DIASTASE IN BLOOD AND URINE IN DIABETES MELLITUS.

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IN a previous paper[1] we have published some of our work on blood amylase, and have reported our findings in normal individuals and in renal disease, illustrating the importance of estimating diastase in both blood and urine. In this paper we shall outline our findings in pancreatic cases, in hepatic disease, and in diabetes mellitus, and then discuss the results in diabetes with reference to pancreas, liver, and kidney. Throughout this investigation the reaction of the urine has been adjusted to P_H 6.7 before estimation of amylase, unless otherwise stated.

A brief summary of our previous results will facilitate comparison with the findings in diabetes.

Normally, the concentration of diastase in the blood lies between 3 and 10 units, and in the urine between 6.7 and 33.3 units. The total quantity of diastase excreted in twenty-four hours varies from 8,000 to 30,000 units. It is useful to calculate the total diastase excreted to reveal instances in which high or low concentrations of diastase may legitimately be attributed to oliguria or diuresis.

In renal disease there may be (*a*) "diminished excretion with retention," in which the value for blood is above 10, and for urine below 6.7; (*b*) "diminished excretion without retention," in which the blood amylase is normal, but the concentration in the urine is lower than in the blood or of the same value; (*c*) "normal excretion," in which the concentration of diastase is higher in the urine than in the blood.

TABLE I.—*Examples of Results in Diseases of Pancreas and Liver.*

Case.	Blood Diastase.	Urine (24 hours). Concentration of Diastase.	Vol.	Total Diastase Excreted.	Remarks.
	units	units	c.cm.	units	
A	23.5	16.7	3,900	65,100	Gunshot wound of pancreas; resulting cyst drained.
	5	3.3	2,780	9,200	Three weeks later, clinically much improved.
B	20	235	330	77,600	Traumatic pancreatic cyst; laparotomy; drainage. Loewi's test negative on three occasions.
	16.7	66	780	51,500	One month later, well on the way to recovery.
	—	16.7	960	16,000	Six weeks later, back at school.
C	40	400	—	—	Acute haemorrhagic pancreatitis; death 24 hours after operation; diastase of cerebro-spinal fluid = 10.
D	8	133	1,600	212,800	Carcinoma of pylorus; bile and pancreatic ducts blocked by growth.
E	5	80	1,540	123,200	Gall stones; pancreatitis; glycosuria.
F	5	100	540	54,000	Talipes equino-varus; no glycosuria; Loewi's test negative; no evidence clinically of pancreatic disease.
1	1	23.5	720	16,900	Malignant disease of liver.
2	1	10	—	—	Carcinoma of liver.
3	2	23.5	360	8,500	Catarrhal jaundice.
	8	10	1,200	12,000	Three weeks later, convalescent.
4	3.3	8	540	4,300	Cirrhosis of liver.
	8	10	780	7,800	One month later, clinically much improved.
5	7	16.7	720	12,000	Cirrhosis of liver.
6	5	16.7	1,020	17,000	Melanotic sarcoma of liver.
7	7	16	1,715	27,400	Acholuric jaundice.

Note.—The reaction of the urine was not adjusted to optimum P_H except in Cases E and 7. The total diastase excreted in twenty-four hours is calculated to the nearest hundred. Case F is included for comparison.

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† Part of this work was included in a thesis for the degree of Doctor of Medicine, Aberdeen, 1922.

Pancreatic Disease.

It is well recognized that active destruction of the pancreas (or sudden obstruction of its ducts) is accompanied by an increased concentration of diastase in the urine, and usually in the blood also. Examples are given in Table I. Occasionally a moderately high concentration of urinary diastase may be found in the absence of any other evidence of pancreatic disease (Case F, Table I).

We conclude that a high urinary index, when accompanied by a raised blood diastase, is diagnostic of active pancreatic disease, but when accompanied by a normal value for blood is merely suggestive.

Liver Disease.

The urinary and blood diastase in the majority of 20 patients has been within normal limits. The blood diastase was subnormal in three cases (all severe), but these low values were accompanied by normal urinary figures for the concentration and total excretion of diastase. In two patients the blood diastase rose as the jaundice and clinical condition improved (Table I).

DIABETES MELLITUS.

Blood Diastase.

Over 200 estimations have been made in a series of 48 patients. In one instance only was the value raised (13.3 units), the estimation being made six hours before death in coma. Fourteen patients had a subnormal blood amylase (1 or 2 units). These low figures have been obtained usually, but not invariably, before treatment or during fasting or on low diets. In many instances they have been accompanied by normal values for concentration or total excretion of diastase in the urine.

In a few cases estimations of blood diastase at intervals of several days or weeks have revealed slight variations, the maximum being 6 units. We have been unable to correlate such changes with the clinical condition, the blood sugar content, or the diet (Table II), and are inclined to regard them as of little or no significance.

TABLE II.

Case and Date.	Blood Diastase.	Blood Sugar.	Glycosuria.	Diet. Carbohydrate.	Protein.	Fat.
CASE 21: F., aged 65.	units	per cent.		grm.	grm.	grm.
2.5.21	6.7	0.23	0	79	69	54
9.5.21	4	0.35	+	22	13	24
31.5.21	8	0.22	0	100	109	120
13.1.22	6	0.31	+++	Low, ill balanced		
12.7.22	7	0.21	Trace	Carbohydrate reduced		
28.7.22	8	0.21	0	156	87	72
15.8.22	5	0.28	+	98	91	93
13.10.22	4	0.42	+++	Broken diet		
CASE 26: M., aged 39.						
17.8.21	3.3	—	+++	Unrestricted		
13.9.21	6.7	0.13	0	101	35	30
1.8.22	3	0.24	+++	55	75	46
15.8.22	2	0.22	Trace	20	15	10
4.9.22	4	0.14	0	80	69	71
CASE 38: M., aged 60.						
17.2.22	2	0.32	+++	Unrestricted		
21.2.22	3	0.185	+++	205	90	17
24.2.22	3	0.16	+	Starvation		
4.3.22	3	0.115	0	80	39	7
8.3.22	3	0.10	0	120	61	27
20.3.22	3	0.18	0	100	101	103
CASE 39: M., aged 53.						
11.3.22	2	0.33	+++	Unrestricted		
15.3.22	1	0.14	0	Starvation		
20.3.22	3	0.155	Slight trace	30	8	0
31.3.22	3	0.25	+++	73	27	16

In our previous paper[1] it was pointed out that blood diastase remains virtually constant throughout the day (estimations at hourly or half-hourly intervals) in normal individuals and in diabetes mellitus. The following are typical experiments in diabetics:

Case 8.—Mild. Blood diastase and blood sugar estimated at 10.15 a.m., immediately before a dose of 50 grams of glucose, taken fasting, and again at hourly intervals until 5.15 p.m. Lunch 1 to 1.15 p.m., and tea 4 to 4.15 p.m. The blood amylase was 5 units on each of the eight occasions. The blood sugar was 0.10, 0.21, 0.14, 0.11, 0.09, 0.07, 0.08, and — per cent. respectively.*

* The — signifies not estimated.

Although the blood sugar was doubled the diastatic index remained constant.

Case 7.—Severe. Examinations before, and at half-hourly intervals after, a meal consisting of carbohydrate (30 grams), protein (23 grams), and fat (13 grams). The serum diastase was 3, 3, 4, 3, 3, and 3 units. The blood sugar was 0.215, 0.27, 0.23, 0.25, 0.27, and 0.27 per cent.

Urinary Diastase.

Until recently the reaction of the urine has been disregarded in estimating the concentration of diastase. Dodds[2] and Sladden[3] have published papers showing that a very considerable error may be introduced if the reaction is not adjusted to the optimum for the enzyme. This fact will necessitate the repetition of much of the work on urinary diastase, and accounts for many of the low results reported, but not for all. We append a few of our most striking figures to show the importance of this adjustment, in confirmation of the findings of the above workers (Table III), together with a few instances in which such correction has made little or no difference. Our corrections have been made according to the plan suggested by Sladden. The reaction has been adjusted with decinormal soda or hydrochloric acid to P_H 6.7, the dilution being allowed for in the subsequent calculation. One per mille soluble starch in 0.5 per cent. sodium chloride has then been added in the usual way.

TABLE III.—*Effect of Correcting Reaction of Urine.*

Case.	Disease.	Blood Diastase.	Urine Diastase; P_H not adjusted.	Urine (24 hours) at P_H 6.7.			N/10 Soda or HCl (ac.) per 100 c.cm. Urine.
				Concentration of Diastase.	Vol.	Total Diastase Excreted.	
				units	c.cm.	units	c.cm.
48	Diabetes mellitus	6	0.5	6	600	3,600	13.8
24	,, ,,	2	1	4	3,100	12,400	17.9
32	,, ,,	3	2	6	2,005	12,000	19.6
47	,, ,,	—	3.3	23	—	—	77.7*
43	,, ,,	5	5	9	1,650	14,900	8.4
54	,, ,,	5	10	16	940	15,000	23.1
26	,, ,,	2	13.3	26	1,210	31,500	32.6
42	,, ,,	4	16.7	25	1,700	42,500	7.4
K613	Chronic interstitial nephritis	5	0.5	4	1,560	6,200	17.9
K632	Albuminuria in pregnancy	2	8	25	1,200	30,000	27.3
F	Cirrhosis of liver	2	3.3	15	960	14,400	50.4
L	Myelogenous leukaemia	3	8	26	600	15,600	30.5
C	Subacute pancreatitis	5	40	80	1,540	123,200	21.0
26	Diabetes mellitus	3	5	8	3,400	27,200	62.9 (ac.)
49	,, ,,	3	8	9	2,300	20,700	9.3 (ac.)
M13	,, ,,	2	10	12	1,440	17,300	16.8
52	,, ,,	4	2	2.3	1,400	3,200	14.7
K608	Chronic nephritis (mixed)	6	0.25	0.5	600	300	5.3

* Night urine.

Several hundreds of estimations of the concentration and total excretion of diastase have been made in a series of 55 diabetics, but only in 20 patients has the reaction of the urine been adjusted. Our remarks on diminished diastase excretion naturally are based solely on the corrected results.

In nearly all diabetics at one time or another the diastatic index is subnormal owing to polyuria, the total excretion being normal. But both concentration and excretion have been subnormal in 4 out of the 20 cases. We attribute such findings to a general depression of metabolism. Raised values have been encountered in only two patients, and then only in a minority of a large number of estimations.

Case 26.—Blood diastase 2 to 6.7 units (6 tests); urinary diastase, concentration 3.3 to 26, and excretion 10,300 to 40,800 units (43 tests, of which only 9 exceeded 30,000).

Case 42.—Blood diastase 4 to 10 units (4 estimations); urine, concentration 8 to 33.3, and excretion 14,400 to 69,900 units (62 estimations, of which 23 exceeded 30,000). The reaction of the urine has been corrected in all these experiments.

The influence of diet has been studied fully in eight patients. Before we realized the importance of correcting the reaction of the urine, it was concluded that the excretion of amylase was generally lowered by fasting or by very low diets. We have repeated our experiments in three patients, making the necessary correction, and have made similar observations on two new patients, the P_H of whose urine was adjusted in the first instance. As a result we now conclude that no marked or constant change in diastase excretion can be demonstrated as a direct consequence of changes in diet (Table IV).

TABLE IV.

Case and Date.	Urine (24 hrs.) at P_H 6.7.			Glycosuria.	Diet.		
	Concentration of Diastase.	Vol.	Total Diastase Excreted.		Carbohydrate.	Protein.	Fat.
CASE 49: M., aged 65.	units	c.cm.	units		grm.	grm.	grm.
9.9.22... ...	11.3	1,290	14,600	+++	Starvation		
11.9.22... ...	10.4	1,620	16,800	0	,,		
16.9.22... ...	5.0	2,160	16,800	0	50	16	4
22.9.22... ...	5.0	3,660	18,300	Slight trace	110	50	29
29.9.22... ...	5.0	2,520	12,600	0	70	83	48
6.10.2.* ...	12.6	780	9,800	+++	60	38	11
7.10.22 ...	10.0	840	8,400	++	25	17	7
10.10 22 ...	5.0	2,220	11,100	0	60	45	26
17.10.22 ...	8.0	1,620	13,000	0	80	72	62
CASE 26: M., aged 40.							
31.7.22	11.6	2,400	27,800	+++	20	28	20
13.8.22... ...	26.2	1,230	31,000	++	Starvation		
18.8.22	8.0	2,820	22,600	0	50	70	25
29.8.22... ...	8.0	2,520	20,200	0	80	71	57
5.9.22... ...	5.0	4,440	22,200	0	80	72	72
22 9.22... ...	7.0	4,920	34,400	0	82	71	75
CASE 21: F., aged 66.							
14.7.22... ...	7.0	1,680	11,800	0	80	47	60
22.7.22	9.0	1,590	14,300	0	121	71	50
27.7.22... ...	12.0	1,500	18,000	0	145	80	65
9.8.22... ...	14.8	1,500	22,200	0	120	91	89
14.8.22... ...	7.5	1,950	14,600	0	94	91	89
CASE 42: F., aged 30.							
17.9 22... ...	13.3	1,950	25,900	0	60	61	47
18 9 22	20.0	1,755	35,100	0	60	60	52
19.9.22... ...	13.3	1,800	23,900	0	60	58	55
29.9 22... ...	10.0	2,500	25,000	0	69	69	57
30.9.22... ...	13.3	2,550	33,900	0	68	69	49
5.11 22 ...	10.0	2,250	22,500	Trace	81	76	46
12.11 22† ...	10.0	2,400	24,000	+++	65	61	48
19.11.22 ...	8.0	2,850	22 800	+	71	59	43
26.11.22 ...	13.3	2,700	35,900	Trace	71	56	39
3.12.22 ...	10.0	2,850	28,500	0	42	50	38

* Exploratory laparotomy (spinal anaesthesia, gas and oxygen), October 5th, 1922; nothing abnormal found.
† Two teeth extracted under gas, November 7th, 1922.

No evidence has been obtained for associating our diastase results in diabetes mellitus with kidney inefficiency. In no instance has there been "diastase retention" (with a single possible exception, blood amylase 13.3 units, urine not examined). Four patients have exhibited "diminished excretion without retention" of the ferment on one or more occasions (the reaction of the urine had been adjusted to P_H 6.7). This diminished excretion may have been due to a general depression of metabolism. Clinically there was no evidence of renal inefficiency and urea tests of renal function were normal.

Increase of diastase in blood or urine has been reported only in *active* destruction of the acini of the pancreas. It is not surprising, therefore, that the majority of diabetics do not show raised amylase values. Their islet tissue may be degenerating as a result of overstrain by excessive diet (Allen), but in the absence of destruction of acini an increase of diastase excretion would not be expected. Conversely, when raised diastase values are found in diabetics, they might be regarded as evidence of active pancreatic injury (inflammatory or otherwise). Only two of our cases have shown such increases, and these were transitory and relatively small. The highest figures found were: blood diastase 10 units; urine, concentration of diastase 33.3 units, volume 2,100 c.cm., and total diastase excreted 69,900 units.

In connexion with their work on the CO_2 content of alveolar air, Bennett and Dodds[4] have made an alternative suggestion—namely, that in diabetes mellitus there may be an excessive flow of pancreatic juice, with a corresponding diminution in internal secretion. It is true that we have not estimated diastase in the faeces, but the great majority of our cases (including many that clinically were severe and untreated at

the time) show either a normal or a diminished amylase content in blood and urine. Our work therefore gives little or no support to this hypothesis.

So far we have found a subnormal blood diastase only in diabetes mellitus, liver disease, one case of albuminuria in pregnancy (Table III, K632), and one case of septic endocarditis. In most instances the urinary diastase was normal, so that the low blood values were not due to a diminished formation of the ferment. It is possible that a lowered renal threshold for amylase was present, such as has been suggested by Langdon Brown[5] to explain the relatively high urinary figures (associated with normal blood diastase) in pregnancy toxaemias. Excluding the pregnant patient, our cases had little or no albuminuria. Otherwise we are at a loss as to what significance (if any) should be attached to these subnormal blood amylase findings.

In conclusion our results confirm the opinion of previous investigators (Allen[6]) that diastase tests are of little or no value in the diagnosis, prognosis, or treatment of diabetes mellitus.

Summary.

Estimations of diastase simultaneously in blood and urine have been made in fifty-five diabetics and a large number of controls, due attention being paid to the reaction of the urine, the diet, etc.

Our findings are in support of those investigators who have concluded that the presence of amylase is more or less accidental, and of little or no value in the diagnosis, prognosis, or treatment of diabetes mellitus.

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BRACHIAL NEURITIS DUE TO CERVICAL RIB.

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MUCH has been published on the condition of cervical ribs and the symptoms which this abnormality may produce, but most of the articles have been contributed to meetings of specialists or to little read journals, and a pathological condition does not become common knowledge until it has been repeatedly brought to the notice of the general practitioner at meetings of societies which he attends or in journals which he reads.

HISTORICAL.

In 1893 Lewis Jones published a report of 6 cases of paralysis of the small muscles of the hand (some supplied by the ulnar and some by the median nerve), which did not progress and so differed from progressive muscular atrophy.

In 1902 Buzzard published a series of similar cases and diagnosed the condition as due to a lesion of an individual root of the brachial plexus, but was puzzled as to the cause.

Apparently neither of these physicians was aware that in 1891, at Edinburgh, Sir David Wallace had read a paper in which he reviewed the older (anatomical) literature on cervical ribs, and had shown a patient with pressure symptoms which Wallace attributed to a rudimentary cervical rib.

In 1895 Stiles recorded a case of his own and referred to 8 or 10 cases in which the cervical rib had been excised.

Thorburn was probably the first to use *x* rays to diagnose the presence of rudimentary ribs, and in 1904 he described before a London society two cases with pressure symptoms.

The connexion between the nerve symptoms and cervical ribs having thus been brought to his notice Lewis Jones endeavoured to trace the cases he had described eleven years earlier, and found that of 14 patients examined 10 showed one or more cervical ribs.

Edwin Bramwell was apparently the first to suggest (in 1903) that the lowest brachial plexus root might be pressed on by a rudimentary or even by a normal first thoracic rib, and in 1911 Sir Harold Stiles removed a portion of first rib, with satisfactory result, from a patient with typical pressure symptoms. Similar cases have been recorded by various surgeons (Stopford stated in 1919 that in less than two years he had met with 10 cases of compression neuritis produced by normal first rib), but, so far from this having become common knowledge, Stiles informs us that it was news to not a few of the American surgeons to whom he lectured on the condition in the States in 1922.

EMBRYOLOGY.

In a limbless animal like the snake, to every vertebra is attached a pair of ribs, and each somatic segment has also its pair of segmental nerves. In the human embryo the arms and legs first appear as limb buds, the arm bud springing from five or six vertebral segments. These segments grow chiefly in a vertical direction, while the limb grows chiefly out at right angles and soon fails to cover the whole vertical extent of the segments from which it was derived. Thus, of the spinal nerves which supply the limb, the upper and lower nerves come to pass more and more obliquely between their points of origin and their point of entry into the limb. The nerves are relatively larger in the embryo than after birth, and they are of sufficient size to interfere with the forward growth of the rib mesoblast, so that in the cervical and lumbar regions the ribs are normally represented by the rudimentary costal processes of the vertebrae only. Occasionally a more or less perfectly formed pair of ribs spring from the seventh cervical vertebra; more rarely the first pair of thoracic ribs are incomplete or rudimentary. The limb bud is not constant in its origin: in some individuals it derives from the cervical segments alone, in others it derives also from the first dorsal segment, and exceptionally from the second dorsal segment also. The brachial plexus, being of course formed from the nerves of whichever segments enter into the origin of the limb, varies accordingly. Wood Jones states that where little or no contribution to the plexus comes from the first dorsal root there is a greater liability to cervical rib; in cases of rudimentary first rib the second thoracic nerve has been found to make a considerable contribution to the brachial plexus.

ANATOMY.

A rudimentary cervical rib is commonly an inch or more in length, and ends in a rounded knob from which a tight fibrous band passes to be attached to the first rib. An intercostal muscle exists between the rudimentary rib and the rib below; anteriorly the muscle fibres are gradually replaced by fibrous tissue. The lowest root of the brachial plexus more usually passes over and rests upon this fibrous band than upon the rudimentary rib itself.

CAUSE OF SYMPTOMS.

Cervical rib is of course a congenital condition. Pressure symptoms rarely occur before adult age. This is explained by the dropping of the shoulder which normally takes place as growth proceeds: in the child the clavicles rise markedly from their sternal ends towards their outer extremities; in adults (especially women) they not uncommonly slope downwards from their sternal ends. Apart from this general factor, there is almost always a definite exciting cause for the pressure symptoms. This may be an acute illness—for example, diphtheria—leading to stretching of ligaments; or a sudden weight lifting; or the pressure, say, of a violin above the clavicle; or unaccustomed use of the upper limb, strenuous such as digging, or intricate such as piano playing or typewriting.

SYMPTOMS.

The lowest root of the brachial plexus contains motor, sensory, and sympathetic fibres, and motor, sensory, trophic, and vascular symptoms may all be present in cases of rib pressure.

Pain.—The patient most usually consults a doctor on account of pain, which commonly extends along one aspect (more often the inner side) of the forearm. The pain is burning, neuralgic, or "pins and needles" in character, and a diagnostic point of importance is that it is relieved by raising the arm above the head, this movement lifting the nerve off the rib or fibrous band over which it has been stretched.

Paralysis.—Wasting of the thenar eminence is the most frequent motor symptom, the opponens pollicis and abductor pollicis being the muscles usually chiefly affected. Careful examination may reveal wasting of some of the interossei or others of the ulnar group of muscles, but the most characteristic clinical picture is one where there is very obvious wasting of the ball of the thumb.

Vascular Symptoms.—A weak radial pulse has been not uncommonly noted; very rarely oedema of the forearm.

Trophic Symptoms.—Gangrene of the fingers is a very rare symptom.