The figures reported here show that over 10% of middle-aged women have circulating thyroid antibodies.

Some of these women probably proceed to overt thyroid deficiency with high titres of antibodies, but the factors which influence progression are as yet unknown.

Theoretical considerations apart, it is hoped that the data here presented will provide an empirical basis for estimating the significance of antibody levels in the diagnosis of thyroid disease.

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PHENFORMIN AS ADJUVANT ORAL THERAPY IN DIABETES

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The sulphonylurea group of drugs were the first to be used successfully in the oral treatment of diabetes (Franke and Fuchs, 1955; Bertram *et al.*, 1955). It soon became apparent that these drugs were ineffective in severe diabetics with a tendency to ketosis, and their use is now restricted to milder diabetics who cannot be controlled by simple dietary restriction. Two drugs of this type are in common use—tolbutamide and chlorpropamide. The latter is the more powerful hypoglycaemic agent and has a more prolonged action (Granville-Grossman *et al.*, 1959). However, not all diabetics who might be expected to respond to chlorpropamide do so in practice. Some newly diagnosed diabetics whose urine is free from ketones fail to respond satisfactorily to chlorpropamide, while others who have responded initially begin to relapse into hyperglycaemia gradually after a time.

Phenformin is a diguanide, and earlier trials showed that, although it is a most potent hypoglycaemic agent and sometimes successful where chlorpropamide has failed, it is poorly tolerated when administered at its maximum therapeutic level, often giving rise to gastro-intestinal disturbances (Hall *et al.*, 1958). Its mode of action is uncertain but differs from that of the sulphonylureas (Marble, 1960). Hence, in patients who show an inadequate response to the sulphonylureas, phenformin

has been used as an addition to these drugs (Beaser, 1958, 1960; Granville-Grossman *et al.*, 1959; Unger *et al.*, 1960). Given in this way, the dose of phenformin can be reduced sufficiently to avoid gastro-intestinal intolerance.

The purpose of this communication is briefly to review the present overall picture of tablet therapy in a diabetic unit, and, in particular, to define the role of phenformin as adjuvant therapy to the sulphonyl ureas.

Overall Picture

Suitable records were available for 1,450 diabetic patients treated at Whittington Hospital Diabetic Clinic. These were divided into three groups: those controlled by simple dietary restriction alone, those taking tablets, and those requiring insulin. These groups are not static. Many diabetics needing insulin or tablets for initial control later remitted and were managed on simple dietary control (Bloom, 1959). Others who were well controlled for many years on dietary restriction later began to relapse and needed tablets or insulin. Some who were well controlled initially by tablets later relapsed and needed insulin.

The large majority of young diabetics required insulin, and only a few could be controlled on diet or tablets (Table I). In those over 50, however, more than 20%

TABLE I.—Treatment of 1,450 Diabetics According to Age

Age:	0-30	31-50	51-70	71+
Insulin ..	111 (87.4%)	150 (52.6%)	210 (31.4%)	137 (37.2%)
Diet alone ..	12 (9.5%)	104 (36.5%)	320 (47.7%)	151 (41.0%)
Tablets ..	4 (3.1%)	31 (10.9%)	140 (20.9%)	80 (21.8%)
Total ..	127 (100%)	285 (100%)	670 (100%)	368 (100%)

were controlled by oral therapy. The majority of patients controlled by tablets were taking either chlorpropamide or tolbutamide (Table II). In recent years

TABLE II.—1,450 Diabetics According to Treatment

Insulin ..	608
Diet alone ..	587
Tablets ..	255
Chlorpropamide ..	107
Tolbutamide ..	94
Phenformin ..	14
Chlorpropamide plus phenformin ..	36
Tolbutamide plus phenformin ..	4

chlorpropamide has been used in preference to tolbutamide in new cases, but patients already satisfactorily controlled by tolbutamide have continued on this therapy. 40 patients, representing 16% of those on oral therapy, or 2.7% of all diabetics, required phenformin in addition to either chlorpropamide or tolbutamide.

Phenformin as Adjuvant Therapy.—Phenformin was used as adjuvant therapy to the sulphonylureas in diabetics showing primary or secondary failure of response to tolbutamide or chlorpropamide. Primary failure was noted in diabetics not responding to diet, and also in diabetics previously taking insulin. Secondary failure occurred in patients who were controlled by tolbutamide or chlorpropamide for at least a month but who then began to relapse on this therapy despite adherence to diet.

Method of Trial

Diabetics Not Responding to Diet and Showing Primary Failure to Respond to Tolbutamide or Chlorpropamide

New cases not severe enough to need insulin were placed on a restricted diet varying from 800 calories a day (80 g. carbohydrate) in very obese patients to 1,500 calories (175 g. carbohydrate) in those of normal weight,

and they were observed each week as out-patients. Patients were taught to test the second specimen of urine passed before breakfast and lunch, and before retiring at night. They used "clinitest" tablets and charted their findings. At each attendance, usually in the afternoon two or three hours after lunch, venous blood was taken for estimation of sugar (Hagedorn and Jensen method). Patients were regarded as well controlled when the urine became free from sugar and the blood sugars were less than 190 mg./100 ml. Tolbutamide 1 g. b.d. or chlorpropamide 500 mg. daily was prescribed only when an adequate trial of dietary restriction failed to lead to good control. Where these tablets also proved unsuccessful, phenformin was prescribed as an addition to previous therapy. If this combination of drugs was unsuccessful the patient was given insulin.

The usual maintenance dose for patients taking tolbutamide and phenformin was 500 mg. of the former and 25 mg. of the latter, both three times daily. In patients taking chlorpropamide and phenformin the usual daily maintenance dose was 350 mg. of the former and 100 mg. of the latter in the form of a slow-acting capsule: before the capsule had become available 25-mg. tablets t.d.s. were prescribed.

Some of these patients were admitted to the ward for in-patient trials as described later.

Patients Previously Controlled by Insulin

Attempted transfer from insulin to tablets was offered to stable diabetics with insulin requirements of less than 30 units a day and where there was no tendency to ketoacidosis. In some patients, however, the attempted transfer was at the patient's request, and sometimes in patients where there seemed little likelihood of success. Diabetics previously controlled on insulin were always admitted to the ward before transfer to oral therapy, since even diabetics on small doses of insulin sometimes became rapidly ketotic when insulin was discontinued. When insulin was omitted, chlorpropamide 500 mg. daily was first administered. Where this failed to control the diabetic state, phenformin was added.

In some of these patients a fuller ward trial was undertaken as described later.

Patients Showing Secondary Failure

These patients had previously been well controlled on either tolbutamide or chlorpropamide, but had begun to show a return of hyperglycaemia and glycosuria despite adherence to diet. Where it was suspected that failure was due to dietary indulgences, the importance of diet was stressed before altering therapy. In some patients admitted to the ward under these circumstances, steady amelioration of the diabetic state occurred on the same tablets and ostensibly on the same diet as was alleged to have been followed at home. In the remainder phenformin was added to the previous therapy and observation continued usually as out-patients.

Separate in-patient trials were conducted on some of these patients.

Results

47 diabetic patients, having failed to respond either to tolbutamide 1 g. b.d. or to chlorpropamide 500 mg. daily, became well controlled when phenformin was added to the previous therapy.

These patients were derived as follows:

1. 18 patients not controlled by dietary restriction had shown a primary failure to respond to the sulphonylurea alone, but became well controlled on the addition of phenformin.

2. 13 patients had been previously well controlled on insulin but showed a return of glycosuria and hyperglycaemia when chlorpropamide was substituted for insulin. Control was re-established when phenformin was added to chlorpropamide. Although insulin requirements had sometimes fluctuated, at the time of transfer one patient was taking less than 20 units, eight were taking between 20 and 30 units, two between 30 and 40 units, and two between 40 and 60 units.

3. 16 patients had responded initially to tolbutamide or chlorpropamide but had gradually relapsed. Three had relapsed within six months, four between six months and a year, six between one and two years, and three between two and three years after the beginning of sulphonylurea therapy. Good control was again established in these patients when phenformin was added.

Of these 47 patients successfully controlled on a combination of a sulphonylurea with phenformin, 7 ultimately relapsed and were transferred to insulin. Table III sets out the length of observation.

TABLE III.—Length of Observation of Patients on Combined Therapy

Months :	1-3	3-6	6-9	9-12	12-18	18-24	> 24
No. of patients so far controlled (40) ..	5	6	9	7	7	5	1
No. of patients who relapsed (7) ..	3		2	1	1		

Two patients died during the recorded period, one of carcinoma of the bronchus and one of cerebral haemorrhage. There was no evidence that current therapy contributed to the cause of death.

Ward Trial

There were two possible explanations for the successful addition of phenformin to chlorpropamide in patients responding poorly to chlorpropamide alone. The continued use of chlorpropamide in these patients could have been irrelevant and the improved response simply due to phenformin. Alternatively, phenformin could have exerted an additive hypoglycaemic effect to that of chlorpropamide, and the resultant normoglycaemia could have been partly due to each. Hence a ward trial was undertaken of a group of patients who showed an inadequate response to chlorpropamide. These patients were observed in the ward for a minimum of five days while taking chlorpropamide, and venous blood sugars were estimated before lunch. Urinary sugar was measured four-hourly. Where glycosuria persisted and blood sugars remained raised above 190 mg./100 ml., chlorpropamide was discontinued, and phenformin 100 mg. once daily or 25 mg. t.d.s. was given in its place. If there was no response to this drug alone after a minimum of five days, both drugs were given together in the same dosage as previously.

Results

In all, 36 patients who had failed to show an adequate response to chlorpropamide were investigated in this way.

Nine patients who failed to respond to chlorpropamide were successfully controlled on phenformin. At a dose level of 25 mg. t.d.s. or 100 mg. daily the urine became

sugar-free and blood sugars near normoglycaemic. Fig. 1 shows an example of a patient who responded in this way.

14 patients who failed to respond to either drug separately showed good response when the tablets at the same dosage were given together. Fig. 2 provides an example of this response. These 14 cases are included in those previously described as having responded to combined therapy.

FIG. 1.—Graph of a patient who responded to phenformin after failure with chlorpropamide.

FIG. 2.—Graph of a patient who responded to chlorpropamide and phenformin given together after failure to respond to the drugs given separately.

13 patients failed to respond to either drug separately or when given in combination, and these patients were transferred to insulin. The number of patients who failed tablet therapy in this manner is of no real significance, since it included some diabetics who were thought unlikely to respond to oral therapy.

Slow Disintegration Capsules

Phenformin given as a single large dose will suppress the blood sugar in from four to ten hours, with maximal effect at six hours (Hall *et al.*, 1958). This means that when smaller doses are used the tablets must be administered two or three times a day to establish adequate control. To overcome this difficulty, capsules have been prepared which contain granules of phenformin mixed with shellac, with the aim of allowing a gradual release of the drug during the day. In order to test the efficiency of these capsules, patients were maintained on a measured diet during the trial, and blood and urinary sugars were measured daily. After a period on tablets, 25 mg. q.d.s. or 50 mg. b.d., the capsules were introduced as a single 100-mg. dose in the morning. On one day during each treatment blood sugars were taken at

intervals during the day. As shown in three cases (Table IV), the blood sugars were broadly similar whether the patient was taking the capsule once each morning or the tablets during the day.

TABLE IV.—Three Subjects, on Two Different Days, Treated with Phenformin Tablets as Multiple Dose or as Single Slow Disintegration (S.D.) Capsule. Blood Sugars Expressed in mg./100 ml.

Case		a.m.		p.m.			a.m.		p.m.	
		7.30	11.30	5.30	12		7.30	11.30	5.30	12
A	25 mg. q.d.s.	160	138	156	146	100 mg. S.D.	160	114	126	116
B	50 mg. b.d.	164	148	170	152	100 mg. S.D.	172	154	180	186
C	100 mg. S.D.	158	140	188	171	25 mg. q.d.s.	160	167	207	155

Out-patients taking phenformin 25 mg. t.d.s. or 50 mg. b.d. were transferred to 100-mg. capsules daily. No deterioration in the diabetic state could be detected after this transfer.

Drug Tolerance

In the main, both tolbutamide and chlorpropamide were well tolerated as previously recorded (Granville-Grossman *et al.*, 1959).

Two elderly patients taking chlorpropamide 500 mg. each morning became confused at night. Even when the dose was reduced to 100 mg. daily confusion persisted for several nights before improvement occurred, and was assumed to be due to hypoglycaemia.

Given at a dose not exceeding 100 mg. daily, phenformin gave rise to minimal peyorative effects. Mild nausea, anorexia, and an unpleasant taste in the mouth were the commonest complaints, elicited as a rule on direct questioning. Nevertheless, in some patients these effects were troublesome enough to warrant discontinuance of this treatment. Some of the patients who had experienced mild nausea when taking phenformin tablets claimed improvement in this respect when transferred to the capsules.

Discussion

Chlorpropamide is both effective and well tolerated by most diabetics who fail to respond to dietary restriction but who do not become ketotic. Whether these patients are newly diagnosed or whether they have been controlled previously on a small dose of insulin, normoglycaemia can usually be maintained by a dose of 500 mg. a day, later reduced to 350 mg. or less. Nevertheless, many diabetics expected to respond to this tablet therapy in practice fail to do so. Others who respond initially to chlorpropamide begin to relapse after a time despite continued adherence to a diet. It is in such cases that phenformin offers the opportunity of prolonging oral therapy without recourse to insulin. Phenformin is a powerful hypoglycaemic agent, but it so often gives rise to gastro-intestinal intolerance when administered in the maximum therapeutic dose that it is not as suitable as the sulphonylureas for general use. However, when given at a dose of 100 mg. a day it is reasonably well tolerated by most, and can be administered conveniently in the form of a single slow-disintegration capsule. Although this is a comparatively small dose of phenformin it effectively controlled hyperglycaemia in some diabetics in whom chlorpropamide was inadequate. In a greater number of diabetics in whom chlorpropamide was unsatisfactory, however, substitution by phenformin was ineffective, but control was obtained when the two agents were administered together. Hence it would seem

convenient in patients responding poorly to chlorpropamide to try the addition of phenformin before recourse to insulin.

Diabetes is a progressive disease, though the rate of progression varies greatly. It is not surprising that some patients at first controlled by the sulphonylureas slowly began to relapse, and this was equally true of patients controlled on combined therapy. In some patients the introduction of combined therapy has meant no more than a delay before insulin was introduced. Nevertheless in other patients treatment by combined therapy has been prolonged, and has been particularly welcomed by elderly patients who would otherwise have required insulin.

Whereas it seems clear that oral therapy as at present described is capable of maintaining normoglycaemia, it remains open to question whether this is sufficient to prevent the degenerative complications so commonly seen in diabetics poorly controlled on insulin, since these complications could possibly be due to factors other than hyperglycaemia. However, quite apart from ultimate complications, hyperglycaemia leads to troublesome symptoms and predisposes to infection. In the present state of our knowledge, these seem valid reasons to justify the use of oral therapy in responsive patients.

Summary

Of 1,450 diabetic patients attending a clinic, 587 (40.4%) were controlled on simple dietary restriction, 608 (42%) required insulin, and the remaining 255 (17.6%) took oral hypoglycaemic agents.

Diabetics deemed suitable for oral therapy who failed to respond to chlorpropamide were given phenformin in small doses as an alternative or as adjuvant therapy. Of 23 such patients, 9 responded to phenformin alone but 14 responded only when the phenformin and chlorpropamide were given together.

Phenformin when administered in a single daily 100-mg. slow-disintegration capsule appeared to offer as effective clinical control as when given in divided doses as tablets.

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Among the 3,334 visitors to Coventry who were treated by local doctors last year were an Ethiopian, a Kuwaitian, a Libyan, a Venezuelan, a Norwegian, three Yugoslavians, and four Sudanese. These figures are given in the annual report of the Coventry Executive Council of the Health Service. On January 1 this year 308,359 persons were on Coventry doctors' lists. On April 1 there were 133 doctors in the city and 84 surgeries. It was stated that five people lost dentures while swimming, one lost them "overboard," six threw them in the fire, and two had them destroyed by dogs. (*Birmingham Post*, May 1.)

BARIUM STUDIES IN THE AGED

BY

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As the possibilities of treatment in the field of geriatrics increase, more and more elderly patients will be submitted to radiological examinations. Some examinations can be carried out almost as easily in the old as in the young. Others, such as the investigation of the alimentary tract by means of barium meals and enemas, may be difficult because of the patient's physical frailty or disability or because his mental state prevents his effective co-operation. Moreover, the barium examinations and the preparation entailed may be distressing for the patient. Barium studies in a series of aged patients have therefore been reviewed in order to determine in how many the results were of practical value and in how many of merely academic interest.

The patients investigated had been treated in the geriatric unit during the past five years and were 70 or more years old. The oldest was 93, and the average age was nearly 80. 148 barium studies (102 meals and 46 enemas) were undertaken on 129 patients (40 men and 89 women). Thirteen patients had both a barium meal and an enema. Five patients had two barium meals and one had two barium enemas. In six cases a meal was attempted but was unsatisfactory because the patient was either not able to co-operate or proved unfit for the examination.

Barium Meals

The findings in the patients examined by barium meal are shown in Table I.

*Clinical Diagnosis of Peptic Ulcer (20 Patients).—*This diagnosis was confirmed in 11 patients (7 gastric ulcers, 4 duodenal ulcers). An additional 16 cases of

TABLE I.—Radiological Findings in 97 Patients (102 Barium-meal Examinations) Grouped According to Diagnosis or the Indication for Investigation.

Radiological Findings	Provisional Clinical Diagnosis or Indication for Investigation					
	Peptic Ulcer	Carcinoma of Stomach	Gastro-intestinal Haemorrhage	Dysphagia	Hiatus Hernia	Total
No abnormality discovered ..	8	15	15	6	2	46
Gastric ulcer ..	7	2	10		1†	20
Duodenal ..	4		3			7
Hiatus hernia ..		1	6	3	5	15
Carcinoma of stomach ..		3				3
Carcinoma of oesophagus ..				2	1†	3
Duodenal diverticulum ..			2*			2
Oesophageal diverticulum ..	1				1	2
Neurological disorder ..				1		1
Achalasia of cardia ..				1		1
Pressure on oesophagus by dilated aorta ..		1				1
Situs inversus ..			1*			1
	20	22	37	13	10	102

* Included among the 15 cases assumed to have no abnormality.
 † Associated with hiatus hernia.