In this series the mortality rate was 10%, and the failure rate with expectant treatment was 12.5%. Thirty-one cases out of 32 with perforated duodenal ulcers recovered under expectant treatment, but only one out of four cases with anterior perforations of the stomach survived. There was a high incidence of chest complications during treatment.

The expectant method of treatment has now been abandoned in favour of early laparotomy in every case.

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SIGNIFICANCE OF RAISED SERUM- ENZYME LEVELS IN PERFORATED PEPTIC ULCER

BY

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Aside from renal considerations, a rise in the amylase content of the blood or urine is generally regarded as an indication of some form of damage to the exocrine system of the pancreas. The gross and the microscopical pathological changes may conform to one of the recognized types of acute pancreatitis or may be so slight as to be imperceptible: instances of the latter have been recorded in which presumably the duct of Wirsung has been affected by the presence of gallstones or of some other agency such as a T-tube left in the common duct for drainage (Millbourn, 1936; Lewison, 1941). In others, a chronic duodenal ulcer burrowing into the pancreas is the disturbing factor (Probstein, Wheeler, and Gray, 1939).

There is experimental evidence to show that the amylase, after its escape from damaged acini or ducts, finds its way into the peripheral blood mainly via the portal system: lymphatic absorption plays a secondary part (Popper and Necheles, 1940; Howard, Smith, and Peters, 1949). It would now appear that a free perforation of a gastric or duodenal ulcer has some claim to be regarded as one of the conditions likely to cause the blood or urine amylase levels to rise. Mikkelsen (1934) cited instances from his own experience in which this complication was associated with hyperdiastasia, but gave no details of the incidence or significance of this finding.

The first large-scale study of the problem was carried out by Hughes (1942). He investigated 40 patients with perforation of a gastric or duodenal ulcer and found four with a urinary diastatic index of the order of 300. I studied the concurrent amylase and lipase changes in the blood in a series of 30 perforated cases, in none of which was the pancreas involved by ulcer (Wapshaw, 1949). Slight deviations from the normal standards were noted in four and substantially raised values in two cases. High though the latter were, they fell short of the values obtained in two cases of acute pancreatitis which were comparable in respect of the duration of illness. Musgrove (1950) has recently added three more to the list, apparently the first to be reported from the Mayo Clinic. One was a perforated reticulum-cell sarcoma; the other two were ordinary perforated peptic ulcers.

The aetiological significance of the increases in enzyme content of the blood or urine is still uncertain. Hughes suggested that they might be due to (1) an overlooked patch of acute pancreatitis; (2) a second peptic ulcer lying posteriorly and adherent to the pancreas; or (3) transperitoneal absorption of the pancreatic ferments contained in the gastric or intestinal contents which had passed into the abdominal cavity. Neither of the first two probabilities was confirmed in the cases which were examined post mortem.

A group of workers at the Mayo Clinic—Pemberton, Grindlay, and Bollman (1950)—stimulated by Musgrove's findings, carried out what seems to be the first experimental attempt to trace the source of the surplus amylase. Not only did they duplicate in dogs the conditions in humans, but they were also able to define the perforations both in time and in location. A decided rise in the serum amylase was observed in animals which suffered perforation within one to two hours after a full meal—that is to say, when the pancreas was secreting to full capacity. If the perforation was delayed for three to four hours the amylase levels in the blood were unaffected. In samples of the peritoneal fluid withdrawn by abdominal paracentesis the amylase concentration of the early group was about six times that of the later. The mortality from peritonitis was very high, particularly among animals belonging to the former group, but, according to the control experiments, peritonitis cannot be held responsible for the hyper-enzymaemia. Pemberton *et al.* concluded that the determining factor was the amylase concentration of the free fluid in the abdomen.

In the course of previous clinical study I independently accumulated data bearing on points studied by the Mayo Clinic team, such as the times of the previous meal and the enzyme activity of the fluid inside the abdominal cavity encountered at operation. It seems of value to place these findings on record. The results are further amplified by the inclusion of repeat serum-enzyme observations which were made in most of the patients 24 hours after the initial readings.

Findings in 32 Perforation Cases

Pathological Data

It must be emphasized again that in none of the cases had the ulcer process implicated the pancreas. The site-incidence of the perforations was as follows: pyloro-duodenal, 29; gastric, 2; anastomotic, 1. Simple closure was carried out on 28 patients, with one death. Two patients were admitted to hospital with widespread peritonitis and died soon after (Cases 1 and 27). There were also two late cases which had developed sub-hepatic abscesses when first seen; both made a good recovery following open drainage (Cases 31 and 32).

In Case 27, at necropsy, a second ulcer was found lying posteriorly and loosely adherent to the pancreas. A few spots of fat necrosis were also observed in the fatty tissue of the lesser and greater omenta of this case. Yet the parenchyma of the gland appeared normal on section, and certainly the enzyme findings in the blood gave no reason for one to think otherwise.

Enzyme Findings in the Blood

Amylase and lipase estimations were carried out with the same sample of blood. In the former, the Somogyi iodometric test was employed. The normal values range between 70 and 200 units per ml. of serum. For

determining the lipase activity the Cherry and Crandall method was used. Normal values do not exceed 1.5 ml. of N/20 NaOH per ml. of blood serum.

The patients were investigated soon after admission to hospital; in 15 of the operated cases the tests were repeated 24 hours later so as not to miss any late enzyme variations. The results are given in the Table. The following summarizes the chief findings.

Initial Readings.—The highest abnormal values for both enzymes were found in a case of two days' standing too ill with peritonitis to be saved by surgery (Case 1). Another with considerably raised readings was a 15-hour perforation

Findings in 32 Cases of Perforated Peptic Ulcer in Order of Duration of Illness. Repeat Serum-enzyme Estimations were Carried Out 24 Hours Later

Case No.	Site of Perforation	Duration of Illness Before Study (hrs.)	Time of Perforation Since Previous Meal (hrs.)	Serum		Peritoneal Fluid	
				Amylase (Somogyi Units) (Normal 70-200)	Lipase (ml. N/20 NaOH) (Normal 0-1.5)	Amylase (Somogyi Units)	Lipase (ml. N/20 NaOH)
12	Stomach	2½		160	0.0		
5	Duodenum	2½	5	46	0.3	94	0.5
2	"	3		177			
26	Pylorus	3		145			
28	Duodenum	4	7		0.1		12.3
9	"	4	2	145	0.2	0	0.1
				190	0.9		
29	Pylorus	4	4½		0.6		6.4
					0.8		
15	Duodenum	4	½	53	0.1	200	9.0
17	"	4½	During meal	184	0.4	6,400	11.4
6	"			84	0.4		
7	Stomach	5	4	133	0.7	3,200	9.2
21	Duodenum	5	3	76	0.3	400	10.2
4	"	6	6	65	0.1		
10	"	6	6	84	0.0		
				56	0.1		
18	"	7	4	88	0.1	710	7.5
				84	0.2		
17	"	7	2	66	0.7	800	4.9
				80	0.5		
14	"	7	5	355*	1.7†	32,000	14.3
				355*	0.1		
30	"	7	½		0.4		4.8
25	"	7	4	168	0.1		
				200	0.3		
23	"	7		106	1.5	133	0.3
22	"	8	5	106	0.7	9,600	10.0
20	Anastomotic ulcer	9	4	106	0.8	400	0.5
11	Duodenum	9	6½	266*	0.2	6,400	13.0
				80	0.0		
8	"	10½	6	248*	0.75	13,330	14.0
				80	0.85		
6	"	11	4	66	0.1		
				123	0.1		
13	"	11	3	266*	2.1†		
				180	0.55		
19	"	12	5	88	0.0	1,770	4.3
				106	0.8		
24	Pylorus	12½	5	88	1.3	3,200	6.5
				300	1.4		
				22½	0.66†		
3	Duodenum	15 (died)		640*	2.5†	48	8.0
27	"	24	"	177	0.7		
1	"	48	"	720*	4.1†	1,600	7.0
31	"	10 days	"	73	0.4		
32	"	18	"	106	0.3		

* Raised serum-amylase readings. † Raised serum-lipase readings.
‡ Result at 48 hours.

(Case 3); this patient also died from peritonitis. Cases 8, 11, 13, and 14 had slightly raised amylase readings. An associated rise in the lipase levels was noted in Cases 13 and 14. These cases all fell within the group which had been ill for 7 to 12½ hours when first examined. The findings in all those seen earlier than the seventh hour were normal, as were also the findings in the two late cases complicated by abscess formation (Cases 31 and 32).

Repeat Readings.—The results obtained on re-examination 24 hours later did not conform to any definite pattern, nor did such changes as were noted in the amylase and lipase concentrations always run parallel. It is noteworthy that the second readings in the four cases which had originally a moderate increase in the serum amylase were within normal limits except in Case 14, which remained elevated. A drop

to normal levels also occurred in the two with moderately raised lipase values. In nine others there was no appreciable difference between the first and second readings. In the remaining two cases (Cases 6 and 24) the second amylase reading was decidedly raised, though in Case 6 it was within normal limits.

Enzyme Concentration of the Peritoneal Fluid

This was examined in 21 cases. The samples were obtained at operation in all except the first in the series, in which recourse was had to paracentesis abdominis ante-mortem. The same two tests were employed as mentioned above. If dilution was required, sterile physiological saline was used.

The results varied between wide limits. For example, the amylase concentration ranged from zero in Case 9 to 32,000 units in Case 14, and the lipase from 0.1 ml. in Case 9 to 14.3 ml. of N/20 NaOH in Case 14. A comparison between those findings and the corresponding results with the blood serum failed to show any correlation such as would lead one to suppose that the concentrations in the latter were augmented from a peritoneal source. It is conceivable that an excess of pancreatic ferments had been carried from the peritoneal cavity into the blood in Case 14, but in the light of the other findings this evidence must be regarded as purely circumstantial.

Time Since Previous Meal

This was noted in 23 cases. One patient perforated during a meal, four within two hours, and in the remainder the lapse of time was three or more hours, the average being four hours.

It was thought at first that the data might give some indication of the functional state of the pancreas at the time when the leakage of the gastric or duodenal contents occurred. However, the results of the estimations carried out on the fluid from the abdominal cavity gave little support to this assumption. Actually the highest concentrations were found among those who had not eaten food for several hours. Nor was there any relationship in respect of time with the findings in the blood serum such as has been reported by Pemberton and his associates.

Discussion

The question at issue is whether or not the changes in enzyme content that have been observed in the blood and urine in certain perforation cases denote a genuine disturbance of the pancreas. It is true that fat necrosis was encountered both by Hughes and by me in patients showing abnormally high readings, but further exploration ruled out a co-existing pancreatitis. The fat necrosis was doubtless the effect of a lipase of high potency which had obtained access to the peritoneal cavity as a result of the perforation. It is difficult, however, to ignore the possibility that the pancreas is sometimes functionally deranged either at the time of perforation or later. The irritant nature of the escaping fluid, particularly when it has become infected, might conceivably lead to changes in the exposed parts of the gland, though parenchymatous changes such as round-cell infiltration or interstitial oedema have not been noted in the deeper parts.

Pemberton and his colleagues were induced to consider this possibility in the course of their studies. By way of a control experiment, they produced a virulent and rapidly fatal peritonitis by the intra-abdominal injections of faecal and other noxious matter, but without

obvious effect on the amylase levels in the blood. It is fair criticism that their experimental conditions did not strictly parallel the clinical, for, whereas the dogs so treated died in the space of four hours, the present investigation leads one to believe that in clinical cases the enzyme levels become materially raised, if at all, only at a later stage. Thus it was found that the cases with abnormal readings had been perforated for a period of 7 to 48 hours; and Musgrove's cases were of one, four, and six days' standing.

When the problem presents itself for the first time after operative intervention, other factors have to be considered, such as the amount of traction required to expose the lesion and even the anaesthetic administered. In regard to the latter, ether is perhaps the drug which calls for the closest attention. Its effects have been studied in animals and the reports are conflicting. Some state that the inhalation of ether has a negligible effect on the serum amylase (Watanabe, 1918; Ross and Davis, 1921), while others believe that it results in a slight increase in concentration (Karsner, Koeckert, and Wahl, 1921; Zucker, Newburger, and Berg, 1932). Lewison refers to the occasional occurrence of abnormal readings after laparotomy, which some allege are due either to the anaesthetic or to intra-abdominal manipulations, but he himself has been unable to substantiate these explanations. With regard to the effects of mechanical trauma, it would seem that the pancreas does not object to gentle handling, but if subjected to damaging injury it registers its protest in the form of a serum-amylase response of moderate degree (McCaughan, 1934).

The experimental evidence brought forward in support of the theory of transperitoneal absorption is convincing. The effect produced by the entry of pancreatic ferments into the blood stream will depend, among other things, on the amount and potency of the secretion of the pancreas at the time of perforation. It was with a view to finding out something of this aspect of the problem that note was taken of the times of the previous meal. The findings suggested that a peptic ulcer is apt to perforate during the interdigestive phases of gastric and pancreatic secretion. The same impression is conveyed by Illingworth, Scott, and Jamieson (1944) in their statistical study of 951 perforations treated at the Glasgow Western Infirmary during 1938-43 when they state that the incidence was highest between 3 p.m. and 6 p.m.—that is, towards the end of the ordinary working day. It is of interest, however, that Strang and Spencer (1950), at Newcastle-upon-Tyne, were unable to correlate the time of occurrence with any particular phase of digestion.

The intraperitoneal findings in the perforation series were inconclusive. So far as could be determined from the data relating to the previous meal, there was no correspondence between the enzyme activity of the free fluid in the abdomen and the different phases of pancreatic function, nor was there any apparent connexion with the enzyme levels in the blood. One hesitates to infer that the possibility of absorption via the peritoneal lining is ruled out on that account. The diversity of the readings may have been due to factors that are beyond analysis clinically; for example, the secretory response evoked by the preceding meal, the degree of enzyme inactivation that is apt to result from an admixture with the acid chyme of the stomach, and the diluent effect of the peritoneal exudate are but a few of the incalculable variables which have to be taken into account.

Summary

Slight increases in the amylase and lipase levels in the blood occur in a small minority of peptic ulcer cases complicated by perforation.

No histological cause for these changes has been found in the pancreas.

A study of the clinical data in the present cases failed to yield evidence either for or against the view, supported by experimental work of others, that the increase in blood levels of the enzymes is due to their absorption into the circulation from the abdominal cavity.

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ADDENDUM.—Since this paper was written another case with raised readings has come to notice. The findings were: male, aged 37; anterior duodenal perforation of 22 hours' duration; serum amylase, 400 Somogyi units; peritoneal fluid amylase, 1,140 Somogyi units; meal one hour before onset of symptoms; recovered after operation.

Medical Memorandum

Persistent Bacillary Dysentery Carrier Treated with Chloramphenicol

Bacillary dysentery is endemic in many mental hospitals, carriers being the main source of infection (Medical Research Council, 1929). Our recent successful treatment of a persistent dysentery carrier with chloramphenicol is felt to be of general interest. The patient had previously remained resistant to sulphonamide therapy during a period of 19 months.

Case Report

In September, 1948, a small outbreak of bacillary dysentery occurred in a female mental ward of approximately 50 patients. There were three clinical cases, and the administration of sulphaguanidine resulted in a prompt cure.

Two months later, on November 5, 1948, the stools of all the patients in the ward were tested and five symptomless carriers were discovered. The infecting organism, both in the carriers and in the previously treated clinical cases, proved to be *Shigella flexneri* (variant X type). Four of the carriers were successfully treated with sulphaguanidine, but the fifth proved resistant. This was a woman aged 28 who had been in an institution since 1936 without previous history of clinical or bacteriological dysentery. She had no general symptoms when examined, and her stools were