Blair, 1960). It is now well established that it is the oestrogens which appear to be responsible for the adverse effects on clotting and platelet function (Poller *et al.*, 1971a, 1971b) and for the thrombotic tendency (Inman *et al.*, 1970). The 19-norsteroid might in theory therefore have produced similar changes to oestrogen-containing oral contraceptives.

The lack of adverse effects on blood clotting with norethisterone is in contrast to our previous findings with all types of conventional combined oral contraceptives where significant rises of factors VII and X as well as other undesirable clotting changes occurred within the first three months of administration. In addition, we have found accelerated cephalin times and Chandler's tube platelet aggregation times with combined preparations. A number of authors have found a tendency to increased platelet adhesion (Ygge *et al.*, 1969) with combined preparations. Von Kaulla and von Kaulla (1970) showed a fall in antithrombin III levels with conventional oral contraception. Several authors have also reported rises in fibrinogen levels with oestrogen-progestogen administration (Nilsson and Kullendar, 1967). The lack of such changes with six months' norethisterone administration is reassuring.

In a previous long-term follow-up of a group taking chlormadinone acetate no change in clotting tests was recorded but acceleration of the Chandler's tube platelet aggregation test was recorded after two years, although this was significantly less than a long-term group on combined oestrogen-progestogen preparations. Longer follow-up will therefore be required to be certain that delayed or cumulative effects do not occur at a later stage of the present study of norethisterone administration.

The absence of adverse effects on clotting and platelets in the group of women not previously having taken oral contraceptives was also supported by the absence of changes in women who changed to norethisterone from chlormadinone acetate and the small group of postpartum patients. None of the patients in this trial suffered from thrombosis but this was unlikely in view of the small size of the groups tested. The absence of clotting

and platelet changes is not proof that oral contraception with 19-norsteroid progestogens will be devoid of thrombotic complications, but the evidence that these undesirable side effects on clotting have been avoided raises the possibility of a reduction in thromboembolic risk when they are used instead of combined preparations.

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Glucose Tolerance and Insulin Secretion in Patients with Chronic Duodenal Ulcer

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Summary

An oral glucose tolerance test has been used to compare carbohydrate metabolism in patients suffering from chronic duodenal ulceration with that in a matched group of normal subjects. A significantly greater rise in blood glucose concentration was observed in the duodenal ulcer group, and this was associated with a significantly greater output of insulin. The reason for these findings may be an abnormal secretion of one or more of the small-bowel hormones.

Introduction

Abnormal glucose tolerance curves have been described after both partial gastrectomy and vagotomy and drainage, and have been attributed in large part to abnormally rapid gastric empty-

ing (Evensen, 1942; Cameron *et al.*, 1969; Holdsworth *et al.*, 1969; Perreau *et al.*, 1969). Less attention has been paid to the question of carbohydrate metabolism in the preoperative ulcer patient. Early studies yielded conflicting results, probably because the techniques of the glucose tolerance tests were not standardized and the methods used for estimating blood glucose concentrations were relatively crude. Furthermore, changes in plasma insulin levels could only be inferred from the observed variations in blood glucose concentration.

The importance of the gastrointestinal hormones in modifying the insulin response to ingested carbohydrate is established (McIntyre *et al.*, 1964, 1965). The altered gastrointestinal physiology accompanying chronic peptic ulcer disease might be reflected in an abnormal pattern of carbohydrate metabolism. We have used an oral glucose tolerance test with measurement of blood glucose and plasma insulin concentrations to investigate a group of patients with chronic duodenal ulcer in an attempt to define any such abnormality.

Patients and Methods

Fifteen patients with a lengthy history of dyspepsia, in whom a radiological diagnosis of chronic duodenal ulcer had been

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obtained, formed the test group. All of these patients were operated on and the diagnosis was confirmed. None was suffering from any of the complications of duodenal ulceration. An additional five subjects with severe pyloric stenosis secondary to duodenal ulceration were studied. The control group comprised 15 healthy subjects, either colleagues or patients admitted to hospital for minor surgical procedures. None had diabetes. All of the patients and controls were within 10% of their ideal body weight and had been taking a normal diet before the test. Details of the subjects are shown in Table I.

TABLE I—Details of Subjects (Mean $\pm$ 1 S.E. of Mean)

	Age (years)	Height (m)	Weight (kg)	Sex	
				M.	F.
Duodenal ulcer ..	45.4 $\pm$ 3.41	1.71 $\pm$ 0.21	65.3 $\pm$ 2.7	11	4
Control	40.7 $\pm$ 4.3	1.70 $\pm$ 0.25	66.5 $\pm$ 2.9	10	5

Procedure.—After fasting overnight the subject drank 350 ml of a 25% glucose solution as rapidly as possible. The first 10 minutes of the two-hour test were carried out with the subject standing, the remainder of the test with the subject sitting upright. Venous blood samples were obtained through an indwelling heparinized cannula before the test and then at 10, 20, 30, 45, 60, 90, and 120 minutes. Blood glucose concentrations were measured by the glucose oxidase method of Morley *et al.* (1968), the coefficient of variation being 4.6% at a blood glucose concentration of 105 mg/100 ml. Plasma immunoreactive insulin was measured in duplicate by the method of Hales and Randle (1963) using a radioactive iodinated insulin and Oxoid membrane filters supplied by the Radiochemical Centre at Amersham. The pre-precipitated antibody and standard human insulin were supplied by Burroughs Wellcome. This assay method gave results with the following standard deviations: ± 2.92 μ U/ml for 115 duplicate determinations in the range 0–49 μ U/ml; ± 6.51 μ U/ml for 64 determinations in the range 50–99 μ U/ml; and ± 7.25 μ U/ml for 55 determinations in the range 100–200 μ U/ml. Samples with a plasma insulin concentration of more than 200 μ U/ml were diluted and reassayed. With this exception all specimens from any one subject were assayed in the same batch.

Results

The changes in blood glucose and plasma insulin concentrations occurring during the test in the normal subjects and duodenal ulcer patients are shown in Figs. 1 and 2 and are summarized in Table II. The ulcer patients exhibited a hyperglycaemia and

FIG. 1—Blood glucose concentrations in 15 normal subjects and 15 patients with chronic duodenal ulcer in response to 350 ml of 25% glucose. Mean values $\pm$ 1 S.E. of mean.

FIG. 2—Plasma insulin concentrations in 15 normal subjects and 15 patients with chronic duodenal ulcer in response to 350 ml of 25% glucose. Mean values $\pm$ 1 S.E. of mean.

TABLE II—Details from Blood Glucose and Plasma Insulin Curves (Mean values $\pm$ 1 S.E. of Mean)

	Blood Glucose (mg/100 ml)			Plasma Insulin (μ U/ml)	
	Maximum	Minimum	Area Under Curve (0–120 min)	Maximum	Area Under Curve (0–120 min)
Duodenal ulcer	163.0 $\pm$ 8.6	92.7 $\pm$ 10.2	6,503.9 $\pm$ 691.3	130.7 $\pm$ 11.3	7,638.1 $\pm$ 856.3
Control	123.2 $\pm$ 7.2	63.5 $\pm$ 6.4	3,031.5 $\pm$ 563.4	90.3 $\pm$ 6.9	4,125.6 $\pm$ 621.2

hyperinsulinaemia, the form of the two curves being similar. Blood glucose concentrations were significantly raised above control levels at 45, 60, 90, and 120 min ($P < 0.05$, $P < 0.01$, $P < 0.01$, and $P < 0.05$). Significantly increased plasma insulin concentrations were found at 60, 90, and 120 min ($P < 0.05$, $P < 0.001$, and $P < 0.001$).

Total insulin secretion was estimated by computing the area beneath the plasma insulin curve from 0 to 2 hours (Perley and Kipnis, 1965). Similarly the area beneath the blood glucose curve from 0 to 2 hours was measured to give an index of glucose tolerance (Burns *et al.*, 1965; Bagdade *et al.*, 1967). A decrease in this area represents an improvement in glucose tolerance. The results of these measurements are shown in Table II. Insulin secretion over the two-hour period was significantly increased in the ulcer patients ($P < 0.01$), yet despite this glucose tolerance was impaired in these patients as is shown by increased areas beneath the blood glucose curves ($P < 0.001$). According to the criteria laid down by the British Diabetic association (Fitzgerald and Keen, 1964), six of the

FIG. 3—Blood glucose and plasma insulin concentrations in five patients with chronic duodenal ulcer complicated by pyloric stenosis. Mean values $\pm$ 1 S.E. of mean.

duodenal ulcer patients (40%) exhibited abnormal glucose tolerance compared with only one of the control group (6.7%).

The blood glucose and plasma insulin levels found in the five patients with pyloric stenosis secondary to duodenal ulcer are shown in Fig. 3. The results show a pattern intermediate between the pronounced hyperglycaemia and hyperinsulinaemia of the patients with uncomplicated duodenal ulcer and the normal glucose tolerance and insulin secretion of the control group.

Discussion

An abnormal hyperglycaemic response to oral glucose has been described previously in patients with chronic duodenal ulcer (Evensen, 1942; Abrahamson, 1945; Platt *et al.*, 1949). In a more recent study, however, Buchanan *et al.* (1967) found that although blood sugar concentrations were higher after oral glucose in patients with duodenal ulcer than in a group of control subjects, the difference attained statistical significance only at 15 minutes after the test began. Despite this they were able to show that the ulcer patients had an insulin output which was significantly greater than that in the control group.

The abnormalities of carbohydrate metabolism which we have found in patients with chronic duodenal ulcer could conceivably be a reflection of a more generalized metabolic disorder. Impaired glucose tolerance with associated hyperinsulinaemia has been described in patients with cirrhosis (Berkowitz *et al.*, 1969) and obesity (Yalow *et al.*, 1965; Bagdade *et al.*, 1967; Abrams *et al.*, 1969). Glucose tolerance and insulin secretion are affected in a similar way by excessive corticosteroid and growth hormone secretion (Berger *et al.*, 1966; Oakley *et al.*, 1970). None of the present patients had any clinical evidence of these disorders, and all had normal liver function tests. Hall (1971) was unable to show any evidence of abnormal growth hormone secretion in patients with duodenal ulcer. The present patients were all within 10% of their ideal body weight and taking a normal diet.

Griffith *et al.* (1968) suggested that patients with uncomplicated duodenal ulcer have an abnormally rapid rate of gastric emptying soon after a meal. Rapid gastric emptying is known to result in a faster rate of rise of blood glucose concentration and higher peak levels in patients who have undergone partial gastrectomy or vagotomy and a drainage procedure (Evensen, 1942; Cameron *et al.*, 1969; Holdsworth *et al.*, 1969; Perreau *et al.*, 1969). However, as the raised peak blood glucose levels are followed by an exaggerated fall towards hypoglycaemia this explanation alone will not account for the results which we have obtained in patients with duodenal ulcer. Conversely, a slower rate of gastric emptying might be expected to give a more prolonged (albeit somewhat flatter) hyperglycaemia phase, such as we have observed in the patients with duodenal ulcer. The results which we have obtained in patients with delayed emptying of the stomach due to pyloric stenosis are against this explanation, showing as they do a pattern intermediate between that of the duodenal ulcer and normal patients, rather than an exaggeration of the ulcer pattern.

A further explanation for the present results is suggested by a consideration of the part that the gastrointestinal hormones play in determining the plasma insulin response to oral glucose. Gastrin, secretin, gut glucagon, and cholecystokinin have all been shown to be released by oral glucose and to augment the output of insulin from the pancreas (Samols *et al.*, 1965; Young *et al.*, 1968; Dupre *et al.*, 1969; Rehfeld and Heding, 1970). It is for this reason that the insulin response to oral glucose is of a greater magnitude than that to a corresponding

intravenous glucose challenge (McIntyre *et al.*, 1964; Dupre, 1964). It may be that the altered gastrointestinal physiology which accompanies duodenal ulceration—in particular the hypersecretion of acid—is accompanied by an increased release of one or more of these hormones. There is some evidence to suggest that the presence of acid in the duodenum increases the secretion of insulin from the pancreas (Dupre, *et al.*, 1969; Kaess *et al.*, 1970) although this has been denied (Boyns *et al.*, 1966). Chisholm *et al.* (1969) perfused the duodenum with acid in normal subjects and observed a prompt release of secretin into the blood stream which was followed by a rise in plasma insulin concentrations. Buchanan and his co-workers (1967) were unable to find any correlation between gastric acid secretion and plasma insulin levels in their duodenal ulcer patients. We have compared the basal acid secretion in the 11 male duodenal ulcer subjects with the total insulin output over the two-hour test period (Table III). There is a significant positive correlation between these two criteria ($P < 0.01$) although the relation is not a linear one (Fig. 4). The abnormal insulin

FIG. 4—Correlation between two-hour insulin response to 350 ml of 25% glucose and basal acid output in 11 male patients with chronic duodenal ulcer. Rank correlation calculated by the method of Spearman (1904). Basal acid output plotted on a logarithmic scale.

response to oral glucose is particularly pronounced in those duodenal ulcer patients who exhibit high levels of basal acid secretion. The finding of hyperglycaemia at a time when plasma insulin levels are raised, suggesting a degree of resistance to the peripheral actions of insulin, is in keeping with the concept of an increased release of small-bowel hormones, since some of these hormones are known to exert, either directly or indirectly, a hyperglycaemic effect (Unger and Eisentraut, 1964; Unger *et al.*, 1967; Ohgawara *et al.*, 1969).

It has been suggested that hyperinsulinaemia may be a factor in the aetiology of duodenal ulceration (Buchanan *et al.*, 1967) acting via the vagus nerves to cause hypersecretion of acid by the stomach. This would seem unlikely since it is not insulin *per se* but rather hypoglycaemia that stimulates gastric secretion (Okada *et al.*, 1930; Roholm, 1930).

Hobsley and Le Quesne (1960) and Sullivan and Boshell (1964) have suggested that a postabsorptive abnormality of carbohydrate metabolism may play a part in the genesis of the dumping syndrome which some patients experience after gastric surgery. Both insulin (Hobsley and Le Quesne, 1960) and oral hypoglycaemic agents (Sullivan and Boshell, 1964) have been used to ameliorate the symptoms of dumping. While we have shown raised concentrations of plasma insulin in the duodenal ulcer patients, these would seem to be relatively ineffective from the point of view of disposing of the glucose load. It may be that the patients who have abnormal glucose tolerance are those who are predisposed to dumping symptoms after operation.

TABLE III—Basal Acid Output and Two-hour Insulin Output in 11 Male Patients with Chronic Duodenal Ulcer

Basal acid output (mEq/hr)	2.26	3.08	3.42	5.32	5.82	6.68	8.68	9.92	12.89	22.48	25.30
Two-hour plasma insulin output (μU/ml/min)	4.473	4.248	6.040	8.120	6.230	10.618	7.078	9.051	10.520	13.876	11.923

There is evidence to suggest that peptic ulceration and cardiovascular disease occur together more commonly than would be expected by chance. Abdominal aortic aneurysm has been linked with peptic ulcer disease (Jones *et al.*, 1970; *British Medical Journal*, 1971), and both Allan and Dawson (1968) and Hall *et al.* (1971) described a high incidence of duodenal ulceration in patients with coronary heart disease and peripheral vascular disease respectively. Sloan *et al.* (1970) described a pattern of impaired glucose tolerance and hyperinsulinaemia in patients with peripheral atherosclerosis, which is similar to the results which we have obtained in patients with duodenal ulcer before operation. An increased insulin response to oral glucose has also been described in patients surviving myocardial infarction (Peters and Hales, 1965). Stout (1968) has shown in experimental animals that insulin stimulates both lipogenesis and cholesterol synthesis in arterial tissue. There are many possible reasons why duodenal ulcer disease and vascular disease may be related. The present results suggest that abnormal carbohydrate metabolism may be common to both.

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Hypertension and Hyperparathyroidism

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Summary

Of 40 patients with primary hyperparathyroidism 13 were hypertensive. Nine presented with hypertension and, of these, seven were discovered to have hyperparathyroidism by the routine determination of serum calcium in 900 patients referred for investigation of hypertension. The association of hypertension and hyperparathyroidism is well recognized but the cause is in doubt. The incidence of primary hyperparathyroidism in patients with hypertension is about 1 in 130, which is considerably higher than in the general population (1 in 1,000-2,000). All patients with hypertension should have a routine serum calcium estimation. Parathyroidectomy in these otherwise asymptomatic cases may prevent renal damage.

Introduction

The clinical manifestations of hyperparathyroidism are many, and patients may present with urinary calculi, renal calcification,

skeletal symptoms, or manifestations of hypercalcaemia. Occasionally on routine screening a raised serum calcium may lead to the diagnosis in patients apparently free from symptoms (Dent, 1962; Gough *et al.*, 1971). Hypertension in hyperparathyroidism was described by Hellstrom *et al.* (1958). In their series of 95 patients 47 (49%) had a diastolic blood pressure of 100 mm Hg or above. George *et al.* (1965) found the incidence to be 20%, and Pyrah *et al.* (1966) between 30 and 50%.

Patients and Investigations

During the period 1960-71, 40 patients with primary hyperparathyroidism were diagnosed in Leicester. Thirty-one presented with renal stones, renal colic, or symptoms of hypercalcaemia. Four patients had diastolic blood pressure of above 110 mm Hg. All had fasting serum calcium levels of 10.4 mg/100 ml or above (normal range 8.8 to 10.3 mg/100 ml.) The diagnosis was confirmed by the removal of a parathyroid adenoma in all patients except one who had parathyroid hyperplasia. In all cases the serum calcium returned to normal after operation.

In the period 1968-71 the serum calcium was measured in 900 patients presenting with diastolic hypertension of at least 110 mm Hg. Raised serum calcium levels were found in seven, none of whom had the clinical features suggestive of hyperparathyroidism or renal stones. In addition there were two