The hourly rate of urinary amylase excretion, serum amylase, and serum lipase

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SUMMARY The rates of urinary amylase excretion/hour and the levels of serum amylase and lipase were measured in 190 normal subjects and patients with no evidence of renal or gastrointestinal disorder. The hourly rate of urinary amylase excretion/hour was found to have an upper limit of normal of 69 IU. The upper limit of normal for the serum amylase was 251 IU/litre and for the serum lipase 1.6 units/ml.

Raised levels of serum amylase and lipase with a normal rate of urinary amylase excretion/hour were found in chronic renal failure.

Part I In control subjects and patients with renal disease

The diagnosis of acute and relapsing chronic pancreatitis may be difficult if a rise in serum amylase which may be transient is missed. The value of determining urinary amylase in the diagnosis of pancreatic disease is not clear, although it has been suggested that the hourly rate of urinary amylase excretion may remain elevated for up to 10 days after an attack of acute pancreatitis (Saxon, Hinkley, Vogel, and Zieve, 1957; Gambill and Mason, 1963). A moderate rise in serum amylase may accompany other acute abdominal conditions, eg, biliary disease, gallstone colic, perforated duodenal ulcer, intestinal obstruction, and ruptured ectopic pregnancy (Kelley, 1957) and may follow upper abdominal surgery (Keighley, Johnson, and Stevens, 1969). In addition it is important to know the effect of impaired renal function on the output of amylase into the urine since acute pancreatitis may be accompanied by renal insufficiency (Dankner and Heifitz, 1951; Meroney, Lawson, Rubini, and Carbone, 1956; Blainey and Northam, 1967).

For a biochemical measurement to be of value in establishing the presence or absence of organic disease it is important to know the normal range and the effect of other diseases on this range. It is also preferable to obtain the blood or urine under clinical rather than experimental conditions.

With these considerations in mind a study of the rate of urinary amylase excretion/hour was undertaken and a comparison made with the levels of serum amylase and lipase. A total of 476 patients were studied. In the first part of the paper we present the findings in healthy adults and control patients together with those in patients with renal or urinary tract disease and in the second part the findings in patients with gastrointestinal disorders and pancreatitis.

Methods

The control subjects comprised a group of out-patients and all patients admitted to a general medical unit over a period of 15 months with no known history of renal or gastrointestinal disease together with a small number of medical staff and students; these were compared with a group of patients with urinary tract disease or elevated blood urea levels.

Values for serum amylase, blood urea, a two-hour urine collection, and, in most cases, a serum lipase were obtained on the same day from each patient. A diuresis was not established and the specimens were not taken at any specific time of day. Serum amylase, serum lipase, and blood urea were estimated in the hospital laboratory using the method of Huggins and Russell, modified by Varley and Hewitt, as described below by the method of Cherry and Crandall (1932),

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and with the AutoAnalyzer respectively. The total two-hour urine volume was recorded and the specimen kept at 4°C until analysed. The amylase concentration of two aliquots was determined by the modified method of Huggins and Russell and the mean of these two results used to calculate the rate of urinary amylase excretion/hour. Replicate analyses of samples kept at 4°C for varying periods of time did not differ significantly.

ESTIMATION OF AMYLASE

The method used to estimate amylase concentrations in serum and urine was based on the modification by Varley (1967) of the Huggins and Russell method. However the present method (Varley and Hewitt, unpublished data) differed from that described by Varley in several details. The incubation mixture was prepared from 2.5 ml of phosphate buffer, 2.0 ml of an 0.5% starch substrate, 0.3 ml of 0.9% saline, and 0.2 ml of serum or urine. Aliquots, each of 0.5 ml, were withdrawn from the incubation mixture at 0, 5, 15, and 30 minutes and treated as described previously (Varley, 1967). Amylase concentration in Somogyi units/100 ml was calculated by multiplying the number of milligrams of starch fermented at five minutes by a factor of 3000, at 15 minutes by a factor of 1000, and at 30 minutes by a factor of 500. Thirty minutes' incubation covered the range 0-250 Somogyi units/100 ml, 15 minutes' 250-500 Somogyi units/100 ml, and five minutes' 500-1000 Somogyi units/100 ml. If hydrolysis was almost complete in five minutes, the estimation was repeated using 0.1 ml of serum or urine. In this paper

the units of amylase are expressed as IU/l (μmol of substrate fermented/min/l). One Somogyi unit/100 ml is equivalent to 1.9 IU/l, or 1 IU is equivalent to 5.4 Somogyi units.

Results

Two-hour urine collections from 263 subjects were examined, but 24 have been excluded because the values for serum amylase or blood urea are missing. The age and sex distribution, and diagnoses of the 190 controls are shown in Tables I and II and for the 49 patients with renal dysfunction in Table III. A few patients had more than one measurement of the serum amylase, serum lipase, and rate of urinary amylase excretion, but only the initial value obtained for each subject is included in the statistical analysis and scattergrams.

Diagnosis	No. of Patients
Heart disease	27
Hypertension	25
Pernicious anaemia	9
Bronchitis	
Carcinoma bronchus	27
Asthma	
Thyroid disease	16
Cerebral disease	11
Arthritis	10
Neurosis	11
Miscellaneous	32
Normal controls	{ Students Staff 10 12

Table II Diagnosis in 190 controls

Age Groups (Yr)	Total Group			Males			Females		
	No. of Patients	Urinary Amylase (IU/hr) Mean (actual range)	Serum Amylase (IU/l) Mean $\pm$ SD (actual range)	No. of Patients	Urinary Amylase (IU/hr) Mean (actual range)	Serum Amylase (IU/l) Mean $\pm$ SD (actual range)	No. of Patients	Urinary Amylase (IU/hr) Mean (actual range)	Serum Amylase (IU/l) Mean $\pm$ SD (actual range)
10-19	4	26 (11-99)	139 ¹ (38-95)	3	28 (11-99)	89 ¹ (38-152)	1	20	285 ¹
20-29	25	19 (9-60)	135 $\pm$ 57 (48-266)	10	23 (13-60)	139 $\pm$ 42 (95-209)	15	17 (9-30)	131 ¹ (48-266)
30-39	23	21 (7-64)	156 $\pm$ 46 (57-219)	13	27 (9-64)	156 $\pm$ 51 (57-219)	10	16 (7-39)	154 $\pm$ 36 (95-219)
40-49	39	21 (4-79)	150 $\pm$ 49 (38-247)	26	23 (4-79)	150 $\pm$ 53 (38-228)	13	17 (9-34)	150 $\pm$ 42 (105-247)
50-59	42	16 (4-55)	156 $\pm$ 59 (48-314)	18	18 (4-55)	165 $\pm$ 51 (48-276)	24	14 (5-45)	148 $\pm$ 67 (57-313)
60-69	42	14 (2-53)	133 $\pm$ 46 (48-228)	23	17 (5-49)	139 $\pm$ 46 (76-228)	19	12 (2-53)	125 $\pm$ 46 (48-228)
70+	15	19 (9-45)	131 $\pm$ 57 (67-257)	5	23 (11-42)	167 $\pm$ 63 (105-257)	10	17 (9-45)	114 $\pm$ 46 (67-209)
TOTAL	190	18 (2-99) 5-69 ²	144 $\pm$ 53 (38-314) 38-251 ¹	98	21 (4-99) 6-74 ²	148 $\pm$ 51 (38-272) 46-251 ²	92	15 (2-53) 4-58 ²	139 $\pm$ 55 (48-313) 29-249 ²

Table I Age and sex distribution in 190 controls

¹Distribution abnormal or numbers too few. ²Mean $\pm$ 2SD

Diagnosis		No. of Patients		Age Range in Years
Renal disease	Urinary tract disease	5	49	18-85
	Blood urea > 45 < 100 mg/100 ml	38	Male 29	
	Blood urea > 100 mg/100 ml	6	Female.....20	

Table III Diagnoses, sex, and age in 49 patients with renal dysfunction

CONTROL PATIENTS

The distribution of the hourly rate of urinary amylase excretion, the serum amylase, and lipase for the 190 control subjects is shown in Figures 1a, 2, and 3. The rate of urinary amylase excretion/hour (Fig. 1a) has a skew distribution, which becomes a normal distribution when the results are translated to a logarithmic scale (Fig. 1b). The mean rate of excretion of urinary amylase/hour was 18 IU/hour with a range of 5 to 69 IU/hour as calculated from the mean $\pm$ 2 standard deviations. The mean serum amylase for this group was 144 IU/l with a calculated range of 38 to 251 IU/l. The selected upper limit of normal for the serum lipase (at the 97.5% level, Fig. 3) gave a value of 1.6 units/ml. The hourly rate of urinary amylase excretion was not significantly

affected by increasing age (Table I), but the mean values of both the hourly rate of urinary amylase and the serum amylase were significantly lower in women than in men ($P < 0.05$, Table I).

RENAL AND URINARY TRACT DISEASE

There were 49 patients in this group (Table III, Fig. 4), five with urinary tract disease, 38 with a blood urea level between 45 (the upper limit of normal in our laboratory) and 100 mg/100 ml and six with a blood urea greater than 100 mg/100 ml. In the last group two patients had a normal rate of urinary amylase excretion/hour in the presence of raised levels of blood urea, serum amylase, and lipase; one had a blood urea value of 400 mg/100 ml, an hourly rate of urinary amylase excretion from 21 to 41 IU/hour,

Fig. 1a Plotted on an arithmetic scale.

Fig. 1b Plotted on a logarithmic scale. Horizontal dotted lines = mean $\pm$ 2SD.Fig. 1
Hourly rate
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whilst the serum amylase was 1,292 to 1,957 IU/l and the serum lipase 5 to 6 units/ml. The other patient had a urinary amylase excretion of 39 IU/hour with a blood urea level of 270 mg/100 ml, serum amylase of 447 IU/l, and a serum lipase of 3.1 units/ml. Both patients died and there was no evidence of pancreatic disease at necropsy. In contrast a patient with a blood urea level of 110 mg/100 ml following a gastrointestinal haemorrhage had a urinary amylase excretion rate of 113 IU/hour, which fell to 49 IU/hour when the blood urea returned to normal but at no time was the serum amylase or lipase raised. Three patients with blood urea levels between 59 and 98 mg/100 ml had serum amylase levels just above the upper limit of normal for this study (295 to 361 IU/litre), but normal serum lipase values and rates of urinary amylase excretion/hour. On the other hand a patient with a hypernephroma excreted 119 IU/hour with a blood urea level of 50 mg/100 ml and a normal serum amylase; the serum lipase was not recorded in this case.

Discussion

The value of measurements of urinary amylase in the diagnosis of pancreatic disease has long been disputed (von Benczúr, 1910; Dozzi, 1940; Sachar, 1952; Saxon, Hinkley, Vogel, and Zieve, 1957; Budd, Walter, Harris, and Knight, 1959; Gambill and Mason, 1963). Interpretation and comparison of published results is difficult since there are so many methods of estimation and a variety of ways in which the results can be expressed. Also many authors do not publish the data on which their conclusions are based. Recently it has been suggested that the hourly rate of amylase excretion into the urine is a more sensitive index of pancreatic disease than is the serum amylase (Saxon *et al*, 1957; Gambill and Mason, 1963). However, in two published series, histograms of rates of urinary amylase excretion for control subjects showed a distribution with a skew to the right (Sachar, 1952; Gambill and Mason, 1964). Similar distributions have been seen when the urinary amylase is expressed as a concentration (van Riet and Hoeke, 1967) and as total 24-hour outputs (Aw, Hobbs, and Wootton, 1967). Comparison of Figs. 1a and 1b clearly shows the log normal distribution of our data: the upper limit of normal for the 190 control subjects was 69 IU/hour. This confirms our impression that the hourly rate of urinary amylase excretion was somewhat higher than the 300 Smith Roe units/hour (63 IU/hour) previously suggested by Gambill and Mason (1964). However, the present results do not take into account any effect on the upper limit of normal that may accompany non-pancreatic gastrointestinal diseases, a point dis-

cussed in part II of this paper. Whilst the apparent tendency for the rate of urinary amylase excretion to decrease with age was not maintained, women had a significantly lower rate of excretion than men, in all age groups.

Most subjects in the present study were patients admitted to the wards or attending as outpatients and provided a more suitable comparative group than normal subjects. Patients with treated pernicious anaemia were included in the control group unless they complained of gastrointestinal symptoms. These patients are usually well and although they have achlorhydria it is likely that many patients of a comparable age are hypochlorhydric (Levin, Kirsner, and Palmer, 1951; Baron, 1963).

Since ill patients may not have been able to tolerate fluids before admission, the two-hour collections from control subjects were not made during an established diuresis. Urine collections are liable to error, but it has been demonstrated by Saxon *et al* (1957) that two-hour collections are as satisfactory as six- or 24-hour collections when hourly rates of urinary amylase excretion are determined and are more convenient unless the patient is dehydrated when a longer collection period may be necessary. Although it has been said that fluctuations in the rate of urinary amylase excretion per hour are less likely to occur than of amylase concentrations, the present authors have found wide variations in the former from day to day (Waller and Ralston, unpublished observations) and even between two-hour collections on the same day in acute pancreatitis (Fig. 6, Table V, Part II). Moreover since blood samples are more easily and rapidly obtained than urine, a value for serum amylase is likely to be more useful than a urinary estimation in the diagnosis of acute pancreatitis.

The present study also provided control ranges for the serum amylase and lipase. Whilst the upper level of 251 IU/l (132 Somogyi units/100 ml) agreed well with the laboratory level of 266 IU/l (140 Somogyi units/100 ml) the serum lipase at 1.6 units/ml was somewhat above the value of 1.15 units/ml for healthy adults obtained in our laboratory.

Alpha-amylase has a molecular weight of about 45,000 (Danielsson, 1947; Blainey and Northam, 1967) and is cleared from the blood by glomerular filtration. Urinary amylase levels are dependent on renal function since the clearance of amylase is directly related to creatinine clearance (Blainey and Northam, 1967). Acute and chronic renal failure are accompanied by retention of both amylase and lipase (Meroney *et al*, 1956; Burton, Hammond, Harper, Howat, Scott, and Varley, 1960). When recovery from acute renal failure takes place hyperamylasuria occurs during the diuretic phase (Howat,

personal communication). In the present series blood urea levels above 250 mg/100 ml were definitely associated with elevations in serum amylase and lipase, but the rates of urinary amylase excretion remained within the normal range. Blood urea levels above 45 mg/100 ml were sometimes accompanied by a slight rise in the serum amylase with normal rates of urinary amylase excretion. In one case, after gastrointestinal bleeding, in which the blood urea was elevated, the serum amylase was normal but the rate of urinary amylase excretion was raised. Therefore, an hourly rate of urinary amylase excretion alone could be misleadingly normal in pancreatitis associated with a transient or chronic renal failure. On the other hand renal disease associated with excretion of large amounts of protein into the urine, such as nephrosis (Corbett, 1913) and toxæmia of pregnancy (Wallis, 1920), is accompanied by elevated rates of urinary amylase excretion.

The elevated rate of urinary amylase excretion in a patient with a hypernephroma and a normal serum amylase level was interesting. One possible explanation was that the tumour produced amylase.

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