primordium is composed of twin buds which lie one on either side of the hepatic rudiment. The fate of the left ventral bud in man is uncertain. Thying (1908) believed that it atrophied completely, which is also the view of Hill (1926) and Keith (1933). Hamilton, Boyd, and Mossman (1946) on the other hand appear to give unqualified acceptance to the view put forward by Felix (1892), namely that the two buds fuse to form the ventral pancreas. According to Hill, the omental pancreatic lobe, which is seen in certain mammals and other classes and lies between the layers of the lesser omentum, is the representative of the left ventral pancreatic bud. The omental lobe occurs as a rarity in Man. The dextral bud makes up the greater part, if not the whole of the ventral rudiment. As explained, it moves through approximately 270° to reach its final destination, so that its duct (i.e. Wirsung's) will approach, and possibly enter, the common bile-duct from the left side. The significance of this point will become evident in/

in considering the aetiology of annular pancreas.

Aetiological Significance of Annular Pancreas.

In 17 of the 20 cases of annular pancreas in which the duct system has been adequately studied, the annulus had a single main duct originating in the portion of the ring overlying the left anterior surface of the duodenum, then sweeping ventrally and around the right side of the duodenum, crossing the gut posteriorly from right to left, and opening into the main pancreatic duct close to the ampulla. This anatomical arrangement indicates that the annulus is derived from the ventral primordium. Lecco particularizes further, taking the view that the anomaly may result from adherence of the tip of the right ventral pancreatic bud to the duodenal wall with the result that during migration dorsally a band of pancreatic tissue becomes stretched around the duodenum (fig. 7,A). Though in agreement with this hypothesis, Baldwin believes that the left ventral bud may sometimes persist and enlarge to form an annulus, (see fig.7,B) a suggestion which would explain the case described by Cunningham (1940) in which the annular duct opened into the common bile-duct in a plane slightly posterior to the entrance of the main pancreatic duct. Chapman and Mossman (1942) think it unreasonable to /

to assume that fixation of the left ventral bud before rotation of the gut accounts for the ring. Since the duodenum has such a small diameter relative to the thickness of its ventral and dorsal mesenteries at the time the ventral bud contacts its dorsal counterpart (i.e. at the 10 millimetre stage), they favour the simpler explanation that the ventral outgrowth spreads dorsally round both sides of the duodenum instead of one, as in normal development. Tieken (1907) was the first to suggest that the annulus was hypertrophic in nature and that it arose as the result of the extension of ventral and dorsal segments of the head of the organ on either side of the related gut (see fig.7,C). Lerat (1910) supported this view and considered that the hypertrophy might result from pancreatitis in utero. The hypertrophic theory however receives little support from the cases in which a careful study of the duct system has been made.

Thür (1929) reported a case in which the duct of the ring opened chiefly into the accessory duct of Santorini, while in Bell's case (1922) the annular duct opened directly into the duodenum above and posterior to the ampulla. It is difficult to believe that the annuli in these two cases arose from the ventral /

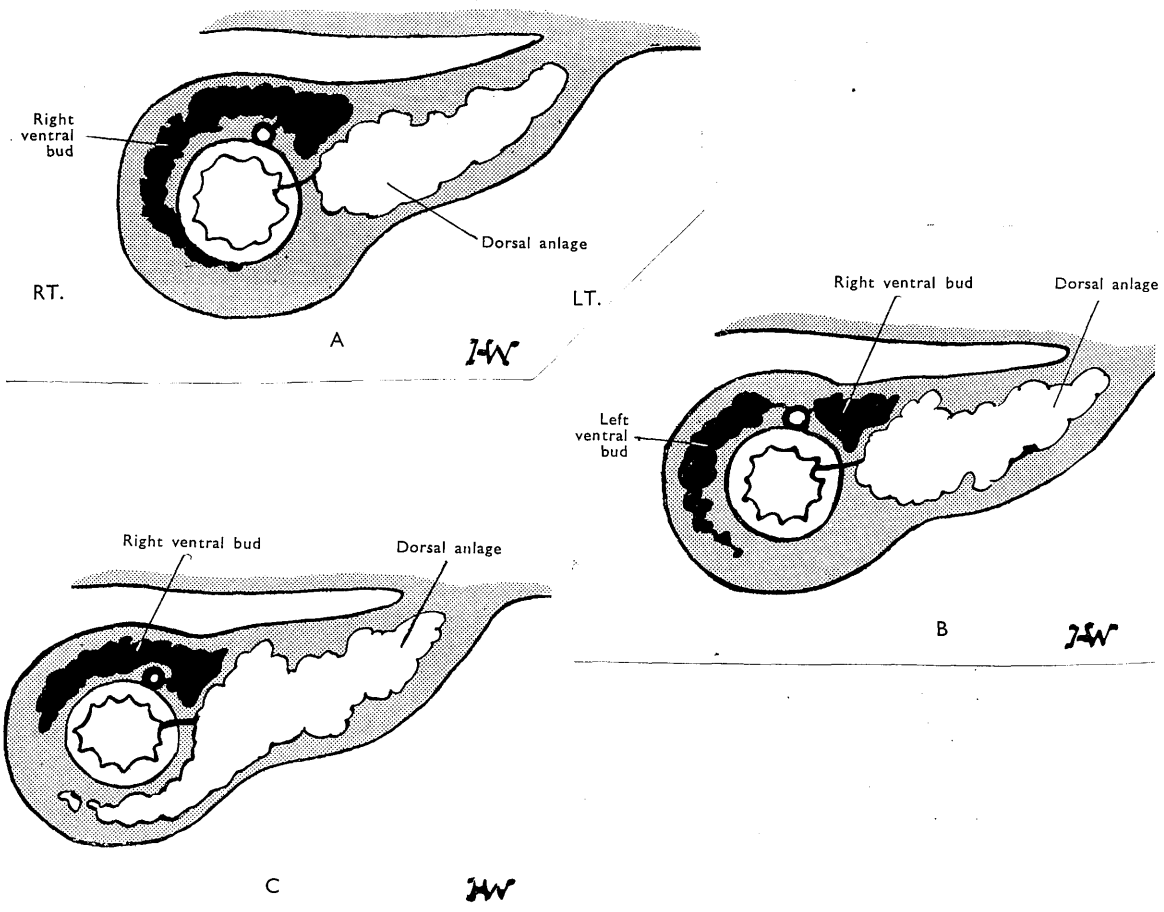


Fig. 7. - Theories of development of annular pancreas. A, Annulus resulting from adherence of the right ventral bud near its point of origin (Lecco's theory). B, Annulus resulting from persistence and enlargement of left ventral bud, with the duct of the annulus entering the common bile-duct (Baldwin's theory). C, Annulus resulting from extensions of both the right ventral and dorsal rudiments. (Tieken's hypertrophic theory). This does not explain the usual duct arrangement.

ventral rudiments. The pancreas, however, is "untidy" in its development as appears from the occasional finding of ectopic pancreatic tissue embedded in the duodenal wall and elsewhere, reminiscent of the condition normally seen in fishes, and it seems not unreasonable to suppose that such ectopic tissue may sometimes come to surround the gut as a result of an error in the developmental rotation of the latter.

There remains the possibility that an atavistic trait accounts for certain of these cases. It is relevant to note that the bird's pancreas is a tripartite structure, the dorsal and two ventral outgrowths remaining separate and each having a separate duct system; the crocodile which approaches the bird in the anatomy of the duodenum, has a double pancreas, one lying ventral to the duodenum, the other dorsal (Hill). In my case the annular duct appears to enter the right or posterior aspect of the common bile-duct (fig. 4), an arrangement similar to that of Cunningham's case. This suggests that the ring pancreas was derived from the sinistral bud, which, as stated above, persists only in certain lower mammals.

There emerges from these otherwise theoretical considerations a practical point bearing on /

on surgical treatment. In the majority of cases the duct of the annulus originates over the left anterior part of the duodenal wall, and the annulus itself is normally somewhat attenuated at this site. Consequently in performing incision or resection of the ring, the site of election should be that part overlying the left anterior surface of the duodenum.

SUMMARY

A case of annular pancreas is reported in which the presenting symptom was jaundice, apparently due to pressure on the lower end of the common bile-duct by the inflamed pancreatic annulus. Partial resection of the ring has been followed by freedom from symptoms.

The aetiology, pathology, diagnosis, and treatment of annular pancreas are briefly discussed.

A RADIOGRAPHIC STUDY OF THE BILIARY AND PANCREATIC DUCTS.

I. Introduction

Excretion radiography has proved disappointing as a means of studying the patency of the extrahepatic bile duct. Quite apart from the fact that cholecystography is contraindicated in cases of obstructive jaundice, the amount of medium which is passed from the gall-bladder, irrespective of its radio-opacity, appears to be so variable that the ducts are visualized only occasionally and rarely with sufficient clarity to allow one to state whether stones are present or not. It appears that the latest cholecystopaque, - "Telepaque" - holds out the promise of showing up the ducts more consistently and with better definition. Nevertheless, the present methods of studying the biliary duct system depend upon contrast /

contrast radiography. These are, to a large extent, standardized and their indications fully understood; yet, it seems true to state that cholangiography was employed only in cases of post-operative external biliary fistula for about 10 years after its introduction. In other words, the earlier attempts were haphazard and the radio-opaque substances used were crude compared with the modern preparations. One of the first papers on the subject was by Reich (1918) entitled "Accidental Injection of Bismuth Paste and Petrolatum into Bile Ducts". Tenney and Patterson (1922) had the satisfaction of demonstrating a gallstone impacted in the ampullary region. Unfortunately, the barium paste which they used was so thick that it plugged the bile duct, and the resulting cholangitis and cholaemia did much to discourage the development of this procedure in the United States (Hicken, McAllister, Franz, and Crowder, 1950). Later in the same year Carnot and Blamoutier injected a barium mixture into a fistula and succeeded in localizing a stone encarcerated in the stump of the cystic duct. The superior qualities of the inorganic and organic halogens as contrasting agents were soon recognised. The first /

first essay with an iodized oil appears to have been that of Lanari and Squirru (1924) who fortuitously obtained a complete picture of the biliary tree following its injection into a hydatid cyst of liver. Duret (1924) injected a solution of sodium bromide into a fistula of the right flank and proved that it communicated with the common bile-ducts. Kempeneer (1926) tried various media but favoured an aqueous solution of sodium iodide. Potassium iodide was regarded by Walzel (1927) as too irritating for clinical use.

Cotte (1929) first suggested that the patency of the bile ducts be investigated by introducing a radio-opaque substance into cholecystostomy and choledochostomy drainage tubes. Credit goes also to Gabriel (1930) in this country for being among the first to carry out cholangiography in cases electively drained, and the first account of its performance during an operation is accredited to Mirizzi (1932) of the Argentine. Numerous authoritative papers on the subject have appeared, notably those by Sturm (1932), Troup (1932), Kretchnar (1933), Saralegui (1934), Robins and Hermanson (1936) and Best and Hicken (1937).

Four methods have been described, (1) Delayed cholangiography, which is carried out under optimum radiological conditions and with little upset to the patient. (2) Immediate cholangiography, which makes greater demands on the radiological staff and requires a certain modification of the surgeon's technique, and (3) Pre-operative cholangiography, whereby the opaque medium is introduced directly into the gall-bladder with the aid of a peritoneoscope. This method has been carried out on a small scale, apparently with success and without mishap (Royer and Solari, 1947), but is unlikely to have a wide appeal. (4) Transhepatic cholangiography was recently described by Noskin, et al. (1953); it entails first tapping percutaneously a dilated bile duct within the liver and then injecting the medium. As it is applicable only to jaundiced cases a preliminary course of vitamin K is imperative to prevent oozing from the liver, only the first two methods will be considered.

II. Delayed Cholangiography.

This is best performed between the 10th and/

and 14th day after operation, that is to say, just before the time for removing the tube draining the common bile-duct or gall-bladder. Earlier workers preferred to wait until the second or third week (Overholt, 1931). The following is a description of the accepted technique (Bockus, 1946; Buckstein, 1948) and that adopted for all but 4 of my cases.

The patients were transported by trolley to the radiological department and there deprived of any objects likely to cast unwanted shadows. The first step was to empty, as far as possible, the bile from the biliary tract by suction, then apply a clamp about 4 inches from the dressing in order to prevent the entry of air. A 20 ml. syringe filled with the opaque medium warmed to body temperature, was inserted into the emerging end of the indwelling tube on the side of the clamp next to the wound, and 5 ml. slowly injected. Its path was followed under the fluouroscopic screen and once it entered the biliary system an exposure was immediately made. Further injections of medium were carried out and successive exposures made until satis-factory records were obtained.

This so-called fractionated method, which /

which on the average amounts to three exposures, is generally regarded as the most reliable means of showing up stones in the biliary tract. It avoids the introduction to begin with of excess of opaque medium which is apt to mask their presence. Another advantage is that the radio-opaque medium does not escape readily into the duodenum, provided that it has not been introduced so forcibly as to overcome the resistance of the sphincter of Oddi.

In 3 of the present cases the medium was introduced by gravity, a method much favoured by Hicken et al. 1950. A small funnel is connected to the indwelling T-tube and the top of the funnel held about 6" above the anterior abdominal wall. Then instilled are about 20 ml. of the contrast agent. Hicken and his colleagues perfuse the bile ducts preliminarily with isotonic sodium chloride solution in order to displace air and flush out any sediment.

III. Immediate Cholangiography.

Given the time and facilities, this method is a greater insurance against an overlooked stone. The /

The technique employed will depend on the exigencies of the operation, and to a certain extent on the type of contrast medium used. The following description takes into account the main adaptations.

A casette tunnel, though not essential, is highly desirable; it is both a convenience to the radiographer and a means of minimizing the disturbance to the field of operation. The one used by the author was large enough to receive a 12" x 10" plate. (Love, (1952) prefers to raise the patient, during a change of casette, by means of a sheet or binder placed across the table about the mid-trunk level). A small Bucky diaphragm was also inserted. Hultén (1938) has a special screening apparatus fixed to his operating table, a refinement which few surgeons can command. All metal instruments should be removed from the field of operation and the towels stitched to the wound edges. Three main methods of instilling the opaque medium have been described. Bettman, Tannenbaum and Areus (1943) prior to removing the gall-bladder, expose the cystic duct and make a transverse slit in it through which is passed a ureteral catheter; this is held in place with an encircling ligature. If the cystic duct is impassable either for anatomical or pathological reasons, they /

they inject the medium directly into the main biliary passage by an ordinary syringe and needle. Best (1938) normally follows the direct route, using a 22 gauge needle with a small bead placed 1/8" from the point, which serves both as a gauge and a plug. Like Bettman et al. he prefers an aqueous solution of organic iodide. Mirizzi (1937) generally uses the more viscid iodized media and has adapted his technique accordingly. He employs metallic cannulae of three sizes, with an olive-shaped adaptor for cases where the duct is unduly wide. Alternatively, he utilizes the gall-bladder and, as a last resort, the common bile-duct, but considers that the thin elastic wall of the latter is unsuitable on account of the tendency for a leakage of bile to occur from the puncture.

As in the delayed method, the ducts are sucked dry of bile. Altman (1941) recommends two exposures - the first after a preliminary injection of 3-5 ml. and the second after an additional 8-10 ml., which should be adequate for most instances. The films are taken during a period of respiratory arrest. The anaesthetist of today has no difficulty in complying /

complying with this request. Four of my own series were done on the operating table; the medium was introduced directly into the common bile-duct in two and via the cystic duct in the others.

IV. Radiographic Considerations

Ideally the antero-posterior view should be stereoscopic with a short exposure and a moving grid (Forsyth, 1950). In practice, however, and under theatre conditions with only a "Victor" 30 in A. mobile set the examination is usually confined to a single antero-posterior view taken with a fast film, fast screen - a high KV(80) - and a short anode-film distance.

The radiographic conditions are, of course, more satisfactory in the X-ray department where all the delayed cholangiograms were made. Stereoscopic views can then be neglected. The unit used was of the 4 valve 500 in A type. The exposure is of the order of 200 - A, 65 - 75KV., depending on the thickness of the patient, 36" distance and 1/2 second. Another essential is a Potter Bucky diaphragm; the films and screens were, of course, standard. The patient was placed supine or preferably tilted slightly by means of a long pad under /

under the left side. This right oblique position gives the best view of the terminal part of the common bile-duct. In a few, a lateral exposure was made.

V. Opaque Media

Two brands of opaque media were used in the investigations about to be described, - (1) 'Neo-Hydriol' and (2) 'Pyelosil'.

'Neo-Hydriol' (May & Baker Ltd.) is an iodized ethyl ester of fatty acids of poppy-seed oil. It is issued in two forms - viscous and fluid, both containing 40%. On account of its lower viscosity, 'Neo-Hydriol Fluid' is highly suitable for showing up narrower channels. The 'Viscous' product, on the other hand, besides requiring a needle or cannula of wider calibre for its injection, often tends to break up into globules with the result that the shadow cast is of varying density or patchy. These difficulties are partly overcome by heating it to body temperature. It has also been asserted that the viscous brand gives too dense a shadow and is, therefore, less suitable for the detection of stones. McNeill Love (1952) also prefers the fluid form.

Fig. 8

Normal choledochogram
Type A
The curved form.

(see text)

Fig. 9

A variation of Type A.

Fig. 10

Another variation of Type A.

Cholangiogram performed through a cholecystostomy tube. The cystic duct appears to cross over the common hepatic and enters from the left side.

With the 'Neo-Hydriol' preparations no harm to the bile ducts or liver appears to result, but the risk of iodism must be borne in mind. Indeed, some workers take the precaution to carry out preliminary tests for iodine idiosyncrasy. None of the cases in my series exhibited any symptoms of the kind.

'Pyelosil', (Glaxo Laboratories Ltd.) is the diethanolamine salt of 3:5 diiodo-4-pyridone-N-acetic acid (B.P. Diodine); it contains 49.8 per cent. of iodine. The virtue of this radio-opaque compound is that the characteristic pharmacological action of iodine is suppressed, so that considerable amounts may be introduced subcutaneously, intramuscularly, or intravenously without producing tissue damage or symptoms of iodism.

'Pyelosil' is issued in three concentrations, the one most suitable for cholangiography in my opinion being 'Pyelosil' 70, which is a 70 per cent. W/V solution.

VI. Clinical Material of the Present Study

The total number of patients investigated was 48. The disorder for which they sought treatment was primarily /

primarily biliary in 38 and primarily pancreatic in 10. The biliary group included cases of chronic cholecystitis with stones, acute cholecystitis, choledocholithiasis, repair of the common bile duct. In the pancreatic group, the following conditions were present - acute haemorrhagic pancreatitis, subacute pancreatitis, and the case of annular pancreas previously described, causing partial obstruction of the common bile duct. It is noteworthy that in four of the cases with acute affections of the pancreas there was no demonstrable disease or stones in the gall-bladder. Chronic calculus disease was found in the other five cases, and in two, small stones had found their way into the common bile duct.

VII. The Normal Choledochogram

In my total of 48 cases, there were 39 in which the findings may be said to conform to the normal picture. 5 showed the presence of stones, and in 2 others, the outline of the biliary passages was obviously altered by disease. There were 2 failures due to incomplete filling of the ducts.

Five different duct patterns were recognised in the normal group.

Fig. 11.

Normal choledochogram
Type B
The angulated form.

(see text)

Fig. 12.

Normal choledochogram
Type C
The vertical form.

The cystic duct and a partial filled gall-bladder are also outlined. Note the left-sided entry of the former.

Fig. 13.

Normal choledochogram
Type D
The zig-zag configuration.
The Ampulla of Vater is well shown in this case.

In by far the largest group (Type A, figs. 8, 9, 10) the common hepatic and bile ducts described a curve with the concavity facing to the patient's right side, some taking an easier sweep than others. There were 23 instances of this type. There were 5 cases (Type B, fig.11) in which the common duct was angulated, presumably at the point where it passed behind or through the pancreas. The common hepatic and bile ducts followed a more or less vertical course in 2 instances (Type C, fig.12). They assumed a zig-zag form in 7 instances, (Type D, fig.13) and they sloped from right to left at an angle almost short of the horizontal in 2 instances (Type E, fig.15).

The extra-hepatic biliary system was found to extend in the large majority of cases from the transverse processes of the 11th and 12th thoracic vertebrae to the levels of the transverse processes of the 2nd or 3rd lumbar vertebrae. In the lateral view the duct usually starts anteriorly and passes downwards and backwards on its way to the duodenum (fig.14).

This account of the normal findings is comparable in most respects to that given by Hicken, Coray, and Franz (1949) who incidentally criticize the standard text books of anatomy for failing to stress /

Fig. 14.

Lateral view showing the duct passing downwards and posteriorly. Some medium has passed into the duodenum. The negative shadows at the lower end of the common bile-duct denote the presence of three pigment stones.

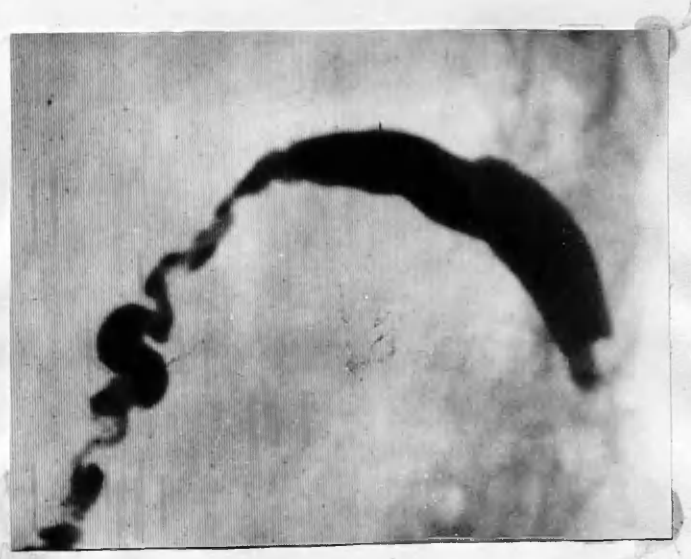


Fig. 15.

Illustrating an almost horizontally placed common bile-duct (Type E). The medium has been injected via the gall-bladder, and has filled only the common bile-duct. The translucent shadow near the latter's lower end denotes the presence of a stone.

stress the lack of uniformity in the morphology of the major biliary passages. Sterling and his colleagues (1949) ignore the less common anatomical variations and refer only to the commoner curved form.

Rhythmic contractions passing down the common hepatic and bile ducts have been described by Overholt (1931) and Mirizzi (1942). Macdonald (1941) noted evidence of muscular contractions towards the duodenal end of the common duct. Like Hultén (1938) and Royer and Solari (1947), I have been unable to detect peristaltic activity. It must be stated that Macdonald administered morphine prior to making his observations, and in my opinion this drug was responsible for the spasticity noted by this author. None of my cholangiograms gave evidence of a constriction at the distal end of the common hepatic duct, such as has been noted by Mirizzi (1940) and interpreted as being due to a special sphincter at that level. Further Gordon-Taylor (1942) found no circular arrangement of muscle fibres in the hepatic duct either in adult or foetal material.

The extent to which the intrahepatic ducts and their finer radicles are visualized depends of course on the amount of medium employed, its fluidity, and /

and also the force with which it is introduced. Quite apart from the presence of constrictive or obstructive lesions, overaction of the sphincter mechanism in control of the bile flow will also play a part in determining the amount of reflex of the medium. Indeed morphine, by virtue of its stimulant action on the sphincter choledochus, has been recommended as a means of producing retrograde filling (Macdonald, 1944). Another method is to place the patient in the Trendelenberg position (Macdonald, 1944). Actually it is rarely necessary to resort to such artificial aids if the fractionated or simple gravity methods are employed. A point to be borne in mind is that defective filling of the ducts in one or more segments of the liver may be due to pathological changes in these ducts or to space-occupying lesions (Rudstrom, 1944; Viaggio, 1945).

The gall-bladder was outlined in 9 cases. Fig. 16 show how it functions as a reservoir, the normal outlet to the duodenum being in these cases blocked by contraction of the sphincter mechanism at the lower end of the common duct due to morphine. Royer and Solari (1947) refer to the appearance of a peculiar wavy or scalloped outline due to peristaltic action, /

A Fig. 16 B

Cholangiograms showing how the gall-bladder fills in the presence of a distal obstruction due in this case to the administration of morphine. The common bile-duct is unusually narrow, but filling of the gall-bladder and the intra-hepatic ducts is seen in B as compared with A.

action, but this was not observed in any of my cases. It must be mentioned that these authors were able to observe the gall-bladder motility under exceptional circumstances, having injected the medium into the gall-bladder by the aid of a peritoneoscope. Kerley (1950) states that such movements have been recorded only twice and believes that an over distended bladder may empty by elastic recoil. This capricious behaviour may account for the difficulty met with in /

in excretion radiography when attempting to cause the gall-bladder to empty itself by giving a fatty meal or other means. In other words, the re-entry of the bile into the main biliary passages from its temporary repository may be determined by gentle rippling contractions of the gall-bladder more often than, as is usually thought, a mass contraction. None of my cases lent themselves to observation of movements of the gall-bladder of one sort or another.

The cystic duct presents a tortuous outline varied in length, width, or direction. In 3 instances it crossed the common hepatic duct either in front or behind, entering from the left side (figs. 10, 12, 23), while in another, it seemed to join anteriorly (fig. 33).

VIII. Pancreatic Ductograms.

Reflux into the duct of Wirsung occurred undoubtedly in 7 out of the 48 cases studied and probably in 2 others, making a maximum incidence of 19.8 per cent. (see examples illustrated by figs.17,18,20B,21,29A,31,32. The findings of others are given in table 1. In this collective study of 1,521 cases, the incidence of pancreatic reflux was 33 per cent.

TABLE 1. The Incidence of Visualization of the Pancreatic Duct During Cholangiography.

Author.	Number of Patients	Number showing Duct	Percentage Visualized
Colp & Doubilet (1938)	35	7	20
Hjorth (1947)	430	202	47
Howell & Bergh (1950)	65	27	41.5
Hultén (1939)	110	26	23.6
Hunt, Hicken & Best (1937)	56	5	9
Leven (1938)	91	21	23
Liedberg (1941)	53	22	41.5
Millbourn (1950)	181	72	39.8
Robins & Hermanson (1936)	25	4	16
Rudstrom (1944)	329	110	33.4
Stenstrom (1940)	57	4	7
Sterling et al.	41	4	9.7
Wapshaw.	48	9	18.7
TOTAL:	1521	513	33.7

Leven rightly points out that this is not a constant feature in any given individual. In his series of choledochograms taken from 91 patients it was demonstrated in 21; of these 21 patients, as many as 71 choledochograms were made and reflux was seen 36 times. Leven found stones in the common duct in 3 with this finding, and a stricture in 2 others. In the remaining 16 there were varying degrees of spasm at the terminal part of the common bile-duct, and he concluded that a stone impacted at the ampulla of Vater was not necessary or even a common factor in the conversion of the duct into a continuous channel. Mirizzi (1942) and Moreno (1950) believe that a rapid reflux into the duct of Wirsung is an indication of over-action or fibrosis of the sphincter of Oddi. Such an explanation involves three suppositions - (1) that the common bile-duct and duct of Wirsung are convertible into one channel, (2) that the sphincter of Oddi is situated distal to the point of fusion of the bile and pancreatic ducts, and (3) that the secretory pressure in the pancreatic duct is lower than that of the bile pressure at the time when the medium enters the pancreatic duct.

As regards the first of these, it has been shown from collective radiographic studies that pancreatic reflux can occur in approximately 33 per cent of individuals.

This is in accord with the anatomical finding of Rienhoff and Pickerell (1945) that a true ampulla varying in length from 3 to 14 millimetres existed in 32 per cent of 250 specimens taken from adult humans. Less is known of the arrangement of the muscle fibres surrounding the pars intestinalis of the bile and pancreatic ducts, popularly designated as the sphincter of Oddi, than current references lead one to believe, and to do full justice to the question requires more space than the present study warrants. Thus, Schwegler and Boyden (1937 (a), 1937 (b),) have described the complex arrangement of muscle fibres which is separable into definite groups and for which they have coined a special nomenclature. They hold, mainly on the basis of their embryological studies, that this sphincter mechanism develops and remains as a separate entity from the primitive mesenchyme. These authors also seem to concentrate their attention more on the annular fasciculi than the longitudinally arranged fibres. The most important component of this "intricate web", as Gordon-Taylor puts it, is believed to be that which surrounds the pre-ampullary segment of the common bile /

bile-duct. Dardinsky (1935), Gordon-Taylor (1942), and Kirk (1944) on the other hand, are of the view that the independent muscle fibres described by Oddi as responsible for sphincteric action, are longitudinal or oblique, not circular, and that they can be traced in continuity with the circular fibres of the duodenal wall. Their explanation is that the duct pierces the outer wall of the duodenum and carries in some of its circular muscle fibres, which become arranged in a longitudinal or oblique fashion. Moreover, they could not find any annular fibres in the submucosa of the major duodenal papilla, which Schwegler and Boyden have described and termed the sphincter ampullae. It is evident that in cases in which the sphincter of Oddi is the factor which directs the medium from the biliary into the pancreatic duct system, the junction of the two must take place proximal to the duodenal wall after the manner illustrated by fig. 32. Further reference to this aspect of the problem is made in the succeeding section on the biliary side-effects of morphine.

Fig. 17.

Showing partial filling of the duct of Wirsung in a case with no apparent obstruction at the lower end of the common bile-duct. A common channel is present, but no flask-like dilatation seen.

Regarding the question of the interplay of bile and pancreatic secretion, Colp and Doubilet (1938) observed that only the terminal part of the main pancreatic duct is filled, and suggested that this is due to the secretory pressure of the pancreas being greater than the resistance of the sphincter of Oddi. One might infer that the excellent ductogram seen in fig. 18 was due to failure of the pancreas to recover its secretory activity by the time the cholangiogram was taken. More space is given to this question in the animal studies (page 226).

Fig. 18.

Illustrating what may be described as a perfect contrast study of the biliary and pancreatic duct systems. This is a case of acute haemorrhagic pancreatic necrosis, for which cholecystostomy was performed. The points of interest are the complete filling of the pancreatic duct, and the visualization of smaller branches, one of which may be the duct of Santorini. The intrahepatic duct system is also well filled, indicating a degree of stasis at the duodenal papilla. Ampulla of Vater well seen. Some medium has passed into the duodenum. Duct visualization does not necessarily indicate that bile has entered intravitam for as Rich & Duff (1936) hold the presence of bile in the pancreas may result from the practice common among pathologists in testing the patency of the biliary tract to exert pressure on the gallbladder while watching the duodenal papilla.

IX. The Biliary Side-Effects of Morphine.

A deliberate attempt was made to divert the injected medium into the pancreatic ducts with the help of morphine, acting on the assumption that it induces a selective spasm of the sphincter of Oddi. The series comprised of 23 subjects, on all but two of whom cholecystectomy had recently performed and T-tubes placed in the common bile duct. Two had their gall-bladders drained. Because of its rapid action, even when given subcutaneously, morphine hydrochloride was administered in gr 1/4 doses in the radiological department. In some it was given before the introduction of radio-opaque medium and in others immediately afterwards.

Considering first the effects on the bile flow, it was noteworthy that those who responded to morphine did so within 5 minutes of its administration. The drug produced no visible effect in 5 (21.7 per cent) of the 23 subjects; in the remaining 18 (78.3 per cent) the terminal part of the /

the common bile duct was compressed to such a degree as to resist the flow into the duodenum of the medium regardless of the amount of pressure with which the latter was introduced. The hold-up lasted for periods varying from 4 minutes to over 2 hours. The findings are grouped arbitrarily in table 2. Radiologically a positive response took the form of a blunting of the termination of the common duct which normally tapers to a point. This effect did not seem to differ in any way from that of a contraction of the sphincter mechanism initiated by a psychological stimulus (page 71). The introduction of more medium merely resulted in outlining more and more of the intrahepatic radicles or in a leak into the tissues around the opening in the duct. Representative prints are shown (figs. 21B, 25). For obvious reasons the interruption in the flow of bile lasts longer in cases with intact gallbladder (figs. 16, 34); King, Comfort and Osterberg (1944) noted in their intubation studies that it lasted for 4 hours.

As mentioned in a preceding section, there are subjects in whom the biliary tract cannot be properly outlined owing to rapid passage of the radio-opaque medium into the duodenum; in such instances the difficulty may /

A Fig. 19. B

A After morphine: the bile ducts and intrahepatic ducts are well filled, and the terminal part of the common bile duct is rounded off. No medium has entered the duodenum.

B 20 minutes later: shows a relaxation of the spasm with medium flowing into the duodenum.

TABLE 2. Effects of Morphine on the Bile Flow

Duration of hold-up.	No. of cases.
Nil.	5
4-6 minutes	3
15 minutes	2
20-25 minutes	3
30-35 minutes	3
40-50 minutes	6
over 2 hours	1

may be overcome by the use of morphine. I had to resort to this method of containing the medium in a case which had had the common bile duct explored for a stone that was overlooked at a previous cholecystectomy.

Pancreatic reflux was noted in 2 (11 per cent) of the 18 cases which responded to morphine. In only one of these could it be stated that morphine was responsible for this diversion (fig. 20). In the other, the pancreatic duct was visualized before the morphine was given (fig. 21). In each instance the effect of the muscular spasm was to compress the transduodenal segments of each thus disassociating the one duct from the other. Doubilet (1948) reported a similar picture.

The findings neither supported nor gave a reason to doubt the concept that morphine acts independently on the sphincter of Oddi. The earlier observors (Reach,1914; Kitakoji, 1930; Lueth,1931; McGowan,Busch and Walters,1936; Colp and Doubilet, 1938) interpreted their observations on this basis /

A Fig. 20 B

A case of acute pancreatitis.

A shows an angulated form of duct with a tapered terminal segment, and an uninterrupted flow of medium into the duodenum. No medium has passed into the pancreatic duct at this stage.

B shows the effects of morphine. The lower end of the common duct has been acutely obstructed and there is a small separate linear shadow which appears to be a partial filling of the pancreatic duct.

C

C shows a resumption of flow of the medium at the lower end of the duct which has become slightly more pointed, and the shadow taken to represent the site of the pancreatic duct is no longer seen.

A Fig. 21. B

A Before morphine: showing an angulated type of biliary duct with the medium partially filling the lower end of the pancreatic duct. The two ducts form a considerable common channel.

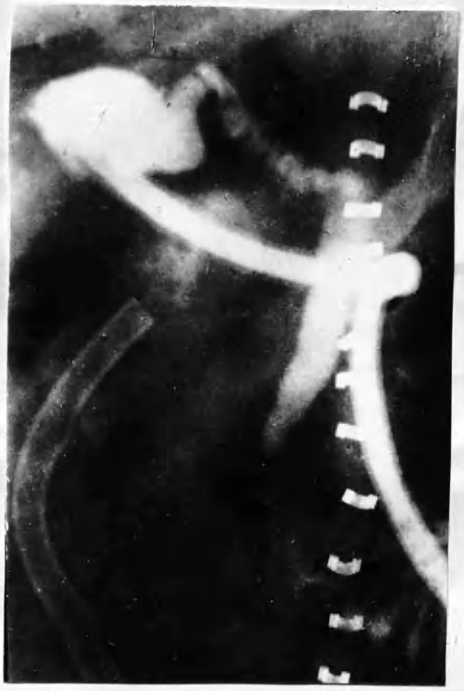
B 5 minutes after morphine: showing disassociation of the two ducts, the result of muscular spasm. The medium has escaped into the surrounding tissues forming a bulbous opacity which might be mistaken for a well filled gall-bladder.

basis and many recent references also agree with this. It is noteworthy, however, that in 1938 McGowan, Knapper, Walters and Snell reported that morphine had the effect of increasing the intraduodenal pressure and attributed this to increase in the second portion of the duodenum. Thus, they were forced to admit the possibility that morphine may act both on the duodenal musculature and on the sphincter mechanism. The drawback, of course, to utilizing cholangiography as a means of study is that it pin-points the attention, as it were, to the exclusion of the more wide-spread visceral effects of this remarkable drug. By resorting to barium meal examinations and placing balloons at different levels in the alimentary tract, it has been shown to cause an increase in the tone, an increase in the frequency of contractions of the small and large bowel and spasm of the pyloric and ileo-caecal sphincters (Plant and Miller, 1926; Yonkman et al., 1936; Krueger, 1937; Rowlands et al., 1950). In /

A Fig.22 B

A After morphine: complete spasm at the lower end of the common bile-duct. Stump of the gall-bladder visualized. An air bubble is seen in the lower part of the common bile-duct attached to the right wall.

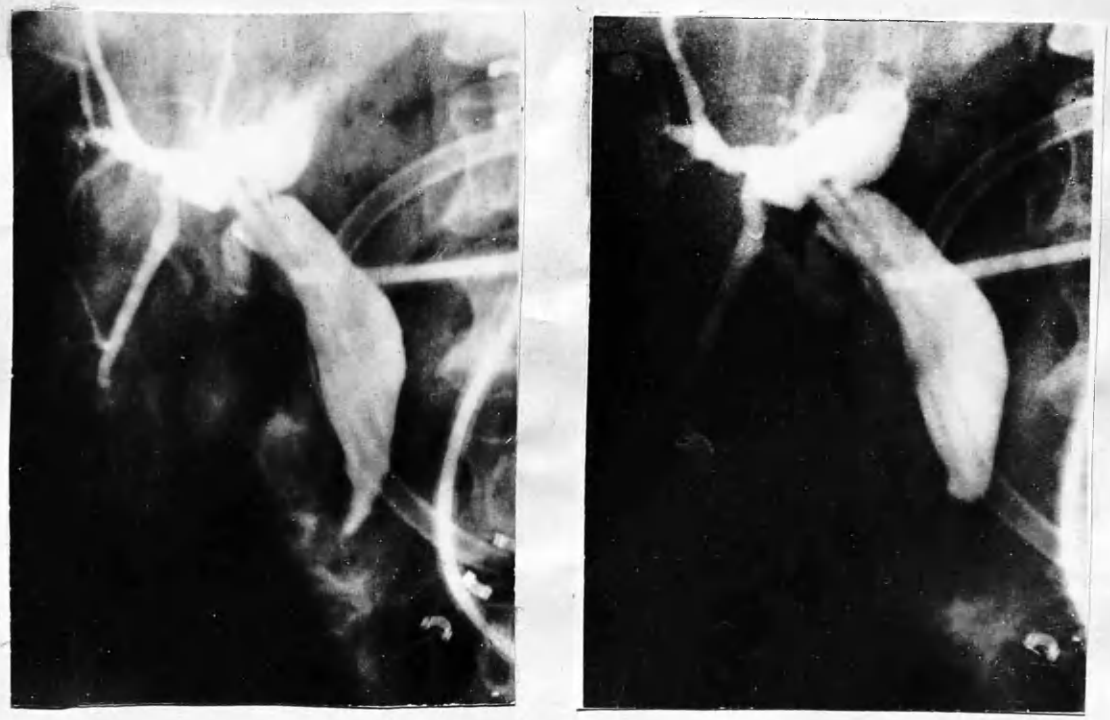
B 20 minutes later: shows the medium passing through into the duodenum. The air bubble has become smaller and appears to have shifted upwards slightly.



A Fig. 23. B

A Medium was introduced through a cholecystostomy. Gall-bladder, cystic duct, and common bile-duct are well outlined. The medium is flowing through the tapering, obliquely placed, and apparently lengthy transduodenal segment into the duodenum. Note the left-sided entry of the cystic duct.

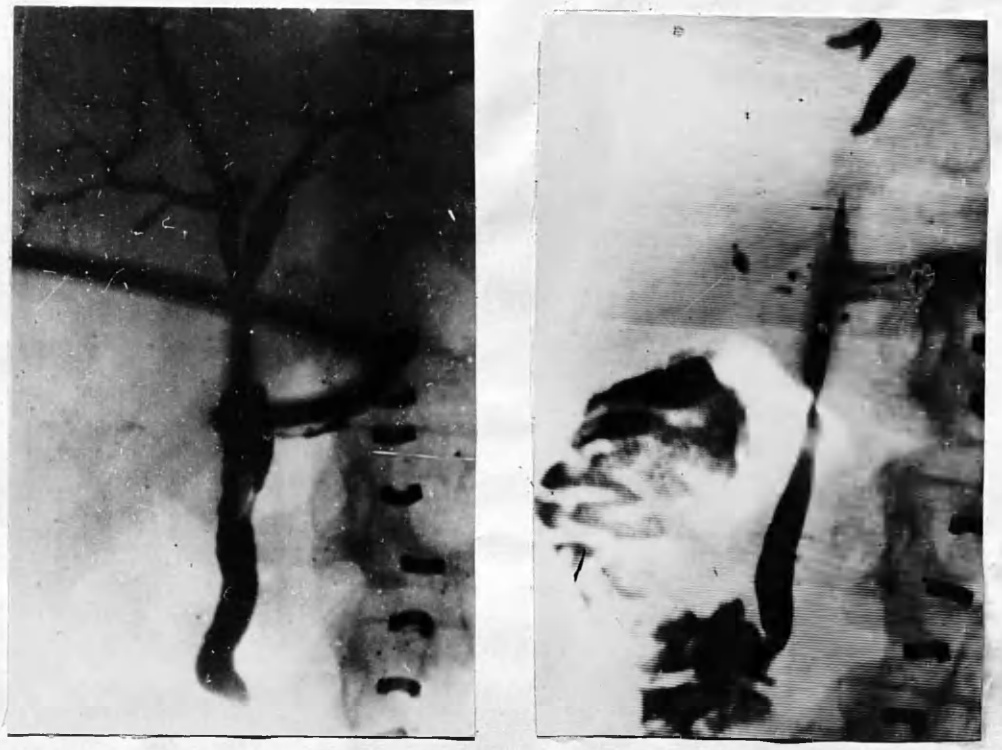
B After morphine: showing a complete hold-up with obliteration of the transduodenal segment.



A Fig. 24. B

A The common bile-duct is short and wide. The main branches of the common hepatic are horn-like, rather than bifurcated, suggesting that they divaricate within the porta hepatis. The lower end of the common bile-duct is pointed and the medium is flowing into the duodenum.

B after morphine: shows the blunting of visceral spasm.



A Fig. 25. B

A After morphine: complete obstruction at the lower end of the common bile-duct with a peculiar twist to the left of an otherwise vertically disposed duct. Also note the extensive filling of the intrahepatic ducts.

B 30 minutes later: shows that the medium has passed on to the duodenum, and there is a questionable filling of the extremity of the pancreatic duct.

In work designed to show how pancreatic reflux can be produced deliberately, Doubilet (1947) attempted to recognise when the sphincter of Oddi was acting by itself and when in association with the duodenal musculature. He tried some with morphine and others with intraduodenal injections of hydrochloric acid. Positive evidence of the formation of a common channel was based on the finding of pancreatic enzymes in high concentration in the bile recovered from a drainage tube lying in the common duct and also on the radiographic evidence of an outlined duct. As he had to admit, however, his observations frequently depended on a "fortuitous conjunction of events".

Morphine is believed to act directly on the intestinal muscle and not indirectly through its effect on the central nervous system (Krueger, 1937). The mechanism of its peripheral action is rather obscure, but has been explained on the basis of the inhibitory effect on cholinesterase resulting in cholinergic stimulation and the liberation of adrenaline which results in adrenergic stimulation (Rowlands et al.1950).

X. Choledocholithiasis

Stones were demonstrable in 5 patients. In two, they were found at operation and removed. Fig. 27 is an example of an immediate cholangiogram. In the three others there was a group of three small non-opaque calculi at the lower part of the common bile-duct (fig. 26); unfortunately the T-tube had been removed before the films came to hand, but there was the comforting fact that they were of such a size as might pass spontaneously. The other case was an aged /

Fig. 26.

Cholangiogram showing three discrete non-opaque shadows at the lower end of the common bile-duct, indicating the presence of three pigment stones.

aged woman with minimal disease of the gall-bladder, on whom it was decided to carry out only cholecystostomy: after the gall-bladder had been cleared of stones, one was discovered lodged in the cystic duct, which was coaxed back into the gall-bladder and removed, the operation then being terminated. Yet fig. 29 shows yet another, apparently a mixed facetted stone, lying in the common bile-duct and taking up different positions. In the third case (fig.28) the stone was unusually large to be overlooked, but the writer has no knowledge of the circumstances of the operation.

Any discussion on the part which cholangiography plays in the detection of biliary calculi must include the wider issue of the management of gall-stones, and particularly those left in the common bile duct. Up till 1926 Lahey (1932, 1938) explored the bile-ducts in only 15 per cent of his cholecystectomies and found stones in 8.4 per cent. Over the succeeding ten years, he stepped up the performance of dochotomy to a third, and in some years a half, of his total per annum and found stones in from 13 to 21 per cent of cases depending on the year. He asserted that many actually originate in the ducts, which is an added argument in favour of a greater readiness to carry the search into them. Even /

Even instrumental exploration does not, however, afford complete assurance. Out of a series of 100 cases, reported by Hicken et al. (1950) in which stones were actually removed from the common duct, there were 12 who still harboured stones after the operation. These authors also refute the belief that spontaneous closure of an external sinus after operation is adequate proof that the common duct is rid of stones; they quote as evidence 35 patients who were proved to have residual stones although their sinuses closed. Accordingly, by carrying out cholangiography more often, the incidence of missing stones might conceivably be reduced.

Attempts to dissolve calculi by the instillation of ether via an indwelling catheter have been made by Walker (1901), Pribram (1932, 1935, 1939). Since ether evaporates rapidly at body temperature and if introduced in large quantities would cause a considerable increase in the intrabiliary pressure, Pribram recommended that it should be introduced in small quantities, 3 times a day, ranging from a few drops to a millilitre, depending on the patient's reactions. The use of a lubricant in the form of liquid paraffin is also advised, and if tolerated, the tube clamped. Walters and Wessen (1937) considered that they were unable to introduce enough ether at one time.

They found that a mixture of one part ethyl alcohol to two parts ethyl ether underwent less rapid evaporation, with the result that as much as 5 millilitres could be introduced at a time. Further, they were able to apply a clamp to the tube immediately afterwards and if any distress occurred this was controlled by means of inhalations of amyl nitrate which has the effect of relaxing the sphincter of Oddi. According to the report of the case, the stone in the common duct became fragmented and was completely expelled into the duodenum. The results of other injections have proved on the whole disappointing. Toxic effects and damage to mucosal lining and hepatic cells were reported in dogs by Probstein and Eckert, 1937; Raffl (1941) on the other hand, found that the biliary mucosa stood up well to 3 ml. injected twice daily. As an alterative, Hicken et al. (1950) advised that a $\frac{1}{100}$ gr tablet of Glyceryl Trinitrate because of its spasmolytic property be placed under the tongue for three successive days. Each morning the patient receives two drachms of magnesium sulphate and also one ounce of olive oil per month. They also suggest that the common bile-duct be gently irrigated through the T-tube, catheter, or fistula, with warm normal saline, and from 10-30 millilitres of warm sterile oil. After each installation the rubber /

rubber tube is clamped to maintain an increase in the intraduct pressure. The same effect was achieved by means of a bile salt preparation given four times a day. This method is only applicable, of course, to the passable stone. The resort to attempts to break up larger stones is worthy of a trial, because if they still remain unaltered, as shown by contrast radiography, or if the patient's symptoms recur in the form of jaundice or pain after the drainage tube is clamped, the only alternative is to repeat exploration of the biliary tract.

Success attended my efforts to get rid of a stone, as illustrated in figs. 29A,B.C. Ether was first used in small quantities, but the patient complained so bitterly of abdominal pain that the procedure had to be abandoned, and it is doubtful if the ether passed beyond the gall-bladder. Next, the patient was put on a course of glyceryl trinitrate tablets gr $\frac{1}{100}$ three times a day, and in addition 20 ccs. warm olive oil were introduced once daily. This was done in the hope that the relaxant effect of the one and the lubricant action of the other would assist the stone to pass. This regimen was continued for three days, and achieved the desired result.

A Fig. 27. B

Operative cholangiogram.

A shows a ureteric catheter placed in the cystic duct through which the medium was introduced. The block at the lower end of the common duct is due to a stone impacted at that level. This was extracted.

B - a choledochostomy has been performed, and the lower end of the common duct, though somewhat ragged, is patent. The dense shadow in the concavity of the bile duct is the medium in the duodenum.

A

B

Fig. 28.

C

Three cholangiograms of the same case showing a large stone at the lower end of the common bile-duct. They form an interesting example of contrast depending on the medium used.

In A and B Pyelosil 70, and in C Neohydriol Viscous was the medium.

Despite the denser shadow with the latter, delineation of the stone is more satisfactory in the Pyelosil photos.

The upper end of the cross-piece of the T-tube was found on withdrawal to be blocked with mucous.

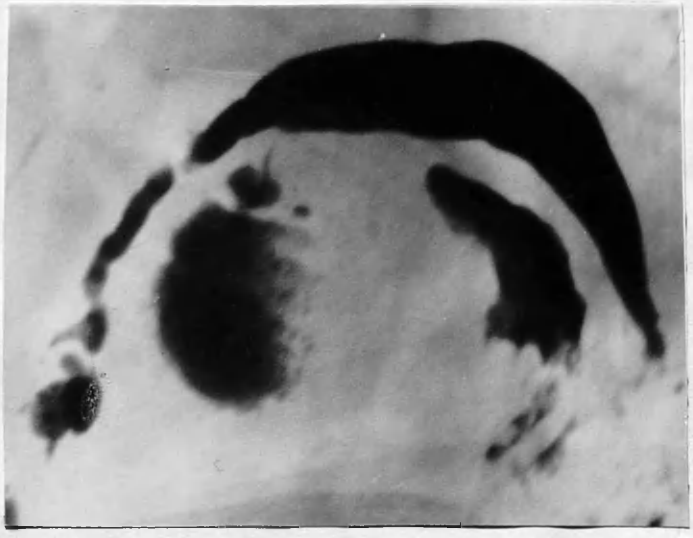
Fig. 29. A

Three cholangiograms of the same case illustrating the non-surgical method of dealing with a stone in the common bile-duct.

A was taken at the time of cholecystostomy. The gall-bladder is incompletely filled. The cystic duct, the common bile-duct, the major intrahepatic ducts, and the duct of Wirsung are well seen. An opaque stone, of cholesterol type, is seen in contact with the left wall of the common bile-duct towards its lower end.

B

B taken some days later shows the stone in a different situation, lying more centrally and causing a more complete obstruction. The blobs of medium are dispersed about the concavity of the biliary outline and are due to medium in the duodenum or possibly an extra-biliary tissue.



C

C shows a normal tapered lower end of the common duct with no stone visible. This was taken to mean that the stone had passed into the duodenum.

XI. Artefacts.

Irregular filling of the ducts with radio-opaque substance must be regarded as the chief source of difficulty when interpreting choledochograms. This may be due either to the presence of air bubbles (see fig. 22), a medium of high viscosity which fails to mix with such bile as may be present, or an inadequate amount of the medium. Air bubbles or pieces of blood clot, bile, or mucous may be removed by a perfusion of normal saline (Hicken et al. 1950., Clute and Lawrence, 1942). If air is trapped serial films will show that it seeks the highest point irrespective of the position of the patient. The drainage tube is apt to get in the way or become blocked at one or other end (see fig. 28). Confusing appearances can be presented by an unusually long segment of the cystic duct, or maybe an extravasation into the tissues beyond the duct (see fig. 21B), or even the presence of medium in the folds of the duodenum.

Other foreign bodies such as blood clots, inspissated bile, fibrin, or other organic debris, not infrequently occur (Best and Hicken, 1938) and some care has to be exercised in differentiating between these and genuine gall-stones. Buckstein (1948) takes the following as his diagnostic radiographic criteria of a stone - (1) a small rounded translucent area completely surrounded by medium, (2) if large and firmly lodged near the duodenum, an inverted cup-shaped defect, (3) if adherent to one wall, a sharply outlined defect in the contour of the duct. All three points are illustrated in the cholangiograms exhibited here. No examples of the other foreign bodies, such as have been mentioned, were encountered.

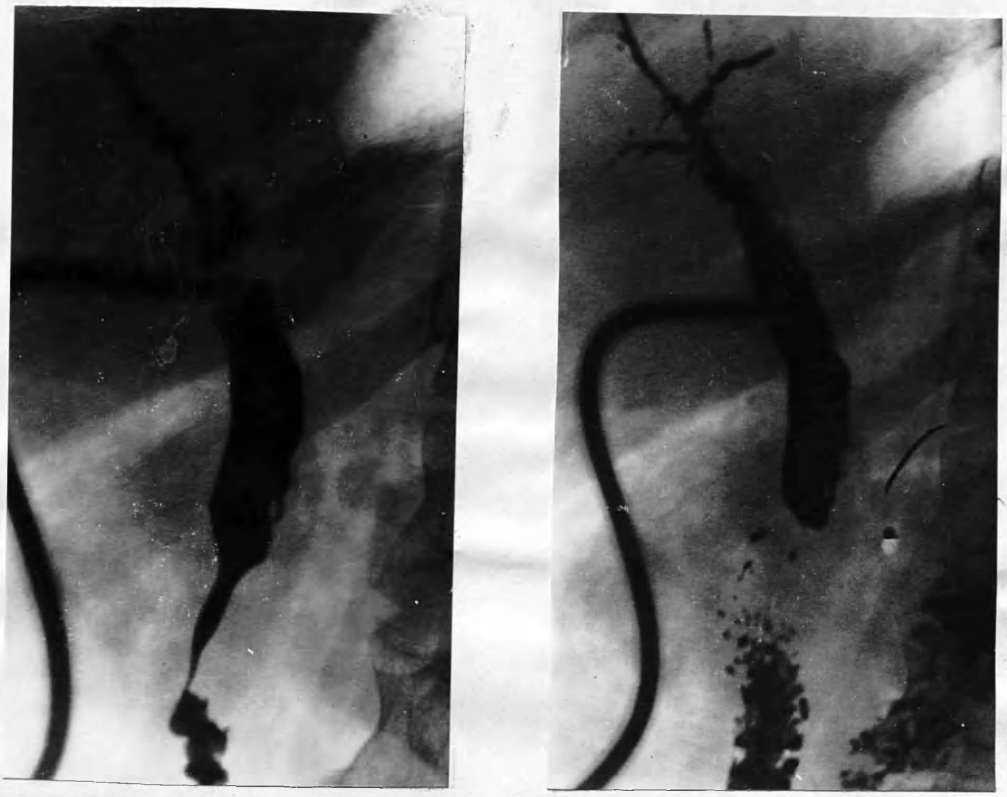
XII. Sphincter of Oddi.

Chronic, so called sclerosing, odditis described by South American authors such as Mirizzi (1942), Moreno (1950), Urrutia and Lavezzo (1951), and by McNeill Love (1952) in this country, was not a feature of the present series. This condition may be a sequel to prolonged spasm or post-inflammatory and tends to narrow the lumen of the terminal segment of the common duct or the papillary area. There were no instances /

instances in the present series of persistent muscular spasm, apart from its artificial production by the exhibition of morphine (vide supra). Figs. 30, 31, and 32 are good examples of spontaneous, temporary spasm. To detect finer degrees of increased resistance demands an experienced and hypercritical eye, but one hazards the opinion that the occurrence of marked filling of the intrahepatic radicles despite the passage of some medium into the duodenum, suggests an over-competent sphincter and possibly some papillary stenosis.

XIII. Pancreatic Lesions.

None of the 9 cases of acute and subacute pancreatitis showed any overt evidence of compression of the lower end of the common bile-duct, such as has been described by Walters and Thiessen (1934) in these conditions. There were no instances of chronic stenosing pancreatitis, tumours of the common bile-duct or the head of the pancreas, in my series. There was cholangiographic evidence, however, of obstruction in the case of annular pancreas reported on page 1 .

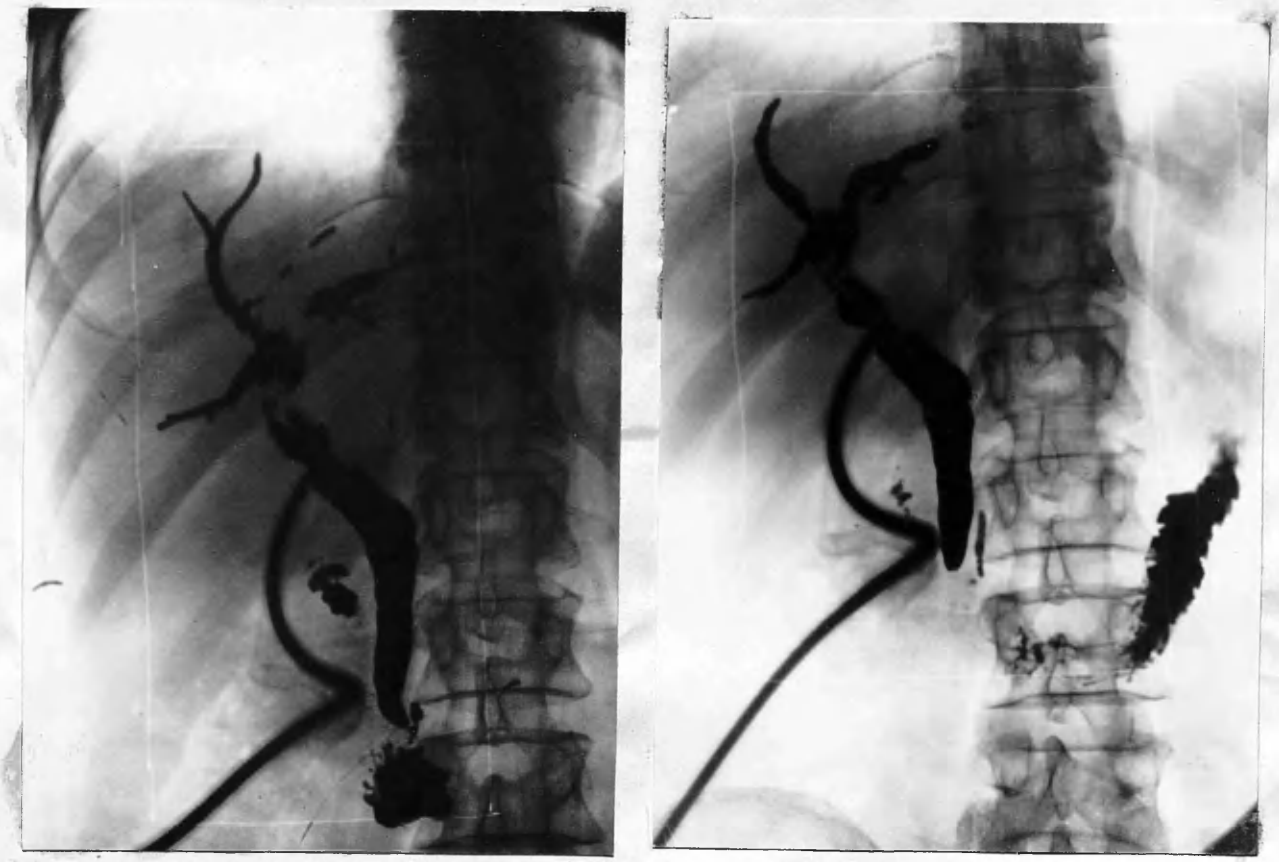


A Fig.30. B

Cholangiograms illustrating obstruction due to muscular spasm involving the pars intestinalis of the common bile-duct.

A is taken after the introduction of 5 ccs. of Neohydriol Fluid. An unduly long tapering terminal segment is seen, with some medium in the duodenum.

B shows complete obstruction at the lower end, involving the narrow tapering part. More medium has passed on to the duodenum from the first injection. The intrahepatic ducts are better filled. This is taken to be an instance of normal spasm.



A Fig. 31. B

Cholangiogram illustrating the effects of muscular spasm on both the pancreatic and the common bile ducts.

A shows well outlined bile ducts with some medium in the duodenum. The terminal part of the pancreatic duct is also seen, and a trans-duodenal segment common to both duct systems. Photo taken after 5 ccs. of medium had been injected.

B shows the effects of spasm of both ducts, causing them to appear dissociated. This occurred after injecting a further 5 ccs. of medium.

Fig. 32.

Cholangiogram obtained by injecting medium through a cholecystostomy tube.
Gall-bladder, cystic duct, and common bile-duct are shown. Some medium had passed into the duodenum before the terminal part of the duct was completely occluded by muscular spasm. No morphine given.

XIV. Untoward Effects.

A few reported instances have implicated either the liver or the pancreas.

Liver. A case of ascending cholangitis following the /

the introduction of Hippuran via. the cystic duct, is reported by Martensson (1946). According to his experimental data, the cholangitis is due to a combination of the injurious effects of osmosis and chemical toxicity on the bile ducts and the propulsion of coliform organisms into the finer intrahepatic bile duct. The danger of forcible injections, especially in the presence of a distal obstruction, are stressed by Rigler and Mixer, (1947). They produced evidence to show that under certain conditions the medium may find its way into the general circulation. In a series of 460 cholangiographic examinations Rigler and Mixer (1947) observed 8 cases in which the renal pelves were clearly outlined by the medium used (Diodrast) 5-30 minutes after it was injected into the common bile-duct, which in all instances was partially or completely obstructed at its lower end by a calculus. Mixer, Rigler and Oddone (1947) summarized the literature concerning the routes by which substances of various kinds find their way from the biliary tree into the general circulation, and carried out experimental studies with thorotrast, /

thorotrast, radio-active phosphorus or infective fluid. It appears unlikely that the dye is absorbed into the blood stream through the intestine or walls of the main biliary ducts. According to their findings in a dog with only a very moderate increase in pressure above hepatic secretory pressure applied during cholangiography, a large volume of diodrast was observed in kidney and bladder. As Rich (1930) has suggested, this probably takes place as the result of regurgitation into the hepatic lymph space (at lower pressure) and hepatic sinuses (at higher pressure). The appearance of Thorotrast in the liver and spleen was regarded by Rigler & Mixer as evidence rather of regurgitation through ruptured biliary canaliculi than absorption through their delicate walls, since it is an insoluble colloidal suspension. Their results with radioactive phosphorus indicated passage into both the blood and lymph spaces of the liver. They also found it a relatively simple matter to force bacteria to take the same routes.

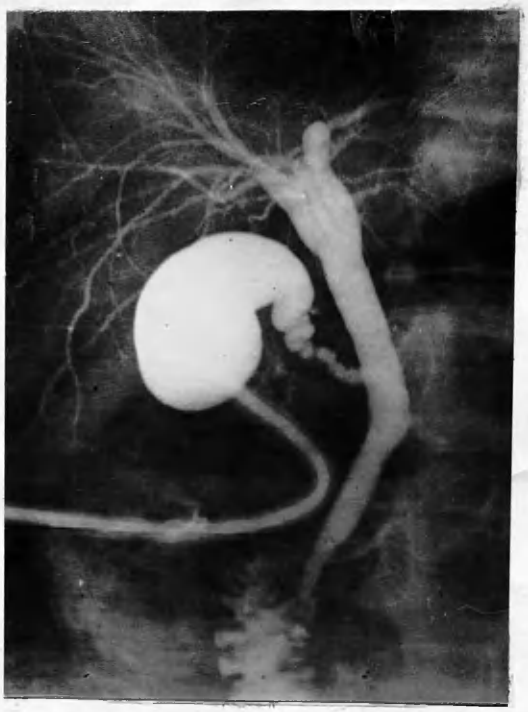
Pancreas. Liedberg (1941) observed an abnormal rise in the urinary diastatic index in 8 (16 per cent.) out of /

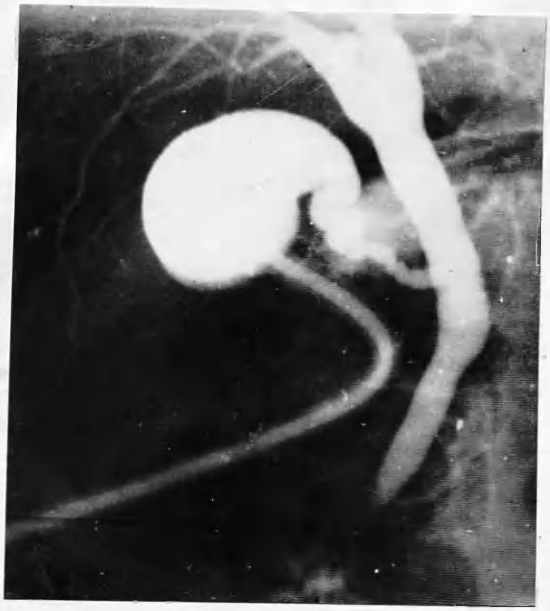
of 50 cases. Raised serum enzyme levels were present in 27 (41 per cent.) of the 50 cases reported by Howell and Bergh. The pancreatic duct was visualized in 25 of these 27 , a correlation which strongly suggests that the biochemical findings are an indication, unsupported though they may be by clinical evidence, of a degree of pancreatic irritation. Acute pancreatitis is alleged to have followed cholangiography on at least two occasions. In the case reported by Gaillard (1950) the diagnosis was based on the clinical findings. The patient collapsed with severe upper abdominal pain and sickness; recovery occurred, however, after supportive measures. The cholangiogram in this case showed filling of the duct of Wirsung and also the duct of Santorini. The other case was reported by Zech (1949) who produced biochemical evidence of raised enzymes in the blood. This case recovered too and the cholangiogram showed a well filled duct of Wirsung.

In the writer's series there was one patient who reacted badly during the investigation. He developed severe epigastric pain soon after Neohydriol Viscous was injected and showed signs of collapse. Recovery /

Recovery followed intensive sedative and intravenous infusion therapy. Strangely enough this happened in a case of acute pancreatitis, on whom cholecystostomy had been performed. Reference to fig.33 will show reflux of contrast medium into the pancreatic duct. It is my impression that the severe reaction was due to over-filling of the gall-bladder, and not an indication of pancreatic embarrassment due to the medium. The patient recovered and has remained well since.

Perhaps more space has been allotted to the potential dangers of cholangiography than they really deserve, because clinical experience has proved it to be a safe procedure. For example, Mirizzi (1942) using Lipiodal, reported 800 cases without complication and in none of the other authors referred to in the foregoing sections is any mention made of recognizable injuries to the bile ducts or related parts. It seems clear, however, that compounds of iodine which contain hippuric acid should not be employed as a cholangiographic medium.





A Fig. 33. B

A case of acute haemorrhagic pancreatic necrosis in which cholecystostomy was performed. The whole biliary system, including the terminal part of the main pancreatic duct, is well visualized. Clearly, the cystic duct enters either in front of or behind the main bile duct.

A shows a common terminal channel of about one centimetre in length, although there is no flask-like dilatation to merit the name of ampulla.

B suggests a degree of spasm at the lower end of the common bile-duct involving the common channel, yet leaving the bile and pancreatic ducts in continuity. The density of the gall-bladder is an outstanding feature (see text).

Certain object lessons can be derived from the experimental work reported in this last section, and these are (1) that forceful injection is to be avoided, especially in the presence of a distal obstruction, and (2) that cholangiography in the presence of an established infection of the biliary tract is also fraught with danger, which at the worst takes the form of cholangitis and possibly bacteriaemia.

SUMMARY.

At the present contrast radiography is essential for good visualization of the biliary tract. Of the four methods available, the delayed and immediate forms of cholangiography were chosen for the present studies, and the former for the most part. The contrast medium preferred was 'Neohydriol' Fluid.

48 patients were studied, 38 having primarily biliary disorders and 10 primarily acute pancreatic disorders. There were two failures among the former group.

Five variations of the normal biliary tract are described and illustrated.

Reflux of the medium into the duct of Wirsung took place in 9 (19.8 per cent) of whom 4 had had acute /

acute pancreatitis. Generally, only the terminal few centimetres are visualized due presumably to the counter-effect of the pancreatic secretion.

The biliary side-effects of morphine are studied in 23 objects. It had no effect in 5: in the remainder a hold-up occurred at the pars intestinalis for periods lasting from 4 minutes to 2 hours. If the pancreatic ducts happened to be filled as well and the point of confluence lay within the duodenal wall, the effect of the morphine induced spasm was to dissociate the two duct systems. It was impossible to state whether or not morphine exerts a selective action on the sphincter of Oddi. The more likely probability is that the duodenal muscularis is also thrown into spasm.

Instances of spontaneous muscular spasm indistinguishable from that seen in the morphinized series are shown.

Reference was made to the problem of stones in the common hepatic and bile ducts and a case presented exemplifying the non-surgical management of same.

The pancreatic and liver complications are discussed, the only mishap in the present series being due to overdistension of the gallbladder. The patient made a good recovery.

ACQUIRED BENIGN STRICTURES OF THE BILE DUCTS

With Particular Reference to those Following Operative Trauma.

INTRODUCTION

There are few problems that tax the patience, courage and endurance of a surgeon so much as a fibrous stricture of the bile ducts and its not uncommon attendant, an external biliary fistula. The task is rendered all the more unpleasant by the knowledge that the condition is usually the result of a previous surgical accident. A minority of the cases are due to pathological conditions such as ulceration caused by gall-stones, obliterative cholangitis, chronic pancreatitis, etc.

This account is based on a personal experience of 7 cases, 4 of which were treated by myself. Two of the latter were established strictures of the main bile duct, the third was due to accidental severance by the author of an accessory right hepatic duct, and the fourth was a case of accidental ligation of the common bile-duct. For permission to include the others I am indebted to Mr. E. G. Gerstenberg, whom I assisted in the operative treatment of a localized stricture, and Mr. J. Leslie Orr in 2 cases of external biliary fistula. First the /

the aetiology of strictures is discussed then my 4 cases are reported in detail, a brief outline of the diagnostic points relating to this condition follows, and finally there is a fairly full description of its surgical management. The problems relating to biliary fistula are considered separately.

Benign strictures of the bile ducts came into prominence as a clinical entity round about the year 1905. It seems more than a coincidence that about this time cholecystectomy began to replace simple drainage of the gall-bladder as the standard treatment for gall-stones and their complications (Walton, 1944). The most authoritative articles on the subject come from the United States. The American writers command respect not only for the candour of their opinions on the causation of strictures but also for their operative inventiveness. It is evident from statistical surveys that operative trauma is responsible for up to 73-90 per cent. of the cases (Walters, 1939., Flickinger and Masson, 1946., Cole, 1946., Cattell, 1947). The Mayo Clinic, the Lahey Clinic, the Illinois Research Hospital, from which these figures were published, and the other large teaching centres appear to encourage the transfer of such cases from their provincial hospitals and this no doubt accounts for the /

the large numbers which they have been able to collect. For example, only 9 of the 181 cases of stricture recorded by Flickinger and Masson were originally treated at the Mayo Clinic. Their figures also revealed the disquieting fact that as many as 23 per cent. of those who developed a stricture after cholecystectomy ought not to have had their gall-bladders removed at all. Further light was thrown on this regrettable aspect of the subject by Gray (1951) of the Mayo Clinic in an address to the Royal Society of Medicine. Between 1941 and 1951, 700 operations for stricture of the common bile-ducts were performed at the Clinic. The annual reports revealed that after 1943 the number of operations performed for a stricture of the bile ducts increased, reaching a peak in 1947, and that a most gratifying and real reduction occurred in the following 3 years. Gray considered that these changes were due to the large number of qualified surgeons who were drafted into military service during the last two years of the war and the first two post-war years, with the result that many small communities were left temporarily to the care of those who had not had adequate surgical training. Some idea of the numbers of strictures treated today in British clinics is obtained from the contributions of Dickson Wright and Wells to the /

the discussion that followed Gray's address. The former had treated 9 cases, for one of which he himself was responsible, and the latter's experience extended to 17 cases. A survey of the records at the Western Infirmary, Glasgow, gives the impression that strictures of the common hepatic and bile ducts are uncommon. Apparently 14 cases with bile duct stricture were admitted during the period 1936-1951. In all the lesion was produced by operative trauma. The operations responsible were cholecystostomy - 1, cholecystectomy - 12, partial gastrectomy - 1. It should be pointed out that 5 of the 14 cases had received their earlier operative treatment elsewhere. During the same period there were 11 cases of external biliary fistulae; one followed rupture of an empyema of the gall-bladder; the rest were undoubtedly post-operative complications. The operations responsible, all done at the Western Infirmary, were as follows: cholecystostomy - 5, cholecystectomy - 4, cholecystostomy plus cholecystectomy - 1.

AETIOLOGY

I. Operative Trauma.

As the foregoing remarks and figures clearly indicate, the operative procedure most likely to lead to/

to injury of the common bile-ducts is cholecystectomy. In a Mayo Clinic review (Walters, 1939) of 60 consecutive cases of stricture covering, like the above, 15 years, 78 per cent. occurred after cholecystectomy alone and in an additional 11 per cent. the damage occurred after cholecystectomy plus choledochostomy. These figures contrast with the 7.5 per cent. which Walters attributed to cholecystostomy alone. It is concluded in Flickinger and Masson's later Mayo Clinic survey (vide supra) that cholecystostomy, or even a planned exploration of the common bile-duct, played only a small part in the production of strictures.

In any inquiry on the cause of a surgical mishap, there are three main considerations, (1) the technical ability of the operator, (2) the nature of the pathological condition for which the surgical treatment was undertaken, and (3) the existing anatomical conditions. It is proposed to deal briefly with these in turn.

1. Technical Considerations. Very often the original operation is reported to have gone smoothly and the surgeon concerned finds it difficult to believe that anything has been amiss. Where there is a minimal degree of inflammatory change around the gall-bladder and bile passages, traction on the cystic duct can sometimes draw/

draw out the common hepatic and bile ducts to a remarkable degree and if the angulation thus caused is not noted or is obscured in a pool of blood, the clamp or ligature intended for the cystic duct may very readily include the common duct. In other words, undue haste, carelessness, and difficulty in obtaining thorough haemostasis account for accidents occurring when the operating conditions are favourable. Allen (1945) was impressed by the fact that in all save one of the cases admitted to the Massachusetts General Hospital the gall-bladder had been removed from the neck towards the fundus, and speculated upon the desirability of beginning the dissection at the fundus. He concluded, however, that any advantages of the latter procedure are offset by the amount of venous oozing from the hepatic bed. Whichever end of the gall-bladder is chosen to begin the dissection, an essential step in the operation is adequate exposure of the tripartite junction of the cystic, common hepatic, and common bile ducts. Contrary to expectation general obesity or a corpulent abdomen are not contributory causes. In fact the majority of patients are thin (Flickinger and Masson, 1946., Gray, 1951).

2. Pathological Considerations. It is tempting to suppose that a high percentage of accidents would occur/

occur in cases where the exposure is rendered difficult by the existing pathological conditions such as inflammatory oedema, adhesions, abscesses, or an internal biliary fistula, but this explanation does not stand scrutiny as a reason for the development of stricture (Gray, 1951). In only 6 per cent. of Flickinger and Masson's series was the gall-bladder removed as an emergency measure. Nevertheless, there are doubtless many British surgeons who tacitly assume that the tendency prevailing in the United States of America, to regard and treat acute cholecystitis as a surgical emergency, is one of the reasons why operative accidents of this kind are so high in that country. Moreover, the amount of space which Lahey and Pyrtek (1950) in their most recent paper on strictures of the bile ducts devote to the technique of removing an acutely inflamed gall-bladder, speaks eloquently of the dangers that beset such a procedure. Walters (1939) also displayed considerable concern when he advised that there is still much to be said for cholecystostomy and recorded in its favour a recurrence of inflammation or stones in only 15-20 per cent., which is decidedly lower than the accepted recurrence rate. This plea for a more conservative approach to the surgery of the biliary tract is presumably intended for those less well equipped to deal with its complexities and/

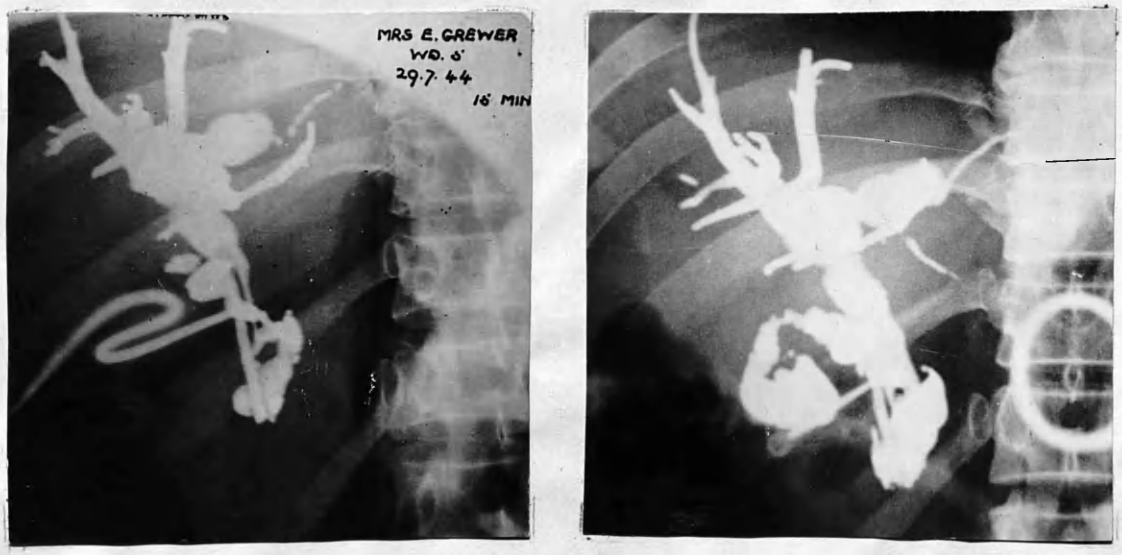
and not to be regarded as a statement of general policy. None the less, one might say that caution is the key-note of all who regard it as their mission to lower the incidence of accidents involving the bile ducts.

Before leaving the surgical aspects of the aetiology of stricture, gastric resection may be mentioned as yet another means of inflicting trauma. One of the strictures in the Western Infirmary series happened thus. Lahey (1945) advised the insertion of an identifying T-tube in the common bile-duct in cases where much of the duodenum has to be sacrificed. Nor must it be forgotten that a traumatic stricture of the common bile-duct can follow a non-penetrating injury of the abdomen. Such a case has been described by Joly (1948). The patient was crushed between two lorries and received extensive damage to the liver and a tear of the cystic duct which implicated the common ducts. Up till 1949, 52 instances of traumatic rupture were reported (Salgado).

3. Anatomical Variations. These also conduce to operative injuries of the main biliary passages. In fact, before embarking on an exploration of the biliary tract every surgeon would do well to remind himself that nowhere else in the body are the conditions so variable. This is equally true of the gall-bladder, the cystic duct, and/

and the common duct, bearing in mind that not uncommon anomaly, an accessory right hepatic duct. The variations in the arrangement of the associated blood vessels is no less confusing. Masterly studies of the different types of abnormalities in this region have been carried out by Kehr (1913), Eisendrath (1920), and Flint (1923).

The following are the most common anatomical variations.



A Fig. 34. B

This is a case of an intrahepatic gall-bladder with gross dilatation of the common bile-duct. The bile duct was full of stones, and choledochostomy performed; gall-bladder left in situ. Note how highly placed both the gall-bladder and the extrahepatic ducts are.

Fig. A was taken after morphine had been given, and shows partial filling of the main bile ducts.

Fig. B, 50 minutes later; more has been introduced and the ducts are grossly dilated. The gall-bladder is now outlined. No medium has passed into the duodenum.

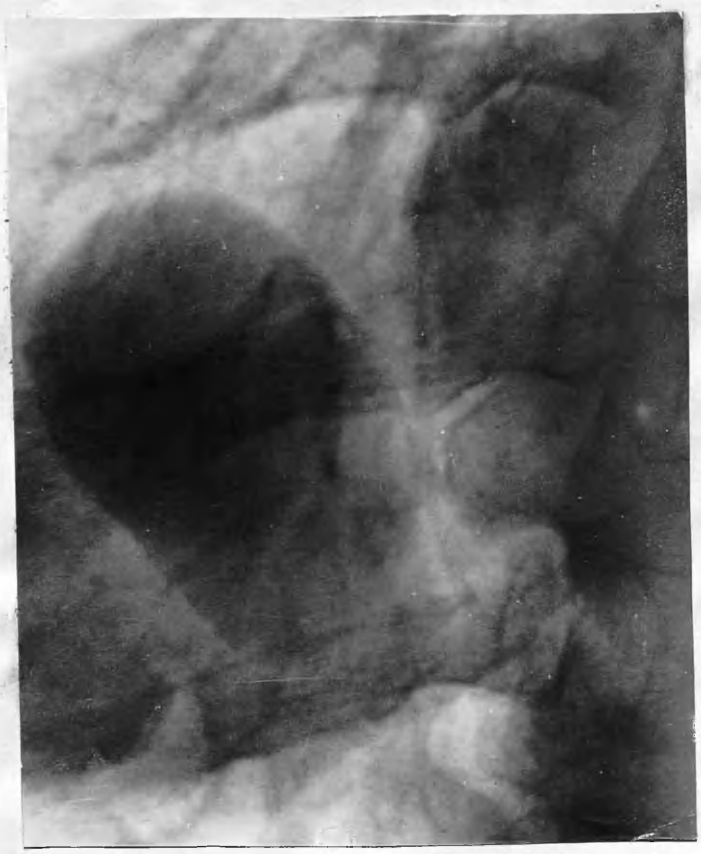


Fig.35.

Cholecystogram showing an inverted gall-bladder.

Fig.36.

Choledochogram showing the medium introduced through a T-tube. The gall-bladder, which was not actually seen at operation owing to the density of adhesions in the area, is partially filled and its fundus overlies the common bile-duct.

1. Anomalies of the Extra-biliary Duct System.

The gall-bladder may be absent, rudimentary, hourglass (of which I have encountered one example), intrahepatic (see fig. 34), or inverted (see fig. 35). A malplaced gall-bladder may lead to some confusion at operation. Such a case was encountered by a colleague who failed to locate such a gall-bladder at operation and proceeded to explore and drain the common hepatic duct. A cholangiogram taken 10 days later (see fig. 36) showed the gall-bladder actually lying across the common bile-duct.

The cystic duct varies in its mode of junction with the main hepatic duct. In 75 per cent. it unites at an acute angle above the upper edge of the first part of the duodenum, the terminal two centimetres running parallel and firmly bound to the common duct with fibrous tissue (Eisendrath, 1920). In 17 per cent. the cystic duct runs for a longer course and in close association with the main duct, and may spiral round the latter (8 per cent.) . Of the 200 specimens studied by Flint (1923), the cystic duct joined the main hepatic duct anteriorly in 8 instances, posteriorly in 3, and on the left side in 1 instance. 3 of my series of cholangiograms show a left-sided entry, and in a fourth the cystic duct appears to/

to join the common hepatic duct either posteriorly or anteriorly (see fig. 33).

Accessory Hepatic Ducts. This abnormality is considered separately in connection with Case I (page 101).

Anomalies of the Right Hepatic Duct, if not recognized can readily cause the most circumspect surgeon to make a serious blunder. Accidents are prone to happen when this duct is unusually long and particularly when it receives the cystic duct (Eisendrath).

2. Arterial Anomalies.

The right hepatic artery normally runs behind the common hepatic duct and gives off the cystic branch just beyond the right edge of this duct in 70 per cent. (Eisendrath). In 12 per cent. the right hepatic artery passes across the front of the common hepatic duct and in 10 per cent. (Cole et al. say 20 per cent.) this artery may run parallel and in close proximity to the cystic duct.

An Accessory Right Hepatic Artery is found in 4.5 per cent. of Flint's 200 specimens.

The Cystic Artery arises in 27 per cent. on the left side of the common hepatic duct which it crosses anteriorly to reach the gall-bladder (Eisendrath).

An Accessory Cystic Artery is seen in about 8 per cent. (Eisendrath).

A common source of bleeding during exposure of the main bile duct is a small artery which runs upwards on its anterior wall. The vessel arises from the main hepatic artery or its gastro-duodenal branch and is found in as many as 50 per cent. of patients (Cole et al. 1949).

II. Ulceration due to Stones.

Local necrosis of the lining of the duct produced by impacted stones is often cited as a cause of distal stricture but actually few proven cases have been reported. Walton (1944) appears to have come across one case; there were none in Walter's (1939) earlier series, and in the 188 cases of stricture published by Flickinger and Masson there were only three examples.

III. Chronic Obliterative Cholangitis.

Judd (1926) drew attention to the relatively large number of cases that developed signs of stenosis of the bile ducts many months and in some cases many years after cholecystectomy, and he makes the point that the surgeon cannot always be held responsible for strictures of late development. In 16 of the 64 cases reviewed by him the common duct was patent at the original inspection, but in some of these there was clinical /

clinical evidence of intermittent obstruction before any operation was performed. An ascending cholangitis, a condition which can easily be overlooked at operation is, in Judd's opinion, a not uncommon aetiological factor particularly in cases with diffuse strictures. Yet in an earlier paper Judd and Burden (1925) stated that 27 of 47 cases of stricture occurred at the junction of the cystic and common hepatic ducts and other 17 occurred slightly lower in the supraduodenal portion of the common duct. These figures, as the authors admitted, may be taken as convincing evidence in favour of a traumatic rather than an infective origin. Gray has raised the point that if cholangitis were the causal factor, the intrahepatic ducts would also be involved, but he has not been able to produce any evidence of this by means of hepatic biopsy. Cole (1946) could not explain to his satisfaction the high incidence of the diffuse type of stricture but thought that it may result from disuse in that part of the duct lying distal to a more localized area of fibrosis; other factors suggested by Cole are infection and impairment of blood supply. Whatever the cause, he is of the view that these strictures take a long time to develop. At least 12 per cent. of Flickinger and Masson's series were classified by them as due to/

to chronic inflammation of the duct mucosa and belonging to the diffuse variety. They offer the novel suggestion that the probable cause is too vigorous use of the gall-stone scoop during attempts to rid the ducts of stones or debris.

IV. Chronic Pancreatitis.

As early as 1896, Riedal associated chronic benign inflammatory affections of the pancreas with obstructive jaundice. Robson (1900) stressed how closely this condition may simulate the commoner malignant lesions in their clinical manifestations. Chronic pancreatitis is characterized, in his experience, by paroxymal attacks of pain and ague-like seizures, wasting, sometimes persistent jaundice, and occasionally the passage of offensive stools. Robson reported 17 cases with obstructive jaundice on whom he had operated: all had a firm inflammatory mass in the head of the pancreas. Treatment took the form of cholecysto-duodenostomy. All except one recovered and did well for varying periods. At the autopsy in this case chronic interstitial changes were present in the head of the pancreas, but it is also noted that there was a gall-stone in the common bile-duct and a large abscess in the liver, findings which cast some doubt on the complicity of the pancreatic lesion.

While it is accepted that the more acute pancreatic affections may be associated with jaundice, which is usually transient and of slight degree, the more intractable forms of jaundice demand a much more critical assessment which should not stop short of an exploratory laparotomy with, if possible, removal of a piece of tissue for microscopic examination. Authentic cases of the constrictive form of pancreatitis have been reported by Walton (1944) and by Peterson and Cole (1945). Cole, Reynolds, and Iraneus (1949) estimated that this was the causal factor in 13 per cent. of their stricture series. Walters (1939) mentioned only one case of this kind in his series - the lesion being a calcified cyst in the pancreas. The present author has yet to see a case of chronic sclerosing pancreatitis associated with stenosis of the common bile-duct, which persisted.

V. Other Aetiological Considerations.

There remain a few cases which do not readily fit into the aforementioned groups. Miller (1927) for example, reported a case of benign stricture in which no stone was found in the gall-bladder at operation and the common bile-duct felt like a thrombosed vein; when opened its wall was found to be thickened. A cholecysto-gastrostomy was done and the jaundice disappeared, but/

but returned one year later. This proved to be due to a spread of the process to involve the common hepatic duct. Delbet (1924) and Lafourcade (1923) reported similar cases unrelated to stone or trauma. Bernard and Mallet-Guy (1933) have suggested that the obstruction in some of the distally placed strictures may result from - (1) a local cicatricial and stenosing lesion, (2) local inflammation associated with spasm and hypertrophy of the sphincter of Oddi, or (3) sphincteric spasm per se. 8 apparently authenticated cases of benign fibrosis of the sphincter of Oddi have recently been reported by Trommald and Seabrook (1950); in 3 of the patients the opening of the papilla was reduced to pin-point size. Lahey and Pyrtek (1950) encountered 24 instances of this type in their total series of 239 cases of benign stricture of the common bile-duct. Carter (1935) has reviewed the literature relating to these odd types and added a case of his own. A new idea formulated by Dragstedt and Woodward (1952) is that some of the post-operative strictures are caused by bile that has been allowed to collect in the vicinity; the necrotizing effect of the bile salts is well known, but as yet there is no definite proof that the accumulation of bile can have such an effect on the bile duct as to lead to stricture.

No.1 - A CASE OF DAMAGED ACCESSORY RIGHT HEPATIC DUCT REPAIRED BY ANASTOMOSIS WITH THE CYSTIC DUCT

According to Flint (1923), the commonest cause of a leakage of bile following cholecystectomy is probably injury to an accessory hepatic duct and not, as so often thought, slipping of the ligature around the cystic duct or a tear of the main bile ducts. An accessory duct was present in about 15 per cent. of the 200 post-mortem specimens which he examined; it arose in the right lobe of the liver, lying at first posterior to the cystic duct, and joined the common hepatic duct at a varying level. Less commonly the accessory duct entered the gall-bladder directly. Flint recalled at least two occasions when he was confronted with the cut end of a duct which did not seem to fit in to the normal pattern and referred to Moyniham as having had a similar experience. Accessory ducts passing directly between the liver and gall-bladder occur in about 8 per cent. of individuals according to Mentzer (1929) and Paul (1948) has described methods devised for dealing with them.

This report concerns a case in which the damage to the accessory duct was not discovered until a/

a week after the gall-bladder had been removed, by which time the abdominal cavity contained several pints of bile. In this case, contrary to my usual custom, no drain was inserted, an omission which added to the chastening effect of this complication. Fortunately, the remnant of the cystic duct was long enough to bridge the gap and so re-direct an appreciable flow of bile into its proper channel.

Case Report.

M.D., housewife, aged 51 years, was admitted to the Broadstone Jubilee Hospital, Port Glasgow, on February 16th, 1949, with cholelithiasis from which she had suffered for the preceding 6 months. She had never been jaundiced and, apart from a rather capricious appetite, was otherwise well. Cholecystography revealed the presence of numerous small stones in a functioning gall-bladder.

Cholecystectomy was performed on the day after admission under spinal anaesthesia. A right paramedian incision was chosen and no difficulty encountered during exposure of the gall-bladder. It had a slightly thickened wall and contained 6 small cholesterol stones. The cystic duct was readily identified and traced as far as its junction with the common duct. The cystic artery, however, could not be exposed to view: instead an /

an aneurysm needle was carefully passed through the fatty tissue lying behind the cystic duct and a ligature applied. After cutting across between the latter and distally applied forceps, no bleeding occurred nor was there a noticeable escape of bile. In fact the wound was so dry after the bed of the gall-bladder had been re-peritonized that it seemed safe to dispense with a drain. The other viscera that lay within reach were regarded as normal.

Post-operative Course. 2 days later the patient began to complain of vague generalized abdominal discomfort with occasional bouts of sickness. These symptoms were at first taken to be the natural sequelae of the operation but, when they persisted despite enemata and particularly when a trace of jaundice appeared, it became obvious that something serious had gone wrong.

Wound re-opened on the 7th day. On opening the peritoneum, a large quantity of bile flowed out. Owing to the altered state of the tissues, it was not possible to make a clean dissection of the vital area but eventually the common bile and hepatic ducts were exposed and they appeared to be intact. The leak occurred from neither of them but from a gaping duct which emerged from the liver at the extreme right of the porta hepatis. It/

It had been cut across almost flush with the liver surface and was about 3 to 4 millimetres in diameter.

The stump of the cystic duct happened to lie in the close vicinity and was of sufficient length and width to anastomose to the accessory duct. Accordingly, the catgut ligature was removed from the cystic duct and its patency checked. A T-tube was found that fitted comfortably into both ducts. These were brought together without tension with a single row of interrupted catgut sutures. The site of operation was also drained by a separate tube.

Further Course. Bile continued to leak alongside as well as through the external limb of the T-tube for about 10 days. Thereafter, it drained only through the tube in daily amounts of about 1 to 2 ounces.

The T-tube was removed after 4 weeks. By that time the jaundice had completely cleared and the stools, which had previously been slightly pale, returned to a normal colour. She was discharged from hospital after a stay of 6 weeks, in a satisfactory state of health.

When seen 18 months later she had no complaints.

Comment.

It is supposed that the distal end of the accessory hepatic duct was ligatured along with the cystic artery, then cut across, and the proximal end left patent. Flint and Moynihan (see Flint) simply tied the proximal end of such accessory ducts with no apparent ill-effects. In a short communication written in 1924, Walters described a method, which he credited to C.H. Mayo, whereby the stump of the cystic duct is utilized to re-establish continuity. The calibre of the anomalous duct was the smaller of the two in their cases but this difficulty was overcome by telescoping the one into the other, using catgut sutures. In my case it was not only possible to accomplish an end-to-end approximation but also to employ an internal splint in the form of a T-tube. To have followed the modern preference for bringing the ducts together over a T-tube inserted through a separate incision in the duct to be repaired (Cole, Reynolds, and Iraneus, 1949), would have meant opening the common bile-duct, a step which was not necessary under the circumstances.

No. 2. A CASE OF A LOCALIZED STRICTURE OF THE COMMON BILE-DUCT.

The case may be conveniently divided into the following four episodes.

1. The Primary Biliary Condition. M.N., aged 39 years, housewife, was admitted on October 31st, 1942, to Killearn Hospital, with recurring attacks of biliary colic extending over a period of two years. She was never jaundiced. She was not seen by the writer at this time.

Operation as described in the records - Kocher approach (19.11.42.) - the gall-bladder contained several stones. Exposure of the cystic duct was difficult, but removal of the gall-bladder was eventually achieved by the retrograde method. Condition of the common duct not mentioned. Liver bed partially closed and the wound drained.

The wound discharged bile for 7 days. 19 days after operation slight jaundice appeared but faded four days later. Wound had healed completely by the 23rd day and she was discharged fit.

2. Incisional Hernia. The patient was readmitted to Killearn Hospital on April 12th, 1943, under my care, with an incisional hernia at the site of the previous /

previous operation scar, but with no other complaint. This was dealt with and she was discharged 4 weeks later.

3. Common Duct Stricture. She was admitted to hospital for the third time on September 10th, 1943, with a history of jaundice, first seen about 2 months previously, some sickness, and diarrhoea. The jaundice had varied from time to time but never quite faded. The stools were clay-coloured. No history of rigors.

The patient was obese. The liver was slightly enlarged and tender. Spleen also palpable. The wound hernia had recurred towards the extreme lateral end.

Operative Treatment (H.Wapshaw), on September 18th, 1943, after a preliminary course of Vitamin K injections. Spinal anaesthesia administered, the dosage being 200 mgm. procaine to level of T.4. A right paramedian incision used. The field of operation was obscured by adhesions but eventually the right side of the lesser omentum and the foramen of Winslow were identified. The common bile-duct was located by blunt dissection and opened through a short vertical slit just above the duodenum. Although the head of the pancreas was somewhat indurated around the area where the common /

common bile-duct terminated, a probe passed down into the duodenum satisfactorily. When the probe was directed proximally, however, it was held up within a short distance. Further dissection above this area revealed a short length of a much dilated common hepatic duct. A second longitudinal incision was made, this time beginning on the proximal side of the stenosed area and carried down across a very tight stricture, but stopping short of the lower incision. The bile which escaped was clear and of a pale greenish colour.

My original plan was to widen the affected area by closing the longitudinal incision through the stenosed area as a transverse wound and to drain the common duct through the lower incision by means of a T-tube, so arranged that the upper limb of the cross-piece extended through the repaired part of the duct. Unfortunately the first part of the manoeuvre appeared to drag too heavily on the tissues, with the result that the fibrosed area began to split transversely. The attempt was, therefore, abandoned and the T-tube was inserted in the upper incision instead, where it lay comfortably. Only two stitches were placed on either side in the longitudinal axis, thus widening the area to a slight extent. One stitch transfixed the tube to prevent accidental dislodgement.

The lower incision in the common bile-duct was closed and was proved to be watertight by introducing saline through the T-tube. A cigarette drain was left in the wound down to the bile duct.

Post-operative course. Bile leaked in some quantity from the wound for 14 days. The jaundice was much less by the end of that time; it had completely disappeared by the 4th week and the stools were now normally coloured. About 2 - 3 ozs. of bile drained each day from the T-tube up to two days before removal of the tube. This was done three weeks after operation.

Patient dismissed from hospital ten days later with the wound healed and apparently well.

4. Recurrence of Jaundice. The patient remained relatively well for 14 months. In November, 1944, the jaundice returned and, although it varied in intensity, it persisted until she was admitted to the Western Infirmary under Mr. James P. Fleming on 15th October, 1945. About the same time she began to suffer attacks of subacute pain in the right hypochondrium, brought on by exercise and relieved by rest. For the 3 months prior to admission she felt listless and noticed that her clothes were too big for her. Her appetite was poor, with a strong distaste for fatty foods. The stools were often pale and the urine dark in colour. She /

She perspired a good deal and complained of pruritus.

On examination the patient showed a moderate degree of jaundice, and appeared tired and listless. There was a considerable loss in weight.

The abdomen was lax but tender in the right hypochondrium. The edge of the liver was palpable about 2 finger breadths below the costal margin.

Operation on 29th October, 1945, by Mr. J.P. Fleming; after cleaving a way through many adhesions, the common bile-duct was found grossly dilated. This was drained, but so much bleeding occurred that further interference was abandoned. The operation notes contain no reference to a stricture.

The patient died on the following day despite infusions of glucose salines. The cause was thought to be liver failure.

Autopsy Findings. The bile ducts were dilated to an occluding stricture 3 centimetres above the ampulla of Vater, where the cystic duct was probably formerly attached. A small mucosal polyp situated in the vicinity of the stricture helped to block the lumen.

The liver was grossly enlarged and the intrahepatic bile ducts greatly dilated.

Comment

Several points call for comment. First of all, it is clear from the surgeon's notes of the original operation that the common duct was implicated at the stage when the cystic duct was interfered with. The discharge of bile from the wound following the cholecystectomy, coupled with the onset of jaundice, transient though it proved to be, were ominous signs that all had not gone well.

Secondly, my own handling of the stricture that developed is not free from criticism. The less radical operation by the Heineke-Mikulicz procedure seemed the safer, and it was not forseen that to convert a longitudinal incision into a transverse one would prove so difficult. The T-tube should probably have been left in much longer than three weeks. Under similar circumstances one would attempt excision of the fibrosed area, followed by an end-to-end closure of the duct.

Finally, there is an apparent discrepancy between the author's and the pathologist's description of the site of the stricture. It will be recalled that /

that in the first attempt at repair a common bile-duct of normal calibre opened into the duodenum and the stricture lay at a higher (more proximal) level, whereas Dr. W.A. Taylor, who performed the autopsy, found that it lay only 3 centimetres from the ampulla of Vater, with much dilatation of the proximal segment of duct. That Mr. Fleming should only find reason to comment on the dilated state of the common bile-duct also suggested that the level of obstruction lay behind or below the first part of duodenum. It is difficult to imagine that the one which I encountered and the one Mr. Fleming had to operate on were two different strictures. The likely explanation is that the stricture which I repaired had recurred and dragged downwards as a result of extensive adhesions or periductal fibrosis.

No. 3. A CASE OF A DIFFUSE STRICTURE OF THE COMMON HEPATIC BILE-DUCT

As in the previous case, a cholecystectomy was to blame for the stricture formation in this patient. Unfortunately the area affected extended from the porta hepatis to the upper border of the first part of the duodenum. Additional difficulties in management were due to the patient having become addicted to morphine.

1. The Primary Biliary Condition was of eighteen years' standing. The patient, a female, was aged 62 years. At no time was she ever jaundiced. Cholecystectomy was performed at the Victoria Infirmary, Glasgow, on the 12th September, 1947. According to the surgeon's notes the gall-bladder was full of stones and lay in a deep recess in the liver. Naturally its removal proved difficult. No stones were palpated in the common duct which was left intact. Wound closed without drainage.

Three days after the operation the patient became jaundiced. The icterus persisted and on the twelfth day it was decided to re-open the abdomen. The common duct was found with difficulty and drained by means of a rubber tube.

She was finally discharged improved but not absolutely fit. It is to be noted that drug addiction was suspected during the stay at the Victoria Infirmary. Her health remained indifferent and four months later she passed a gall-stone in the stool, which was identified by her doctor. A short time later she began to suffer from what appeared to be left-sided renal colic and passed a small urinary calculus.

About six months after the discharge from hospital, the patient began to complain of a variety of symptoms which were at first regarded as due to chronic pancreatitis. The sympton-complex took the form of vague and sometimes severe supra-umbilical pain, which tended to radiate down the left side and towards the left flank, and she lost weight. Her mental health became suspect and she was admitted to the psychiatric wards of Stobhill Hospital, but was dismissed in statu quo ante. How much of her trouble was really due to the craving for morphine remained uncertain.

2. Stricture of the Common Bile-Duct. Twenty months later she was admitted to the Western Infirmary, Glasgow, for further observation. In addition to the symptoms already described, she complained of flatulence, irregularity of the bowels, feeling as if something was bearing down into the pelvis, and occasionally pain /

/pain while passing urine.

On examination she was a thin, anaemic woman, slightly jaundiced, and appeared to be in a hypochondriacal state. There was photographic evidence that the patient had lost much weight since the cholecystectomy. The blood pressure was 140/90 mm.Hg., pulse rate 112 per minute. The heart sounds were of poor quality. The other systems appeared normal.

There were two large scars on the abdominal wall, the liver and spleen were not enlarged. The colon was readily palpable. Tenderness was elicited at most parts and particularly to the left of the mid-line between umbilicus and subcostal margin. There was no rigidity.

Rectal and vaginal examination revealed no abnormalities.

Barium Meal gave normal findings.

Straight K.U.B. Film showed the kidneys to be normal in size, shape, and position. There was a small opacity overlying the lower pole of the left kidney.

Faecal Analysis. Stool contained a few undigested meat fibres seen on microscopic examination, but no excess of fatty material or starch. Total fat of dried faecal solids was 25.6% which is only slightly above the average.

Cystoscopic examination did not reveal any cause for dysuria.

Her general behaviour during stay in hospital left much to be desired. There were many "scenes" particularly in the presence of an audience, which appeared to be her way of satisfying a craving for attention and sympathy. For these hysterical fits or attacks of pain, sterile water was often given in the hope that she might thereby be weaned from morphia. On frequent occasions it was noted that sterile water was "beneficial", although speaking in the light of later knowledge, she must at times have suffered genuine visceral pain.

Laparotomy (H.Wapshaw) was carried out on 12.5.49. The old scar was excised and the adhesions in the right upper abdomen separated to disclose the duodenum. This took some time. The right margin of the gastro-hepatic omentum was eventually exposed. It was extensively cicatrized. Neither the common bile nor hepatic ducts were identified. The pancreas was examined and seemed to be normal to palpation.

Bleeding was troublesome from the branches of the hepatic artery and on one occasion from the portal /

portal vein. After extensive dissection in an upward direction, the right and left branches of the hepatic duct were found. They were dilated.

At that stage, the anaesthetist became concerned about the patient's condition and advised early termination of the operation which had now lasted two hours. Therefore a rubber tube was inserted quickly into the right hepatic duct in the hope that an external fistula would form, which could be implanted into the bowel at a later period.

15 days later the drainage tube was removed and rapid healing of the fistula occurred. The patient was dismissed soon after with a healed wound, and in effect no better off than when admitted.

Comment

It is very evident from the original records of this case that a serious mishap had occurred during the removal of the gall-bladder and that the laparotomy performed 12 days later had not improved matters.

The attempt to repair the resulting stricture, failed completely. Had she been able to withstand a more prolonged operation, a high hepatico-jejunostomy with a Y-tube support might have been the procedure of choice. As it was, the tube stitched into the right /

right hepatic duct did not achieve its purpose of creating a fistula which could be transplanted at a later date. The stricture in this case must have been long, narrow and tortuous, and considering the amount of interference it is hard to understand how the natural bile flow became re-established.

No. 4. A CASE OF ACCIDENTAL SEVERANCE OF THE COMMON BILE-DUCT

The patient gave a long-standing history of indigestion, and cholelithiasis was diagnosed by means of excretion radiography. The surgeon who performed the cholecystectomy incorporated the common bile-duct unwittingly in the ligature intended for the cystic duct. Scrutiny of the operation notes makes it clear that the accident arose through the presence of adhesions around the neck of the gall-bladder, because the surgeon seemed to have difficulty in identifying the cystic duct, although he states that this was eventually found, separated, and ligated. The gall-bladder was removed in the usual manner, and a rubber tube placed down to the site of the gall-bladder.

Bile continued to drain from the wound, and this was regarded as not unusual until a week later when the stools became clay coloured and slight jaundice appeared. Till then it was suspected that the leakage of bile was due to slipping of the ligature in the cystic duct, or possibly accidental severance of an /

an anomalous duct or even the right branch of the hepatic. The appearance of the acholic stools pointed to a more serious cause. The author had the privilege of carrying out the exploratory laparotomy, and the following are details of the reconstructive procedure carried out fourteen days after the original operation.

Biliary-intestinal anastomosis by utilizing loop of jejunum, with entero-anastomosis. (9th April 1953).

A fresh incision was made to inner side of the first one and the peritoneal cavity opened without interfering with the track of the sinus. On separating the omental adhesions to the under edge of the right lobe of liver, a large collection of bile was discovered in Morison's pouch. The under surface of the right lobe of liver and the surface of the first and second parts of the duodenum were covered with sloughs, possibly due to the necrotising effect of the bile. The necrotic material was curetted and sponged off the adjacent viscera.

A probe was passed down the fistulous track: it passed across the pyloro-duodenal junction and ended in the region of a ligatured duct. A search was made for the supra-duodenal segment of the common bile-duct /

duct but only the portal vein could be found. When the ligature was removed from what was thought to be the cystic duct, it became obvious that the common bile-duct had been tied mistakenly for it and cut across in error. The distal end of the duct could not be found. Since there was a loss of about 1.5 to 2 cms. of duct, it was decided to expose the hepatic duct and perform a biliary-intestinal anastomosis.

The hepatic duct was cleared for about 1.5 cm. and the patency of the right and left branches checked with a bougie. An upper loop of jejunum was chosen and a 2-layer anastomosis carried out with interrupted "Mersilk" sutures. A short length (6 cms. approx.) of narrow rubber tubing was used as a temporary splint. This was fixed by means of one catgut suture, then entero-anastomosis performed, the stoma being 5 cms. in length. The apex of the loop was finally tacked to the under surface of liver to prevent a drag on the anastomosis. Morison's pouch was drained with a rubber tube: wound otherwise closed.

Post-operative Progress: The patient withstood the second operation very well. A bilious discharge leaked from the wound for a few days. The only complication was a break down of the wound at the part /

part opposite the external fistula. This was due to interference in the blood supply caused by the second incision. The general health and strength rapidly improved. The stools became normally coloured by the 6th day and the jaundice had gone about the same time. The patient was discharged home on the 13th day, but still attending for dressings. So far the small length of rubber tubing used for the anastomosis has not been passed to the patient's knowledge.

Comment

The specimen of the gall-bladder was examined soon after the removal but nothing unusual noted beyond the presence of gallstones and signs of chronic inflammatory change. Walton (1944) cited a case operated on by himself in which death from biliary peritonitis took place a few days after cholecystectomy. At autopsy, a portion of the common duct was seen to be torn away. Fortunately, the gall-bladder had been kept, and there, attached to the cystic duct was the missing piece of tissue. In the above case one could not state the circumstances that led to the accident. No particular difficulty was encountered during the exposure or re-constitution of the biliary pathway. The common duct was, however, undilated and therefore not so easy to /

to deal with; the use of a small piece of rubber tube temporarily anchored by means of a single catgut stitch greatly facilitated the performance of the union between the duct and the jejunum.

DIAGNOSIS

It goes without saying that the sooner an injury to the bile ducts is discovered the easier its repair will be. Usually the accident escapes notice at the time. An unexpected leakage of bile from a cholecystectomy wound in the immediate post-operative phase is highly suspicious of such an accident, although slipping of the ligature placed around the cystic duct, or damage of an accessory right hepatic duct (Flint, 1923), such as occurred in my first case, are other possibilities.

The four cases treated by the author discharged bile through their cholecystectomy wounds. In 3 or them the bile ceased to flow after a few days whereupon jaundice developed. The one in which the common bile duct was tied the discharge continued for 14 days but this was coming from a bilious collection in Morison's pouch.

In approximately 40 per cent. of the cases due to operative trauma (Gray, 1951), the first indication that all is not well is jaundice appearing within a few days after the operation. Many others do not become jaundiced until the second post-operative week and a few several months later, though most of the latter will complain of symptoms referable to the biliary system in /

in the interim. The convalescence was normal for 1 to 12 months before obstructive symptoms appeared in 27 per cent. of Flickinger and Masson's series. It is probably fair to assume, to quote Wilson (1939), that if a patient has had a normal convalescence and remained well for a period of two years, the operator cannot be blamed for any subsequent disease in the biliary tract.

Recurring chills and phases of anorexia and nausea suggest strongly attacks of cholangitis and hepatitis. These symptoms were well exemplified in Case 3. The combined effects of this complication and the progressive dilatation of the intrahepatic ducts due to mechanical obstruction, result in time in a considerable degree of enlargement of the liver. In Mr. Gerstenberg's case the patient suffered from transient attacks of jaundice during her menstrual periods following a Heineke-Mikulicz repair and these recurred after a normal menopause, coinciding more or less with the times of the previous periods. It is difficult to account for the apparent regularity of these episodes, and I have not seen reference to any similar case. When last seen the liver was enlarged to about 2 finger breadths below the costal margin, and it is not improbable that there is still a degree of stenosis that /

that may be aggravated by periodic congestion.

The subjective complaints of the patients vary with the emotional reaction of the individual to stress and the secondary effects of the biliary obstruction on the liver and possibly on the pancreas (Gray, 1951). Case 3 was again a good example: photographs of the patient taken before cholecystectomy showed her to be a robust woman.

The other conditions to be considered in the diagnosis are an overlooked stone lying in the common bile-duct, infective hepatitis or malignancy.

THE SURGICAL MANAGEMENT.

Benign strictures of the bile ducts may conveniently be classified as - (1) Localized Strictures and (2) Diffuse Strictures. The former are a sequel to minimal damage; and the most amenable to direct surgical attack are those that develop in the immediate supraduodenal zone. Unfortunately, the localized type occurred in only 10-20 per cent. of reported cases (Cole, 1946). However, the real concern of the surgeon is not so much the extent of the cicatricized area, as its location. Thus, extensive narrowing of the intra- or retro-pancreatic segment of the common bile-duct can /

can readily be short-circuited by an anastomosis between the common bile-duct and the duodenum; on the other hand, damage to the common hepatic duct or its branches is, indeed, a vexata quaestio and its surgical management calls for the greatest technical skill and daring.

General Considerations.

A tedious, but unavoidable, prelude to any reparative procedure is the separation of adhesions binding the duodenum and transverse colon to the adjacent surface of the liver. This stage of the operation may take as long as 1 - 2 hours. The time is not infrequently further prolonged by the need to stem leaks from punctures or tears in the portal vein. It is, therefore, sound policy to assess carefully the patient's fitness to withstand a major and prolonged operative procedure, but under certain circumstances surgical intervention is unavoidable and worthwhile even although the patient is in poor condition. With overt manifestations of hepatitis surgery should be postponed until a remission sets in, and to hasten recovery simple medical and chemo-therapeutic measures ought to be instituted.

The preoperative care consists largely of giving a high protein, high carbohydrate, and low fat diet, correction of secondary anaemia if present, and /

and of hypoprothrombinaemia by administration of vitamin K. If the preoperative period is short, oral feeding may be supplemented by the intravenous administration of fluid, electrolytes and glucose. An ample supply of fresh blood should be available for the actual operation.

Exposure. The structures that usually require to be separated from the under surface of the liver before the affected duct is reached are the omentum, hepatic flexure of the colon, duodenum, and stomach. Walters (1950) claims that it is a help to begin the dissection from far to the right beneath the right lobe of the liver and work inwards towards the hepatico-duodenal ligament. The identification of the hepatic artery and the portal vein is the next essential step before directing attention to the damaged area of the duct.

Forms of Repair.

Excision with end-to-end anastomosis (fig. 37) is widely regarded as the ideal form of repair for a localized stricture. One layer of catgut or silk suture is all that is required. To insert another would carry the risk of narrowing the lumen unnecessarily. The use of some support either in the form of a rubber T-tube or one made of vitallium (see below) serves as an added insurance against both leakage and the tendency /

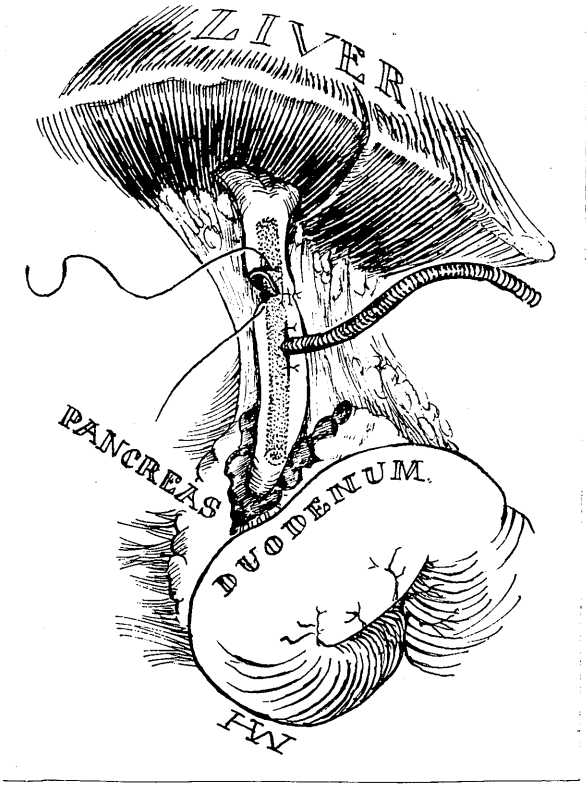


Fig.37. End-to-end anastomosis. T-tube inserted through a separate incision in the distal portion of the common bile duct. Extra length has been obtained by dissecting the latter out of the head of the pancreas after reflecting duodenum to the left (Cattell's manoeuvre).

tendency to further stenosis during the healing process. It has become the accepted practice when using a rubber T-tube to insert it through a separate incision in the common duct, which is made on whichever side is more suitable. The length of time that it may be allowed to remain in position has been arbitrarily stated by some to be 3 months (Cole, Reynolds, and Iraneus, 1949) and by others 6 months (Gray, 1951).

While excision of the cicatrix with a mucosa-to-mucosa closure is recognized as the form of repair that offers the best results, there are good grounds based on animal experiments for concluding that many patients so treated develop another stricture at the site of anastomosis despite the use of fine suture material and careful surgical technique (Douglas, Lounsbury, Cutter, and Wetzel, 1950). The constant flow of bile over the healing surface is a factor tending to cause further stenosis; but even if one wished to eliminate this temporarily the opportunity for diverting the flow rarely presents itself. Walters (1950) has recently brought forward clinical evidence that the results of choledocho-choledochostomy leave much to be desired (<u>vide infra</u>). My first case may be regarded as an instance of end-to-end repair.

The gap left after excising a hepatic duct stricture is generally too wide for an end-to-end approximation. The procedure of Cattell (1947) is a means of gaining extra length by mobilizing and reflecting the second part of the duodenum to the left and dissecting out the retro- or intra-pancreatic portion of the common bile-duct (see fig. 37). Speaking from personal experience, this causes much bleeding from minor veins, which is difficult to control. This procedure will fail to achieve its aim in cases where the common duct follows a nearly straight course , several examples of which were shown in the radiographic studies (vide supra). Cattell does not discuss this possibility. However, desperate conditions call for desperate measures and the procedure has been favoured by certain responsible workers (Lahey and Pyrtek, 1950). A simpler manoeuvre, possibly just as effective as a means of allowing the two ends of the bile duct to come together, is to mobilize the duodenum along with the head of the pancreas and displace these viscera upwards in one piece.

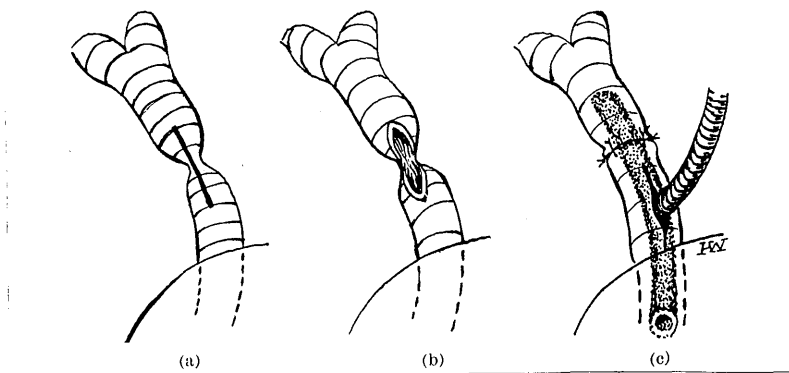


Fig.38. The Heineke-Mikulicz procedure. (a) and (b) lines of incision through the stenosed area. (c) Plastic procedure completed with a T-tube inserted in a separate incision in the common bile duct.

In cases where the stenosed area is inseparably adherent to the portal vein, it may be widened by the Heineke-Mikulicz manoeuvre (fig.38). Unfortunately the bile duct, unlike the bowel or ureter, is in these instances a stiff and friable structure, not having a muscular coat. Accordingly, attempts to convert a longitudinal incision through the stricture into a transverse wound are likely to be very difficult, as was the writer's experience (vide supra). A temporary splint, /

splint, e.g. a rubber T-tube, is highly desirable and should be inserted, as previously mentioned, through a separate incision in the bile duct.

Few cases are suitable and few likely to benefit from instrumental dilatation of the stricture. Walton, (1944) cited two so treated with apparent success apart from slight recurrent attacks of jaundice. Lahey and Pyrtek, (1950) have performed this operation on 41 cases and obtained good results in most (see later); it is noted that they took the precaution to leave in a tube for a considerable time.

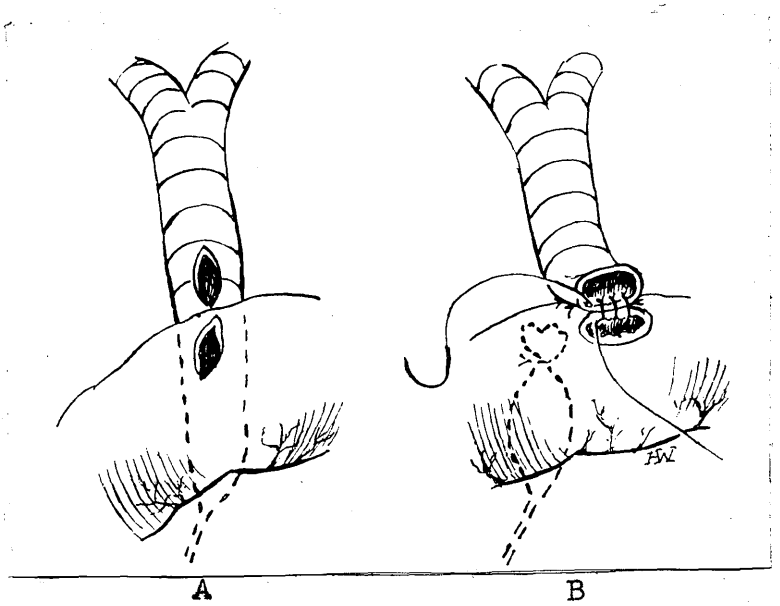


Fig.39. (A) illustrates a side-to-side choledocho-duodenostomy. (B) illustrates an end-to-side choledocho-duodenostomy.

Distal strictures lend themselves to some form of short-circuiting procedure. This may take the form of a side-to-side choledocho-duodenostomy with, wherever possible, a longitudinal stoma in the common bile-duct (hepatico-duodenostomy is the term applicable when the common hepatic duct is used for the anastomosis). Alternatively, the common duct may be cut across, the distal end permanently occluded and the proximal implanted into the duodenum (see fig. 39). With the latter procedure, it is a matter of individual preference whether or not the site of anastomosis is provided with a tubular support. Given suitable conditions, either of these operations yields satisfactory results. Localized strictures at the duodenal orifice may only require to be slit after opening that part of the bowel, or by passing a sphincterotome down from above (McNeill Love, 1952), i.e. the operation which is otherwise known as sphincterotomy, but there must be few capable of being relieved in this way. Cattell (1946) maintains the patency of the widened orifice by a T-tube with a long cross-piece, one end of which is passed through into the lumen of the duodenum. This must be left in situ for some months.

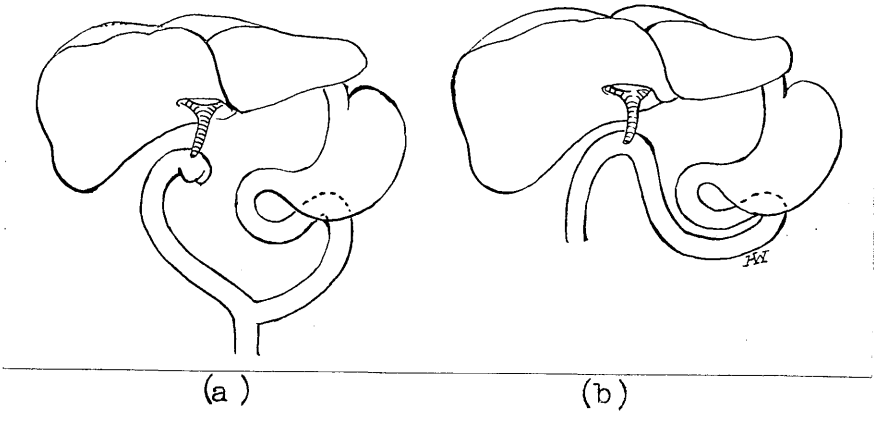
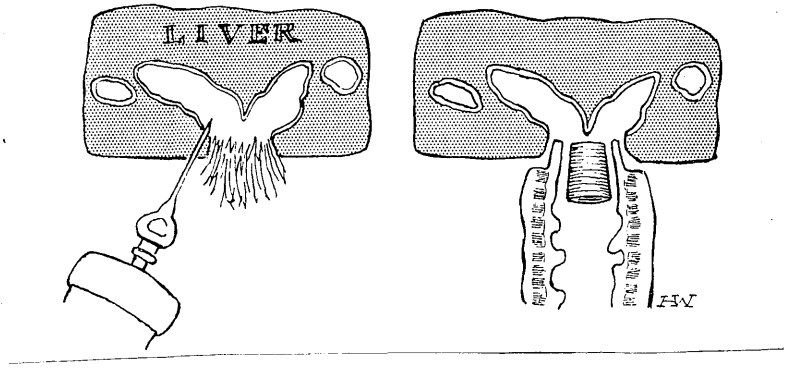


Fig.40. Choledocho-jejunostomy (a) Anastomosis en-Y Roux (b) Utilizing a loop of the upper jejunum.

The use of the Roux Y-arm of jejunum, first popularized by Whipple (1927), has proved a useful means of re-establishing the bile flow in high strictures (see fig.40). According to Cole, Reynolds and Iraneus, its chief advantage over the use of an upper loop of jejunum, lies in the almost total elimination of the danger of regurgitation of food and intestinal secretion of cholangitis. This complication is liable to occur even with an entero-anastomosis between the arms of the loop for the reason that the food etc., tend to follow the original route (Cole, 1946). An upper jejunal loop with an entero-anastomosis was utilized for the repair of case 4 of my series.

The worst types to treat and, unfortunately, the commonest, are those with extensive stricture formation. The part affected usually lies above the duodenum or pancreas and the limits are difficult to define. In an attempt to reduce the time and manipulation involved in searching for the distal segment of duct in these cases, Dragstedt and Woodward (1952) open the second part of the duodenum and pass a catheter up the common duct, thus locating the level of the stricture: they next excise the strictured area and if possible carry out the anastomosis with the proximal end of the bile duct over the same catheter. More often it is necessary to define the fringe of common hepatic duct at the porta hepatis and carry out a hepatico-jejunostomy utilizing the Roux principle. The worst cases of all to treat are those in which the proximal remnant of duct has become strangled by scar tissue and lies buried in the liver substance. The dilated duct is located by needling, then exposed by paring away the intervening liver tissue and an opening made into it. The method chosen for restoring bile duct continuity should take into account the likelihood of a stricture reforming in the area that has been cored out. Cole et al. (1949) favour a hepatico- /

hepatico-jejunostomy on the lines previously described, but with the following ingenious modification. The free edge of the Y-arm of jejunum is divested of its serosa and muscularis so as to leave a cuff of mucosa 2 cms. long, which is supposed to line the passage that leads from the surface of the liver to the exposed duct (see fig. 41). If the two main branches of the common hepatic duct have been spared Lahey et al. (1950) recommend that they be sutured together and then converted into one lumen by snipping across the spur thus fashioned: an end-to-end anastomosis with the distal segment can then be carried out (see fig. 37).



(a) (b)

Fig. 41. A method of treating a stricture at the porta hepatis (after Cole, Reynolds and Iraneus). (a) Showing the syringe method of locating the major intra-hepatic branches of the bile duct. (b) The cicatrix has been removed, the ends of the major hepatic ducts exposed, and bile continuity achieved via an isolated arm of jejunum. To facilitate the anastomosis a segment of a rubber catheter has been inserted.

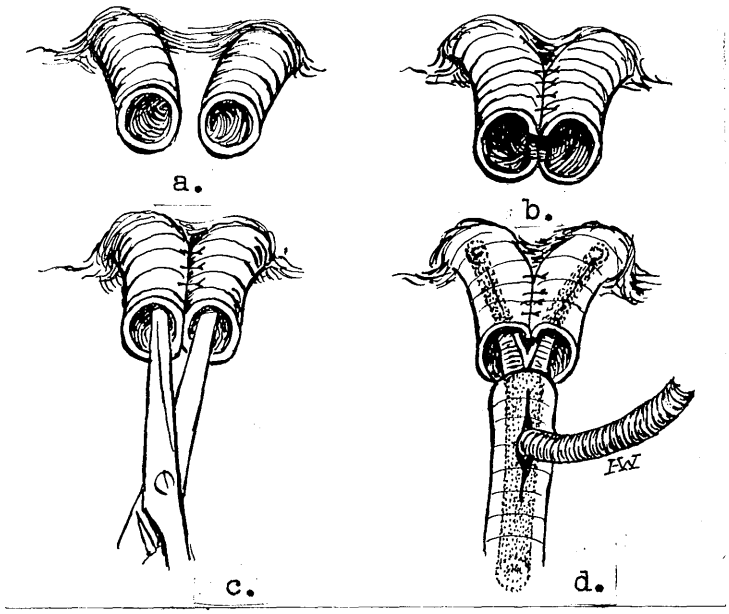


Fig.42. A method of repairing a stricture involving the branches of the common hepatic duct (after Lahey and Pyrtek). (a) The two branches of the duct defined. (b) Showing the two branches stitched together and the intervening spur being cut with scissors. (c) Showing the two lumina converted into one. (d) Showing the distal portion of the hepatic duct and its fused branches approximated over the Y-tube.

This outline would not be complete without reference to the earlier methods devised by Walton (1915) and Hoag (1937). It is generally admitted, however, that the former's method of raising a flap of duodenal wall to /

to replace a damaged stretch of duct, has not fulfilled its earlier promise. The main criticism is that it rids the patient of one disability only to expose him to the threat of another, namely, ascending cholangitis. Hoag described a somewhat similar procedure whereby the gastric mucosa is drawn out through an incision in the sero-muscular coat. This is converted into a small tube which is apposed to the end of the duct over a piece of rubber tubing. Attempts to make good the loss of part of the duct by the use of other autoplastic materials such as omentum wrapped round a catheter (Sullivan, 1909), fascial, venous, or peritoneal grafts (Lord and Chenoweth, 1943), or an isolated segment of jejunum (Kirby and Fitts, 1950), have so far been largely confined to the field of experimental surgery.

Tubes.

The procedures that particularly call for prosthetic materials are the straightforward local excisions with end-to-end closures and high hepatico-jejunostomies, where there is little of the duct to spare. Temporary splintage is generally preferred to a buried tube. To serve the former purpose, rubber tubing is ideal; for the latter there are now available tubes made of vitallium, tantalum, bouncing clay or silicon (Lahey, 1945) and polythene plastic (Grindlay, 1947).

Rubber prostheses may take the form of a simple catheter or a T-tube. In cases where it is necessary to utilize the branches of the hepatic duct in the anastomosis, it is convenient to use a Y-shaped cross-piece or, if that is not obtainable, the upper component of a rectangular cross-piece might be slit so that segments, at least, can be accommodated in the separate branches of the hepatic duct (see fig. 42).

Ordinary catheters are used by McArthur (1923) in the performance of choledocho-duodenostomy and by Allen (1945) in hepatico-jejunostomy. Their techniques are similar as regards the bell-shaped end which is utilized for the anastomosis. McArthur leaves the other end dangling in the duodenum, whereas Allen prefers to bring it out through a stab wound in the jejunal wall to the exterior. Each anchors the tube externally by means of a silk stitch so that the time of its release can be controlled, the one being allowed to pass in the stool, and the other simply pulled out. Cole, Reynolds, and Iraneus use merely the bell-shaped end in the hepatico-jejunostomy which they devised for cases with strictures at the porta hepatis (see fig. 41). Whichever form is used, a high grade of rubber is essential, among the best /

best obtainable in this country being the brand named after Kehr, another pioneer in this field of surgery (1913). Rubber may in time come to be replaced by pure latex rubber, which has the virtue of being mouldable into a single unit thus, eliminating any weakness or defect at the point of union of the two limbs (Maingot, 1953).

Vitallium is a hard alloy which cannot be bent, moulded, or machined, but must be cast; being weldable, it can be fitted with a flange or tab. In comparison the other materials appear less suitable (Pearse, 1941). Thus, tantalum is malleable but cannot be welded and plastics are liable to cause tissue irritation.

The main disadvantage of a buried tube, irrespective of composition, is a tendency to become dislodged or blocked, or to damage the mucosal surfaces with which it lies in contact. Its removal, if that becomes necessary, is, of course, a major undertaking. Flanged tubes are preferable, but even they are liable to be displaced, particularly if used in an anastomosis of the duct to the duodenum where they are exposed to the tug of the food-stream (Cole et al.).

EXTERNAL BILIARY FISTULA.

A persistent discharge of bile from a surgical wound generally indicates that the operation has either (1) failed to eliminate gall-stones or other causes of obstruction or (2) damaged the main biliary passages. In just over 50 per cent. of the cases cholecystostomy has been performed (Balfour and Ross, 1921; Hicken, White, and Coray, 1942), which suggests that the exploration of the biliary tract was not as thorough as it might have been. In a few the fistula is deliberately made for decompressive purposes. This was attempted as a last resort in Case 3 in the hope that an external fistula would form and be transplanted later on. The rapid closure of the wound dashed this hope. One of the cases encountered in the Western Infirmary series was secondary to an empyema of the gall-bladder which discharged its contents to the exterior.

It is difficult to imagine how some patients tolerate this distressing condition for so long. A case that came under my care was of 21 years' standing. Those that refuse surgical relief or are bad risks might conceivably be benefited by some adaptation of the bag devised for collecting the effluent of an ileostomy, rubber /

rubber solution being used to achieve a water-tight seal, although I have not heard of such a device being employed. There is the other side of the question, namely, the surgeon's personal feelings when faced with this predicament. He would do well to recall Wilkie's inspiring maxim (Aird, 1948) that the ultimate criterion of high aptitude for a surgical career, is not dexterity of hand or brilliance of intellect but the ability to see weekly for six months a patient with a biliary fistula and never mention the word 'bile'.

The surgical treatment will depend on the cause of the fistula. A cholecystectomy may be all that is required, as proved to be the case in one of Mr. Orr's cases. More often the source of the trouble lies in the common bile-duct, i.e. gall-stone or a stricture. Whichever is present, it is recommended that the common duct be approached through a fresh incision (Hicken et al. 1942). Apart from the difficulties of the exposure, the removal of stones is, as a rule, a relatively simple matter. If a stricture exists, a repair is carried out along the lines described above. The external opening of the fistula, which is generally lined for some centimetres with skin, can then be cored out and the wound drained.

The general opinion in the United States is /

is that attempts at transplanting the fistulous tract are not worthwhile. Isolated instances of complete cure following this procedure have been reported by Lilienthal (1923), Lahey (1924), St. John (1926), Williams and Smithwick (1929). The results of fistulo-duodenostomy, or -gastrostomy, are on the whole disappointing. For example, of the 6 instances mentioned in Flickinger and Masson's series 3 died soon after and 1 continued to have symptoms. Of the 14 cases so-treated by Lahey et al. (1950) only 2 had permanent relief. Walters (1939) operated on 7 cases and could claim only 2 successes. The reasons for failure are stenosis of the tract, either at one part or throughout its length, and cholangitis due to regurgitation of the gastric or duodenal contents. If transplantation of the tract be decided on, the dissection should keep wide of the lumen in order to preserve the vicarious blood supply as far as possible and, as Lahey (1930) has pointed out, there is no need to tunnel deeper than the margin of the liver. It is also Lahey's practice to lop off the area of skin encircling the external opening and insert a piece of rubber tubing before connecting /

/connecting the fistula to stomach or bowel. To remove the cutaneous fringe means leaving a raw area which is apt to undergo stenosis. In the other case treated by Mr. Orr, the tract was implanted with the skin attached and without a tube, in the manner described by Lilienthal and St. John; the result was satisfactory. Regurgitation may be reduced to a minimum by uniting the fistulous tract to a loop of jejunum and then by-passing this point by means of a jejuno-jejunostomy (Aylett, 1949).

GENERAL RESULTS OF REPARATIVE SURGERY

It is probably true to say that these reconstructive undertakings, major though they are, are on the whole well tolerated, the operative mortality rate being about 12 per cent. (Walters, 1939; Flickinger and Masson). But any feelings of complacency that are apt to be engendered on that account are rudely dispelled when one comes to evaluate their therapeutic outcome. Approximately 40 per cent. of the patients subjected to surgery have undergone at least one previous attempt at repair, which means that results which may be classified as satisfactory are to /

to be expected in 50 to 60 per cent. (Gray, 1951). It is widely accepted that local excision of the stricture with an end-to-end approximation gives the best results. Besides restoring the normal anatomical arrangement, this operation has the virtue of preserving the sphincter of Oddi. Walter (1939, 1950) is inclined to favour choledocho- or hepatico-duodenostomy. In his more recent paper 75 per cent. so treated were permanently relieved, in contradistinction to the 50-55 per cent. who were cured by an end-to-end closure. The results of Lahey and Pyrtek's series collected over the period 1940-1948 deserve detailed mention. The outcome was satisfactory in (1) 60 per cent. of the group in which an end-to-end anastomosis was carried out (76 cases), (2) 75 per cent. of Heineke-Mikulicz repair (17 cases), (3) 75 per cent. following dilatation and tube implantation (41 cases), and (4) 63.4 per cent. following biliary-intestinal anastomosis (45 cases).

Speaking in more general terms, an evaluation of the results of reparative surgery should, according to Flickinger and Masson, take into account the possibility that many who have had chills, fever, jaundice, and perhaps an enlarged tender liver at one time, may /

may later become free of these symptoms. In other words these conditions may arise from an infective cholangitis rather than a mechanical obstruction. A simple way of deciding the issue is to note the colour of the stool or, if thought necessary, take samples of the duodenal content. Flickinger and Masson's figures speak for themselves. 36 per cent. of all patients were absolutely well two or more years after operation; 31 per cent. had symptoms of cholangitis or obstruction, and half of these required further surgical interference. As might be expected, the most gratifying results were obtained in cases where the segment of common duct was long and of sufficient diameter to ensure a well-placed anastomosis with the duodenum or jejunum. Of those that fulfilled those conditions, 62 per cent. were well after 2 to 12 years, and less than a third of them had had transient symptoms of cholangitis, which disappeared in the course of time.

The question of the need for an indwelling tube should be carefully considered. The consensus of opinion seems to be that a temporary support, i.e. one made of rubber, is likely to prove moreuseful than a buried tube made of metal or a plastic material. Even /

Even the former may not justify its use; thus, Flickinger and Masson found that when a T-tube was employed for a choledocho-duodenostomy the results were somewhat inferior to those without a tube. Pearse (1946) speaks highly of vitallium tubes. In a report of 266 cases, collected from a group of surgeons who used a vitallium prosthesis for reconstruction of the common bile-duct, the outcome was satisfactory in 80 per cent. Plugging of the tube occurred through bile salt deposition in 11 per cent. Of those on whom a choledocho-duodenostomy was performed over a vitallium tube, the results were satisfactory in 38 per cent. The judgement of the representatives of the major clinics in the United States is much more reserved as regards the usefulness of vitallium tubes, and in this country, Professor Wells of Liverpool is decidedly opposed to them.

My own experiences in this field are summarized in Table 3.

TABLE 3. Summary of Essential Data Relating to Personally Observed Cases.

Case	Original Operation	Complication	Duration	Form of Reconstructive Surgery	Result.
1	Cholecystectomy	Severance of an Accessory R Hepatic Duct	7 days	End-to-end anastomosis with the stump of cystic duct	Good
2	Cholecystectomy	Localized Stricture	10 months	Heineke-Mikulicz plastic procedure	Recurrence of jaundice 14 months later
3	Cholecystectomy	Diffuse Stricture	20 months	Attempt to produce an external fistula by inserting a tube into R branch of hepatic duct	Failure
4	Cholecystectomy	Ligation of common bile duct	14 days	Hepatic-jejunostomy utilizing a loop of bowel with an entero-anastomosis	Good
5	Cholecystectomy (Mr. Gerstenberg's case)	Stricture of common bile duct near insertion of cystic duct		Heineke-Mikulicz	Recurring attacks of mild jaundice but generally satisfactory
6	Cholecystectomy (Mr. Orr's case)	External biliary fistula	Many years	Transplantation of fistula into the stomach	Good
7	Cholecystostomy (Mr. Orr's case)	External biliary	21 years	Cholecystectomy	Good

S U M M A R Y

The evidence is almost overwhelming that the majority of cases of benign stricture of the bile ducts are the result of surgical interference involving cholecystectomy, although other factors are occasionally responsible. The precautions which will minimize this late surgical complication are discussed.

The essential points in regard to diagnosis are recorded.

Certain forms of repair give better results than others, but one must be prepared for disappointment in about half of the cases treated surgically. Local excision with an end-to-end anastomosis of the two segments of the duct and, alternatively, the short-circuiting procedures which utilize either the duodenum or jejunum, are regarded as more reliable than those that depend on autogenous duct substitutes. In cases complicated by an external biliary fistula, a bolder approach is indicated and each must probably be tackled in the light of the special circumstances.

The writer's four cases are reported in detail and three other personally observed cases are referred to in the text.

MALIGNANT TUMOURS OF THE EXTRAHEPATIC BILE DUCTS

Primary growths of the extrahepatic bile ducts apart from the ampullary group are seldom seen by surgeons and the number published annually is small. Critical scrutiny of large consecutive autopsy series has, however, shown the incidence to vary from quite a low figure to one of disquieting frequency. For example, McLaughlin (1933) estimated its incidence at 0.073 per cent., Neibling, Docherty and Waugh (1949) at 0.26 per cent: and Dick (1939), Masuda (1935), Kirchbaum and Kozoll (1941) found it to be 0.42, 0.45, 0.46 respectively. Neibling et al. approached the problem from the clinical standpoint and found that at the Mayo Clinic in a 10 year period of operative experience comprising 14,000 biliary tract conditions the incidence was 0.5 per cent. Some surgeons can claim considerable personal experience of the tumours; thus Brauschwig and Bigelow (1945) operated upon 7, Siler and Zinninger (1948) on 10, Miller (1951) of Edinburgh on 3, while Saypol (1951) in one year encountered 4 among 90 patients requiring biliary surgery.

The operability of tumours arising in the extrahepatic bile ducts can be measured in terms of site, degree of spread, and extent to which the liver has been damaged by the obstruction. The case which forms the basis of this chapter was favourable for radical surgery on all counts. The tumour was excised and a biliary-intestinal anastomosis performed. The patient has remained well since the operation was done in November, 1951. I propose first to describe this case and to follow with a critical account of the more important pathological, clinical and therapeutic aspects of these tumours.

CASE REPORT

W.S. male, age 64, Civil Servant, was admitted to Mr. E.G. Gerstenberg's wards in the Western Infirmary, Glasgow, on November 13th, 1951, complaining of abdominal pain of threeweeks' duration, which appeared to be confined to the right iliac fossa. The pain lasted almost continually for spells of a few days, with intervening periods of comparative freedom. He was also aware of a considerable persistent swelling on the right side of the abdomen for the same period. Jaundice had appeared 10 days prior to admission, but seemed to have lessened slightly in the last few days. Appetite was fair throughout. The bowels moved regularly, but the stools had become paler than usual.

He had lost weight in recent weeks, and was easily fatigued.

Past History:-

He had had jaundice as a child. In 1930, he was operated on for haemorrhoids. His left leg was amputated following an accident in 1940.

Family History and personal habits presented no significant features.

General Examination:-

The patient showed a degree of emaciation. He was jaundiced. There was no cyanosis or oedema. His left leg had been amputated at the thigh.

The tongue was moist but furred. The abdominal wall was very lax and there was a fullness in the right side which was occupied by a firm, slightly mobile, sausage-shaped mass. This was slightly tender to pressure. The liver was palpable about four fingerbreadths below the costal margin. Per rectum nothing abnormal was felt.

Cardiovascular System:-

No abnormality was detected on routine clinical examination. Temperature 96.8°F. Pulse 88/min. Resp. 20/min. Blood Pressure 110/75. 1st heart sound /

sound at the mitral area was split.

Respiratory System: -

Chest was increased in its antero-posterior diameter. There was a degree of scoliosis. Respiratory murmur vesicular, no adventitial sounds.

Urine:-

Bile was present. Microscopically no organisms were seen.

Operation 20.11.51 (H. Wapshaw).

Pre-operatively the patient received several injections of Vitamin K preparation.

Anaesthetic, - C_3H_6-O_2, N_2O/O_2 (Oro. Tube): Flaxedil 80 mgm: Pethedine 50 mgms. and 25 mgms intravenously.

Right paramedian incision; bleeding slight. The liver was enlarged about 6 cm. below the sub-costal margin and the gall-bladder grossly dilated, being about 17 cm. in length; the fundus was very thin and appeared on the point of rupture. The cystic duct and common hepatic duct were also distended due to a small scirrhous tumour approximately 1 cm. in extent situated precisely at the point of junction of cystic and common hepatic ducts. The distal part of the common bile-duct was much contracted.

To facilitate access the bile was removed from the gall-bladder by trocar and cannula: it was colourless and mucoid in consistency. The next step was exposure of the tripartite junction of the cystic, common hepatic, and the common bile ducts; this was effected with relative ease and without apparent damage to portal vein or hepatic artery. There was a soft slightly enlarged lymph gland to the left of the tumour, which was not removed.

Next, the gall-bladder was excised by cutting the dilated cystic duct about 2.5 cm. away from the tumour, and the gall-bladder bed reperitonised to control oozing. Then the common bile-duct was transfixed, ligated and cut across about 1 cm. below the tumour. Finally, the tumour was excised by cutting through the common hepatic duct 1 cm. above the upper margin of the tumour.

The jejunum was then examined and adhesions removed from its mesentery to display the vascular pattern. The bowel was cut across 25 cm. from the duodeno-jejunal flexure; the distal end was turned in and closed and then brought up through a gap in the /

the meso-colon; and hepatico-jejunostomy performed, the common hepatic duct being anastomosed to a separate opening in the jejunum. Restoration of bowel continuity was achieved by an end-to-side anastomosis between the proximal portion of jejunum and the distal portion below the meso-colon at a point about 12 cm. below the bile duct anastomosis. To prevent traction the jejunum was fixed to the under surface of liver and omentum tacked round the upper anastomosis by means of catgut sutures.

The upper part of the wound was drained by a tube and the wound closed in layers.

Histological Report.

(1) Tripartite junction. The specimen consisted of the junction of the cystic duct with the hepatic duct. A firm white tumour completely occluded the cystic duct at the junction. The tumour extended to within 2 mm. of the excised margin of the common hepatic duct and within 0.75 cm. of the excised margin of the common bile duct. (fig. 43).

Microscopy showed a well differentiated adeno-carcinoma of bile duct origin infiltrating locally /

locally and evoking a considerable scirrhous response. The excised margins were clear of tumour tissue but near the margins perineural lymphatic invasion has occurred. (figs. 44, 45).

(2) Gall-bladder measured 15 cm. x 13 cm. The wall was extensively infiltrated with blood. No lesion of the mucosa was seen.

Microscopy showed the gall-bladder wall heavily infiltrated with blood due to trauma. There was no gross infiltration by carcinoma.

The post-operative course was surprisingly satisfactory so far as the biliary condition went, and the wound healed satisfactorily. Unfortunately, however, retention of urine developed, for which an indwelling catheter was required. Melancholic tendencies and feelings of unworthiness became manifest especially at night.

The jaundice had largely cleared by the 14th day and stools and urine were normally coloured by the same time. Despite this improvement it was thought that he was losing ground, and it was decided to carry out liver and renal function tests. The results, however, seemed to rule out any breakdown of function of either organ.

Blood urea	26 mgms. per 100 c.c.
Thymol Turbidity	2 units
Thymol flocculation	negative
Alkaline phosphatase	20 King units
Icteric Index	25

As he was still unable to pass urine naturally it was decided to perform a supra-pubic cystostomy; this was done on the 6th December, 1951, under local anaesthesia.

The patient was allowed up 30 days after the original operation.

Mr. W.W. Galbraith was called in consultation and advised a transurethral resection of the prostate, which was successfully performed on 10th January, 1952.

Last Progress Note (September 1953):

Patient looked extremely fit with excellent complexion and good appetite. He had gained three stones in weight. Abdominal wound sound.

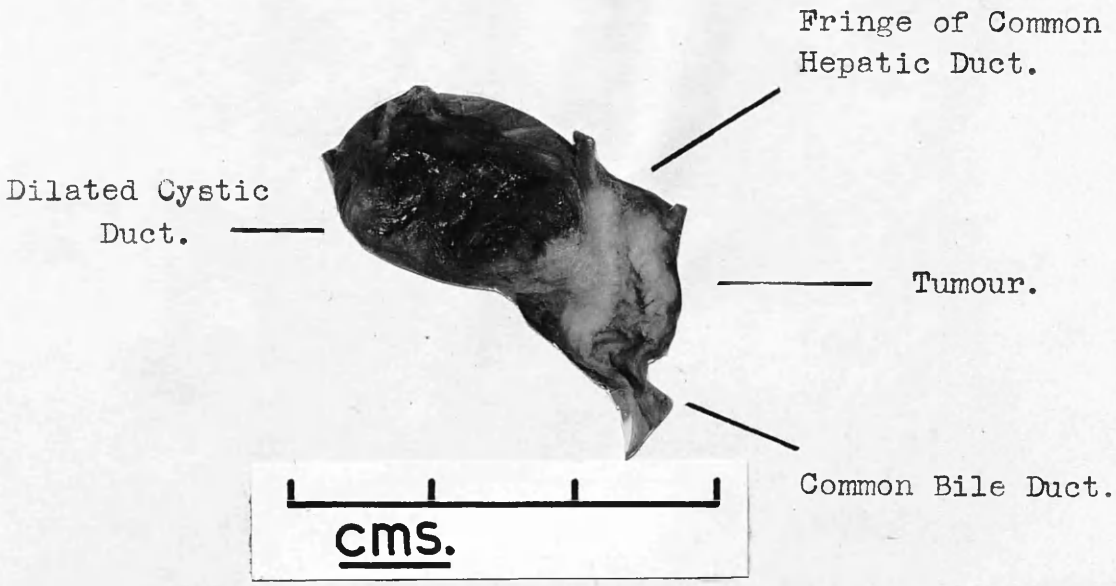


Fig.43. Gross specimen consisting of the excised tumour which appears lighter in colour in contrast with the adjacent parts of common cystic, common hepatic and common bile ducts. Alongside is a 2 cm. scale.

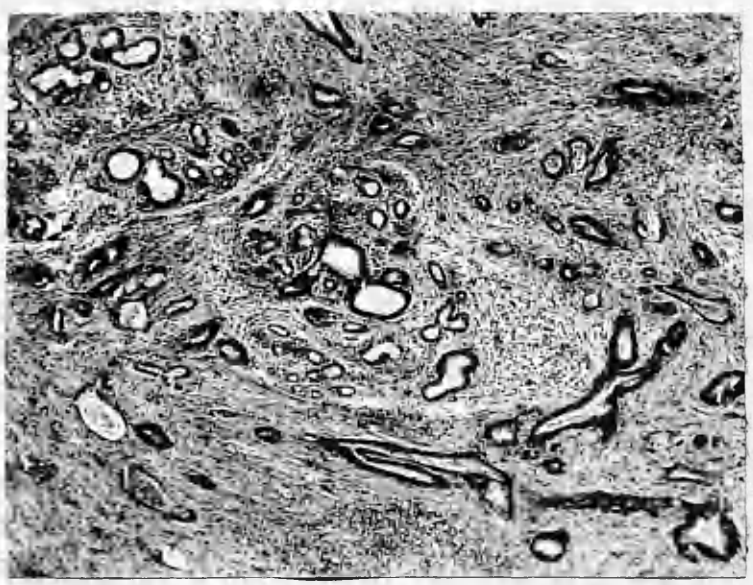


Fig.44. showing tumour with well defined acini embedded in dense fibrous tissue (x 100).

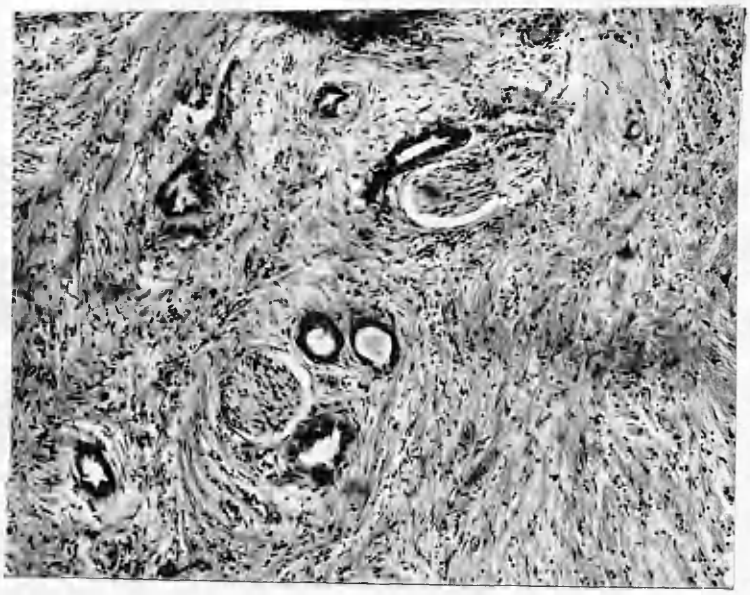


Fig.45. from another portion of the tumour showing 2 nerves in transverse section with perineural involvement (x 200).

COMMENT

The majority of these growths appear as localized nodules obstructing the lumen of the bile duct and associated with proximal dilatation (Neibling et al., 1949). Occasionally they infiltrate almost the entire length of the bile duct before its patency is reduced to the extent of producing clinical jaundice. The similarity of some such tumours to benign strictures has been noted by Bell (1944), and the commonest site is undoubtedly the common bile-duct (Renshaw, 1922: McLaughlin, 1933: /

McLaughlin, 1933: Kirschbaum and Kozoll, 1941). Some authorities stress the most frequent point of origin as being precisely at the junction of the cystic duct with the common hepatic and common bile ducts (Rolleston and McNee, 1929; Marshall, 1932; Stewart, Lieber and Morgan, 1940; Neibling et al., 1949). The next most common site, is the distal end of the common bile-duct, and the least common is the common hepatic duct and its branches. Only 5 proven cases of primary carcinoma of the cystic duct have been reported according to Farrar (1951).

The common histological picture is an adenocarcinoma with well defined acini lined by cylindrical cells. For this reason, coupled with the frequent presence of dense fibrous stroma, Ewing (1946) regards most of these tumours as of low malignancy. This is the scirrhous form. The case reported by the writer was of this type. Papillomatous forms occur in 5 per cent. (Neibling et al.,1949) to 10 per cent. (Marshall, 1932). Instances of encephaloid, mucus-producing or squamous epithelioma types, and even melanoblastoma have been recorded, but are decidedly rare (Kirschbaum and Kozoll, 1941). Moll (1925) has described a case of sarcoma /

sarcoma composed of round and oat-shaped cells. One wonders if, in view of the modern concept of the nature of oat-cell tumours, this author has perhaps interpreted his findings erroneously. The unique association of a localized lymph node sarcoidosis alongside a carcinoma of the bile duct is described by Gherardi (1950).

Carcinoma of the bile ducts is from all accounts decidedly commoner in men than in women, in contrast to the greater frequency of primary carcinoma of the gall-bladder in women. Most of the patients are over 50 years of age.

Gall-stones are present in about one third of the cases recorded, their incidence in primary carcinoma of the gall-bladder being nearer 70 per cent. (Rolleston and McNee). They were present in slightly more than half of Neibling et al.'s cases, which is much higher than their incidence in the population as a whole or in any comparable group, and these authors justifiably raise the question of the aetiological significance of gall-stones occupying the bile ducts in the pathogenesis of extrahepatic duct tumours. Most observers are inclined to regard the stones as blameless.

The clinical manifestations may be described as inconstant. Jaundice, marked loss in weight, not infrequently vague gastro-intestinal upsets and upper abdominal pain of varying degree, make up the symptom complex in order of frequency. To illustrate the difficulty of arriving at a correct and timely diagnosis, Brauschwig and Bigelow (1945) reported 7 cases of advanced malignant tumours of the bile ducts, in 4 of which jaundice was present for only 2 to 7 weeks. Nevertheless, it is present at some time or other in approximately 90 per cent. of cases. Abdominal pain may occur in as many as 61 per cent. according to Neibling et al., who have made a special study of its relation to nerve involvement by tumour cells. The dyspepsia is not characteristic and is apt to be a late manifestation. There was ascites in 50 per cent. and occult blood in the faeces in 55 per cent. of the series reported by Kirschbaum et al.

The question of how far pain in malignant conditions is attributable to invasion of the nerves by tumour, is receiving increasing attention of late. In 1935 Masuda reported involvement of nerves in 12 of his 15 cases of carcinoma of the bile ducts and Moore (1944) suggested that this may account for the pain. Neibling et al. (1949) made a special study of this problem. Sections /

Sections of 90 cases were examined and nerve filaments were identified in 46. In 29 (63 per cent.) of these, the nerves were invaded by tumour cells; the part most frequently affected was the perineural sheath. It was not clear, however, whether the involvement of the sheath constituted involvement of a true space, or whether the tumour cells were within lymphatics or small blood vessels. Less commonly, the malignant cells directly replaced or invaded nerve bundles. Two results of neural invasion were considered by Neibling et al., (1) abdominal pain and (2) its relation to jaundice. With regard to pain, this was present in 20 out of 29 cases in which nerve involvement was seen. On the other hand, in 17 cases where nerves were noted but no tumour cells, only 9 had pain. With regard to jaundice, they postulate that the blockage of bile ducts may either be mechanical or the result of loss or lack of contractility of the lower part of the common bile-duct resulting from an invasive process which interfered with essential nerve impulses. Neibling et al. carefully worked out a statistical case for their theory, that the jaundice may on occasions be of the latter type. It is difficult to comprehend the mechanism involved unless there /

results in some jaundiced cases, particularly where the tumour is not sufficiently occlusive, a persistent spasm of the sphincter of Oddi and/or the contiguous duodenal musculature. Perineural invasion was a feature in the case presented (fig. 45) but examination of the gross specimen left one in no doubt that the obstruction had been a mechanical one. My criticism of the theory just outlined is that the histological findings have been interpreted in terms of deranged physiology and more evidence is required before it is granted full acceptance.

In an extensive review of the literature, Stewart et al. (1940) found that surgical treatment had been instituted in 50 cases with an immediate post-operative mortality of 68 per cent. and an ultimate mortality of 98 per cent. All 7 cases operated on by Brauschwig et al. (1945) had advanced tumours but one survived for 1 year. Quite apart from the ethical issues involved in undertaking such hazardous attempts at palliation, the question arises whether the expectation of life is likely to be much greater than if nothing were done. Miller (1951) and Saypol (1951) take the view that palliative resections are worth while. Of the 10 cases subjected to operation by /

by Siler and Zinniger (1948) only one was resectable and one suitable for a palliative procedure; in the rest only exploratory laparotomy was possible. The operable case lived for 17 months, the others from 4 - 92 days. Tumours affecting the juxta-hepatic region are generally hopeless propositions, although Barnes and Zarr (1947) have successfully excised one along with the gall-bladder and, incidentally, utilized the cystic duct to restore biliary continuity in a manner similar to that adopted by the writer in the case of damaged accessory hepatic duct. Tumours affecting the lower reaches of the common bile-duct may be tackled via the duodenum or preferably by a formal pancreatico-duodenectomy. The latter procedure is discussed in full by Pickrell & Blalock(1944).

With regard to prognosis, most authorities believe that metastases are uncommon and, when present, a late feature of carcinoma of the bile ducts (Renshaw, 1922; Rolleston and McNee, 1929; Marshall, 1932; Dick, 1939; Pickrell and Blalock, 1944). On the other hand, Kirschbaum et al., basing their observations entirely on autopsy material, found evidence of metastases in 76.7 per cent., varying from involvement of regional lymph nodes to generalized carcino-matosis. The liver /

liver was the most common site and there were several examples of blood spread. It would appear that the cholaemia which follows obstruction to the bile duct is largely responsible for the fatal outcome. The case reported here, like a few others for which success has been claimed, must be regarded as exceptional, because in general there appears to be little room for optimism in the management of tumours of the extra-hepatic bile ducts. According to the latest survey of 90 cases by Neibling et al. 63 per cent. of patients had metastases at the time of operation and yet the patients on the average had become aware of their illness owing to onset of jaundice only 8 weeks before operation. There were 14 per cent. in whom the growth had not advanced far enough to cause jaundice and yet in three quarters of these patients metastatic deposits or extensions were noted at operation. In my case the duration of the jaundice was only 10 days and pain 3 weeks. If seen earlier, some form of malignancy might have been suspected considering the loss of appetite and weight, but unfortunately there is no certain means of arriving at a diagnosis in these cases until more compelling symptoms force the patients to seek advice.

SUMMARY

Growths of the extrahepatic bile ducts are considered distinct from those affecting the liver, gall-bladder or ampullary area.

The majority are localized adenocarcinomata and the commonest site appears to be the point of junction of the cystic and common ducts.

The clinical features are inconsistent, the more prominent being jaundice and abdominal pain.

The probable significance of perineural invasion is discussed.

The results of surgery are on the whole disappointing.

An illustrative case is presented. Radical excision was carried out 2.1/2 years ago and the patient remains well.

THE PANCREATIC SIDE-EFFECTS OF MORPHINE

Prior to the publication of Lagerlöf's studies (1945, 1947) information regarding the influence of morphine on the pancreas was very fragmentary. In 1907 Bickel and Pincussohn observed in two dogs with pancreatic fistulae that it first decreased and later increased the output of the external secretion. Cohnheim and Modrakowski (1911), using dogs each with a duodenal and an ileal fistula, found that morphine depressed the natural response to food. Babkin (1928) also noted a diminution in the duodenal content after its administration to animals. A more remote effect which has been reported in rabbits, is an increase in the diastatic index of the urine (Sato, 1940). Reference to the radiological studies (page 49) shows that morphine has been known for a decade and a half to impede not only the flow of bile but also the external secretion of the pancreas.

The first recorded studies of its effects on the secretory activity of the pancreas in humans are by Lagerlöf. Primarily interested in the fat-splitting enzymes in the blood, particularly those elaborated by the pancreas, he conceived that morphine might serve as a safe means of deranging the function of the gland. He/

He compared the effect produced by the intravenous administration of purified Secretin on the content of digestive ferments in the blood with the effect of Secretin given along with morphine. For the recovery of the duodenal juice he made use of the gastro-duodenal tube, thus minimizing the amount of gastric juice entering the duodenum. Secretin given alone produced an abundant flow of pancreatic juice of high bicarbonate content unassociated with any appreciable change in the lipase levels in the blood. When it was given along with morphine there resulted a reduction in the volume of the duodenal fluid and a concomitant lowering of the secretory rates of amylase, trypsin and, to a lesser extent, the bicarbonate of the pancreatic secretion: the amount of bilirubin in the duodenal contents was also diminished. These changes were maximal approximately 30 minutes after morphine. Soon afterwards there appeared in the blood a lipase that had not previously been present. Lagerlöf interpreted these findings as being due to over-action of the sphincter of Oddi interfering with the delivery to the duodenum of the bile and pancreatic secretion and leading to absorption of a portion of the latter into the blood-stream. He could not, however, exclude altogether the possibility that morphine depresses/

depresses the function of the pancreas. The procedure just outlined has come to be known as the Morphine-Secretin test, the focus of attention having shifted to the response on the part of the serum-enzymes (vide infra). Lagerlöf also made the arresting suggestion that the nausea and abdominal discomfort, sometimes amounting to pain, which not infrequently follow the administration of morphine, may be symptomatic of a drug-induced pancreatitis.

This paper is principally concerned with the serum-enzyme effects of morphine on healthy humans. Some were investigated in the fasting state, others were given a substantial meal prior to morphine and in a third group an attempt was made to exalt the so-called vagus response of the pancreas to food by giving a parasympathetic stimulant before the morphine. Carbaminoylcholine chloride (B.P. Carbachol) was chosen since it has been shown in the previous section to exert a vagus-like action on the pancreatic secretion (Wapshaw, 1952).

A. BIOCHEMICAL STUDIES

1. Methods.

In the majority of the experiments both the amylase and lipase estimations were carried out with the same sample of venous blood. For the former the Somogyi (1934; 1938) iodometric test was employed for which the normal range /

range of values is 70 - 200 units per millilitre of serum, although for each individual the value varies very little. The lipase activity was determined by the Cherry and Crandall test. (1932). By this method it is ususual for normal values to exceed 1.5 ml. N/20 sodium hydroxide per ml. of serum. The author's own normal findings (Wapshaw 1948) are cited in page 200 for the purpose of comparison with the findings on dogs.

A rise in the serum amylase of 50 per cent. over the pre-medication reading was regarded as significant. It was more difficult to decide what constituted a positive lipase response; but in view of results in the literature and after considerable experience an increase of at least a 100 per cent. over the pre-medication control reading was taken as a positive result.

2. The Effects of Carbachol.

This was a control study. 28 normal volunteers were investigated. These were divided into two equal groups. The first group fasted during the experimental period. The second received a meal consisting of soup, a meat dish with potatoes and vegetable, and a milk pudding, 45 minutes before the injection of Carbachol. Each subject received 0.5 mg. Carbachol intramuscularly, which is twice the upper therapeutic dose. Only lipase estimations were carried out in this series.

(a) The Fasting Group. 3 out of 14 subjects showed a /

TABLE 4 THE EFFECT OF CARBACHOL ON THE SERUM LIPASE.

(a) Doses of 0.25 mg intramuscularly on 14 Fasting Subjects.

Case.	Before Carbachol.	Lipase: in ml/N/20 NaOH/ml. Time of Observation in Hours after Carbachol.			
		2	3	4	5
1.	0.10				0.03
2.	0.60		0.70		
3.	0.70			0.80	
4.	0.10		0.30		
5.	0.50				1.10
6.	0.30			0.60	
7.	0.70			1.70	
8.	0.70			1.20	
9.	0.70			0.80	
10.	0.70	1.40			
11.	1.00		1.00		
12.	0.90		0.90		
13.	0.70		0.10		
14.	0.10		0.20		

(b) Doses of 0.50 mg intramuscularly on 14 Fed Subjects.

1.	0.60			1.20	
2.	0.10				Zero
3.	Zero			Zero	
4.	0.20				0.40
5.	0.10	0.10			
6.	0.6	0.80			
7.	0.60	0.80			
8.	Zero		Zero		
9.	0.40		0.70		
10.	0.50			0.10	
11.	0.20			0.10	
12.	0.30			0.10	
13.	0.40			0.20	
14.	0.70		0.90		

a slight but apparently significant increase in the lipase concentration 2 to 5 hours after Carbachol. The most pronounced increase was a rise from 0.7 ml. to 1.7 ml. N/20 NaOH per ml. serum. (table 4a, Nos.5,7,10)

(b) The Fed Group. Only one of the 14 subjects had altered readings. The control reading in this case was 0.6 ml. and 4 hours after Carbachol the reading was 1.2 ml. (table 4b, No.1)

3. The Effects of Morphine Hydrochloride.

84 individuals were investigated. They were divided into three groups each comprising 28 subjects; all received a subcutaneous injection of 1/4 gr. morphine hydrochloride. Those in the first fasted throughout the experimental period. The second group had a meal (see above) 60 minutes before the administration of morphine. The third received a similar meal and 45 minutes later an intramuscular injection of 0.5 mg. Carbachol; after 15 minutes further, the morphine was injected. Thus, it was arranged that the morphine was given at a time when the pancreas was likely to be in a state of active secretion.

(a) The Fasting Group. An increase in the amylase and lipase levels was observed in 5 of the 28 subjects (18 per cent.). The highest rise for amylase was 3 times the pre-medication reading in that subject and the highest for/

for lipase 20 times (see table 5).

(b) The Fed Group. Raised levels were noted in 9 of the 28 investigated (32 per cent). The highest rise for amylase was 9.1 times the pre-medication reading and the highest for lipase 14.7 times (see table 6).

(c) Food plus Carbachol. Raised levels were observed in 19 subjects (68 per cent). The maximum responses were observed in the same case (No. 15, table 7) and amounted to 22 times and 17 times the pre-medication values for amylase and lipase respectively. In several the changes were marked within the first hour, but more usually maximum augmentation occurred 2 to 4 hours after the morphine injection. A comparison of the two sets of readings indicated that the lipase concentration was more readily affected than the amylase concentration.

B. BODILY REACTIONS

Carbachol. The somatic effects varied from case to case. Some subjects were apparently unaffected. Others complained of flushing of the face and neck, diaphoresis, salivation, a desire to void urine or go to stool, and one suffered from fairly severe precordial distress.

Morphine Hydrochloride. One fifth of all the subjects complained of nausea and about half of those affected vomited. The detailed incidence of sickness in the /

TABLE 5 *Effects of ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Fasting Subjects (only the 5 instances of positive responses are shown)*

No.	Amylase (units/ml.)						Lipase (ml. N/20 NaOH/ml.)					
	Fasting Reading	Hours after Morphine					Fasting Reading	Hours after Morphine				
		1	2	3	4	5		1	2	3	4	5
1	100			180								
2	180				460		0·5				1·8	
3	177			530			0·3			4·6		
4	220			260			1·8			3·2		
5	160			320			0·1			2·0		

TABLE 6 *—Effects of Food and ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Subjects (only the 9 instances of positive responses are shown)*

No.	Amylase (units/ml.)							Lipase (ml. N/20 NaOH/ml.)						
	Fasting Reading	Hours						Fasting Reading	Hours					
		1	2	3	4	5	6		1	2	3	4	5	6
1	177				200			0·2				2·6		
2								0·1					2·6	
3	84					188		0·4					1·2	
4	114				640			0·4				5·9		
5	100	400		914				0·8	6·4		7·6			
6	100			640				1·1			5·3			
7	123			530				1·3			3·1			
8	139			800				0·5			3·4			
9	160			800										

TABLE 7 *—Effects of Food, 0.5 mg. of Carbachol, and ¼ gr. (16 mg.) of Morphine Hydrochloride on Serum Enzymes in 28 Subjects (only the 19 instances of positive responses are shown)*

No.	Amylase (units/ml.)											Lipase (ml. N/20 NaOH/ml.)									
	Fasting Reading	Hours										Fasting Reading	Hours								
		1	2	3	4	5	6	7	8	9	10		1	2	3	4	5	6	7	8	9	10
1	100	94	213									1·2	1·3	4·6								
2	80	85			220							0·7	0·7			3·9						
3	40	44			53							0·7	1·4			2·4						
4	50					88						1·1					2·4					
5	66			177							106	Zero			2·5							0·9
6	46				145							,,				1·6						
7	55					114						,,				0·6						
8	66	118		172								0·6	4·0		2·7							
9	80	340		420								0·4	5·2		5·1							
10	100	710	1,600									0·8	8·0	9·6								
11	60	760	940									0·7	3·5	6·6								
12	168	530		650								1·1	7·0	6·5								
13	94	200		578								1·6	4·5		6·0							
14	123	640		1920								0·9	7·4		10·1							
15	70				1600				800			0·6				10·2				4·3		
16	55	96		320								1·2	7·5		10·7							
17	160	400			580							0·9	5·0			1·6						
18	73					920						0·9					8·5					
19	80				580							1·3				5·8						

the three groups was as follows - fasting, 21 per cent; fed, 18 per cent; fed and received Carbachol, 25 per cent. In some the feeling of sickness, often with giddiness, came on soon after the injection of morphine; in others it did not come on for one to two hours; it passed off after about two hours.

There was no correlation between the occurrence of sickness and the enzyme findings in the blood.

Pain developed in the epigastrium in 3 subjects. One belonged to the fasting group and the other two to the group which received food and Carbachol. One of the latter was in considerable distress when examined, not only with pain that radiated in the lumbo-dorsal region, but also vomiting and retching. None of the three, however, exhibited signs of intra-abdominal irritation, and all the unpleasant effects had passed off within a few hours.

The serum-enzymes were slightly raised in two of the three affected with pain. The one with the severe pain was No.4 in table 7 , and the other No.2 in table 5.

DISCUSSION

It is generally accepted that the amylase/

amylase concentration in the blood remains constant irrespective of the state of nutrition or the relative abundance of carbohydrate in the diet (Carlson and Luckhardt, 1908; Cohen, 1925; Somogyi, 1934). Opinions differ, however, as to whether or not the blood is normally endowed with the capacity to split the glycerine esters of the more complex fatty acids and there is no agreement as to what effects the ingestion of fat may have on this property. Crandall (1935) and Lagerlöf (1945) hold that the olive-oil splitting esterase or lipase is normally confined to the pancreatic secretion and that it finds its way in to the general circulation only when the gland becomes the seat of disease. Others believe that its presence in the blood is consistent with sound health (Comfort and Osterberg, 1940; Johnson and Bockus, 1940; Wapshaw, 1948).

There is evidence that certain parasympathetico-mimetic drugs modify the digestive activity of the blood. Thus, Methacholine chloride B.P. (acetyl-beta-methylcholine chloride, 'Mecholyl') was observed by Autopol, Schifrin and Tuchman (1934) and Friedman and Thompson (1936) to cause in dogs a rise in the amylase concentration, which attained maximal levels within a few hours. Friedman and Thompson tied off the pancreatic/

pancreatic ducts in dogs and found that the subsequent response on the part of the serum-amylase to Methacholine diminished pari passu with the degree of acinar atrophy which resulted from that procedure. In similar experiments Popper, Olsen and Necheles (1943) were likewise able to correlate their serum lipase findings with the amount of parenchymatous loss. Indeed, the latter authors went so far as to suggest that the serum-enzyme response to Methacholine, especially when administered together with Secretin, might serve as a means of detecting pancreatic insufficiency.

Myhre, Nesbitt, and Hurley (1949) performed the Mecholyl-Secretin test (as it is designated in the United States of America) on a group of 24 healthy subjects. Only 70 per cent. of them yielded positive responses in the blood, which is obviously too low a normal register for a test that is intended to discover faulty function. The impression gained from the present investigation was that Carbachol would also be unsuitable for this purpose.

As regards the effects of morphine, the serum-enzyme levels were raised in 33 of the 84 subjects examined i.e. 39 per cent. Taking each group separately, positive responses occurred in 18 per cent. of the fasting group, /

32 per cent. of those furnished with a meal and 68 per cent. of those who received Carbachol in addition to food. Peak levels were reached between the second and the fourth hours and by the tenth hour the readings approached normal. Some very remarkable findings were recorded; in fact, judging from previous experience (Wapshaw 1946), the increments in certain instances were of such a high level as to justify a biochemical diagnosis of acute pancreatitis; but the lack of supporting clinical evidence allayed any misgivings on that score. Lagerlöf expressed the view that although a certain parallelism exists between the lipase and amylase responses the former is the more marked. The present findings agree with this.

The increased incidence of positive findings in the third group of the morphinized series, that is to say, those on whom presumably the most testing conditions were imposed, corresponds with that reported by others. Thus, Myhre et al. (1949) found that morphine and Secretin modified the amylase levels in 70 per cent. of 30 normal subjects. It would appear that Burke, Plummer, and Bradford (1950) subjected the pancreas to a still greater stress by giving concurrently morphine, Methacholine, and Secretin, since according to their results 79 per cent.of/

of the 68 individuals so treated exhibited raised enzyme readings. In the present series, the disparity between the results of the three groups, all of whom had morphine, leads to the view that the mobilisation of the serum-enzymes is conditioned by (1) the potent action of the drug on the sphincter of Oddi and the surrounding duodenal musculature (see page 55) and (2) the functional state of the pancreas at the time when the morphine takes effect. The proportionately higher readings in the Carbachol group was also regarded as evidence that this drug enhances the natural secretory response to food. Whether or not Carbachol, itself a powerful excitant of visceral muscle, reinforces the action of morphine on unstriped muscle, thereby increasing the compression of the pars intestinalis of the pancreatic ducts, is an interesting question. There is experimental evidence that it does. The next paragraph refers to a few papers dealing with the interaction between morphine and choline, as it affects visceral muscle.

La Barre (1924) in rabbits found that the stimulating action of morphine on tone was reinforced by choline and by excitoperistaltic substances that could be obtained from perfusates of normal loops of intestines. The tonic effect due to choline was also reinforced by previous exposure of intestinal loops to morphine. Morphine /

Morphine did not increase the tone of the loops which had been decholinized by long continued washing with Ringer's Solution. Choline, in his opinion, forms some complexes or combinations with morphine which possess a tonic action superior to those of the constituents, that is to say, choline plus morphine is more effective than choline followed by morphine or morphine followed by choline. Keeser (1933) concluded from his experiments that under the influence of morphine there is increased decomposition of lecithin, with a consequent release of choline, which in its turn leads to increased synthesis of methylguanidine, so that the action of morphine is in part identical with those of choline or methylguanidine. Considerable amount of research has also been carried out on the action of morphine and its derivatives on contractions of leech muscle due to choline, acetyl-choline, etc. (Quastel and Tannenbaum, 1937; Kahane and Lévy, 1939; Dastague and Beeson, 1940). Finally, it is relevant to note that acetyl-choline can produce a spasm of the sphincter of Oddi in animals (Kitakoji, 1930; and Lueth, 1931). Reverting to my own work, the findings with Carbachol alone both in the intubation experiments, reported in 1952 by the author, and the present serological studies, suggest that it does not seriously hamper the flow of the pancreatic /

pancreatic secretion, which it stimulates, though judging from reported data, Metacholine may conceivably have such a dual effect.

The nausea and abdominal discomfort that so often affect those under the influence of morphine are generally ascribed to excitation of the vomiting centre in the medulla (Goodman and Gilman, 1941). This explanation ignores such visceral side-effects as pyloric spasm (Schroeder, 1933), a general increase in the motility of the intestinal tract (Plant and Miller,1926, 28; Carlson, 1933), and spasm of the mechanism controlling the bile flow, which has already received attention. (page 51). The overall incidence of nausea in the present series was 21 per cent. and did not bear any obvious relation to the functional state of the pancreas at the time when the morphine was given. Clinical support for Lagerlof's assumption that the nausea and abdominal discomfort which some of his subjects complained of, may be of pancreatic origin is lacking. None of the subjects in the investigations of Myhre et al. exhibited symptoms which were referable to the pancreas. Burke et al. cited one instance of epigastric pain following morphine, but it is noted that this particular subject had previously undergone cholecystectomy, and the pain could well have been due to a rise in the intra-biliary pressure. There were three instances of associated epigastric pain, one in the /

fasting group, and the other two in the carbachol group; in two the enzyme levels showed a rise, but only of slight degree. All three were completely free of pain and nausea within a few hours, and enjoyed their evening meal.

It would be premature to conclude that these findings have any direct bearing on the aetiology of acute pancreatitis. They do infer, however, that morphine may cause the pancreas a considerable degree of embarrassment, although these short-term experiments indicate that the disturbance was largely functional.

SUMMARY.

The influence of morphine on the pancreas was investigated in 84 normal subjects. The observations included a study of (1) the ensuing changes in the amylase and lipase levels in the blood, and (2) the somatic effects of the drug.

The serum-enzyme concentrations were significantly raised in 39% of the series. These changes appear to be due mainly to a state of secretion-retention within the pancreas, for which the excitant action of morphine on the sphincter of Oddi and contiguous muscularis, with consequent absorption of the ferments into the general circulation, is responsible. The present findings suggest that this effect is conditioned also by the functional state of the pancreas.

Carbachol alone does not materially affect the enzyme concentration of the blood, though it would appear to intensify the effect of morphine in this respect.

The incidence of nausea among the morphinized group was 21%. Three instances of transient epigastric pain are recorded. It is questionable if these bodily reactions, though attributable to morphine, have a pancreatic basis.

THE FUNCTIONAL EFFECTS OF PINCHING OF THE PANCREAS.

The pressure applied to the pancreas was more sustained than usually called for in the course of any surgical procedure but of a degree that might be considered well within safety limits. Six cases of clinical appendicitis were chosen. The morbid changes present were so insignificant that they may be regarded as normal subjects.

The anaesthetic took the form of a high spinal (Nupercaine) and the level of anaesthesia varied from the 4th to the 6th thoracic segments. This was proceeded by ½ gr. Ephedrine and 0.5 g. Sodium Thiopentone. None received morphine before or during the period of observation. It seems unlikely that this form of anaesthesia had any adverse effect on pancreatic function: according to Lake, Nickel and Andrus (1951), a sympathectomy which sacrifices ganglia T9 to L1, does not modify it to any a preciable extent.

The procedure was as follows: after opening the abdomen by means of a right paramedian incision and removing the appendix, the part of the pancreas which lay in front of the aorta, that is to say, about mid-body /

mid-body was located. By so doing one expected to have an area that was likely to be constant for each subject and one that would not seriously compromise the duct system. Pressure was applied by means of the adducted fore- and mid-fingers of the right hand and maintained thus for two minutes.

The serum amylase readings were taken before and three hours afterwards. The findings are presented in table 8. It will be seen at a glance that this maneouvre produced no appreciable change in the amylase levels and presumably did not cause any functional upset.

TABLE 8

Showing the Effect of Digital Compression of the Pancreas on the Serum Amylase Concentration

	Somogyi units per ml.	
Case.	Before Compression.	3 Hours after Compression.
1	100	98
2	150	140
3	130	140
4	220	180
5	110	130
6	200	220

THE PATHOGENESIS OF ACUTE PANCREATITIS

With Special Reference to the Bile and Obstructive Factors.

INTRODUCTION

The influence of the bile factor and of its anatomical implications still figure prominently in references to the aetiology of the acute affections of the pancreas. Those who are inclined to look elsewhere for the cause of this obscure group of conditions, which may be collectively referred to as "acute pancreatitis", regard the so-called "common channel theory" as too rigid in its interpretation and one that is ill-supported by clinical and morphological findings. In fact, the weight of argument in its favour rests partly on the frequent association with chronic calculous disease of the gall bladder (see table 8), which is at best circumstantial evidence, and partly on the susceptibility of the pancreas to intraduct injections of bile as shown by experiments on animals.

TABLE 9. INCIDENCE OF CHOLELITHIASIS IN ACUTE PANCREATITIS (After IVY & GIBBS)

Author	No. of cases of acute Pancreatitis.	Cases with Cholelithiasis	
		Number.	Per Cent.
Egdahl (1907)	105	44	42
Fallis & Plain (1938)	26	15	58
Guleke (1904)	437	256	59
Lewison(1940)	35	28	80
McWhorter(1932)	64	25	39
Wapshaw	24	11	45.8
TOTAL:	691	379	54.84

It is now well nigh a century since Claude Bernard (1856) demonstrated the noxious effect of bile on the tissues of the pancreas. Lancereaux (1899) suggested that reflux of bile into the duct system of the gland might be the cause of acute pancreatitis in humans. Substance was given to this hypothesis when Opie (1901) reported the discovery during an autopsy of a small gall stone "snugly filling the diverticulum of Vater" and staining of the duct of Wirsung with bile. He /

He instanced 8 similar cases out of a collective series of 32 patients. Subsequent studies have shown the presence of such a stone to be uncommon (see table 9), as evidenced by the findings of the authors presented.

TABLE 10 . INCIDENCE OF ACUTE PANCREATITIS WITH A SMALL STONE AT THE PAPILLA OF VATER

Author	No. of cases of acute Pancreatitis.	Cases with stone at Papilla	
		Number.	Per Cent.
Egdahl (1907)	44	3	6.8
Guleke (1904)	437	6	1.4
Rich & Duff (1936)	24	2	8.0
Schmieden & Sebening(1927)	1278	57	4.5
Smyth (1940)	245	32	13.0
Wapshaw	24	2	8.0
TOTAL:	2052	102	4.9

Similar uncertainty attaches to clinical data purporting to show the influence of the obstructive factor and here again we must fall back on animal /

animal experiments for more complete evidence.

The results presented here are based on investigations carried out on dogs. The scope of the experimental research is limited to studies on the effects of ligation of the major duct of the pancreas with or without the introduction of bile or a solution of one of its salts. In the discussion that follows I have attempted a critical review of literature relating to the bile and obstructive factors, incorporating impressions drawn from my experimental and clinical experiences.

As the canine pancreas differs very considerably from that of humans, it was considered appropriate to begin with a brief study of the main points of difference.

THE ANATOMY OF THE CANINE PANCREAS

The pancreas in the dog is a V-shaped structure, the two limbs coming to form the acute angle in the region of the pylorus (Sisson,1917; Bradley and Graham,1948). The right limb, the "caput pancreatis" is contained within the mesentery of the meso-duodenum. The left limb - the "cauda pancreatis", passes to the left across the vertebral column behind the omental bursa dorsal to the stomach and ends at the left kidney (fig.46). In the subsequent text the junctional area is referred to as the head of the gland.

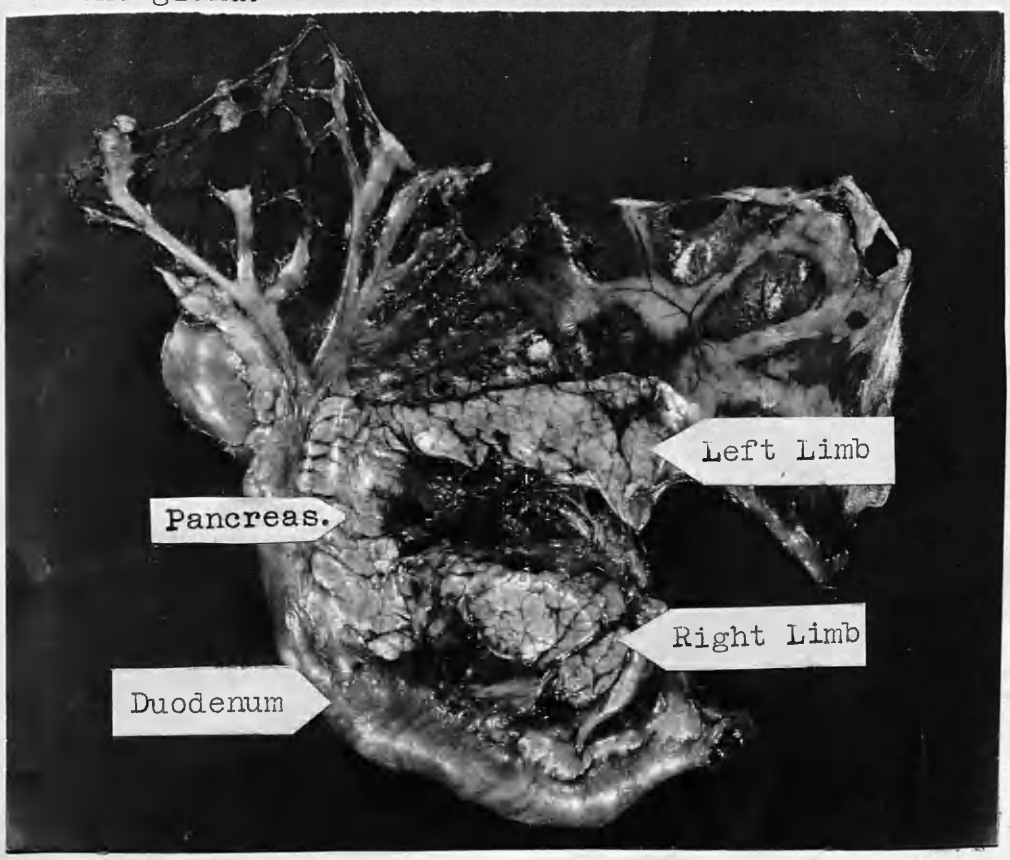


Fig. 46. Gross specimen showing the pylorus, duodenum with pancreas attached.

There are two, sometimes three, ducts. The duct of Wirsung is often missing; when present it is small and drains part of the left lobe. It usually unites with the common bile-duct at the duodenum; it may merge with the common bile-duct at a more proximal level, or again, open separately into the duodenum. The so-called accessory duct of Santorini is the main secretory pathway in the dog. It is about 2 millimetres in diameter and not more than 5 millimetres in length, being in fact a common channel formed by the fusion of the ducts which drain the right and left limbs of the gland.

Fig.47. Skiagram of Specimen. (fig. 46). Opaque medium was injected in the principal duct. The two branches well outlined, that in the right limb more extensively. The attempt to inject the upper smaller duct has failed. The course of the common bile duct is indicated by green dots.

This principal duct opens into the duodenum 3 centimetres or so below the entrance of the common bile-duct and at a distance of about 4 centimetres beyond the pylorus. The ductogram (fig.47) shows the relation of the principal duct to the common bile-duct. In this case there is no communication between the ducts of Santorini and Wirsung, but often one exists.

The histological appearances do not seem to differ materially from those of the human pancreas. (figs.48, 49).

Fig. 48
Normal principal duct with its fibrous wall. An entering ductule (bottom right) is cut in transverse section. (x100)

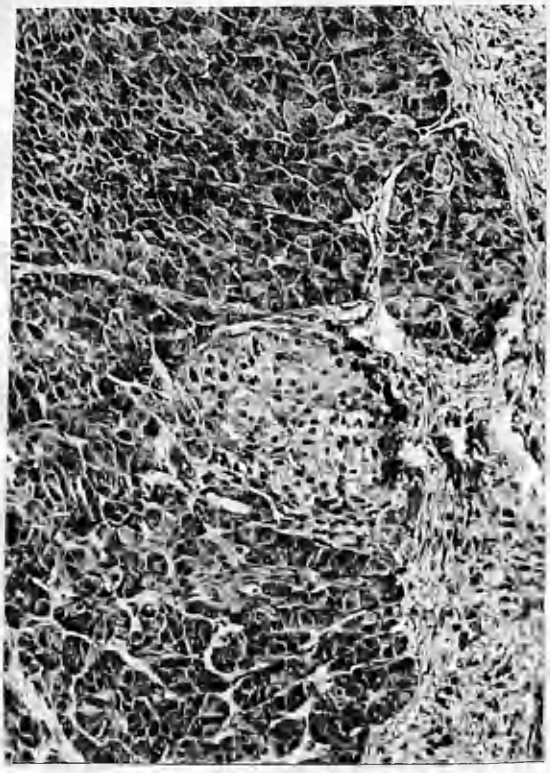


Fig. 49
Field showing in centre a large islet of Langerhans surrounded by normal acini. (x150)

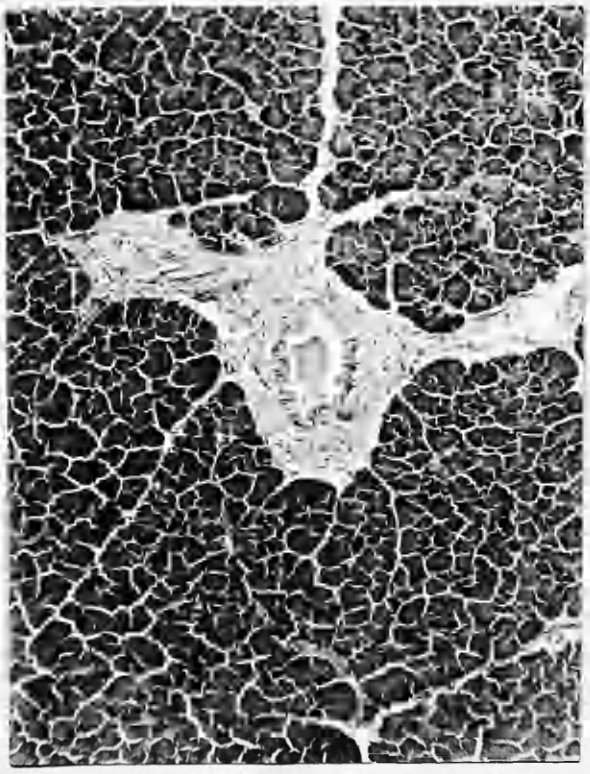


Fig. 50 Field of normal canine pancreas showing medium sized duct surrounded by acinar tissue. (x150)

Fig. 51 Field of normal canine pancreas showing acinar tissue and several islets of Langerhans.(arrows) (x100)

MATERIALS

1. Sixteen dogs were used. They were fed on horse flesh, boiled potatoes, water and milk. The animals' weight ranged from 5 - 20 kg., the average being 8 kg.

2. Canine bile was obtained under aseptic conditions by puncturing the gall-bladder through the right lobe of liver. All samples proved to be sterile on culture.

3. A 20% solution of sodium taurocholate salt (saturated) was prepared in sterile physiological saline. Prior to use, this solution was passed through a Seitz filter to minimise the bacterial content. The pH was 7. This concentration is about double that normally found in canine bile(Tejerina-Fotheringham,1948).

METHODS.

The general operative technique followed the same pattern in each of the 4 sets of experiments. After an overnight fast, the dogs were anaesthetised as follows. Each was premedicated by 1½-3 grams 'Nembutal' per os half-an-hour beforehand and this was followed by open ether anaesthesia administered by means of a perforated tin containing a wad of cotton wool. This anaesthesia was employed throughout alike in major and minor procedures. With sterile technique, the abdomen was entered through a vertical midline incision. The duodenum, which loops round the pancreas - both mobile structures in the dog - was turned over to the left in order to expose the posterior aspect of the pancreas.

In each experiment the terminal portion of the main secretory pathway in the dog, was the focus of attention. It was exposed by teasing the fibrous tissue interposed between the area of the pancreas lying in juxtaposition to the second part of the duodenum. Bleeding was arrested usually by means of hot saline packs but sometimes the use of haemostat and ligature was necessary. When the duct was/

was located a blunt-pointed metal cannula was inserted through a small opening made in the wall and held in position by an encircling ligature of cotton thread. Another ligature was applied between the opening and the duodenal wall. When the cannula was withdrawn the first ligature was tightened further. The smaller duct of Wirsung was left untouched.

18 experiments were carried out. The first series comprised 4 experiments designed to investigate the biochemical effects of simply exposing the duct to view. The same dog* was used for two of the experiments in this series, and this dog was again used for one of the next series. In the second series (4 dogs) the principal duct was tied with a linen thread. In the third series (5 dogs) bile was injected in quantities varying from 4.0 to 0.5 ml. by means of a syringe into the principal duct which was then doubly ligated as already mentioned. In the fourth series (6 dogs) the sodium taurocholate solution was introduced into the principal duct at a pressure of 180 mm water, and again ligature applied. There were two deaths: one as a result of severe haemorrhagic pancreatic necrosis following the injection of 4 ml. bile, the other an anaesthetic death. The surviving animals /

*Series 1, Experiments 1 & 2: Series II, Experiment 1.

animals in the second, third and fourth sets of experiments, were killed with chloroform injected into the heart and immediate autopsies carried out.

Histological studies were made on representative portions taken from different parts of the pancreas. These were fixed in formalin and sections stained with haemalum and eosin. Lesions of the following grades of severity were recognised.

Grade I. Minimal to moderate oedema of interlobular septa with slight diffuse inflammatory reaction. Infrequent areas of fatty necrosis but no significant acinar damage.

Grade II. Similar to I with more severe inflammatory reaction and some haemorrhages. More areas of fatty necrosis and scattered foci of acinar necrosis.

Grade III. More pronounced than II with frequent areas of fat and glandular necrosis and commencing replacement fibrosis of the damaged tissue in the later stages.

Simultaneously amylase and lipase estimations were carried out in most of the experiments. The blood was taken from the femoral artery: in some, the vessel was /

was exposed for this purpose, in others it was entered with success percutaneously. About 8 ml. was an adequate specimen: it was collected in a centrifuge tube containing 3 drops of 50% potassium oxalate solution evaporated to dryness, and after thorough mixture with avoidance of frothing, centrifuged and plasma decanted off. Plasma was found preferable to serum because in dogs the latter tended to show delayed coagulation. The biochemical methods were the same as those employed in studies in humans (see page 168). It was necessary, however, owing to the higher potency of the dogs' amylase, to dilute the plasma samples before carrying out the estimations. The pre-operative findings are given in tables 11 & 12. For purposes of comparison, my findings in a larger normal human series, are included. The range of amylase values in the canine series is of a much higher order than that found in the human series and compares with those obtained by Rush and Cliffton in dogs (1952). The results of the lipase estimations in dogs paralleled the results in humans, and were very similar to the findings in dogs reported by Cherry and Crandall (1932), and Nochman Pratt and Benotti (1948).

TABLE 11 NORMAL AMYLASE ACTIVITY IN HUMANS AND DOGS

Measured in terms of Somogyi.

Units per millilitre.

(Personal Observations)

Species.	Range of Readings	Mean of Readings	Standard Deviation	Coefficient of Variation
83 Humans.	40-230	100	44	44
30 Dogs.	500-2,200	1,230	460	37

TABLE 12 NORMAL LIPASE ACTIVITY IN THE SAME SERIES

In ml N/20 Na OH per millilitre.

76 Humans.	0-1.6	0.44	0.29	66
30 Dogs.	0-1.2	0.28	0.30	107

In presenting results the pathological findings will be described first. The biochemical findings are next presented in tabular form, and there follows the analysis of the data. Since no tissue was taken for examination from any of the animals in the duct exposure series, the procedural data of this series are omitted, and only the biochemical findings presented.

PATHOLOGICAL FINDINGS.

SERIES II. SIMPLE LIGATION OF THE PRINCIPAL DUCT

EXPERIMENT 1.

Dog No.17. Weight 6 kg. Date of Operation 3/3/42.
Date of Autopsy 7/3/42.

Gross Findings: The pancreas felt firmer than normal but showed no other noteworthy feature.

Histology: There was widespread oedema, exudation and round cell infiltration. In parts the acinar cells on the periphery of the lobules did not take on the eosin stain so well as those more deeply placed.
Grade I changes.

EXPERIMENT 2.

Dog No.18. Weight 9.8 kg. Date of Operation 5/4/42.
Date of Autopsy 6/4/42.

Gross Findings: The pancreas was not appreciably altered.

Histology: Grade I changes in their mildest form.

EXPERIMENT 3.

No Histological Studies undertaken.

EXPERIMENT 4.

Dog No. 20. Weight 8 kg. Date of Operation 21/4/42.
Date of Biopsy 3/5/42.
Date of Autopsy 50 days after operation.

Gross Findings: 12 days after operation: The whole gland appeared to be slightly shrunken, firmer and paler than normal. A piece of tissue was taken from the extremity of the left limb. The biopsy produced less bleeding than one would have expected. Wound closed. Good recovery.

Histology: A considerable degree of interlobular fibrosis with minimal acinar changes at the periphery of the lobules (fig. 56).

Gross Findings: 50 days after operation: The left limb of the pancreas was adherent to the undersurface of the liver, but was apparently healthy. The right limb was shrivelled and fibrous. Fragments were removed for histological examination from right and left limbs and from the intermediate segment lying adjacent to the duodenum.

Histology: In the right lobe there is advanced fibrosis with fragmentation of the lobules and much loss of secretory tissue. The islet cells appear normal. In the left lobe the acinar tissue was more normal.

SERIES III. FORCED INJECTION OF BILE INTO PRINCIPAL DUCT.

EXPERIMENT 1. 4 ml. of sterile bile injected.

Dog No. 9. Weight 10 kg. Date of Operation 22/4/41.
Date of Autopsy 23/4/41.

Gross Findings: The pancreas was swollen, indurated and haemorrhagic at its head and right limb. Foci of fat necrosis were found throughout the abdominal cavity.

Histology: Grade III changes in the affected parts. (figs. 64, 65, 67).

EXPERIMENT 2. 2 ml. of sterile bile injected.

Dog No. 11. Weight 9 kg. Date of operation 30/7/41.
Date of Autopsy 9/8/41.

Gross Findings: The pancreas was nodular and hard throughout. Areas of necrosis were visible under the peritoneal covering.

Histology: Grade III changes in all areas examined, with fibroblastic stromal change.

EXPERIMENT 3. 2 ml. of sterile bile injected.

Dog No.32. Weight 6 kg. Date of Operation 3/12/42.
Date of Autopsy 5/12/42.

Gross Findings: The whole pancreas was swollen hard and oedematous looking. Areas of haemorrhage and necrosis were seen after section. Some patches of fat necrosis were present on the surface of the gland and in adjacent parts.

Histology: Grade III changes in all areas examined.

EXPERIMENT 4. 2 ml. of sterile bile injected.

Dog No.33. Weight 6.3 kg. Date of Operation 8/12/42.
Date of Autopsy 10/12/42.

Gross Findings: The head and right limb of the pancreas were the seat of haemorrhages and patchy necrosis.

Histology: Grade III changes in areas affected. A remarkable feature was the degree of fibroblastic reaction in the stromal spaces.

EXPERIMENT 5. 0.5 ml. of sterile bile injected.

Dog No. 31. Weight 20 kg. Date of Operation 15/11/42.
Date of Autopsy 19/11/42.

Gross Findings: The pancreas was oedematous and indurated, particularly in the head and left limb. The right limb was of normal colour and consistency. No areas of fat necrosis were seen.

Histology: The changes were relatively slight and may be classified as Grade I to Grade II. In sections taken from the head and left limb there were a few widely scattered areas of acinar damage of a very localized character: this was usually in association with minor ducts (figs. 59, 60).

SERIES IV. INTRODUCTION OF SODIUM TAUROCHOLATE SOLUTION AT 180 mm WATER PRESSURE

EXPERIMENT 1. The amount of fluid which entered was estimated to be 0.2 ml.

Dog No.21. Weight 7 kg. Date of Operation 26/5/42.
Date of Autopsy 29/5/42.

Gross Findings: The head and right lobe of the pancreas were swollen and appeared to be congested at parts. There were some spots of fat necrosis in the parietal wound and mesoduodenum.

Histology: The interlobular and subcapsular spaces were widened and occupied by a fibrillary network in the meshes of which were many round cells. There were a few widely scattered areas of acinar destruction of a very limited character. Grade I mainly with minimal acinar drainage.

EXPERIMENT 2. The amount of fluid which entered was negligible - 0.01 ml.

Dog No. 24. Weight 9 kg. Date of Operation 29/6/42.
Date of Autopsy 1/7/42.

Gross Findings: The head and right limb of the pancreas were firm, swollen and congested. There was no evidence of fat necrosis.

Histology: Interstitial oedema in evidence but few round cells seen. In parts fibrinous exudate with spindle cells were noted. Grade I change.

EXPERIMENT 3. Amount approximately same as in previous experiment.

Dog No. 25. Weight 9 kg. Date of Operation 23/7/42.
Date of Autopsy 11/8/42.

Gross Findings: The pancreas was not much affected apart from some induration and swelling of the head and right limb. The ligamentum teres and area around the exposed duct were affected with fat necrosis.

Histology: Interstitial oedema is the only notable feature. Grade I changes.

EXPERIMENT 4. The amount of fluid introduced was 1.00 ml.

Dog No.27. Weight 9.5 kg. Date of Operation 24/8/42.
Date of Autopsy 26/8/42.

Gross Findings: The head and right limb of the pancreas were swollen, firm and congested. The left limb appeared normal. There was fairly widespread areas of fat necrosis in the abdominal cavity.

Histological Appearances: Grade II - Grade III.

The interlobular spaces were much widened and infiltrated by numerous round cells and blood cells. A few areas of acinar destruction were observed. (fig. 63).

EXPERIMENT 5. The amount of fluid introduced was 0,3 ml.

Dog No.28. Weight 9 kg. Date of Operation 25/8/42.
Date of Autopsy 27/8/42.

Gross Findings: The head of the pancreas was swollen, congested and covered with a clot of blood. Some bile staining on surface of the gland. The right and left limbs looked and felt normal. There were some flecks of fat necrosis on the surface and congestion of the adjacent part of the duodenum.

Histological Appearances: Grade I changes in all parts.

Fig. 52 (Series II , Exp.2.)
Interlobular oedema 24 hrs after ligation of the principal duct. There is no cellular infiltration. (x50)

Fig. 53 (Series IV , Exp.1.)
Exudate in interlobular spaces. The cellular component is minimal. This was taken 48 hrs after exposure to the effects of sodium taurocholate; so little entered the pancreas that the above changes are more likely to be the result of duct ligation per se. (x75)

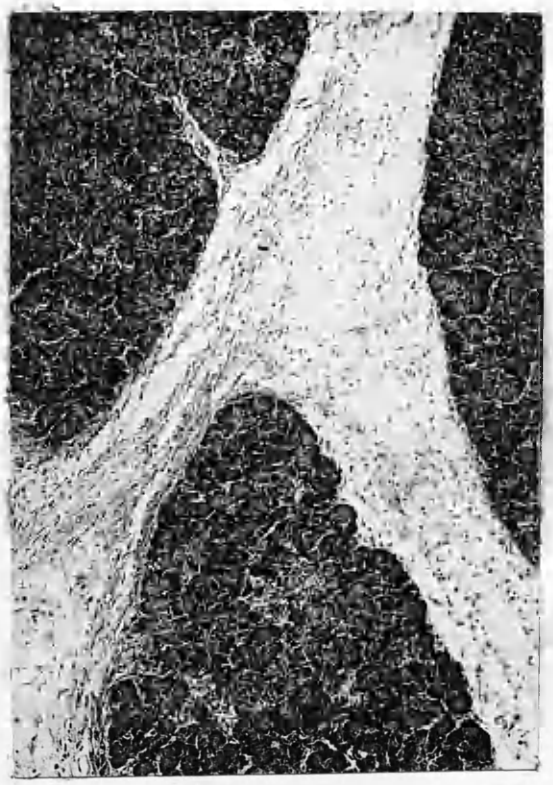


Fig. 54 (Series II, Exp.1.)
A mild degree of inter-lobular oedema with a little cellular infiltration following simple ligation of the principal duct. Autopsy 24 hrs after operation. (x100)

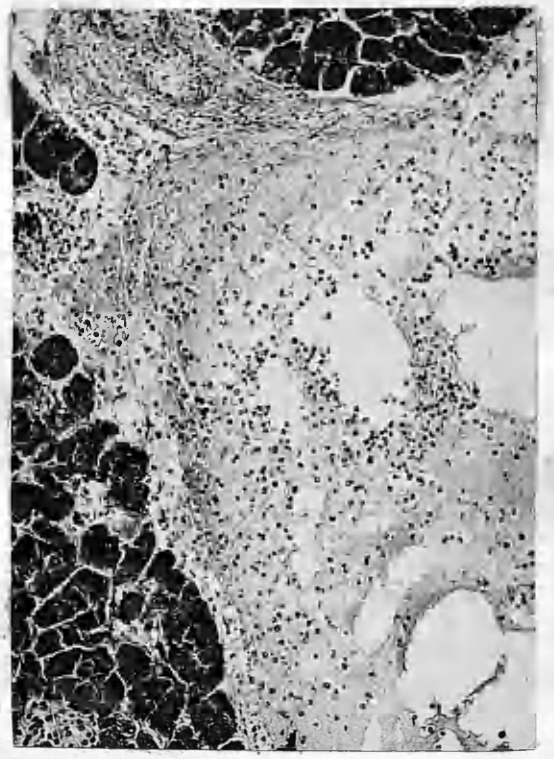


Fig. 55 (Series II, Exp.1.)
The inflammatory exudate with a conspicuous polymorphonuclear component following simple ligation. Autopsy 24 hrs after operation. (x200)

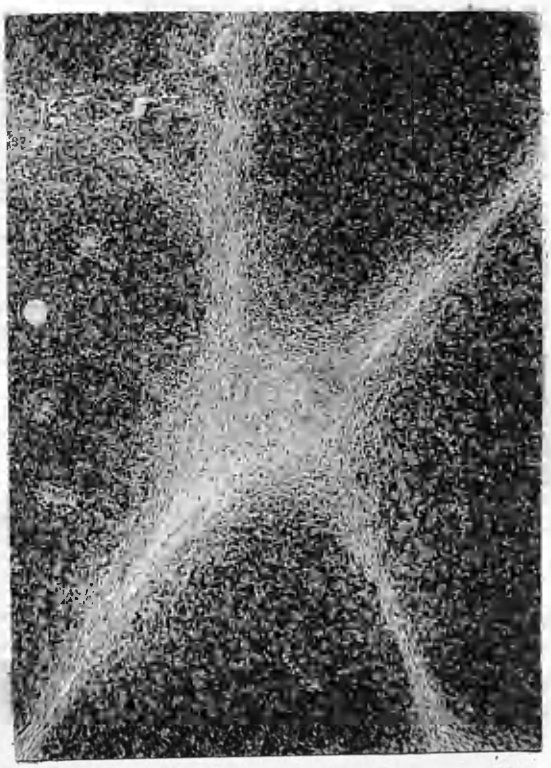


Fig.56 (Series II , Exp.4.)
Commencing interlobular fibrosis 12 days after ligation of the principal duct. Note a considerable degree of acinar replacement and lymphocytic infiltration at the periphery of the lobules. (x60)

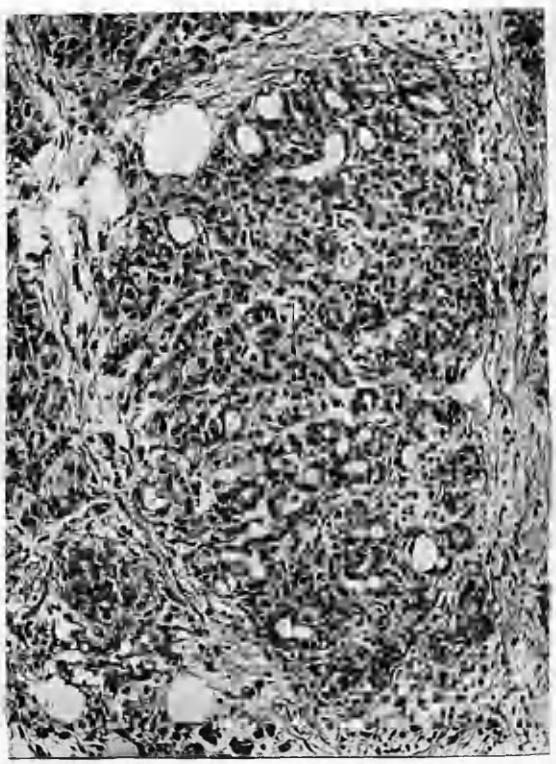


Fig.57 (Series II , Exp.4.)
An area with irregularly dilated ducto-acinar units. This animal had the principal duct tied 12 days previously. (x150)

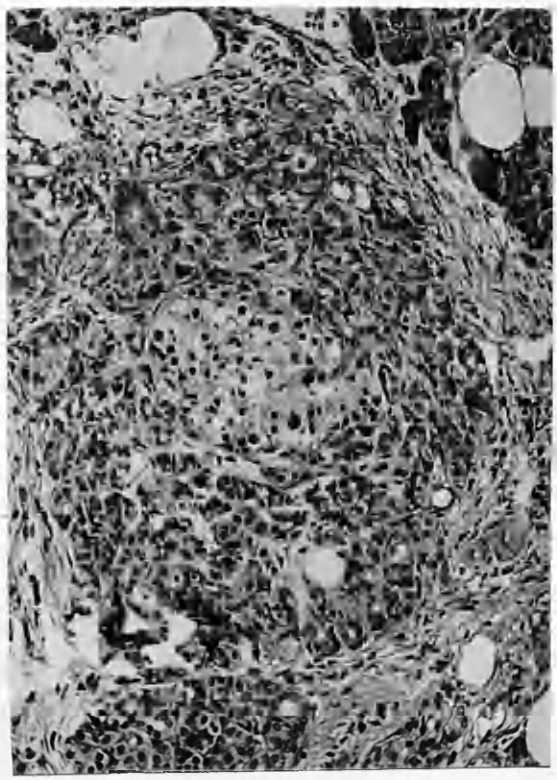


Fig.58 (Series IV, Exp.1.)

Situated in the centre is an islet of Langerhans. Its elements appear to be intact but the surrounding acinar tissue stains poorly and the cells are misshapen. Taken from an animal exposed 48 hrs previously to the effects of sodium taurocholate solution. (x150)

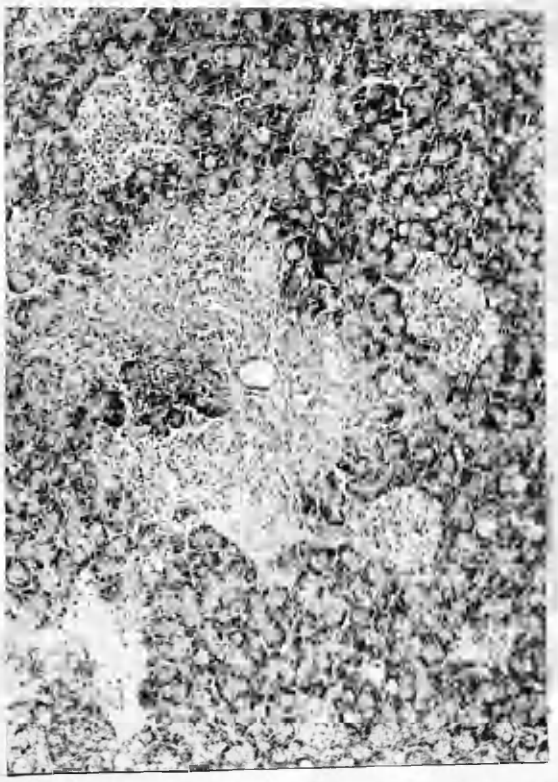


Fig.59 (Series III, Exp.5)

4 days after the injection of 0.5 ml. bile. In the immediate vicinity of the central ductule is an area of inflammation and exudation. The lining of the small duct appears to be simplified. There are 5 islets in the field and they appear larger than normal, possibly as the result of oedema. (x100)

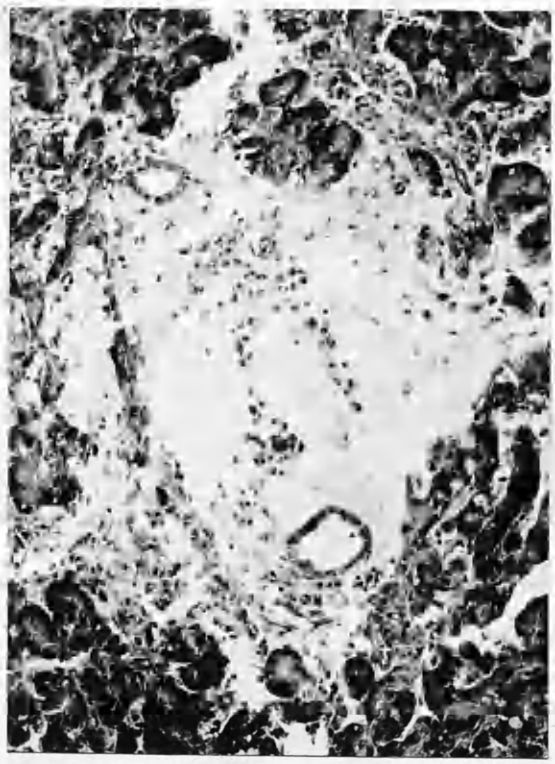


Fig. 60 (Series III, Exp. 5)
A higher power of the previous figure. Minimal changes are seen in the lining epithelium of the two ductules and there is an associated area of inflammation and exudation. It is questionable if there is any actual acinar damage. (x200)

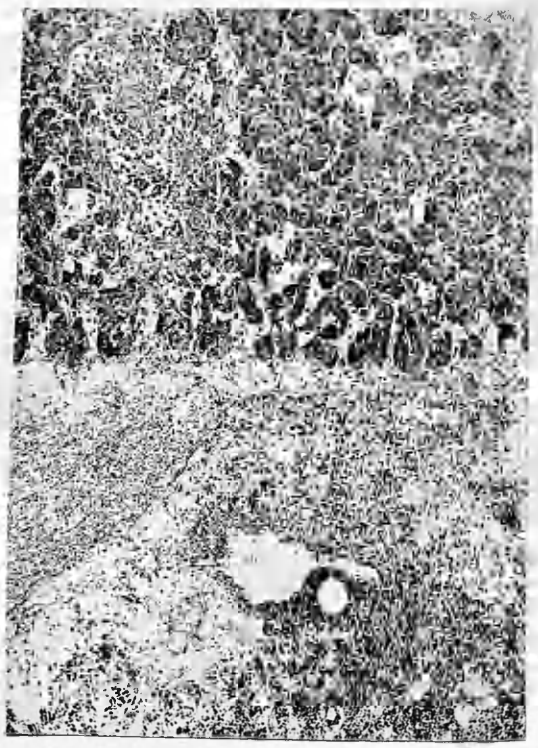


Fig. 61 (Series III, Exp.2)
The effects of injecting 2 ml. of bile 48 hrs previously. Not only is there a marked inflammatory reaction outside the lobule but there is also fragmentation and at some parts actual loss of acini due to leucocytic infiltration and haemorrhage. (x100)

Fig.62 Series III, Exp.3)

The effects 48 hrs after injecting 2 ml. of bile. In the centre the main duct is seen surrounded by minor tributaries. At the upper part the lining has been denuded and there is the suggestion of epithelial regeneration. Extensive lobular destruction has occurred and the inflammatory reaction in the interstitial tissue is intense. (x50)

Fig. 63 Series IV , Exp.4)

A vein cut in transverse section surrounded by the intense inflammatory exudate. Its walls are fragmented. This could be regarded as an example of the vascular lesion described by Rich & Duff. Taken from an animal exposed 48 hrs before to the effects of 1 ml. of sodium taurocholate solution. (x50)

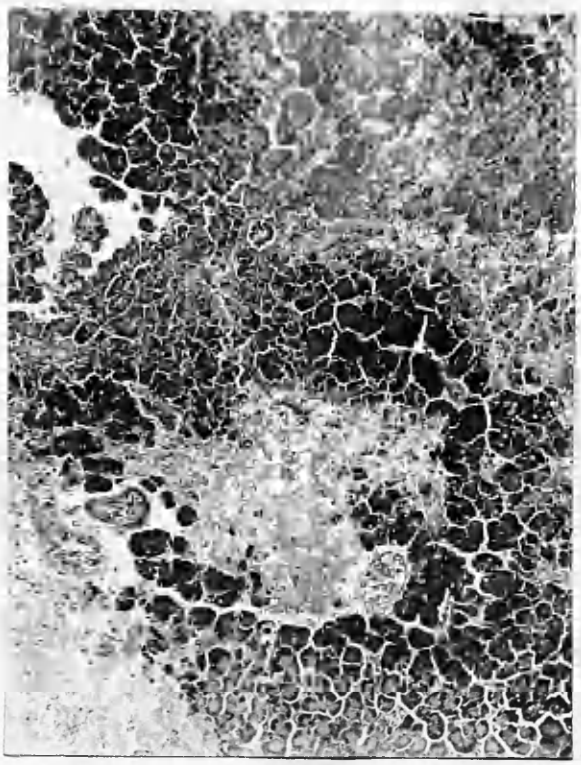


Fig. 64 Series III, Exp. 1)

Section taken 24 hrs after injection of 4 ml. of bile into the principal pancreatic duct. It illustrates patchy coagulative necrosis so often seen in bile induced pancreatitis, without polymorphonuclear and lymphocytic infiltration. (x100)

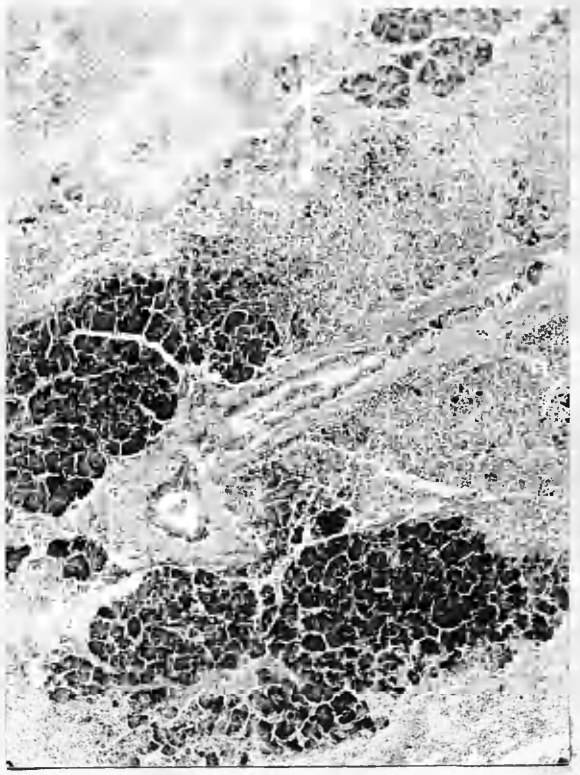


Fig. 65 Series III, Exp. 1)

An example of widespread acinar destruction 24 hrs after the injection of 4 ml. sterile bile. (x75)

Fig. 66 (Series III, Exp.2)

The effect 48 hrs after injecting 2 ml. bile into the pancreatic duct. Note the patchy loss of acinar substance in the interior of the lobule. This is a common picture in bile induced pancreatitis. (x150)

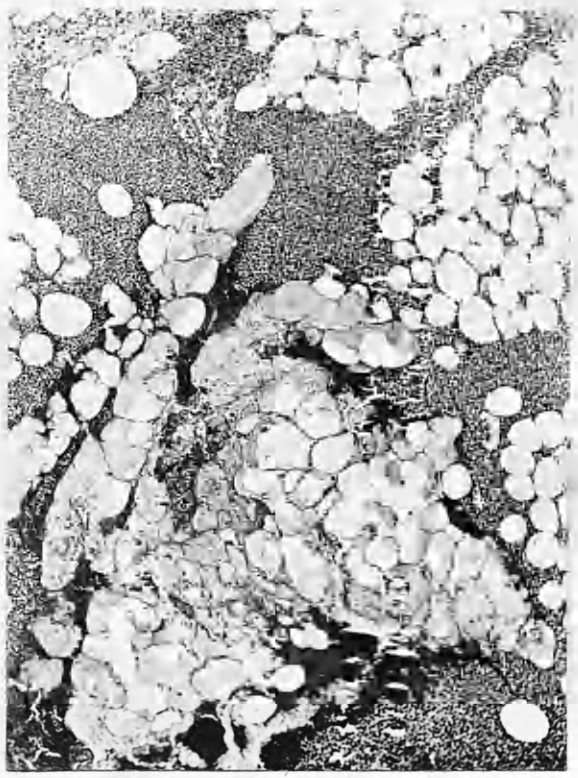


Fig. 67 (Series III, Exp. 1)

Showing an area of fat necrosis surrounded by areas of closely packed round cells. This was from the dog in which 4 ml. of bile was injected into the duct. (x50)

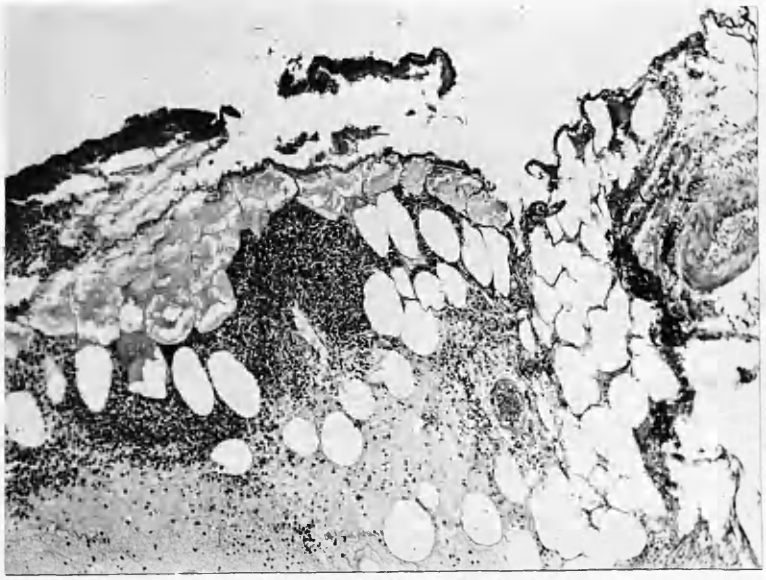


Fig. 68 (Series III, Exp. 1)

Showing surface fatty necrosis with subjacent aggregation of leucocytes and exudate formation in a bile induced pancreatitis. (x50)

TABLE 13.

SERIES NO. I. The Effect of Exposure of the Principal Duct on Plasma Enzymes.

Exp.	Estimation Time	Amylase Units/ml.	Lipase ml. N/20 Na OH /ml.	Amylase Ratios of Maximal to Normal Reading	Lipase Maximal Readings	Means		Standard Deviation	
						Amylase Ratios	Lipase Maximal Readings	Amylase Ratios	Lipase Maximal Readings
1.	Before Exp. 3 hrs later 1 day later	2,560 6,400 6,400	0.10 3.00 0.60	2.50	3.00				
2.	Before Exp. 4 hrs later 1 day later 4 days later	1,600 6,400 4,260 3,760	0.10 4.50 5.00 Zero	4.00	5.00				
3.	Before Exp. 4 hrs later	1,280 4,800	0.10 4.10	3.75	4.10	3.11	3.10	0.91	2.04
4.	Before Exp. 1 day later 2 days later	1,060 2,320 1,060	Zero 0.30 0.30	2.17	0.30				

TABLE 14.

SERIES NO. II. The Effects of Ligation of the Principal Duct on Plasma Enzymes.

Exp.	Estimation Time	Amylase Units/ml.	Lipase ml. N/20 Na OH/ml.	Amylase Ratios of Maximal to Normal Reading	Lipase Maximal Readings	Means: Amylase Ratios	Means: Lipase Maximal Readings	Standard Deviation: Amylase Ratios	Standard Deviation: Lipase Maximal Readings
1.	Before Exp. 2½ hrs later 1 day later	1,280 6,400 21,300	0.10 3.90 7.10	16.64	7.10	10.60	5.75	8.25	4.79
2.	Before Exp. 2¾ hrs later 1 day later	1,330 2,600 5,330	0.50 2.40 4.10	4.01	4.00				
3.	Before Exp. 3 hrs later 1 day later	2,130 2,080 6,400	0.1 0.3	3.00	0.30				
4.	Before Exp. 3½ hrs later 1 day later 4 days later 8 days later 12 days later	1,850 2,600 34,700 32,000 4,000 2,130	Zero Zero 11.60 6.30 1.10 0.60	18.76	11.60				

TABLE 15.

SERIES NO. III. The Effects of Bile Forcibly Injected into the Principal Duct on Plasma Enzymes followed by Ligation.

Exp.	Estimation Time	Amylase Readings	Lipase Readings	Amylase Ratios of Maximal to Normal Reading	Lipase Maximal Readings	Means		Standard Deviation	
						Amylase Ratios	Lipase Maximal Readings	Amylase Ratios	Lipase Maximal Readings
1.	Before Exp. 3 hrs later 1 day later		0.30 1.90 6.90		6.90				
2.	Before Exp. 1 hr later 3 hrs later 1 day later 3 days later 10 days later		Zero 4.0 7.3 5.0 Zero 0.8		7.30				
						20.50	6.58	11.98	1.81
3.	Before Exp. 1 day later 2 days later	800 13,500 24,600	0.8 7.9 4.1	30.75	7.90				
4.	Before Exp. 1 day later 2 days later	910 10,660 21,300	0.14 6.9 7.4	23.41	7.40				
5.	Penultimate day Day before 3 hrs later 1 day later 2 days later 4 days later	1,160 1,160 2,560 8,530 6,090 3,080	0.3 0.2 2,8 3.3 3,4 2.67	7.33	3.40				

TABLE 16.

SERIES NO. IV. The Effects of Introducing Sodium Taurocholate Solution into Principal Duct at Low Pressure on Plasma Enzymes followed by Ligation.

Exp.	Estimation Time	Amylase Units/ml.	Lipase ml. N/20 Na OH/ml.
1.	Before Exp.	508	0.20
	4 hrs later	2,600	1.50
	1 day later	16,000	3.50
	3 days later	21,000	4.80
2.	Before Exp.	1,450	0.10
	4 hrs later	2,740	1.40
	1 day later	40,000	5.50
	2 days later	29,000	6.60
3.	Before Exp.	1,280	0.40
	4 hrs later	3,200	3.20
	1 day later	12,000	5.40
	2 days later	16,000	10.00
	4 days later	1,600	1.20
	5 days later	1,440	0.04
4.	Before Exp.	1,280	Zero
	4 hrs later	4,240	1.20
	1 day later	8,510	6.90
	2 days later	11,550	8.60
5.	Before Exp.	800	0.25
	4 hrs later	1,600	3.60
	1 day later	1,280	0.40
	2 days later	1,420	2.00

Analysis of Biochemical Findings.

The wide variations in the after-results which were especially noted in series II, III and IV, rendered their interpretation difficult. Accordingly it was decided to analyse the results on a strictly statistical basis comparing one series of experiments as a group with another rather than isolating single experiments for study. There was another question, namely the validity of comparing the results of injecting a normal body fluid under high pressure (series III) with those of injecting an abnormal solution under low pressure (series IV). After due consideration, it was decided to exclude series IV from the analysis.

As the figures for amylase showed, one could not be certain that a dog with a high pre-operative value would have a high reading afterwards. It was, therefore, decided to take the ratio of the most abnormal (i.e. the highest) to the normal readings in each set of experiments instead of using the most abnormal reading per se. In other words, the analysis took the form of the study of the factor by which the amylase readings were increased following operative trauma of one sort or another.

With the lipase figures, a comparison of the maximum /

maximum after-results was, on the other hand, considered preferable to taking ratios because of the nature of the initial readings, some being zero. This meant a consideration of the amount by which the lipase readings had increased following operative trauma.

AMYLASE FINDINGS:

The analysis was divided into two parts.

(1) A comparison between the results of injecting bile at high pressure (series III) followed by duct ligation with the results of ligating the duct alone (series II).

The result of series III gave a mean of - 20.50 and a standard deviation of ± 11.98. There appears little difference between the standard deviation thus obtained, i.e. 11.98, and the standard deviation ± 8.25 which resulted from duct ligation per se. Nor can the difference in the means - 20.50 : 10.60, be regarded as significant since such an apparent difference in the means can occur in these figures once in every four trials. One might conçlude that there is a suggestion that the introduction of bile followed by ligation, has more effect than ligation alone, but statistically, the difference in the results is not significant inasmuch as these differences can occur by chance. It is equally true, of course, that /

that there is insufficient evidence to say that the former forms of trauma have not more effect.

(2) A comparison between the pooled results of series II and III with those obtained from simple exposure of the pancreatic duct (series I).

The mean of the pooled results was 14.84 and the standard deviation ± 10.49. These were compared with the corresponding results of series I which were 3.11 and ± 0.91 respectively.

The difference in the standard deviation is significant and would occur by chance once in 500 trials. The difference between the means is significant and would occur approximately once in 200 trials. Accordingly, one concluded with a measureable degree of certainty, that the simple operation of exposing the pancreatic duct to view does not cause such a disturbance in the amylase concentration in the blood as ligation of the duct with or without the introduction of bile or taurocholate salt.

LIPASE FINDINGS:

Considering firstly series II and III, the means of the maximum readings were 5.75 : 6.58 respectively, and the standard deviations were ± 4.79, ± 1.81 respectively.

From these figures one might assume that there is little difference between the changes in the plasma lipase concentration due to ligating the principal pancreatic duct alone and due to ligating the duct after the introduction of bile at high pressure. The after-results of series I were then compared with the pooled results of series II and III. There was no greater spread between these two sets of readings, - the standard deviations being $\pm$2.04 (series I) as against $\pm$ 3.23 (series II and III). The respective means were 3.10 : 6.21, which is a difference that would occur by chance in approximately eleven per cent of trials. It was concluded that the results in series II and III were significantly higher than those in series I, but the evidence is not as conclusive as in the case of amylase.

DISCUSSION.

1. The Bile Factor.

Pressure Effects. The damaging effect of bile forcibly injected into the duct system of the pancreas was known before it was suspected as being causally related to acute pancreatitis (Bernard, 1856; Flexner, 1897; Oser, 1898). It was largely through Opie's work (1901 : 1910) that the bile factor or the so-called 'common channel theory' came to be so widely accepted. According to Flexner (1906) the extent of damage depends on the composition of the bile, the salts being noxious and the colloids affording some protection. It is, however, generally realized that the lesions within the pancreas resulting from intraduct injections of bile are not specific and may be found in animals similarly treated with gastric juice (Hlava, 1890), duodenal juice (Polya,1908: 1912), a weak solution of hydrochloric acid (Flexner, 1900), or trypsin (Rich and Duff, 1935). It has been found under experimental conditions that bile must be introduced into the main duct in quantities /

quantities of about 2 ml. and over, and with considerable force before the characteristic haemorrhages and destruction of acini and fatty tissue make their appearance (vide seq.) When injected directly into the substance of the gland there is little change beyond local oedema (Wangensteen et al.; Thistlethwaite and Hill, 1952). Claims that an intraduct injection of infected bile is more harmful than sterile bile such as have been made by Clasen et al. (1934) and McCaughan (1934), must be regarded with reserve to judge from the variable results reported by those who have conducted large scale investigations using only sterile bile. For example, in the observations of Iraneus (1941) on forty dogs, there was minimal damage in fifteen, and mild to moderately severe lesions in twenty five. Baxter et al. (1938) also using sterile bile reported structural change of varying degrees of severity. When present the acinar loss tends to be patchy and affect the central portion of the lobules; widening of the interlobular spaces is usually present. Leucocytic infiltration, which may be accompanied by exudate formation, are other common features. These changes were encountered by the author in the experi- /

experiments in which quantities of bile varying from 2 ml to 4 ml were injected (figs. 61, 62, 64, 65, 66.) Commencing recovery is indicated by the appearance of new fibro-blastic tissue, so that by the first week the interlobular spaces are filled by young fibrous tissue which may pervade the inter-acinar spaces (fig. 56) Misshapen and distended cells are frequently seen. As found also in the present work, Iraneus noted loss of parts of the lining in the major ducts (fig. 62) and related to the latter were irregular nests of epithelial cells with tubular formation: he regarded these groups of cells as proliferating epithelium. At no part was there any sign of acinar regeneration in his sections. This observation lends weight to the view expressed earlier by Grauer (1926) that the duct epithelium is the source of growth repair in the pancreas. As long ago as 1918 Cooke and Whipple emphasised the remarkable reparative power of the pancreas following injections of large amounts of sterile bile, but their work did not seem to be fully appreciated by the surgeons of their day. The islet tissue usually excapes (fig. 58) but there may be seen slight disruption of cytoplasm with some loss of /

of nuclear stain. A so-called specific vascular lesion which is characterised by rapid necrosis and hyaline change in the walls of the arteries and veins allowing an escape of blood into the surrounding part, has been reported by Rich & Duff: its significance will be discussed later. Fig. 63 may illustrate this lesion. It is not a constant finding (Innerfield et al. 1952).

Investigators who introduced small quantities of bile have been unable to produce lesions such as these described; for instance, Popper (1942) injected 0.1 ml. Archibald & Kaufmann (1947) injected 0.75 ml. and Coffey (1942) even found 2 ml. inadequate in dogs. The writer considered 2 ml. effective as a means of producing experimental pancreatitis, but with 0.5 ml. the acinar damage was minimal. (figs. 59, 60)

Certain workers have attempted to simulate the conditions which may obtain in some human cases of pancreatitis by converting the bile and pancreatic ducts into one communicating channel; but varied results are reported. Archibald (1919), using cats, claimed that he was able to produce such a state of affairs by inducing spasm of the sphincter of Oddi, that acute pancreatitis resulted. Wangensteen et al./

et al. (1931) achieved a similar anatomical continuity by ligating the Vaterine ampulla in cats. Then, according to their observations, either an injection of air into the gall bladder, or stimulation of the bile flow by means of a high fat diet, or stimulation of the flow of pancreatic secretion by means of pilocarpine, produced acinar damage of varying degree. Mann & Giordano (1927) and Bisgard & Baker (1940) used goats, which are eminently suitable for this type of experiment for the reason that the pancreatic duct joins the common bile duct at a point well proximal to the duodenum. Each found that ligation of the channel common to both systems did not produce acute pancreatitis, but when bile was injected under pressure into the pancreatic duct, gross damage resulted. Tejerina-Fotheringham (1948) also failed to produce positive evidence of damage in rats, which have a duct arrangement similar to that of the goat, by ligating the common channel. Archibald (1919) expressed the view that the conditions necessary for structural changes are, - (1) a change in the constitution of the bile brought about either by infection, or an excess of salts, (2) undue resistance of the sphincter of Oddi, and /

and (3) abnormally high biliary pressure. The response on the part of the pancreas to injections of 3 to 10 ml. of such innocuous fluids as Indian ink and Lock's solution tinted with trypan blue, were studied by Rich & Duff (1936). In neither experiment did any damage result. The inky particles found their way into the interstitial spaces through clefts between the acinar cells and separated them. Following the introduction of a simple dye, all that was noted at the end of 24 hours was stromal oedema, the ducts and acini being intact. They concluded that the acinar units were able, by a simple process of mechanical separation of the constituent cells, to allow the escape of pancreatic secretion or injected fluids of a harmless nature and that the cells fell back into place thus sealing off the defects.

It will be obvious from the preceding remarks that the question of the differential pressure existing in the biliary and pancreatic duct system has an important bearing on the present problem, and it will not be out of place to consider this matter in more detail. From studies on monkeys and dogs it has been shown that the pressure within the pancreatic duct varies from about /

about 260 to 350 mm water (Herring & Simpson, 1909; Mann & Giordano, 1923; Jordan Jr. & Hallenbeck, 1952). Jordan & Hallenbeck concluded from their studies that the maximum secretory pressure fluctuated from minute to minute: in some dogs it was as low as 180 mm water. An increase did not produce any significant change in the rate of the secretion of the pancreatic juice until the pressure was at or near the maximum when there occurred an abrupt fall in the rate of secretion. According to Herring & Simpson, when the duct or ducts are obstructed the pressure of the pancreatic secretion rises to a level closely approximating that reached by the bile in obstruction of the common bile duct. A rapid fall was also noted by them when the pressure reached this maximal level. They further noted that in the presence of obstruction the rise and fall of the pancreatic secretory pressure are more rapid than the rise and fall of bile pressure. Harms (1927) reported that during the height of digestion in unanaesthetized dogs the secretory pressure of the pancreas is higher than that of the biliary pressure, an event which would favour the passage of pancreatic juice into the biliary channel rather than the reverse./

reverse. The biliary pressure, however, is also liable to undergo wide fluctuations. Mann & Giordano considered the influence of the gallbladder less effective in this respect than the mechanical effects of the abdominal muscles and the diaphragm: during retching, for example, pressures as high as 1,000 mm water were recorded in the biliary system of the dog. These authors argued that if the intra-abdominal pressure were equally distributed, or affected each viscus alike, no harm would be likely to result from such muscular efforts, but if not, the act of vomiting, coughing, etc. might conceivably drive the bile into the pancreas provided the anatomical conditions were also favourable. It is unfortunate that Mann & Giordano did not record the secretory pressure of the pancreas under the conditions of their experiments. The lowest pressure within the pancreas which causes amylase to make its appearance in the blood in humans was estimated at less than 300 mm water by Howell and Bergh (1950), who were able to check the validity of this observation by radiographic studies of the incidence of pancreatic reflux in their patients. Mann & Giordano were unable, in dogs, to introduce bile into the pancreatic /

pancreatic duct at pressures under 350 mm water. In most instances bile did not enter the pancreatic duct with pressures less than 500 water, but it entered in all experiments with pressures approaching 800 mm. At 1,000 mm water they succeeded in introducing as much as 10 ml. which was achieved after a period of 2½ to 3 hours, and yet the only notable change was oedema of the gland. This is a most important observation as will be seen when the mode of action of bile comes to be discussed. According to the author's observations, small amounts of bile salt, up to 1 ml. solution, passed into the duct of the pancreas at a pressure of 180 mm water, but whether this was the cause of the minor degree of acinar damage which was noted in some of the experiments, it is difficult to say. This much may be stated, that the only dog showing Grade III changes in the pancreas was that in which 1 ml. of bile salt solution was introduced.

Ivy & Gibb (1952) have referred to the probability that any pressure exerted through the duct of Wirsung in humans would be equalized through its connection with the accessory duct of Santorini. According to their survey of the literature bearing on this point the accessory duct could function in 40 per cent. of

of normal cadavers if the chief duct were occluded, but apparently the connection between the two ducts is sufficiently wide to permit a free flow of secretion in only 15 per cent. of persons. It may be noted that the minor duct was left untied in the author's series, as it was thought that by so doing, conditions approaching those encountered in human cases of pancreatitis would be reproduced and would allow an influx of bile or a solution of its taurocholate salt at a pressure approaching the minimal level. It seems certain, however, that the mere presence of bile in the main pancreatic duct cannot do much harm as a rule, since collective studies of the incidence of pancreatic reflux have shown (see radiographic studies) that the opportunity for the bile and pancreatic secretion to intermingle exists in about 30 per cent. of normal persons.

Irritant Action. There are some who believe that bile, under circumstances not yet clearly understood, is particularly destructive to the secretory elements of the pancreas. Its irritating properties are well known to surgeons who take every precaution to prevent pooling in the peritonital cavity by providing adequate drainage for its escape. Tatum (1916) observed its effects by experiments in vitro on small blocks of tissue removed from different organs (excluding the pancreas); the most pronounced change was loss of affinity for stains and fragmentation of the nuclei of the cells at the surface. When previously boiled or frozen and then immersed in bile the tissues were not appreciably affected. He assumed that the cytolysis was the result of a co-enzyme or activating substance in the bile which reacted with the autolytic enzyme in the tissues examined. Based as it was on histological evidence alone, this conclusion was open to criticism. Bradley & Taylor (1917) repeated Tatum's experiments but found that bile did not change significantly the rate of autolysis of liver, heart or spleen and therefore deduced that it would not function either as an activator or as a co-enzyme. These authors offered /

offered the alternative suggestion that its cytolytic effect may be due to the solvent action of bile salts on cell lipoids. When injected into the pelvis of the kidney (Dragsted et al.), a salivary duct (Sellards,1909) and the subcutaneous tissue (Rich & Duff), some structural change and exudate formation is observable, but in none of these experiments have lesions on the scale encountered in destructive pancreatitis been recorded. Archibald (1919) considered bile to be capable under conditions already mentioned (vide page of producing acinar necrosis. Dragstedt et al. also regard bile as suspect. They further hold that its toxic properties are to some extent neutralized by the proteins of the blood stream, so that exudate and haemorrhages are protective. The tryptic ferment which, in their opinion, does not affect living cells, digests the serum proteins, thereby setting free the bile salts to exert their baleful influence once again. Thistlethwaite and Hill (1952) advanced the theory that acinar destruction is in part due to the direct cytolytic effect of the bile and in part to local vasospasm. The importance of the latter is discussed later in another regard (page 269) It is difficult to reconcile these /

these views with the failure to reproduce the lesions of pancreatitis by injecting bile directly into the substance of the gland, or the introduction of large amounts of bile via the ducts using pressures under 1000 mm. water (Mann & Giordano). Rich & Duff (1935), who are inclined to belittle the importance of bile as a factor in the pathogenesis of acute pancreatitis, adduced experimental evidence in support of the view that bile is instrumental in setting free the proteolytic and other ferments from effete acinar components which set about digesting the already damaged gland. They took the changes in the walls of the arteries and veins as their criterion for the presence or absence of tryptic activity and found that whereas an injection of bile into the subcutaneous tissue left the vessels unharmed, an injection of trypsin caused necrosis and haemorrhages of the kind frequently encountered in experimental pancreatitis. My own findings in the experiments in which 0.5 ml. of bile was injected with force might be taken as evidence of a local effect. The instance of acinar damage in those in which 1 ml. of bile salt solution was introduced at 180 mm. water also support that contention.

It is pertinent to mention that the chemical com- /

composition of canine bile differs from that of white rats, cats, goats and man in that the predominant salt in the former is sodium taurocholate, which is strongly cytolytic(Tejerina-Fotheringham, 1948). In man there are only small amounts of this salt, the glycocholate being the principal; and it is also the less irritating when injected into the pancreatic duct of the dog(Tejerina-Fotheringham). In the dog, ox and pig, all of which have sodium taurocholate as the main constituent, the anatomical arrangement of the terminations of the biliary and pancreatic ducts is such as to make it impossible for biliary-pancreatic reflux to occur.

Lastly, one might consider the vitality of the tissues normally exposed to bile for it would seem that living cells are endowed with some protective property. For example, non-infected bile does not, so far as can be ascertained, adversely affect the mucosa of the gall-bladder, yet if after cholecystectomy there is a delay of even a few minutes in transferring the specimen to fixative, extensive shedding of the cells lining the villi will inevitably result (Cappell, 1951). Accordingly, one may reasonably suppose that bile is /

is only destructive to the cells of the pancreas which have previously been traumatized by say the impact of an inrush of bile or by some other factor such as vasospasm.

Influence on Proteolysis. "The natural commingling of bile and pancreatic juice in the duodenum is strongly suggestive of harmony of action and it might be reasonably assumed that in pancreatic proteolysis the presence of bile would be in no wise inimical" (Chittenden and Albro, 1898). These words were addressed to the subject of the role of bile in the natural process of protein digestion. They assume a peculiar ambiguity when considered in the light of the concept that bile, when diverted into the pancreas, acquires the sinister property of not only aiding, but initiating the process of proteolysis, i.e. without the catalytic action of the enterokinase of the duodenum. It is not known who first proposed this theory, but almost general acceptance is given to the view that this is among the common predisposing causes of acute pancreatitis. A search of the literature for supportive evidence has proved difficult, since biochemists seem to have long ceased to interest themselves in this aspect of the bile's part in the body /

body economy. In fact, the literature on this subject was for the most part written at the latter part of the last century when investigative findings were largely qualitative and the methods employed outmoded by present standards.

According to Delezenne (1902a), Bernard was the first to report that bile increased the tryptic power of the pancreatic juice. Heidenhain (1875) observed that when an aqueous solution of dried bile was added to a glycerine extract of pancreas the proteolytic action of the latter was not diminished but apparently increased: a similar stimulating effect was also noted after the addition of 1 per cent. Lindberger (1883) found that the inhibiting action of organic acids upon trypsin-proteolysis may be overcome to some extent at least by the presence of bile salts. Crittendon and Cummins' (1895) findings obtained more equivocal results in that the addition of a 10 per cent. solution of bile to neutral or alkaline pancreatic extract modified only slightly the rate and extent, of proteolysis: it induced a slight stimulation under some conditions and under others a marked inhibitory effect. Martin and Williams (1890) gained the impression that bile and, to a less extent, sodium glycocholate hastened proteo-

proteolytic activity of a pancreatic extract as measured in terms of the effect of egg-albumin: it must be observed that their extract exhibited a certain amount of digestive power before the bile or its salt were added. Rachford and Mouthgate (1895) studied the effects of pancreatic juice freshly obtained from a rabbit on blood fibrin after the addition of fresh rabbit's bile: the proteolytic power of trypsin was increased by one quarter. Crittendon and Cummins (1898) used fresh bile of the ox, dog, cat and sheep with human pancreatic extracts. Their results showed that bile did not increase the proteolytic power of the enzymes of neutral extracts of the pancreas. Some slight stimulation might be produced but they could not guarantee that this was of constant occurrence or sufficient in degree to have much physiological significance. Delezenne (1902b)found bile capable of increasing the tryptic activity of the pancreatic juice but only when the latter already possesses some power to digest albumin. He further stated that the action of bile on proteolysis was not to be compared with the activating properties of duodenal juice or enterokinase. Quagliariello (1910) reported that sodium glycocholate had no influence on /

on tryptic digestion. Fenger and Hull (1919) who used hog's pancreas because this species showed a similarity in its digestive apparatus to that of humans, found that all of their extracts exhibited some proteolytic activity prior to the addition of bile: bile alone was devoid of any measureable enzyme action. In their conclusion they suggested that besides its ability to augment the activity of lipase, bile may protect the fat-splitting process against any interference on the part of trypsin. Passing mention may be made to the question of the presence of a proteolytic ferment in the bile. Gegalov (1900) reported its existence in the bile of carnivora but its action was only a weak one. This observation has been extended to man by Tschermak. Pavlov (1910), who cited these references in his famous lectures on the work of the digestive glands, considered that this property was not of major importance, and certainly one which is ignored by subsequent authorities (Sobotka 1937).

In the interpretation of these various reports due regard must be made to the nature of the substrate used to test the proteolytic activity of the bile. As Pavlov (1910) has pointed out, the majority of these /

these experiments dealt with extracts of the pancreas, and consequently in the main with the zymogen and not with the ready-made juice, and he considered it doubtful whether the results would hold good for the actual conditions of digestion. Effront (1917) added confusion to the issue when he stated that fresh extracts of the pancreas are liable to show slight proteolytic power. He stated that the pancreas of an animal killed in a digestive phase is likely to furnish an extract capable of being activated very readily, the results being less satisfactory when the animal is killed during a fast. Extracts of calf and dog pancreas in general activate easily, but not so the feline pancreas. Some investigators employed freshly obtained pancreatic juice. As a rule, this does not contain trypsin but rather its zymogen, but it too may develop spontaneously the power to digest protein (vide infra). These two probabilities give reason for doubt regarding the general belief that bile is an activator of the percursor of trypsin. Wangensteen et al. (1931) made the point that the regularity with which necrosis follows the injection of bile into the pancreas bespeaks the importance of effective activation /

activation of trypsinogen in the production of acute pancreatitis. This appears a somewhat specious argument which ignores the possibility of a local necrotizing effect. Some have strongly asserted that infected bile is a sine qua non (Coffey, 1942; Taylor, 1949; Tejerina-Fotheringham, 1948). There is no tangible evidence that infected bile is any the more destructive than sterile bile, so far as I am aware, but I have not examined this aspect of the problem sufficiently to be able to express an opinion. It would entail a very comprehensive investigation, taking into account such problems as the virulence of the organisms, their proteolytic activity and that of any leucocytes that may be present, and finally the question of the bacteriostatic effect of the bile on the particular organism involved. The bacteriology of the bile and the peritoneal collections was studied in most of my own cases, but such a record is of doubtful value when one cannot be certain whether or not the bile factor was at fault. It may be of interest to note that the samples of bile in the gall-bladder and the peritoneal fluid taken from the case represented by fig.18 yielded sterile cultures. Lastly, if refluxed bile must be infected in order to produce acute pancreatitis, "it cannot" to quote Cattell (1953) "be concluded a priori that the presence of bile is an inciting factor".

2. The Influence of Duodenal Juice.

Regurgitation of duodenal juice deserves mention as a factor in the production of acute pancreatitis inasmuch as it involves not only bile but also enterokinase. One could imagine this happening in cases in which the biliary and pancreatic ducts open separately into the duodenum. According to Ivy and Gibbs (1952) only 9 such cases of acute pancreatitis have been reported. This anatomical arrangement was present in two of my series. In one, acute pancreatitis followed as an early complication of a Polya gastrectomy to which the patient had been subjected elsewhere. Death ensued and on autopsy the accessory duct of Santorini proved to be the major one and although it appeared to be quite patent throughout its length there was the possibility that the terminal part was distorted as a result of the interference necessary to close the duodenal stump. In the other case the duct of Wirsung was of normal dimensions but entered about 1 cm. distal to the point of emergence of the common bile duct.

Although this regurgitation hypothesis has the support of a considerable body of opinion, particularly on the /

the Continent (Bottin, 1932), grounds for criticism are the rarity of acute affections of the pancreas in cases of small bowel obstruction and the disinclination for barium to regurgitate into the ampulla of Vater during X-ray examinations of the upper intestinal tract (Beal & Jagoda, 1921: Feldman, 1938).

It is usually assumed that the natural safeguard is the sphincter of Oddi. But there is another protective mechanism which was well known to the older anatomists but is now almost completely disregarded, viz. the arrangement of the mucous folds at the transmural portion of the biliary - pancreatic ducts or duct (i.e. common channel or ampulla). Their minute anatomy has been more carefully studied by Dardinski (1935) and Kirk, (1944). These folds are more conspicuous in the ampulla of Vater. They are 2-4 millimetres in length and 2-3 mm. in width. The end of one fuses with the end or side of the adjacent one and by this union forms a pocket. The more distal ones actually protrude through the orifice of the papilla. Extensions of muscularis into the cores of the villi have been noted which suggests that they are retractile and not merely passive appendages. The intrapapillary portion of /

of the pancreatic duct contains similar folds but smaller in size and not so intricate an arrangement. Figs.67, 68, 69, illustrate the two types. The tissues shown are in a state of good preservation because I took the specimen while performing a partial pancreatic-duodenectomy for a carcinoma of the duct of Wirsung (see page 263)

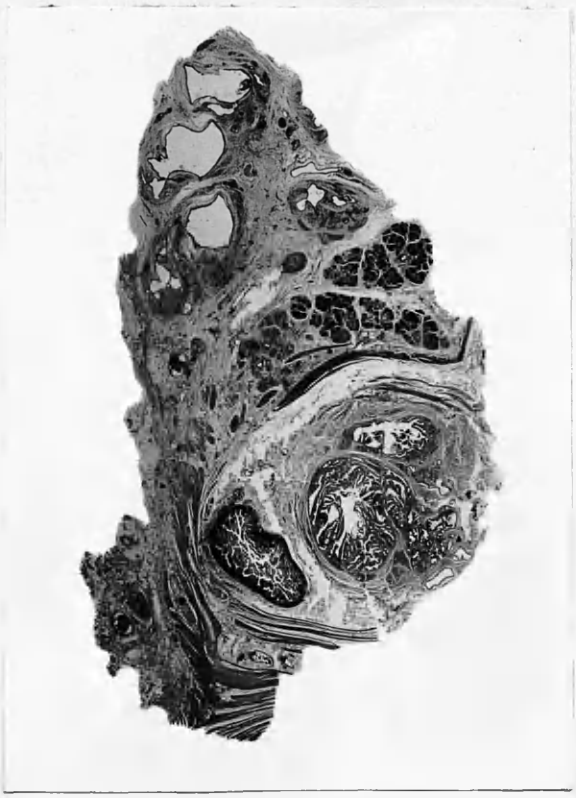


Fig. 67

Section through the transmural segments of the common bile duct (on right) and main pancreatic duct (on left). Note fibrous condition of the pancreatic substance and the dilated duct in the upper part of specimen. (x4)

Fig. 68

High power view of the pancreatic duct showing villous formation of the mucosal lining. Components of the sphincter of Oddi are seen in the periphery. (x8)

Fig. 69

High power view of the common bile duct. The more intricate arrangement of the villous folds of this duct as compared with the pancreatic duct is obvious. Outside are small intramural ductules common in this area.

The Tryptic Activity of the Pancreatic Juice.

"Every observor who has been occupied for any length of time investigating the functions of the pancreas will leave this field with a feeling of dissatisfaction in consequence of the extremely large number of fruitless experiments he is obliged to subtract from the total number of his investigations; for not even the greatest care, nor the ripest experience in the making of pancreatic fistulae, will overcome the incomprehensible sensitiveness of the organ, which only too often annuls its function for a length of time after the operation, a function which it does not resume even under the influence of the most favourable secretory conditions. A degree of uncertainty, therefore, always clings to the results of such observations, which is not set aside even by frequent repetition of the experiments. I must openly confess that I have never undertaken a series of experiments which entailed the sacrifice of so many dogs and with such poor results".

(Heidenhain, 1875)

"The formation of the active enzymes from inactive pancreatic juice or from inactive extracts of the pancreas has been extensively studied but the literature is surprisingly confused and contradictory".

(Northrop, 1937)

The early observers (Kühne, 1867; Heidenhain, 1875) believed that trypsin existed in the glandular cells of the pancreas as an inert zymogen and only became active when secreted. The type of fistula employed at that time was surrounded by a fringe of duodenal mucosa which, as Shepovalnikov (1899) demonstrated, contained the activating principle, enterokinase. The observations of Bayliss & Starling (1905) also indicated that this /

this ferment is limited to the small intestine. Delezenne (1902b) on the other hand, has also demonstrated its presence in lymphatic glands. Mellanby and Woolley (1913) brought forward evidence that enterokinase is contained in small but definite amounts on practically every tissue of the body, the most interesting finding being in the fresh extracts of pancreas taken from animals. How this kinase operates, was for many years poorly understood, but it has now been established that it is by a true enzymatic action (Kunitz & Northrop, 1938-39). The study of the proteolytic ferments has now, of course, been placed on a different plane since it has become possible to isolate and crystallize in purified form not only the three main proteases of the pancreas, - trypsin (Northrop and Kunitz, 1932), chymotrypsin (Kunitz and Northrop, 1934-35) and carboxypeptidase (Anson, 1935) but also the precursors, - trypsinogen (Kunitz and Northrop, 1934) and chymotrypsinogen (Kunitz and Northrop, 1935). Northrop and his associates have demonstrated that the amorphous forms contain small amounts of inhibitor and other substances, which may be regarded as impurities, and which adversely influence the activation of the zymogen, whereas with the pure crystallized form activation occurs readily. Amorphous /

Amorphous preparations of trypsinogen, for instance, are stable in solution and can only be activated by the addition of kinase, large quantities of trypsin, or concentrated solutions of magnesium and ammonium sulphate. After crystallization, trypsinogen becomes rapidly transformed to trypsin as soon as it is dissolved in neutral solution (Northrop, 1937). For that reason one would imagine that the effects of bile or crystallized trypsinogen, would be difficult to control and, so far as can be ascertained, there is no record that such an experiment has been tried (Northrop, 1953). Whether the study of the chemistry of pure products or systems is likely to be advantageous in the quest for the cause of acute pancreatitis, is a moot point. Some may argue against this approach to the problem on the grounds that it ignores the vagaries of pancreatic secretion which can only be appreciated by the study of living subjects. This criticism is sustained by the knowledge that contrary to the standard teaching outlined above, pancreatic juice freshly collected from a fistula, and which has had no contact with the duodenum or its content, may on occasion exhibit proteolytic properties. The anomaly of spontaneous activation was known to Heidenhain (1878) and /

and has also been recorded by Babkin (1904), Savitch (1909), Mellanby and Woolley (1913), Waldschmidt-Leitz(1925), and others. Northrop (1937) considered that this occurs by means of an auto-catalytic reaction and ascribed the transformation to some internal rearrangement in the molecular structure of the trypsinogen, which consists presumably in the hydrolysis of a polypeptide ring. Chymotrypsinogen is changed into the active form by the presence of trypsin. The so-called "vagus" juice, i.e. that which is evoked by stimulation of that nerve is particularly prone to become active (Savitch, 1909; Anrep, 1916): certain drugs, e.g. pilocarpine (vide infra) and a heavy meal have been shown to have a similar effect (Guleke, 1908; Rich and Duff). The type of meal may be important as implied by the observations made by Frouin (1907) and Chechulin (1923) that trypsinogen of pancreatic juice obtained from dogs on a meat diet is activated by enterokinase 50-80 times more readily than that of pancreatic juice secreted by the same animals on a bread and milk diet. Another /

Another influencing factor is apparently the reaction of the pancreatic juice. Heidenhain (1885) noted that the addition of an alkali retarded auto-activation whereas an acid facilitated the process. Mellanby and Woolley (1913) found that whatever agent neutralizes the alkalinity of pancreatic juice and does not destroy the trypsinogen produces rapid activation. The same correlation has been established in regard to "vagus" juice (Kudrevezki, 1890; Savitch, 1909). "Pilocarpine" juice which is usually partially active, also exhibits a lower alkalinity than that of "secretin" juice which is usually inactive (De Zilwa, 1904). These findings suggest that the normal alkalinity of the pancreatic secretion may be a safeguard against spontaneous activation.

The addition of calcium chloride to pancreatic juice in vitro appears also to convert trypsinogen into trypsin (Delezenne, 1905), but it is a slow process lasting about 7 hours (Effront, 1917). Mellanby & Woolley (1913) hold that the calcium does not initiate but only accelerates the rate of trypsin production. The presence of calcium in the pancreatic juice of a dog under the influence of various secreting agents was investigated by Pozerski (1905). All samples which were examined after the /

the administration of secretion were inert and none contained calcium, whereas pilocarpine produced a secretion which actively digested coagulated egg albumin and contained calcium in appreciable quantities. Mellanby & Woolley (1913) put forward the explanation that calcium possibly has the effect of removing the inhibitory alkali from the pancreatic juice and the enterokinase present is thus provided with the most favourable conditions for generating trypsin from trypsinogen. Even assuming as they believed that enterokinase is normally present in the pancreatic juice it is difficult to understand the chemical basis for this explanation. Northrop and his associates do not include calcium among the list of activators of amorphous trypsinogen and perhaps too much emphasis has been placed in the past on its influence on the proteolytic activity of the pancreatic juice.

The fact remains that spontaneous activation, whatever its mechanism may be, remains a potential source of danger which has been underlined by the recent reports of the effects of prolonged stimulation with parasympathomimetic drugs. Mecholyl tends to produce a severe hyperacute inflammation of the pancreas which may progress to focal haemorrhages, and may even be associated with /

with vacuolization of acinar cells and fat necrosis (Tucker, 1948; Werner, Sinion & Hoff, 1950). The contributing factors appear to be the nature of the resultant secretion and a degree of contraction of the ducts which Anrep (1915) described following vagal stimulation. There is also some evidence that the choline derivatives cause the sphincter of Oddi to contract (see page 181). A more mechanical block may arise as a result of congestion, oedema and even patches of ulceration of the duodenal mucosa, which have been observed in dogs following repeated administration of Mecholyl (Wener, Hoff & Sinion, 1948).

The opportunities for carrying out adequately controlled observations in humans with a pancreatic fistula are limited. Glassner (1903) and Wohlgemuth (1907) each reported a case in which they attempted to estimate the tryptic activity of the escaping secretion with negative results, Any appraisal of the results in such cases is likely to be difficult, however, since as a rule the precise location and depth of the fistula is unknown. The author has of late had such a condition to deal with following radical treatment for a chronic duodenal ulcer. The following are the main points.

W.McI., a male, aged 45 years, had subtotal gastrec- /

gastrectomy performed on 5th May 1953 for a duodenal ulcer of 12 years' standing. The mobilization of the ulcer-bearing area was not unduly difficult, and only the first part of the duodenum had to be sacrificed. The stump of the latter was enfolded without difficulty. Gastrojejunal anastomosis was fashioned behind the mesocolon according to Polya's method. The patient's condition during the immediate post-operative period was unsatisfactory, and there was generalised abdominal discomfort and distention which was relieved to some extent by continuous gastric suction and intravenous infusion. On the tenth day it was decided to reopen the wound. In the thin layers of the parietes there was some serous fluid and fibrin, but no sepsis or blood. The upper compartment of the abdomen was thoroughly explored. It contained about 10 oz of clear fluid, and the surrounding tissue was coated with masses of jelly-like material. There was no trace of bile or pus. The duodenal stump and the gastrojejunal anastomosis were examined carefully, but no sign of leakage was detected. To check this, dilute gentian-violet solution was introduced by stomach tube but none appeared in the peritoneal cavity. The abdomen was drained by means of a wide bore rubber tube, which was connected to an aspiration pump.

At first the possibility of a leakage from the thoracic duct was considered, but it soom became clear from estimation of the enzyme content on the fluid, that one was dealing with escaping pancreatic secretion. The only explanation that can be offered for the fistula is damage to a high placed accessory duct, and possibly one which conveyed most of the pancreatic secretion to the duodenum. Since it appeared that one was dealing with a pure pancreatic fistula, observations were carried out which are presented in Table 17. For these I am indebted to Dr. E. Hendry, Biochemistry Department of the Western Infirmary, Glasgow. The test used for the presence of trypsin was that directed by Charney & Tomarelli (1947). The results were equivocal so far as concerns factors governing proteolytic activity of the escaping fluid. There was no definite correlation between the findings in the fasting fractions and those following food plus pilocarpine or carbachol. Nor was it certain that the stimulation of the pancreas by such means produced exclusively an increase in volume of the secretion. The experiment lasted one week and towards the end of this period, the fistula was tending to close, a factor that may have affected the conditions of the experiment.

TABLE 17 . Observations on a Case of External Pancreatic Fistula which followed a Subtotal Gastrectomy dated 5th May 1953. The ph of the initial sample of the fluid was 6.7

		Tryptic Activity. % Protein digested.	Volume in ml.	Amylase Wohlgemuth units per ml.
20/5/43.	Initial Sample.	2		4,000
22/5/43.	Fasting Period.*	15		
23/5/43.	Fasting Period.	10	64	
23/5/53.	Food plus Pilocarpine. +	8	128	
25/5/43.	Food plus Carbachol. ⊕	11	185	
26/5/43.	Fasting Period.	5	110	4,000
26/5/43.	Food plus Carbachol.	1	94	10,000
27/5/43.	Fasting Period.	2	38	10,000
27/5/43.	Food plus Carbachol.	3	90	6,670

* Fasting Period lasted from 3 a.m. to 9 a.m.

\+ Fluid collected between 9 a.m. and 3 p.m. during which time 2 meals were given and after each gr $\frac{1}{100}$ Pilocarpine.

⊕ Fluid collected between 9 a.m. and 3 p.m. during which time 2 meals were given and after each 0.5 mg. Carbachol.

It is pertinent to mention that the pancreatic juice may exhibit toxic properties when permitted to flow unchecked into the peritoneal cavity although the authorities are not agreed upon this question. Guleke (1908) found that all his dogs died. Dragstedt et al. (1934) considered that its presence was innocuous irrespective of its proteolytic activity. The more recent work of Noskin et al. (1952) indicates that such a leakage of pancreatic juice is usually associated with a high mortality. This survey of the factors controlling the tryptic activity is far from complete. It is also unbalanced in that no mention is made of the anti-tryptic factor. What part it plays in the etiology of acute pancreatitis is uncertain. Rich & Duff offered a view that this condition may result from a temporary deficiency of the anti-ferment. Its potential therapeutic value is considered later.

The Structural Effects of Duct Ligation.

The results of this apparently straightforward procedure have proved more varied than might be expected. This is explained partly by inherent differences in the pancreas of various species used for the experiment and partly on the time chosen in relation to the secretory activity of the gland. Acinar atrophy, for example, generally starts after 48 hours, but develops earlier in cats and rabbits (Clerc & Loeper, 1909; Milne & Peters, 1912). Some have noted that the pancreas assumes an oedematous appearance within the first 24 hours irrespective of function (Gould & Carlson, 1911; DeTakats, 1929; Gibbs & Ivy, 1951; Thistlethwaite & Hill, 1952). While others have concluded that this appearance is found only when the gland has been subjected to active stimulation (Hess, 1909; Wangensteen et al., 1932; Popper & Necheles, 1942; Lium, Portmouth & Maddock, 1948). On microscopic examination the oedema is seen to take the form of widening of the interlobular spaces with infiltration of leucocytes (figs.54,55); sometimes the latter is not a feature, as may be deduced from figs. 52, 53. The oedema or glassy /

glassy appearance is due to extravasation of the pancreatic juice, and naturally its extent will depend on the amount of secretion contained in the duct system and the productive capacity of the gland at the time when the ligature was applied and subsequently. Widening of the interlobular spaces with varying degrees of leucocytic infiltration was observed by the author in the three experiments in which the duct was ligated in the fasting state. And in one fibroblastic change was evident by the third day, and well advanced fibrosis by the 12th day. In fasting rabbits, Wang, Wang & Grossman (1950) observed dilatation of the larger ducts 12 hours later, and also vacuolation of some of the acinar cells with loss of affinity for stains. After 24 hours some of the intralobular ducts become dilated and after 48 hours the end chambers were affected and the parenchyma was degenerated and becoming replaced by fibrous tissue. The number of ductules appeared to be increased. Later the glandular elements were reduced to clusters of cells. Fig. 57 is an illustration of dilatation of the ducto-acinar terminals. In dogs, the structural changes usually take 48 hours to become established, but otherwise follow the same course. Provided continuity with the duodenum is not established, as may /

may readily happen (Milne & Peters, 1912), the end picture is dominated by diffused fibrous tissue, thick walled vessels, focal accumulations of leucocytes and increase in fatty tissue. The islet cells do not as a rule suffer (Johnson & Wiés, 1932), but instances of atrophy have been recorded (Milne & Peters) or, as is more probable, these cells become so altered as to be indistinguishable from those of atrophic or distorted acini. After 24 weeks de Takats could not find any sign of acinar tissue. The islet elements were considerably enlarged and well preserved. The rest of the glands consisted of connective tissue arranged in a wavy circular configuration around the islet cells. The effects of long standing obstruction are demonstrated in figs. 71 & 72 which were taken from a case mentioned earlier, which a partial duodeno-pancreatectomy was performed by the author for a carcinoma of duct of Wirsung. The latter being so dilated, there was no difficulty in making a ducto-intestinal anastomosis. The operation was further simplified by the fact that the patient had had a partial gastrectomy two years earlier.

Fig.70

Transverse section of the neck of the pancreas showing grossly dilated duct of Wirsung and extensive fibrosis of the gland substance. At the ringed part several nests of cancer cells were found indicating that the line of section had been carried through tumour tissue. (x4)

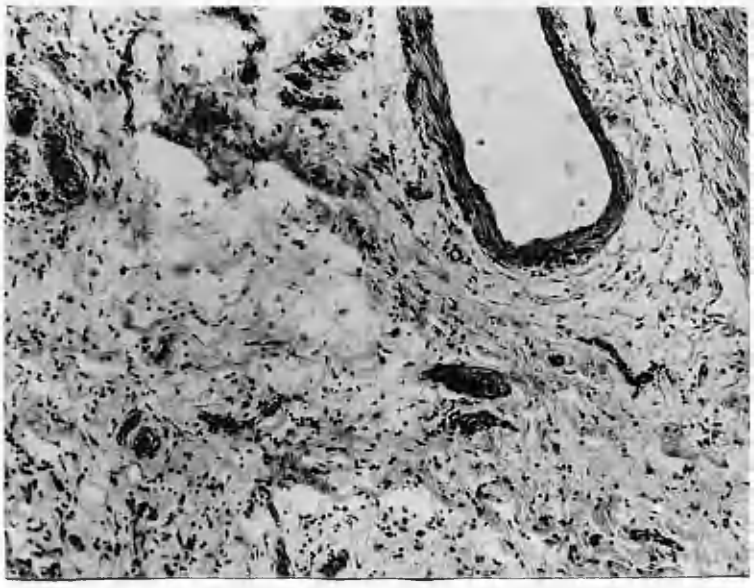


Fig. 71 A non-invaded part of the pancreas showing gross fibrous replacement with scattered lymphocytic infiltration. (x100)

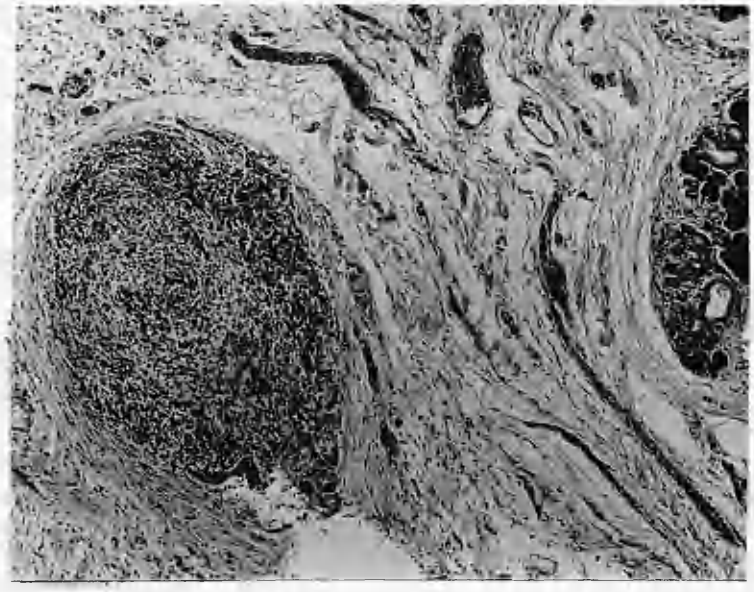


Fig. 72 Another part of the field showing on the left the aggregation of lymphocytes and on the right a few surviving acini. (x100)

Gibbs & Ivy (1951) compared in the dog the effect of tying the major duct with the effect of applying a pressure to this duct of 300 mm. water from a reservoir of saline. In controls in which the duct was simply exposed, as in the author's first series of experiments, only a few inflammatory cells were apparent under the capsule of the pancreas but no oedema. Following simple ligation there appeared within 24 hours a considerable degree of oedema which had spread through the interlobular spaces and under the capsule. Polymorphonuclear and other inflammatory cells were numerous but none were noted among the acini. At this stage there was no acinar degeneration, no separation of acini, or dilatation of duct terminals. The acinar cells were well stocked with zymogen granules. When the duct system was subjected to a pressure of 300 mm. water the oedema appeared sooner and was more pronounced than in the previous experiment. There was also more intense infiltration of cells between the lobules and many had found their way into the interacinar spaces. In some /

some instances total disappearance of acini had occurred, but this was limited to small foci which tended to lie in the vicinity of the smaller ducts. Numerous erythrocytes were present in the tissue spaces. Vacuolization of acinar cytoplasm was largely limited to the latter group.

The Effects of Hypersecretion. It has, of course, been long known that the most pronounced changes ensue when the ducts are tied during or preceding an active phase of pancreatic secretion. In fact, Hess (1909) was encouraged by his experimental findings in the belief that acute pancreatitis may be due to the stimulating effect of a meal on a pancreas in which the secretion can find no outlet, either through the main duct or through the accessory duct. Coffey (1942) avulsed the minor ducts in 6 dogs and ligated the major one. Then following the intravenous administration of pilocarpine, 4 dogs expired in less than 10 hours and at autopsy gross evidence of pancreatic damage was found. Lium, Portsmouth & Maddock (1948), after applying a ligature to the main duct while the pancreas was in an active secretory phase, found lesions varying from mild oedema to the beginnings of acinar destruction and in parts entire lobules undergoing dissolution. The stimulants used were food, secretion, Mecholyl. In the author's /

author's experiments, the animals were not subjected to artificial stimulations nor were they fed before the duct was ligated, and the histological changes were, as might be expected, grade I in degree. My observations on the effects of obstructing an actively secretory gland are confined to humans, viz. the experiments carried out in which the blocking agent was morphine. The interruption in the flow of pancreatic juice in these subjects could not have lasted more than 4 hours (see page 168) and yet the disturbance in the serum enzyme concentration was in some instances very considerable and, one might even say, of a degree to justify the diagnosis of acute pancreatitis. Against this was the lack of abdominal pain although the presence of this might have been masked by the morphine.

There are insufficient data as yet to allow of a critical assessment of the supposition that a sudden interruption in the flow of pancreatic juice is a factor in the pathogenesis of acute pancreatitis. There appears to be an overreadiness to equate the presence of aggregations of polymorphonuclear amd other cells with the presence of an infective process, whereas their presence is probably explained on a chemotactic basis, i.e., the extravasated pancreatic juice, or again to speak of acinar /

acinar necrosis as if it implied a different significance from the parenchymatous atrophy which naturally ensues in an obstructed pancreas. Gibbs and Ivy, for example, interpreted their histological findings (see page 266) in the dogs in which a pressure of 300 mm. saline was applied as having reproduced the picture of acute purulent, haemorrhagic and necrotic pancreatitis. I agree with the view expressed by Shingleton et al. (1952) that pancreatitis produced in this manner resembles the milder forms of pancreatitis encountered in humans. In their study of the effects of ligating both pancreatic ducts in dogs during stimulation with pilocarpine and secretin, the variety of pancreatitis was relatively non-lethal although it is to be noted that 2 out of 10 died. Nevertheless, there appears to be some missing link and this may well be the vascular factor. In a comprehensive study of the conditions which in combination with the presence of obstruction produced the maximum damage to the pancreas, Popper, Necheles & Russell (1948) observed that the administration of secretin or blockage of the lymph flow from the pancreas or venous blockage merely resulted in pancreatic oedema, whereas a temporary occlusion of the pancreatic artery for 15 minutes under the same conditions resulted in gross acinar damage. /

Damage of a similar kind had been recorded earlier by Smyth (1940) following injections of droplets of mercury into the main artery to the pancreas in dogs. According to Ivy, Grossman and Bachrach (1950) the pancreas will digest itself if it is deprived of all or much of its blood supply, the implication being that one of the effects of ischaemia is to convert trypsinogen into active trypsin (Ivy and Gibbs, 1952).

Acute Interstitial Pancreatitis in Humans. The similarity between the more immediate effects of duct ligation, and those found in the clinical condition known as acute oedema of the pancreas or interstitial pancreatitis, is too striking to be ignored. In fact, this form is coming to be called an obstructive pancreatitis. The earliest accounts of this condition were given by Salsted (1890), Villard and Brause (1909), Mercade (1919) and Zoeppfel (1922). Zoeppfel, who reported four cases, placed emphasis on the glassy appearance assumed by the pancreas. Elman (1933; 1937a,1937b,1942) has reviewed the literature and collected many cases of his own. The extent of the oedema appears to be quite remarkable spreading in some cases into the mesocolon, transverse colon, and adjacent duodenum. The gland is swollen and hard, with a glassy surface which /

which occasionally presents a bilious tinge. Elman took this to indicate that bile has penetrated into the intestices of the gland and that this was the usual casual mechanism: others have considered this form as purely an obstructive condition (Casberg, 1939; Cole, 1937, Dunlop & Hunt, 1938). Besides the oedema, infiltration of polymorphonuclear leucocytes was a common finding on microscopy. The cellular structure was not affected in any of the specimens examined.

About half of the author's series of cases were of the subacute variety of pancreatitis but only one patient showed gross evidence of oedema on operation. The patient, an elderly female, was thought at first to be suffering from intestinal obstruction, and it is noted that Elman (1933) made the same mistake in six of his cases. The duration of illness in my case was 6 days during which time she suffered epigastric pain of moderate degree, frequent bouts of sickness and constipation. At operation the gland was swollen, nodular and hard, and had a glassy surface. The root of the small bowel mesentery was thickened and oedamatous to the extent of a few inches. In some parts the small bowel was distended and at others contracted. The oedema of the root of the mesentery might well have been responsible for /

for the intestinal spasm. Biopsy was taken from the head and body of the gland (figs. 73 & 74). The biliary tract seemed to be normal on external examination, and as the patient was over 70 years of age, it seemed unjustified to search further for the cause of the disease. The patient made a satisfactory recovery.

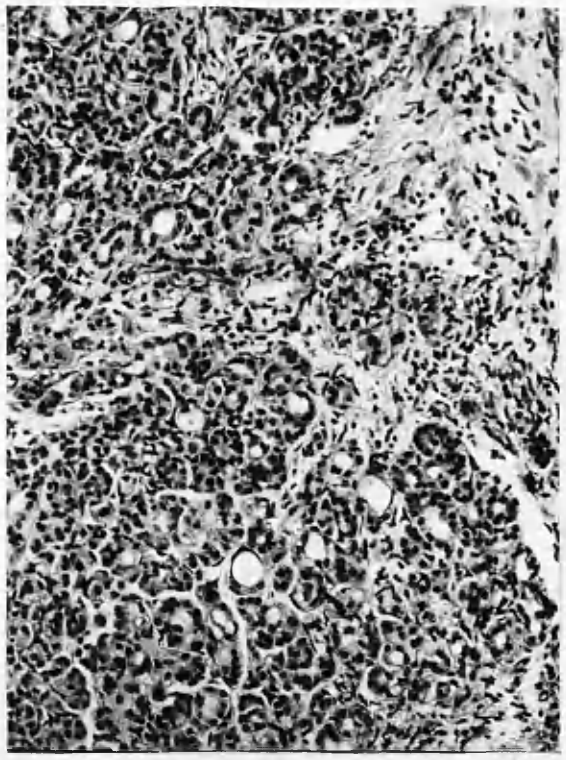


Fig. 73

Acute interstitial pancreatitis showing a loss of general architecture with dilatation of ductules or acinar terminals. Towards the upper right of field some glandular units have atrophied and are being infiltrated with round cells and fibroblasts. (x190)

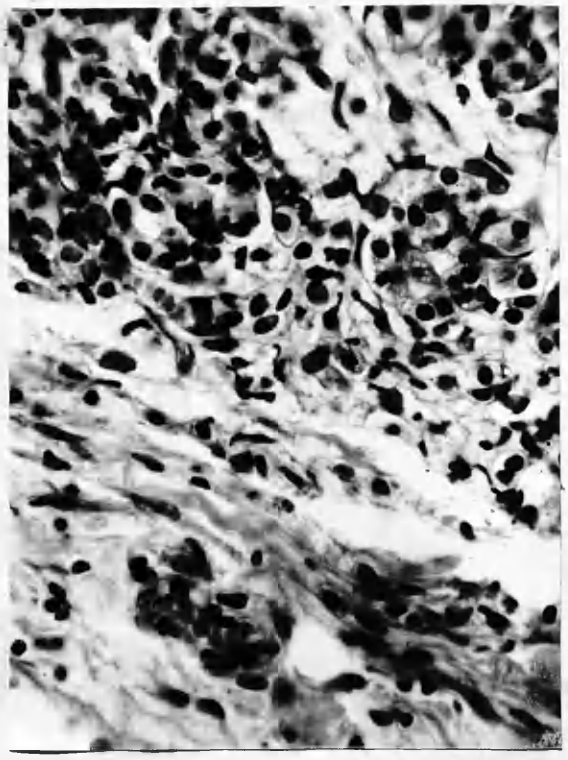


Fig. 74

Another part of the field at much higher magnification to show the acinar distortion and nearby fibroblastic change. (x400)

Lastly, there is the more factual evidence that ligation of the pancreatic ducts can be carried out if need be in the radical operation for growth affecting the head of pancreas without fear of inducing necrosis or even appreciable oedema of the gland. (Cattell, 1953). This surely lends substance to the view that duct occlusion per se should be relegated to a place of lesser importance in the aetiology of acute haemorrhagic or necrotic pancreatitis.

The Serum Enzyme Changes.

Amylase & Lipase. It is firmly established that obstruction of the main secretory pathway to the pancreas is followed by a prompt rise in the serum amylase concentration (Schlesinger, 1908; Clerc & Loeper, 1909; Johnson & Wies, 1932; Golden et al. 1939) which is usually paralleled by a similar rise in the lipase titre (Cherry & Crandall, 1932; Nochman et al. 1948). The question at issue is whether the amplitude of the increase is proportional to the extent of the damage. Wohlgemuth (1909) and McCaughan (1934) working with dogs, each onserved that ligature of the smaller (upper) duct produced less effect on the amylase levels than ligature of the larger one, and the most marked effect resulted when both were tied. This is understandable considering the gross disparity in the areas subserved by these two ducts in the canine species. Further support for belief that there is a correlation with the extent of the pancreatic obstruction is found in the observations by De Takats and Nathanson (1929) in their comparison between the enzymatic effects of tying a mass ligature round the tail of the pancreas and those of tying one round the head. Others /

Others contend that the enzyme changes are proportional to the parenchymatous damage inflicted by irritants of different kind injected into the pancreas via the main duct. Thus, Clasen et al. (1934) noted that an injection of a saline suspension of B.coli in bile produced the most virulent inflammatory reaction and the greatest increase in serum amylase. Sodium taurocholate produced a pathological lesion and enzyme changes next in severity, while sterile bile produced the least effect. McCaughan (1934) was encouraged from his animal studies to draw the same conclusion. Baxter et al. (1938) considered that the rise in serum lipase was dependent on the amount of oedema or inflammatory reaction caused by retrojection of bile up the main duct of the dog, although it is noted that they advanced the suggestion that in the more severe grades of experimental pancreatitis the level reached may not be so high owing to extensive destruction of the blood or lymph vessels. This is a significant admission of the variability of their results, which was also a feature of the author's results both in the dogs in which the main duct was simply ligatured, and in those in which bile was injected prior to the application of the ligature. Thistlethwaite & Hill (1952) studied the effects of ligation in /

in the fasting state, after vagal stimulation plus arterial occlusion (pancreatic vessels,) and after an intraduct injection of bile. There was little appreciable difference in the ensuing changes in the serum amylase except for slightly more precipitate rises in those animals showing number 2 and 3 grades of pathological damage. Gibbs & Ivy (1951) formed the opinion that the application of a pressure of 300 mm. water from a reservoir of saline evokes a serum amylase rise comparative to that of simple duct ligation but in the former group of experiments it took half the time that was taken in the latter to attain maximal levels. The general impression gathered from analysis of the writer's findings was that the rise in levels of amylase and lipase do not bear a definite relationship to the severity of the damage to the pancreas. The common factor in my series was obstruction, the principal duct being ligated in all experiments except those in which the duct was exposed but not tied. A slight but decided rise was observed in the latter group. Gibbs and Ivy, on the other hand, found that exposure of the duct did not disturb the serum amylase levels. How much the enzyme equilibrium is affected will probably depend on the extent of dissection required to expose the duct.

Maximum levels are usually reached within 24 hours according to some observors (Wohlgemuth, 1909; Gould & Carlson, 1911) and 72 hours according to others (Schlesinger; McCaughan). In the author's experiments the peak values lay between these times. It is generally accepted that the flooding of the peripheral blood with surplus pancreatic ferments is a transitory phenomenon, lasting not more than a few days. In Schlesinger's original experiments the abnormal values were not maintained beyond the third post-operative day. In Wohlgemuth's dogs they had returned to normal levels by the 8th to the 10th day. In Johnson and Wies' dogs they were sustained for 5 to 12 days, and 8 to 18 days in McCaughan's. In the author's observations on humans with morphine as the means of obstructing the pancreatic ducts, appreciable increases in both amylase and lipase concentrations were noted as early as one hour after giving of the drug and the highest levels were reached between the third and fourth hours.

The explanation given by Schlesinger for the changes, viz., that resorption of the starch-splitting ferments takes place as a result of passive back pressure, is generally accepted as the correct one, and according to Nochman et al. the same holds good for the olive-oil splitting ferments. /

Popper and Necheles (1940) studied the pathways taken by the enzymes to reach the peripheral circulation. They found that compression of the portal vein delayed or prevented a rise in concentration of amylase in the peripheral blood. When the portal vein was released a pronounced rise did occur in the peripheral blood and in samples of lymph taken from the thoracic duct. They concluded that the enzymes were absorbed directly from the pancreas into the blood stream, and that lymphatic absorption played a minor rôle. Their experimental findings have been confirmed by Howard, Smith and Peters (1949). Recently Janowitz and Hollander (1951) have suggested that the excretion of certain digestive enzymes may be partly into the lumina of the glands and partly into the blood stream. There is evidence of a quantitative nature in favour of this for the peptic activity of the stomach but there is as yet no proof that the same obtains for the ferments of the pancreas. Janowitz and Hollander refer to this as the exocrine-endocrine partition and suppose that a rise in the amylase or lipase concentration of the blood may not merely be a spill over, as it were, into the blood stream, but an upset in the balance of the partition.

Secondary and sometimes tertiary rises in amylase concentration (Gould and Carlson) and in lipase concentration (Cherry and Grandall) may occur 3 and 5 weeks respectively after ligation of the ducts. A secondary rise was also noted by de Takats et al. following ligature of the tail of the pancreas, but not after tying the tail plus head. Gould and Carlson explained these episodes on the following basis. The initial increase in pressure resulting in widespread extravasation tends to have an injurious effect on the secretory units leading to diminished activity and possibly pressure atrophy. This is followed by a period of diminished secretion, followed by renewed activity and a further rise of pressure, which can only be relieved by absorption of the excess secretion into the blood. The consensus of opinion is that enzyme equilibrium again becomes stabilized within a few weeks. Golden et al, (1939) dispute this on the grounds that the earlier workers failed to demonstrate complete dissociation of the pancreas from the duodenum and that in long term experiments the pancreatic juice may have destroyed the tissue around a ligature and so caused a communucation with the duodenum to reform. To prevent this, Golden and his colleague tied off all the ducts and interposed /

interposed omentum between the pancreas and the duodenum. Two of their 4 dogs showed a raised blood amylase concentration persistently for many months. At the termination of the experiment, virtually no secretory tissue remained on post-mortem examination, and Golden et al. were at a loss to explain the sustained rise in amylase levels. Popper and Sorler (1941) repeated their experiment and extended the scope to include the blood lipase. Two of their dogs lived for a period of one year following complete isolation of the pancreatic secretion from the alimentary canal, but there was no permanent increase of either the amylase or lipase concentration, although one dog had secondary and tertiary rises within the first few weeks of the start of the experiment. The drop in the serum amylase levels following complete obstruction may be taken to mean either recovery or depression of the secretory capacity of the pancreas. Wang, Wang and Grossman (1951) ligated the main duct in rabbits and cannulated the ducts proximally. Repeated examinations of the pancreatic secretion under these conditions revealed that the amylase response to secretin and pancreozymin was much reduced in 24 hours and poor after 4 days; by the 10th day or so no amylase could be /

be detected. These observations indicate, as Ivy and Gibbs point out, that an incomplete obstruction may be a more potent factor in the genesis of acute pancreatitis than a complete one. The question arises how much the serum enzyme changes can be related to the aetiology of this disease. My clinical findings (Wapshaw, 1948) and the experimental data presented were remarkably variable and encourage the view that such tests are a poor yardstick of the severity of the pancreatic damage. It does, however, appear fairly certain that most pronounced increases in amylase or lipase levels result from some form of interference with the flow of pancreatic secretion whether this be a mechanical block or an inrush of bile, whereas those that follow local trauma to the gland are relatively slight. This view is supported by my experiments in humans (pages 168 & 185). McCaughan (1934) noted slight amylase increases from crushing the tail of the pancreas in dogs: gentle manipulation had no effect. Only moderate increases in the serum amylase levels were reported by Wohlgemuth and Noguchi (1912) after ripping or piercing the organ with a knife.

Trypsin. For many years it has been thought that the constitutional upset associated with acute pancreatitis is due, inter alia to trypsin toxaemia (Guleke, 1908). Oddly enough, until very recently this theory has depended on the variations in the anti-tryptic index (Petersen, Jobling and Eggstein, 1916; Coffey, Brinig and Gillespie, 1951). Reliable means of detecting an increase in the proteolytic activity of the blood are now available (Lasher and McCabe, 1950; Rush and Cliffton, 1952; Hoffman, Jacob and Friedlander, 1953). However, the problem is complicated by the presence of a natural proteolytic principle, plasmin or, as the recent Conference on Blood Clotting and Allied Problems (1953) preferred to call it, fibrolysin. It occurs initially in an inactive form and when activated participates in the normal clotting process. It is uncertain whether the increase in the proteolytic activity observed in certain cases of acute pancreatitis is due to conversion of the precursor of this proteinase into the active form by pancreatic trypsin or merely results from excess of the latter. The fact that acute and subacute pancreatitis is sometimes associated with alterations in the clotting /

clotting mechanism such as a reduction in the plasma prothrombin (Bechgard, 1941; Strombeck, 1941; Brogstron, 1944) and prolongation of the coagulation time (Lasher & McCabe, 1950; Storer & Kazdan, 1953) has stimulated an interest in the effect of trypsin on the coagulability of the blood. Apparently in small amounts it produces clotting in vitro, while experimentally in vivo it fails to do so, possibly owing to the presence of circulating antisubstance (Innerfield et al., 1952). In large doses trypsin has a powerful anti-coagulant effect both in vitro and in vivo when applied to artificially formed intravascular thrombi in rabbits. Reports on the general effect of trypsin injected intravenously into normal subjects are conflicting. For instance, Mersley and Freis (1944) noted in animals severe shock with hepatic and renal changes and extensive intravascular clotting. Yet Innerfield et al. administered it in crystalline form to 101 human subjects and found that the only untoward reaction was an occasional mild chill towards the end of the infusion. The above short survey of the subject has been given, because no personal observations on the subject have been made. Two interesting inferences may be drawn (1) that some factor in the pancreatic /

pancreatic secretion has a bearing on the blood clotting mechanism, and (2) that acute and possibly subacute pancreatitis may affect the coagulability of the blood.

Therapeutic Applications.

On the premise that acute pancreatitis is essentially a proteolytic process the search for a more effective form of treatment is actively proceeding along two main lines. The aim of one is to minimize the local effects of trypsin by interrupting the nerve impulses which control its production; the other is an endeavour to combat its more widespread effects by means of anti-tryptic agents.

As regards the latter, an inhibitor substance crystallized from the soy bean is being used, but so far trials have been limited to dogs with bile-induced pancreatitis. The first to report its action, Coffey et al. (1951) and later Rush & Cliffton (1952), were favourably impressed with their results and concluded that it gave some protection against shock. On the other hand, Hoffman, Jacobs & Friedlander (1953) have since found little difference in the mortality of the untreated and the treated animals. Nor were the trypsin levels affected by the inhibitor substance. The soy bean tryptic inhibitor by virtue of its anticoagulant properties, may cause spontaneous haemorrhages /

haemorrhages and it is regarded by some as being toxic to the liver (Noskin, Popper & Necheles, 1952).

As regards interruption of nervous influence, the secretory action of the vagus can be checked either by neurectomy or by the exhibition of a so-called blocking drug. The beneficial results of vagotomy were recently reported by Schaffarzick, Ferran & McCleary (1951). They obstructed the pancreas during a secretory phase and compared the functional and structural changes in the vagotomized animals as against the control series. They took as their criteria of betterment a lowering in the levels of the expected increase in amylase concentration and also the reduction in histological changes in the former group. Ripstein & Thompson (1951) also gave a good report of its value in ameliorating the more serious effects of intraduct injections of a bile-trypsin mixture: and McCleery, Kesterson & Schaffarzick (1951) were convinced of its therapeutic value in patients with chronic recurrent pancreatitis. During the past few years splanchnicectomy has been practised as a pain-relieving measure for the relapsing form of pancreatitis (Reinhoff & Baker, 1947; Ray & Neill, 1947; de Takats, Walters & Larsner, 1950.) It may /

It may be said in favour of splanchnicectomy, that it is not only a means of severing pain-conducting fibres, but may also modify the secretory output of the gland for it has long been known that the amount of pancreatic juice secreted after splanchnic nerve stimulation is qualitatively similar to that secreted after vagal stimulation although perhaps in amount smaller. (Kudrevetski, 1890; Babkin, Hibb & Sergeyeva, 1939). According to recent evidence (Lake et al. 1951), however, the performance of an extensive sympathectomy in humans with a normal pancreas has no appreciable effect on secretory function: moreover, Ripstein & Thompson (1951) hold that this operation serves merely to eliminate or mitigate the pain of acute pancreatitis, but does not alter the course nor lessen the mortality of the condition. It would appear that neurectomy, whether vagotomy or sympathectomy, is likely to be replaced by drugs endowed with the property of interrupting the impulses passing along these nerves, in other words chemical neurotomy.

Methantheline bromide (Banthine) has received the approval of the Council on Pharmacy and Chemistry in the U.S.A. (1952) as a means of controlling (1) the /

the factor of excessive vagal stimulation in such conditions as peptic ulcer, and (2) disorders of the intestines and gallbladder characterized by hypermotility, among several other conditions. Encouraging reports have appeared of its value in the treatment of acute pancreatitis. Banthine is primarily anti-cholinergic in action; in larger doses it acts on the autonomic ganglia, and in still larger doses has a curare-like effect. Depending on the amount given it produces a pronounced inhibition of the secretory response of the pancreas to a meal rich in protein for periods ranging from one to four hours in dogs (Annis & Hallenbeck, 1951) and has a similar effect in humans (Shingleton, Fawcet & Vetter, 1951; Capper & Tovey, 1954). Since the drug also reduces the concentration and total output of hydrochloric acid from the gastric mucosa, the hormonal influence of secretin is temporarily suspended as well. The general effect, in other words, is to put the pancreas completely at rest. Banthine has been used both in human cases (Ripstein & Thompson) and in dogs (Shingleton, Anlyan and David, 1952) suffering from severe forms of acute pancreatitis, with promising /

promising results. In this country Davies, Moore & Wynn-Williams (1953) have found that hexamethonium relieves the agonising pain of this disease for periods up to six hours and advised continuing the administration for a period of 5 days. Capper & Tovey were also impressed by the clinical improvement conferred by this drug, but considered the side-effects, especially the tendency to lower the blood pressure, a serious drawback; they suggested that methantheline or the more recent propantheline bromide (Probanthine) or even atropine pushed to limits of dosage, give equal relief without affecting the blood pressure to such a degree. Probanthine is believed to have a greater potency than Banthine in respect of its blocking effect both on the effector sites of the parasympathetic nervous system and on the ganglia of both the parasympathetic and sympathetic divisions. Banthine is, of course, not free from side-effects, the commoner being drying of the salivary secretions, mydriasis, and difficulty in emptying the bladder and rectum (Grimson, 1950). Schwartz et al. (1953) found that Probanthine produced less annoying side-effects in a large series of patients previously treated with /

with Banthine. A point that seems so far to have escaped consideration is the functional state of the affected pancreas. Studies of the duodenal content by using secretin as a secretogogue have shown that the severe forms of acute pancreatitis in particular cause a marked diminution both in volume and the total enzyme content of the above, which may last several weeks (Diamond & Siegal, 1940; Wirts, 1951). Accordingly, the value of these blocking drugs may well depend entirely upon their pain-relieving properties.

To close with a discussion on the therapeutic application of the knowledge that has been furnished from the foregoing work is perhaps presumptuous and implies an endorsement of the theory that overstimulation of the vagus nerve is largely responsible for the pathogenesis of acute pancreatitis. While there is strong evidence that acute retention during a hyper-secretory phase is a precipitating factor, other factors must be taken into account, such as access of bile to the gland tissue, or some vascular disturbance. If, on the other hand, a process characterised by the continued output of active secretion and proteolytic digestion of the pancreas /

pancreas is the ultimate result, then a nerve blockade seems a rational procedure. For reasons already stated, however, any benefit derived from the anti-cholinergic drugs may be more dependent on their blocking action on the sensory fibres of the vagus than on the secretory.

SUMMARY.

Since I have made only a selective survey of the literature bearing on the pathogenesis of acute pancreatitis, any attempt to reach a conclusion is decidedly open to censure. Nor have my researches been extensive enough for the results to carry much weight by themselves. Accordingly, the following statements should be regarded as more in the nature of impressions.

To establish the complicity of bile is more difficult than is generally imagined for the following reasons. (1) The damage which follows forcible intraduct injection is not specific and can be reproduced by other noxious fluids, such as hydrochloric acid, intestinal fluid, and trypsin. (2) The response to intraduct injections of the same volume of bile, which is found in any given series of animal experiments, is very varied. The matter was considered from three aspects. - firstly, the amounts and force used, secondly, the local irritant action of bile, and thirdly, its influence on proteolysis.

Sterile homologous bile in quantities of 2 ml. and over, when injected by the main ducts of the pancreas produces patchy cytolysis, fat necrosis, and haemmorhages.

Lesser amounts of bile inflict minimal changes. When introduced at pressures not much above the normal secretory pressure of the pancreas, bile is less lethal to this organ. The highly irritant action of sodium taurocholate may account for the excessive damage caused by 1 ml. instilled at a pressure of 180 mm. water. The general inference is that both the amount of bile and the force with which it is introduced, are telling conditions.

It is difficult to be decided on the question of the alleged local cytolytic action of bile. There is some reason to believe that bile is more prone to affect only cells whose cellular structure has received prior damage.

A diligent search of the literature has failed to trace any evidence to support the contention that bile is capable of activating trypsinogen.

The factors controlling the tryptic activity of the pancreatic juice may yet turn out to be a promising topic for investigation, but there is at present no tangible evidence that spontaneous activation, by say vagal stimulation, provides the conditions favourable for the development of haemorrhagic necrosis.

The early changes in the obstructed pancreas are characterised by the histological picture of widened interlobular spaces, and an "inflammatory" infiltrate /

infiltrate consisting of polymorphs, plasma cells, and lymphocytes. On the other hand, very little structural change may result. There is evidence that the most florid changes occur in association with active secretion. In contrast to the widely dispersed intralobular destruction seen in bile-induced pancreatitis, the acini which are affected, if at all, are those lying at the periphery of the lobules. The likelihood that this experimental picture has its counterpart in the clinical conditions known as acute oedema or acute interstitial pancreatitis, is admitted. It is questionable if the features described are a transitional phase and prone to progress to that of haemorrhagic necrosis. A search for an additional factor is indicated and this may well be temporary ischeamia. Another may be a temporary failure on the part of the anti-tryptic mechanism.

Significant changes in the amylase and lipase concentration of the blood plasma have been recorded in animals who have had the pancreatic duct tied. They reach their peak around the second post-operative day and return to normal takes place over the succeeding /

succeeding 10 days or so. Further studies are needed on the serum proteolytic changes before we can finally decide whether or not they have a prognostic significance. The same applies to the observations made on the anti-tryptic index of the blood.

As regards the management of acute pancreatitis, it seems that we are on the threshhold of a therapeutic advance. The results of chemical neurotomy are promising, but further studies are needed before we can finally assess the worth of the drugs employed or their mode of action.

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