THE BLOOD DIASTASE AND LIPASE CHANGES IN ACUTE PANCREATITIS

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Little has been published in this country about the pancreatic function tests that entail the study of the digestive ferments of the blood. It would appear that in America such tests as the viscometric, the copper reduction, and, to a lesser extent, the iodometric methods of estimating the serum diastase have superseded the urinary methods, which are our main stand-by, and in many clinics abroad the serum lipase tests are in common use.

The investigations here presented concern two serum tests—the one for diastase, and the other for lipase—and take the form of a study of their relative merits as aids to the diagnosis of acute pancreatitis.

Blood Diastase

It has long been known that the blood and the extracts of many of the organs and viscera of the body are endowed with starch-splitting properties (Magendie, 1846; Bernard, 1856; Foster, 1867). Carlson and Luckhart (1908), while engaged in a study of the diastatic activity of the various body fluids, observed that the levels in the blood were apt to remain unaltered in health, and cumulative evidence of this is to be found in the papers of Corbett (1912), Cohen (1925), Somogyi (1934), and Lewison (1941). Somogyi observed 100 normal subjects over a period of two years without noting any significant variation in the serum diastase level of any one individual; he found, however, that it varied widely from person to person, but was unable to establish a correlation between his findings and nutritional factors, sex, or age. The diastase content of the urine is well known to be subject to some physiological variation.

The physiological role of this ferment is not understood, nor do we know precisely the nature of the mechanism that governs its activity. Oelgoetz, Oelgoetz, and Wittekind (1935) have suggested that the diastase which normally finds its way into the intestine is absorbed in order to complete the digestion of partially split food products that may have gained entry into the lymph and blood streams. Experimental evidence is not in entire agreement with this hypothesis. Elman and McCaughan (1927) drained off the pancreatic juice by producing a total external fistula in the dog, and yet no diminution in serum levels occurred, while Crandall (1935) failed to bring about an increase by the introduction of a large quantity of fresh pancreatic juice into the bowel of normal animals. King (1914), whose attention was solely directed to the urinary diastase, did, however, report an increased output by the latter means. Most authors seem to incline to the view that the enzyme is a by-product of tissue metabolism which, once in circulation, is destined either to destruction or elimination via the kidneys. King has further suggested that it may help to maintain colloid equilibrium. The amount of diastase contributed by the pancreas to the blood has been the subject of much physiological research. We know that the infliction of trauma to the gland, ligation of its major duct, and the forced injection of chemical irritants lead to a conspicuous rise in serum diastase, and that total pancreatectomy is followed by its temporary diminution in the blood, but, as McCaughan (1934) has demonstrated, the

return to normal levels takes place in either event about the same time—namely, the tenth day. In general, the other workers in this field report similar results. The compensatory mechanism responsible for this nicety of adjustment is, however, beyond the scope of this paper.

Blood Lipase

When we turn to consider the fat-splitting enzyme we find that the earlier workers, such as Doyon and Morel (1902) and Arthus (1902), held the opinion that the blood is not lipolytic under normal conditions. Cherry and Crandall (1932) also subscribed to this view despite the finding of a few positives among their controls. More recent contributors to this branch of study have succeeded in proving to their satisfaction that lipase is a common constituent of normal blood (Comfort and Osterberg, 1940; Johnson and Bockus, 1940). Cherry and Crandall made the practical observation that the emulsions of olive oil and pea-nut oil are the most satisfactory for demonstrating the increase in the lipolytic activity of the blood in cases of acute pancreatitis and of dogs that have been subjected to duct ligation. With ethyl butyrate there was no measurable change in the blood in subjects thus affected. Their findings were confirmed by Comfort and Osterberg (1934). For this reason the former urged that the name "lipase" be applied to the ferment particularly active on oils and that "esterase," which is often synonymously used, be retained as the generic name for the whole group.

Scope of Work

The present study is based on the serum enzyme findings in 10 cases of acute pancreatitis. The pathological picture, which was known through operation in nine of the patients, was varied, but it was possible to divide the cases into two main groups—the severely and the mildly affected. Of the former, six (Cases 1, 3, 4, 6, 7, and 10) showed pancreatic necrosis and haemorrhages, and in three (Cases 5, 8, and 9) the pancreas was indurated and slightly swollen. The remaining case (No. 2), which was treated conservatively, probably belonged to the latter group.

The serum diastatic activity was estimated by the iodometric method of Somogyi (1938). The test is technically simple and gives a sharply definable end-point. It can be performed within 30 minutes. The preparation of the starch substrate is a complicated process which takes three days to complete, but the finished product has the advantage that it can be stored for several months. The range of the normal indices is 70 to 200 units of diastase per millilitre of serum.

The serum lipolytic activity was estimated by the Cherry and Crandall (1932) modification of the Loewenhardt method. The patient's serum is allowed to act on an olive-oil emulsion for 24 hours under optimum conditions of pH and temperature. The fatty acids set free are then neutralized by an N/20 solution of sodium hydroxide. The lipolytic power of the serum is measured in terms of the number of millilitres of alkali used per millilitre of serum. In view of the disagreement over the normal presence of lipase a control series comprising 76 subjects was investigated. Five were found to be lacking in lipase. The highest normal titre was 1.5 ml., but, as may be gathered from the mean of the readings, which was 0.45 (standard deviation = ± 0.35), the majority of the normal titres fell below unity. The range of normality was taken to be 0 to 1.5 ml., which agrees with that accepted by Comfort and Osterberg (1940). The values did not alter materially in a control study to investigate the influence of meals containing an excess of fat.

These two procedures were carried out on each patient at the earliest opportunity and repeated several times during the stay in hospital. The results are shown in the Table.

Biochemical Results.—An analysis of the results showed that the highest readings for both enzymes were obtained in Case 8, which was shown by delayed laparotomy to be relatively benign as regards the pathology; the values amounted to 26.5

and 6.5 times the upper limits of normality for diastase and lipase, respectively. They presented an interesting contrast with the findings in the severely affected cases, Nos. 1 and 3, which were also examined on the first day, but a few hours later, because their readings were of a decidedly lower order. The findings beyond the second day of illness were so variable from case to case that a detailed description of each seems to be uncalled for. It suffices to state that the majority of the readings had dropped to physiological limits by the end of the first week. A comparison of the readings of the two groups of patients was made in order to find out whether there existed

In clinical work it is much more difficult to prove that such a relationship exists. Wohlgemuth (1929) has alluded to the wide differences that may be found in the readings of apparently equally affected cases, and advanced the theory that they depended on the proximity of the lesion to the major ducts. Unger and Heuss (1927) were of the belief that the height of the rise in diastase had a prognostic significance, since all their cases with an output in the urine of over 1,000 units (Wohlgemuth) died within a few hours of operation. This flooding of the system, so to speak, with

Table showing the Serum Enzyme Findings in Ten Cases of Acute Pancreatitis

Essential Clinical Data	Time of Observation	Serum Diastase Units per ml. Serum	Serum Lipase ml. N/20 NaOH per ml. Serum
Case 1.—Man, 65 years. June, 1941. <i>Acute haemorrhagic necrosis</i> with scattered foci of fat necrosis, and free fluid. Died in 8th week after progressing to the suppurative stage	14 hours 2nd day 3rd " 7th " 27th " 57th "	4,000 2,130 475 320 290 46	5.30 0.50 0.50 1.00 Zero
Case 3.—Man, 66 years. Dec., 1941. <i>Acute haemorrhagic pancreatitis</i> of the caudal half. No fat necrosis or free fluid. Survived after a prolonged illness	15 hours 2nd day 3rd " 4th " 12th " 15th "	1,600 860 530 320 406	3.10 1.30 1.80 0.20
Case 4.—Man, 70 years. April, 1942. <i>Acute pancreatic necrosis</i> : false cyst in lesser sac containing 2 pints turbid fluid; fat necrosis of omentum. Survived after a long illness	4th day 7th " 12th " 15th "	457 84 106 57	2.13 0.21 0.08 0.30
Case 6.—Woman, 48 years. Oct., 1942. <i>Acute pancreatic necrosis</i> but no visible haemorrhages; spots of fat necrosis in surrounding parts. Survived	8th day 18th "	94 145	0.98 1.36
Case 7.—Woman, 63 years. Nov., 1942. Pancreas swollen and hard but hidden by matted swollen omentum; numerous points of fat necrosis; brown effusion in peritoneal cavity. Survived	4th day 5th "	110 80	0.21 0.35
Case 10.—Woman, 52 years. Feb., 1944. <i>Acute haemorrhagic necrosis</i> with much free brownish fluid tinged with bile in abdominal cavity. Died on 3rd day	3rd day		1.08
Case 5.—Woman, 45 years. Aug., 1942. Severe upper abdominal pain and vomiting; slight jaundice. At operation on 5th day the pancreas was diffusely swollen and indurated. No signs of haemorrhages on its surface or fat necrosis in the vicinity. Gall-bladder slightly oedematous, but no stones found in it or in common bile duct. Survived	5th day		0.9.
Case 8.—Woman, 49 years. June, 1943. Severe epigastric pain and sickness for 6 hours before admission; slight jaundice; collapsed. Operation after 21 days: pancreas slightly nodular and firmer than normal. Biopsy revealed focal areas of acinar necrosis histologically. Gall-bladder showed early chronic change: it contained one pigmented stone 1.5 cm. in diameter. Survived	6 hours 3rd day 6th " 48th "	5,300 460 228	9.80 5.80 2.94 1.35
Case 9.—Man, 49 years. Jan., 1944. Severe pain in right hypochondrium for 2 days referred to intrascapular region and right shoulder-tip. Cyanosed and jaundiced. Laparotomy on 2nd day revealed a hard nodular pancreas. Biopsy showed evidence of subacute inflammation. Gall-bladder free of stones. Survived	10th day		1.40
Case 2.—Woman, 57 years. July, 1941. Severe upper abdominal pain for 3 days. Slight jaundice. Tender right hypochondrium. Non-functioning gall-bladder. Survived without operative intervention	4th day 6th " 8th "	1,280 228 228	2.60 1.70 1.70

any correlation with the underlying pathology. The observations made will be introduced into the subsequent discussion.

Discussion

There is some experimental evidence to support the belief that the serum enzyme changes encountered in acute pancreatitis provide a measurable index of the degree of functional upset. Wohlgemuth (1909) and McCaughan, using different laboratory methods, compared the effects of ligating the two pancreatic ducts with those of tying one, and each found that complete obstruction produced a more conspicuous and more lasting rise in the serum diastase. Clasen, Johnstone, Orr, and Rice (1933) observed that the variations in diastase levels in experimentally produced pancreatitis were commensurate with the amount of glandular damage caused by the intraduct injection of chemical irritants. Baxter, Baxter, and McIntosh (1938), who were among the first to study the serum lipase changes in experimental pancreatitis, arrived at the same conclusion.

pancreatic ferments has proved to be such a transient incident in the experience of most observers that it is considered futile to attempt to establish a correlation between the grade of severity of the lesion and the gradient of the rise in enzyme activity. The highest readings recorded in the present work were found in a subacute case of only six hours' duration. It was unfortunate that the earliest of the hyperacute group was not seen until eight hours later. Mikkelsen (1934) has placed on record two interesting cases which, when investigated, had been ill for only three hours, and at that time no alteration in diastase could be detected. On repeating his tests one hour later he found that the typical enzyme response had manifested itself. Accordingly, taking into account the present findings, it would appear that the peak values are to be found between the fourth and sixth hours from the start of the condition.

While a single diastase estimation may be uninformative there is some evidence to show that serial estimations may furnish a clue to the character of the lesion. Elman (1942)

has produced convincing evidence that a precipitate drop in levels denotes a subacute pancreatitis and that a slow subsidence is often found in association with widespread pancreatic destruction. The diastase readings in Cases 1 and 3 of my own series exemplify the latter relationship, but, as may be seen, an early return to normal activity is not incompatible with the presence of a gross necrotic lesion.

A gain in lipolytic power was also noted in the patients subjected to investigation. It was found to be particularly marked in those who were examined on the first day of illness. It is interesting to observe that the maximum level was attained in the same case in which the maximal diastase reading was found—i.e., Case 8. The later determinations, taking the series as a whole, showed a steady decline, which was more rapid in some than in others, and by the end of seven days most of the readings were normal. In other words, the fluctuations in lipase activity paralleled fairly closely those of diastase. The graphic presentations of all the results illustrate this point (see Graphs 1 and 2). It has

GRAPH 1.—Showing the serum diastase findings in seven cases of acute pancreatitis.

GRAPH 2.—Showing the serum lipase findings in ten cases of acute pancreatitis.

been claimed by those who favour this test that an excess of lipase in the blood persists longer than an excess of diastase (Crandall, 1935; Comfort and Osterberg, 1940; Johnson and Bockus, 1940). Yet Lewison (1941) after an extensive clinical trial, using both methods, failed to detect a constant difference in the rates of fall in the levels of the two enzymes. There was a slower fall in lipase values in

two of the present series. The lipase test does score over the diastase test when it comes to the question of the diagnosis of the pancreatitis of mumps, because the results of the latter are apt to be vitiated by the alterations in serum diastase which the parotid lesion may occasion. The main objection to the particular lipase test chosen for this comparative study is the 24-hour incubation period required for the complete digestion of the olive-oil emulsion, but now that the balance of favour has swung over towards conservatism in the treatment of acute pancreatitis this delay need not be regarded as a bar to its wider clinical application.

Summary

The relative merits of two serum enzyme tests have been considered.

The blood normally contains enzymes that are active on starch and vegetable oils. Their activity varies from person to person, but is constant for each individual.

The diastase and lipase findings in 10 cases of acute pancreatitis are reported.

It was found that the two tests were equally satisfactory as indicators of acute pancreatitis. Their clinical application seems to be limited to the initial stages of the disease owing to the nature of the specific enzyme reaction. Evidence is given to show that serial diastase estimations may furnish information regarding the grade of severity of the disease.

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Manchester University Medical School Gazette, which first appeared in June, 1898, has just published a special golden jubilee number. This is handsomely produced and illustrated and includes a number of special articles. Prof. Geoffrey Jefferson, F.R.S., contributes an article on three Manchester pioneers in neurology, James Ross, Sir William Thorburn, and R. T. Williamson. Dr. E. Bosdin Leech briefly recounts the history of the *Gazette*, which appeared originally as the "Manchester Royal Infirmary Students' Gazette," and Dr. A. E. Barclay has an interesting article on the early days of radiology in Manchester. There are in addition the familiar articles on "By-paths of Medical History" over the initials "W.B." and the usual contributions on such subjects as common infections of the hand. This special issue is one which should interest all former students of the Medical School at Manchester.