While platelet-fibrin micro-emboli undoubtedly occur, it would appear from the operative material in this series that this is not the whole explanation. The patient with a type I plaque (Fig. 4) is at risk on two counts: he may develop micro-emboli, or a haemorrhage into the plaque may occlude the artery or convert the lesion into type II. Such a localized dissection occurring in atheromatous plaques has been described in detail by Winternitz, Thomas, and LeCompte (1938) and Winternitz (1954).

The type II plaque has two possible sequels: it may rupture and discharge its semi-solid content into the internal carotid artery with resultant cerebral emboli and leave the smooth web-like plaque (type III) or the rough necrotic area (type IV), or it may organize to the most commonly found type V. The risk of trial compression over the carotid artery bifurcation in patients with such a lesion is obvious, and may account for some of the neurological signs elicited during clinical examinations. The patient with a type IV plaque is at particular risk from emboli of either platelets or detached debris, and Gunning *et al.* (1964) have suggested this possibility. It is also possible that both type I and type IV plaques may build up to a type V. On numerous occasions we have noted similar lesions to those described while operating on occlusive vascular disease in the abdominal aorta and peripheral vessels of the limbs. Presumably they also produce small emboli which for the most part are lost in the vascular bed of the limbs and pass unnoticed by the patient. However, when the end-organ of the arterial supply is an essential organ, such as the brain, the need for removing a potential source of such emboli is clearly indicated.

Summary

The clinical investigation and results of 65 carotid endarterectomies in 55 patients presenting during 1957–64 are analysed. Fifty-one patients had intermittent attacks of cerebral insufficiency produced by carotid artery stenosis, and four had completed stroke secondary to carotid artery thrombosis. In the former group 42 patients were alive and well in June 1964, 30 of these being completely free from

symptoms; there was one operative death. All four patients in the latter group died within one month of operation.

Ten patients with bilateral disease were operated upon; staging of the operation at an interval of four to eight weeks is recommended in such cases.

Hypothermia was used in 38 patients, plastic-tube bypass in 4, and local anaesthesia in 13. The relative merits and demerits are discussed.

An analysis of the atherosclerotic plaques encountered in 47 operations permitted classification into five different types. The possible mechanisms of formation and the relationships to symptomatology are discussed.

It is a pleasure to acknowledge the contribution of the physicians and neurologists who referred the patients, and particularly of Dr. C. H. Edwards, of St. Mary's Hospital; also the help of the many general practitioners who assisted in the follow-up of the patients. We are also indebted to Dr. David Sutton for the arteriographic studies, to Dr. P. N. Cardew for photographic reproductions, and to Professor W. T. Irvine for access to the records of the earlier patients in this series.

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Effects of Tolbutamide Upon Gastric Secretion and Emptying

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It was suggested that endogenously produced glucagon and insulin might play a physiological part in controlling gastric secretion and emptying (Aylett, 1962a).

This communication deals with the response of gastric secretion and emptying to stimulation by intravenous tolbutamide in duodenal-ulcer subjects. The method of measuring gastric secretion and emptying was adapted from that of Hunt (1954), as described by Aylett (1962b).

Method

Quantitative water test meals were given, marked with a known amount of phenol red. The patients fasted from 10 o'clock the previous night; starting at 9 a.m. the 750-ml. test meal was poured into the stomach via a polyvinyl tube passed

through the mouth. This meal was allowed to "digest" for 20 minutes, then the unemptied gastric contents were recovered by suction, using an electric pump. Each "meal" was preceded by a washout of 250 ml. of tap-water. A similar washout was given after the meal to check the completeness of recovery.

Estimations were made, on recovered gastric contents, of the concentrations of acid, chloride, potassium, sodium, and phenol red, and of the phenol-red content of the final washout. With the use of Hunt's equations, these measurements, together with the volume of recovered gastric contents and of the final washout, enabled the 20-minute output of these gastric electrolytes to be calculated, together with the volume of gastric contents emptied.

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A "control" water meal was given (in most cases preceded 30 minutes beforehand by an intravenous injection of 10 ml. of normal saline). On another day a similar meal was given 30 minutes after intravenous injection of 10 ml. of 1% sodium tolbutamide.

Venous blood for glucose estimation was taken fasting and 10 minutes after the start of each meal. Glucose concentration was estimated, using the glucose-oxidase method (Huggett and Nixen, 1957).

Results

In four of the eight duodenal-ulcer patients tested there were mild hypoglycaemia symptoms after intravenous tolbutamide. The remaining four subjects had no symptoms after injection.

Blood-glucose Levels.—The mean fasting venous blood-glucose level was 65.5 mg./100 ml., S.D. 6.47. The mean level 10 minutes after the start of control meals was 68.5 mg./100 ml., and for the tolbutamide meals 49.3 mg./100 ml. (see Fig. 1). The fall of blood-glucose level after tolbutamide was significant $0.002 > P > 0.001$.

Gastric Secretion.—(a) *Control Meals*: The mean quantity of acid secreted was 8.29 mEq, of chloride 13.0 mEq, of potassium 1.83 mEq, and of sodium 3.86 mEq. The mean volume of gastric secretion was 82.9 ml., with a mean concentration of potassium of 22.0 mEq/l., and of sodium 50.9 mEq/l. (see Fig. 1). (b) *Tolbutamide Meals*: The mean quantity of acid secreted was 12.3 mEq, of chloride 18.1 mEq, of potassium 2.26 mEq, and of sodium 3.95 mEq. The mean volume of secretion was 114 ml. and was increased in six out of eight subjects with a mean concentration of potassium of 20.1 mEq/l. and of

by a small fall of blood-glucose level. However, there was no relation between the blood-glucose level and the amount of gastric secretion produced. There was a linear relationship between the log % of fasting blood-glucose level and the log volume of gastric contents emptied. Regression analysis showed significance at less than the 2.5% level (see Fig. 2).

FIG. 2.—Control and tolbutamide meals. Relation between log % of fasting blood-glucose level and log volume of gastric contents emptied. $F=8.8771$ (Snedecor's variance ratio test).

Discussion

Unger and Madison (1958) showed that intravenous sodium tolbutamide produced a fall of blood-glucose level in normal subjects. Since Loubatières (1944) suggested that hypo-

FIG. 1.—Gastric secretion of electrolytes, volume of gastric secretion, concentrations of potassium and sodium in the secretion, and volume of gastric contents emptied for control and tolbutamide meals; together with the blood-glucose levels, fasting and 10 minutes after the start of meals. Mean values: 750 ml. water/phenol red, 20-minute meals.

sodium of 37.7 mEq/l. (see Fig. 1). Thus tolbutamide tended to increase the secretory output, with some fall in concentration of potassium and sodium in the secretion. However, these changes were not statistically significant.

Gastric Emptying.—(a) *Control Meals*: The mean volume of gastric contents emptied was 555 ml. (see Fig. 1). (b) *Tolbutamide Meals*: The mean volume of gastric contents emptied was 641 ml. (see Fig. 1). The larger volume of gastric contents emptied after tolbutamide was statistically significant, taking paired data ($0.05 > P > 0.02$).

Gastric Function and the Blood-glucose Level.—The increased gastric secretion after tolbutamide was accompanied

glycaemic sulphonylureas stimulated endogenous insulin production, there has been much experimental evidence in support of this view (Lazarus and Volk, 1962; Lacy, 1962; Mehnert, 1962). It has also been suggested that tolbutamide converts circulating insulin from an inactive to an active form (Lacy, 1962). Antoniadis *et al.* (1962) showed that insulin circulated in the blood as a biologically active "free" insulin and also as an inactive complex.

Glucagon-free insulin was shown to increase gastric secretory output and emptying rate (Aylett, 1962c). It is not known, however, what influence "free" and "inactive" forms of insulin have upon gastric function.

In the present study an increased output of gastric secretion and an increased rate of gastric emptying occurred, together with a small fall of blood-glucose level after tolbutamide. Hypoglycaemic symptoms did not occur in four of the subjects. The result for gastric secretion agreed with that of Weiss and Sciales (1961) for directly aspirated secretion.

An increased gastric emptying rate after tolbutamide does not seem to have been reported previously. However, this result is compatible with the increased gastric motility found by Dupuy *et al.* (1959) after a hypoglycaemic sulphonamide.

The present results are interpreted as showing that insulin, in amounts which the body can secrete in response to stimulation by tolbutamide (or converted to the biologically active form by this substance), can produce measurable effects upon gastric function. While this may lend some support to the view that insulin is concerned as one of the normal mechanisms controlling gastric secretion and emptying, absolute proof would depend upon measurable change of secretion and emptying rate in response to change of plasma-insulin level within the normal range.

The Hunt-type water-test-meal method used is not a weak stimulus to gastric secretion, the stimulus probably being dependent upon the volume of the meal. The secretory response was often a high fraction of the maximal histamine response; by using the maximal histamine response alone, and also in conjunction with a water meal, it was shown that the Hunt-type water meal gave a satisfactory assessment of secretory state and emptying rate (Aylett and Tonkin, 1964). However, for accurate interpretation of small changes in gastric secretory output and emptying rate a more sensitive method of measuring these parameters than that yet available might be required.

Hypoglycaemic sulphonamides (Ito *et al.*, 1960) increased the pancreatic glucagon content of animals. In this the effect was similar to that of injected insulin. Glucagon injected together with insulin suppressed gastric secretion as effectively as when the same dose of glucagon was given alone, while gastric emptying was partially slowed (Aylett, 1962c). It is possible therefore that the effects of insulin or tolbutamide on gastric function are counterbalanced to some extent by increased endogenous glucagon production, tending to "damp" excessive "swings" in response to stimulation.

The effects of tolbutamide on gastric secretion were similar to but milder than those found after insulin injection by Saemundsson (1948), Bernstein (1952), and Aylett (1962c)—that is, increased output of electrolytes and the volume of secretion, together with some fall in the concentrations of potassium and sodium.

In the present study gastric secretory output was unrelated to blood-glucose level. This was similar to results previously described for the secretory responses to insulin and glucagon (Aylett, 1962c) and for gastric secretion in diabetic subjects (Aylett, 1965). Traditionally it has been assumed that the stimulation of gastric secretion by insulin was dependent upon a sharp fall of blood-glucose level. The present results with tolbutamide and previous ones with relatively small doses of insulin (Aylett, 1962a) do not support the need for marked hypoglycaemia as a stimulus.

However, the results after tolbutamide do show a relation between gastric emptying rate and change of blood glucose similar to that after glucagon and insulin injections (Aylett, 1962b). This might be a subsidiary mechanism for the smooth

control of gastric transit of food in relation to glucose utilization, local osmotic effects being more powerful (Aylett and Tonkin, 1965).

Much more study of the relation between gastric function, the pancreatic hormones, and glucose metabolism is obviously required.

Summary

Intravenous sodium tolbutamide in duodenal-ulcer subjects led to increase in gastric secretion of acid, chloride, and potassium, and in the volume of secretion. The concentrations of potassium and sodium in the secretion tended to fall. These effects were similar to but milder than those producible by insulin.

Tolbutamide led to an increased rate of gastric emptying of water meals. This change was similar to that of insulin.

There was an associated fall of blood-glucose level (mild enough not to produce hypoglycaemic symptoms in half the number of subjects).

The results are interpreted as showing that increased endogeneous availability of insulin in response to tolbutamide produced the observed changes in gastric function.

There was no relation between gastric secretion and the blood-glucose level. However, there was a relation between gastric emptying rate and change of blood-glucose level, emptying tending to increase with the degree of fall of blood glucose in relation to the fasting level.

The results are discussed in their possible relation to gastric physiology.

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