In the West Indian populations studied by them Miall *et al.* (1962) had noted that mean arterial pressures were higher in women from the rural than from the urban areas. They could not attribute this difference to excess weight, differences in reaction to the examination, migration, or to a genetic basis. In our West African series urban blood pressures were generally higher than rural values in comparable age groups. Yet the diet, socio-economic status, habitus, and degree of activity of the two groups differed in no striking way. It also seems noteworthy that the blood pressure at all ages was higher in the male urban groups than in the other groups. No definite factor can be said to account for this difference

TABLE II.—*Proteinuria on Two Occasions in Rural and Urban Populations*

Years	Male		Female	
	Total	No. with Proteinuria	Total	No. with Proteinuria
	Rural			
15–19	46	8	62	9
20–29	56	9	80	14
30–39	43	7	52	11
40–49	40	11	49	7
50–54	8	1	17	5
	193	36	260	46
	Urban			
15–19	3	1	12	1
20–29	261	23	113	10
30–39	144	12	82	6
40–49	71	16	19	2
50–54	17	3	3	—
	496	55	229	19

The relatively high incidence of proteinuria in this series may be partly attributed to urinary schistosomiasis, which is known to be endemic in Western Nigeria. The higher incidence of proteinuria in males of both populations may also relate to the prevalence of gonococcal urethral stricture in these groups. As very few of those with proteinuria had hypertension it would seem likely that such hypertension as was found in the rural and urban areas was predominantly essential in origin. This is in general agreement with the findings of Callander (1953) in Nigerian soldiers and army recruits, in whom the incidence of proteinuria was 2·5%.

FIG. 3.—Mean systolic and diastolic pressures in Negro population samples. O——O Nigeria rural. Present series, 1967. × - - - × Nigeria urban. Present series, 1968. △ - - - △ U.S. (Comstock, 1967). ●——● W. Indies (Miall *et al.*, 1962).

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Phenformin-induced Hypoglycaemia in Normal Subjects*

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Summary: Study of the effect of phenformin on the blood glucose level in normal subjects before and during 70 hours of starvation showed a statistically significant hypoglycaemic effect after 40 hours of starvation. This effect was not due to increased glucose utilization.

Another finding in this study was a statistically significant decrease in total urinary nitrogen excretion during starvation in subjects given phenformin. These findings show that the hypoglycaemic effect of phenformin in starved normal subjects is due to inhibition of gluconeogenesis.

Introduction

Phenformin (phenethylbiguanide) is an oral non-sulfonylurea blood-glucose-lowering agent which can act in the absence of insulin. Reduction of hyperglycaemia and glycosuria is well known in patients with diabetes mellitus treated with phenformin. Previous investigations have failed to show any blood-glucose-lowering effect in normal man (Fajans *et al.*, 1960 ;

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Madison and Unger, 1960). In a recent study Searle *et al.* (1966), using ^{14}C-glucose, suggested that phenformin increases the turnover of glucose in normal subjects. Other experiments contradict this finding and seem to indicate that the drug inhibits gluconeogenesis in obese individuals (Kreisberg, 1968).

The present study was undertaken in order to try to distinguish between these contradictory propositions by examining the effect of phenformin on the blood glucose of starving normal subjects, who depend entirely on gluconeogenesis to maintain the blood glucose level.

Material and Methods

Thirteen healthy male volunteers aged 19 to 31 years with normal intravenous glucose tolerance and without a family history of diabetes mellitus were investigated. Before the investigation they were interviewed and the possible hazards and consequences of the experimental procedure were explained in order to obtain informed consent. All subjects were in hospital for the investigation, during which they were starved for 70 hours. Seven normal subjects were treated with phenformin in timed disintegration capsules, 50 mg. every 12 hours, for 72 hours before and during the starvation period.

Intravenous glucose tolerance tests (Lundbæk, 1962) were performed twice in each subject, on the morning before and the morning after 70 hours of starvation. Blood glucose values during the intravenous glucose tolerance tests were determined in arterial blood collected from a catheter introduced into the brachial artery by the Seldinger technique. The rate of glucose disappearance was expressed as the k value, which indicates the slope of the straight line relating blood glucose concentration to time plotted on semi-log paper. Venous blood glucose values were determined every six hours during the period of starvation.

Blood glucose was determined by a modification of the glucose oxidase method (Christensen, 1967).

During the 70-hour period of starvation the urine was quantitatively collected and total urinary nitrogen excretion was determined by the Kjeldahl method.

Results

The mean k values obtained by the intravenous glucose tolerance tests are shown in the Table. The mean k values in the phenformin-treated subjects and in the control group were found not to be statistically different, neither before nor after starvation. The well-known grossly abnormal glucose tolerance was noted in all the starved subjects.

Intravenous Glucose Tolerance Tests in Starving Normal Subjects

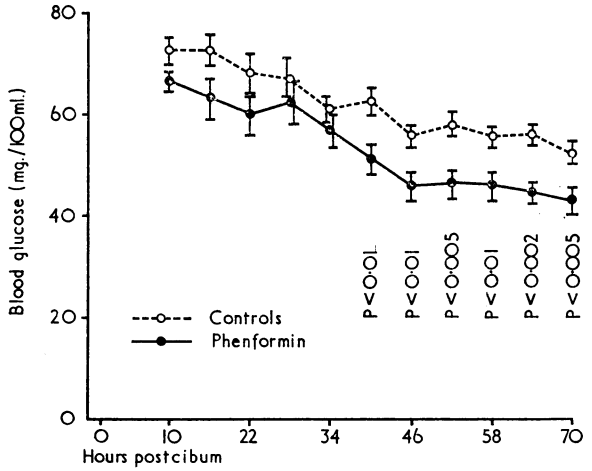
	Mean k Values (min.$^{-1}$ ± S.E.M.)	
	Before Starvation	After Starvation
Control subjects (n = 6)	1·40 ± 0·08	0·80 ± 0·04
Phenformin-treated subjects (n = 7)	1·17 ± 0·09	0·80 ± 0·05
Statistical analysis control subjects versus phenformin-treated subjects	P > 0·2	P > 0·5*

* 95% confidence limits for the true difference: 0·00 ± 0·20.

The mean fasting arterial blood glucose values obtained before the starvation period was 80 mg./100 ml. (S.E.M. ± 2 mg.) in the phenformin-treated subjects and 80 mg./100 ml. (S.E.M. ± 2 mg.) in the control group.

The mean venous blood glucose values during the starvation period are shown in the Chart. The mean blood glucose values were lower in the phenformin-treated subjects than in the control group during the entire period of starvation. The differences between the mean values in the two groups was found to be statistically significant during the last 40 hours of starvation.

The mean total urinary nitrogen excretion during the starvation period was found to be 39·3 g. (S.D. ± 5·1 g.) in the control group and 32·6 g. (S.D. ± 5·6 g.) in the phenformin-treated subjects. The difference between the mean values in the two groups was statistically significant ($t = 2{\cdot}233$, $P < 0{\cdot}05$).



Venous blood glucose values in starving normal subjects (mean values ± S.E.M.).

Discussion

Previous studies have failed to show any hypoglycaemic effect of phenformin in fasting normal subjects even when the drug was administered for 9 to 12 days (Fajans *et al.*, 1960; Madison and Unger, 1960). Correspondingly, the present investigation shows no decrease in fasting arterial blood glucose levels in normal subjects given a normal diet and treated with phenformin for three days. In contrast, during a 70-hour period of starvation a significant decrease in venous blood glucose level was found in phenformin-treated normal subjects.

The phenformin-induced hypoglycaemia observed in normal subjects during starvation may be caused by two different actions of the drug—decreased glucose production from the liver and kidney or increased peripheral utilization of glucose, or a combination of both. The utilization of glucose, as judged by the intravenous glucose tolerance test, was found to be decreased in phenformin-treated starving subjects but no more nor less than that in the controls. Furthermore, no increase in peripheral glucose uptake has hitherto been found in phenformin-treated fasting normal subjects (Madison and Unger, 1960). It therefore seems unlikely that the hypoglycaemic effect of phenformin is caused by an increased glucose utilization.

It is of considerable interest to note that a hypoglycaemic effect of phenformin is present in starved but not in fed normal subjects. After two days of starvation the liver is depleted of glycogen, and glucose production takes place exclusively by gluconeogenesis. In the present study the hypoglycaemic effect of phenformin is most pronounced and only statistically significant after 40 hours of starvation, at a time when glucose is formed exclusively by gluconeogenesis. Furthermore, during starvation the total urinary nitrogen excretion is decreased in the phenformin-treated subjects. These two findings indicate that phenformin inhibits gluconeogenesis in starving normal subjects.

This hypothesis is in good agreement with previous studies in obese diabetic and non-diabetic human subjects (Kreisberg, 1968) and with the finding of an inhibition of gluconeogenesis by biguanides in animal experiments (Williams *et al.*, 1957; Meyer *et al.*, 1967; Altschuld and Kruger, 1968).

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Erythema Nodosum due to Pasteurella pseudotuberculosis

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Summary: Two children developed erythema nodosum due to Pasteurella pseudotuberculosis. Neither case showed typical signs of P. pseudotuberculosis infection, but this cause was shown by positive agglutination tests. It is suggested that this organism is a more common cause of erythema nodosum than is at present recognized.

The purpose of this report is to draw attention to a cause of erythema nodosum in children and young adults which may easily escape notice. In recent years *Pasteurella pseudotuberculosis* infection has been recognized on the Continent, especially in France, as an underlying cause of erythema nodosum occurring either as a separate clinical entity or in association with mesenteric lymphadenitis (Evreux and Magard, 1967; Lèques and Verdaguer, 1967; Le Coulant *et al.*, 1967). In this country Bouton and Hall diagnosed *P. pseudotuberculosis* infection in a 14-year-old girl admitted to Alder Hey Children's Hospital, Liverpool, with erythema nodosum and a four-month history of intermittent abdominal pain (cited by Mollaret, 1962).

In the following cases the patients did not show the abdominal symptoms characteristic of *P. pseudotuberculosis* infection. In one case the erythema nodosum followed a non-specific febrile upper respiratory illness and in the other erythema nodosum was the only clinical manifestation.

Case 1

A girl of 6 years was referred by her general practitioner on account of erythema nodosum. Her mother stated that on 29 August 1968 she complained of loss of appetite and general malaise. By 1 September she had become febrile, her temperature reaching 39·5° C. over the next three days. At that stage the family doctor noted numerous reddish blue lumps on both shins and referred her to one of us (D. S. W.). Examination on 12 September showed a classical resolving erythema nodosum on both legs with typical bruised discoloration. Although the patient was afebrile and had no other complaints or abnormal physical signs, the mother stated that she had not yet recovered her normal health. During the succeeding 10 days complete recovery occurred.

Investigations.—Hb 80%; W.B.C. 6,900/cu. mm.; E.S.R. (Westergren) 74 mm./hour; antistreptolysin-O titre, less than 200 u./ml. Chest x-ray examination showed no evidence of tuberculosis or sarcoidosis. Tuberculin test negative at 1/1,000 dilution. Brucella and salmonella agglutinins negative.

Serum taken from the patient on 12 September was found to agglutinate *P. pseudotuberculosis* (type I) to a titre of 1/1,280. An intradermal test with *P. pseudotuberculosis* antigen produced a positive result (erythema 10 mm., induration 5 mm.) 24 hours after the injection. Serum taken from the patient three months later showed no agglutinins for *P. pseudotuberculosis*.

Serum specimens from five other members of the household were examined with negative results. At about the time the patient became ill the family had acquired a stray cat which was unwell and had sticky eyes. Blood was taken from the animal, but unfortunately an insufficient amount was obtained to allow the agglutination titre to be determined.

Case 2

A girl aged 15 had a history of recurrent "bilious" attacks, occurring at intervals of two to three months, over a period of two years. The attacks, which lasted one day, were characterized by vomiting and headache but no diarrhoea. One of these attacks (11 January 1969) coincided with the development of small, tender nodules on both legs and arms. There was no fever, and the patient remained well subjectively. Because of the persistence of the lesions she was seen by her general practitioner, who referred her to one of us (D. S. W.). On examination she showed typical resolving erythema nodosum on legs and arms. There was no lymphadenopathy.

Investigations.—Hb 100%; W.B.C. 7,800/cu.mm.; E.S.R. 37 mm./hour; antistreptolysin-O titre, less than 200 u./ml. Chest x-ray examination showed no evidence of tuberculosis or sarcoidosis. Tuberculin test negative at 1/1,000 dilution. Intradermal test with *P. pseudotuberculosis* antigen produced a pronounced reaction (induration 10 mm., erythema 20 mm.) at 48 hours.

Serum taken on 19 January agglutinated *P. pseudotuberculosis* type IV to a titre of 1/1,280 and *Salmonella typhi* O to a titre of 1/160. Tests for other salmonella agglutinins were negative. The specificity of the agglutination test for *P. pseudotuberculosis* type IV is affected by the antigenic relationship which exists between type IV and O factor 9 of the salmonella D group to which *S. typhi* belongs. In order that a serological diagnosis can be made it is necessary to absorb the patient's serum with a strain of the D group. In the present case the patient's serum was absorbed with a strain of *S. typhi*. After absorption agglutinins to type IV were still present at a titre of 1/640, indicating infection with *P. pseudotuberculosis*.

Comment

Many different agents have been incriminated as causes of erythema nodosum. In recent years tuberculosis has become

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