CURRENT DRUG THERAPY

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Oral Hypoglycemic Drugs

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Sulfonylureas

THE sulfonylureas are sulfonamide derivatives. The two most commonly used are tolbutamide and chlorpropamide. Their action is now generally accepted to be due to the release of pancreatic insulin, a mechanism which requires that the pancreas be able to produce some insulin. Hence, clinical experience has limited the use of the sulfonylureas to patients meeting certain criteria, described below. These agents may also cause a decrease in hepatic glucose output, but this is unlikely to be their sole effect.

Criteria usually accepted for the successful use of these agents are that the patient be more than 40 years of age; the diabetes be of less than 10 years' duration; there be no previous history of acidosis; and the insulin dosage be no higher than 40 units daily, and preferably between 20 and 30 units daily.

These criteria are not absolute, and probably the best method of selection of patients is still a clinical trial after due consideration of the criteria. Secondary failure after an initial response is most often due to poor selection of patients.

Tolbutamide has the outstanding advantage in low incidence of complications. Side effects are mainly mild urticarial rashes and transient digestive upsets. Hypoglycemic episodes are unusual, owing to the short duration of its action—the half-life is four to eight hours. Tolbutamide is the drug of first choice and the usual dosage is 0.5 g. before breakfast and supper with increases to 1 g. before each meal as necessary. If a dose of 3 g. daily is not effective, still larger doses will not usually produce the desired diabetic control.

Chlorpropamide.—Clinical experience has suggested that this agent may produce a higher percentage of favourable responses than tolbutamide. Both primary and secondary failures have been less common. The incidence of side effects is higher than with tolbutamide, and these include gastrointestinal upset, chest pain, muscle weakness, skin rashes, leukopenia, jaundice and prolonged hypoglycemia—the half-life is 30-36 hours. Because of hypoglycemia, care must be taken with its use in the elderly. The usual dosage is 0.25 g. daily in a single dose before breakfast, with increases as necessary to a maximum of 0.1 g. daily.

Biguanides

Phenformin (DBI)) is the most widely used oral hypoglycemic agent. The drugs in the biguanide group are entirely unrelated to the sulfonylureas. Phenformin does not stimulate the production or release of insulin from the pancreas as the sulfonylureas do. In some way the drug promotes glucose disappearance by means of anaerobic glycolysis, perhaps through increased peripheral utilization of glucose. Its exact mechanism of action remains in doubt.

Selection of patients is by clinical trial only. The restrictions generally accepted in the selection of patients for trial with sulfonylureas do not apply to phenformin. However, some patients do not respond at all to this agent. The drug may be useful in brittle diabetics of all ages in "smoothing" out the diabetic control when combined with insulin. Under these circumstances the dosage of insulin may be reduced by one-third to one-half.

Following the administration of phenformin a fall in blood glucose begins in about two hours and continues to some extent for six to 14 hours. The drug therefore is administered two to four times daily. In patients not receiving insulin one may begin with 25 mg. before breakfast and supper, with increases as necessary to a total of 175 mg. daily; that is, 50 mg. three times daily and 25 mg. at bedtime. When insulin is being given concurrently, the same dosage program may be used with gradual reduction of insulin as the dose of phenformin is increased.

There is no advantage in administering phenformin with insulin to persons with stable diabetes. In such patients, if phenformin alone does not produce excellent control of diabetes, insulin alone should be used. In *unstable diabetics* in whom phenformin permits a lowering of the insulin dose in addition to making the course smoother, both agents may be continued.

Timed-disintegration capsules of phenformin are now available containing 50 mg., which permit the administration of a dosage of 50 to 100 mg. before breakfast and supper.

The side effects of phenformin are common. Early in treatment these consist of gastrointestinal disturbances, metallic taste and ketonuria;

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the later effects are less well defined but include fatigue, weakness and on occasion weight loss. The side effects disappear on discontinuing the drug or lowering the dose. No demonstrable tissue or organ damage has been reported. The range between the therapeutic dosage and the toxic dose is often narrow, for example 25-50 mg.

The place of phenformin in the treatment of diabetes is still a matter of some controversy, because experience with the drug is short, the mode of action is obscure and the long-term effects are unknown. Until more time has passed, many feel that the drug should be considered as still on clinical trial.

CASE REPORT

Peritonitis Caused by *Candida Albicans*

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CANDIDA peritonitis that is not associated with bacterial peritonitis is not commonly encountered. One recently published report[2] described a patient with esophageal perforation who had been treated with massive doses of antibiotics and developed a pure monilial peritonitis. Amphotericin B was administered and the patient survived.

The more extensive use of antibiotics, antimetabolites and corticosteroids, and the prolonged survival of debilitated patients have resulted in an increase in mycotic infections, as illustrated by a recent report by Louria, Stiff and Bennett[1] of a large series of patients with disseminated moniliasis.

The following case is presented to draw attention to the possibility of such infections, and to report the pathological findings in a case of peritonitis caused solely by *Candida albicans*.

A 38-year-old white man was admitted to the Vancouver General Hospital on April 27, 1963, with a four-day history of right upper quadrant pain, anorexia, chills, fever and severe prostration. He was a schizophrenic patient and had not sought medical attention until that time. His past history revealed that at the age of 25 he had been treated for a peptic ulcer by conservative measures.

Physical examination at the time of admission indicated that he was in a state of profound shock and dehydration. An abdominal radiograph revealed the presence of free air within the peritoneal cavity, and a diagnosis of a perforated peptic ulcer was made. His shock was treated by intravenous metaraminol bitartrate and hydrocortisone, which he required for three days. He was not considered a reasonable surgical risk and was treated conservatively with intravenous penicillin, intramuscular tetracycline and supportive measures.

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His urine output was only 200 ml./24 hours and a diagnosis of acute renal failure was made. His blood urea nitrogen (BUN) and serum potassium gradually rose until May 2, when peritoneal dialysis with fluid containing tetracycline was started. It was continued until the time of his death nine days later. The dialysis was quite successful in preventing uremia and there was only a slight rise in the BUN and serum potassium terminally. Cultures were done at the time of the insertion of the intraperitoneal catheter and again three days later. At both times a moderate pure growth of *Candida albicans* was obtained. Urine cultures failed to demonstrate any growth.

On May 6, bowel sounds were first heard and it was thought the perforation had sealed. He remained semicomatose and required a tracheostomy and a Bird respirator to assist his respirations.

Early on May 7 his level of consciousness improved and he generally appeared somewhat better. Later in the day he became worse and 400 ml. of coffee-ground material was noted in the gastric suction. A tarry stool was passed the next day.

The patient continued to sink deeper into coma and shock, and when his serum potassium began to rise an ion exchange resin enema was given. His urine output had remained unchanged during the course of his illness. The peritoneal dialysate was noted to be very cloudy on the last day of his life.

Pathological Findings

The gross examination was unremarkable except for evidence of cachexia, pulmonary edema and the abnormal findings within the peritoneal cavity.

The peritoneal surfaces of all the organs were covered by a thick, shaggy white coat. The superficial portion of the fibrinous coat could be easily scraped off, while the deeper portions appeared firmly attached to the peritoneum. The white material was thickest over the pyloric portion of the stomach and the first part of the duodenum where a perforated ulcer was found. All of the loops of bowel and the greater omentum were matted together by the white covering and by recent filmy adhesions which were easily