FIG. 4.—Case 2. Consecutive records while under anaesthesia. (a) Ventricular extrasystoles with depression of S-T intervals in some complexes; rate 120. (b) Ventricular extrasystoles with suggestion of coupling. (c) Normal rhythm. (d) Patient "light." Recurrence of extrasystoles, without depression of S-T intervals. (e) Normal rhythm. (f) Normal rhythm.

There is felt to be evidence that isopropyl chloride exerts a direct toxic action on the myocardium, and extreme caution should be shown in its use. Flagg (1939) reminds us that too many people have tried too often to avoid the use of ether, and it is open to question whether, perchance, in casting out the admittedly unpleasant devils of ether and chloroform we are not making way for seven other far worse devils.

Summary

The pleasant qualities of isopropyl chloride are emphasized.

The high incidence of cardiac irregularities are noted and a death under this anaesthetic is recorded.

Electrocardiographic studies showing severe though temporary changes during the administration of the anaesthetic have been made.

REFERENCES

- Flagg, P. J. (1939). *The Art of Anaesthesia*. Philadelphia.
MacDonald, T. J. C. (1950). *Brit. J. Anaesth.*, **22**, 92.
Roualle, H. L. M. (1950). *British Medical Journal*, **2**, 712.

Dextran has already received some notice as a possible substitute for plasma in transfusions. It is a complex gummy carbohydrate synthesized by certain bacteria from glucose, and according to a recent press report plans are now going forward for its commercial production. Meanwhile laminarin, a polysaccharide from seaweed, is also under investigation as a plasma substitute and as a replacement for the talc of surgical powder. It is extremely similar to ordinary starch in chemical composition, being largely composed of glucose units linked in chains, but the points of glycosidic linkage differ in the two substances. There are five possible points on the glucose molecular ring at which other glucose molecules can be attached: in ordinary starch, positions 1 and 4 on opposite sides of the ring are so used, whereas in laminarin it is positions 1 and 3 which form the links. Dr. F. M. Woodward, director of the Institute of Seaweed Research, estimates that, if all the 200,000 tons of brown seaweed annually available round Scottish coasts were harvested, there could be a yearly production of 40,000 tons of laminarin. At the same time about 30,000 tons of mannitol would be available, and roughly the same amount of alginic acid, used for making synthetic fibres for the textile industry.

RAISED BLOOD PYRUVIC ACID LEVEL IN DIABETIC ACIDOSIS THE VALUE OF COCARBOXYLASE IN TREATMENT

BY

I. C. GILLILAND, M.D., M.R.C.P.

Medical Tutor, Postgraduate Medical School of London

AND

M. MENCER MARTIN, M.B., M.R.C.P.

Formerly Lund Research Fellow, Postgraduate
Medical School of London; Diabetic Depart-
ment, King's College Hospital

Ketosis is a familiar early complication of severe and uncontrolled diabetes mellitus: its causation is understandable, but the steps by which, unchecked, it progresses to coma and shock are not all understood. Usually the standard treatment with insulin and fluids will rapidly resuscitate a patient from diabetic coma: but recovery may be slow or even fail to take place if treatment has been delayed. Prolonged severe diabetic ketosis is evidently complicated by functional disturbances other than those reversible by insulin. One such complication which has recently been clarified is the depletion of potassium and phosphates in the tissues (Guest, 1942; Martin and Wertman, 1947). That disordered carbohydrate oxidation may be another is suggested by the recent finding of a raised pyruvic acid level in the blood in diabetic acidosis (Markees and Meyer, 1948; Markees, 1949).

Pyruvic acid is believed to occupy a central position in the metabolism of carbohydrates; it is an intermediate product in the body's oxidation of these and other metabolites. The first step in the oxidation of pyruvic acid is effected by the pyruvic oxidase enzyme system, which is active only in the presence of certain co-enzymes, including cocarboxylase (Banga, Ochoa, and Peters, 1939). Accumulation of pyruvic acid in the blood suggests a failure of this enzyme system, as is the case, for example, in aneurin deficiency, which results in lack of cocarboxylase (vitamin B₁ diphosphate).

Markees and Meyer (1949) and Boulin *et al.* (1949) have suggested that the administration of cocarboxylase may be a useful supplement to the standard treatment of diabetic coma. They have claimed that the addition of cocarboxylase hastens the recovery from diabetic coma in alloxan-diabetic rabbits (Markees, 1949) and in some human cases (Markees and Meyer, 1949; Boulin *et al.*, 1949), but control data are not given.

This report presents the results of testing the above claims both in alloxan-diabetic rabbits and in four acidotic diabetic patients. Control observations of the rate of recovery under standard treatment have been compared with the results obtained when this treatment is supplemented by cocarboxylase and riboflavin as advocated by Markees and Meyer (1949).

Method

I. Animals

Plan.—After the induction of alloxan diabetes the rabbits were observed for the development of diabetic acidosis. Eight to ten days after the administration of alloxan a number of the rabbits which had become diabetic gradually passed into a phase of progressive

diabetic acidosis with ketosis and a raised blood pyruvic acid level. The first signs were usually the presence of acetone in the urine (FeCl_3 test) and in the breath, and a slowing of respiration. When, usually 12 to 24 hours later, the animals were clearly noticed to be ataxic or unable to stand, they were classed as being in "diabetic precoma." Pairs of rabbits were selected that had reached approximately the same stage of precoma at about the same time after alloxan administration; the treatment to be tested was then instituted. Observations were carried out over an eight-hour period. If one of a pair died during that time the pair were rejected from further observation. Each pair received identical general treatment: 10 to 50 units of soluble insulin intravenously, repeated subcutaneously after two hours, and 100 ml. of normal saline intravenously two-hourly for the first four hours. In addition, one of each pair was given two-hourly 25 mg. of cocarboxylase intravenously and 10 mg. of riboflavin subcutaneously. Blood samples were withdrawn by cardiac puncture every two hours after the onset of treatment. The collection of blood from an ear vein was found to be too slow and unreliable for frequent sampling (Friedemann and Haugen, 1943).

Preparation of Diabetic Animals.—Rabbits weighing between 2,000 and 2,500 g. were used in all experiments. They were kept in metabolic cages and were fed on a constant diet with water *ad lib.* Diabetes was induced (Duffy, 1945) by giving the rabbits 200 mg. of alloxan per kg. body weight in a 4% solution intravenously, the solution being almost neutralized with NaOH immediately before use. A 5% glucose drink was offered for the subsequent 24 hours and given by stomach tube when hypoglycaemic symptoms were noted.

II. Patients

Four patients in diabetic acidosis were tested—two were mildly acidotic and two moderately to severely acidotic, though not actually comatose. All four patients were dehydrated; the two more acidotic patients were vomiting and one was drowsy. The breath of each of the patients contained acetone, and the urine was loaded with sugar and acetone (FeCl_3 test).

The two severely acidotic and the two mildly acidotic patients were paired and each pair was given identical treatment. The severely acidotic patients received subcutaneously 50 units of soluble insulin four-hourly and the less acidotic patients 20 units of soluble insulin four-hourly with saline in addition as required. One of each pair was also given 200 mg. of cocarboxylase (vitamin B_1 diphosphate) intravenously and 10 mg. of riboflavin subcutaneously every two hours.

The blood samples from the two mildly acidotic patients were estimated only for pyruvic acid.

III. Estimations

The blood samples from both rabbits and patients were analysed for the alkali reserve by the method of Van Slyke and Cullen (1917), for blood sugar by the Harding modification of the Schaffer-Hartmann method (King, 1947), and for pyruvic acid by the method of Friedemann and Haugen (1943).

Results

Rabbits.—No difference was observed in the rate of recovery from acidosis between rabbits treated with

cocarboxylase and riboflavin and those not so treated. All the rabbits that survived lost their ataxia and became more lively, and fed themselves by the conclusion of the eighth hour of the experiment. There was no observable difference between the pairs in these clinical respects. Data of blood pyruvic acid, alkali reserve, and blood sugar are shown in Fig. 1.

FIG. 1.—Fall in level of pyruvic acid and blood sugar, and rise in alkali reserve in individual rabbits, as well as the means of observations on cocarboxylase-treated and on control animals. $\times$ — $\times$ = control animals; $\bullet$ — $\bullet$ = cocarboxylase-treated animals.

In non-acidotic diabetic rabbits the mean blood pyruvic acid level was found to be 1.32 mg. per 100 ml., with a range of 0.81–2.1 mg. (12 obs.), which compares well with a mean of 1 mg. and a range of 0.3–2.2 mg. reported by Markees and Meyer (1949).

Patients.—The observations on the rate of recovery in the four patients are shown in Fig. 2. No difference, either clinically or in the measurements, was observed in those given cocarboxylase and riboflavin. This might conceivably have been because our patients were not comatose.

Discussion

Although in controlled diabetes mellitus both the blood pyruvic acid level (Bueding *et al.*, 1942) and the cocarboxylase level (Goodhart and Sinclair, 1940) are normal, our findings corroborate those of Markees and Meyer (1948, 1949), that the blood pyruvic acid level is raised in diabetic acidosis both in alloxan-diabetic rabbits and in diabetic patients. But we have been unable to confirm their claim that the giving of

FIG. 2.—Fall in pyruvic acid levels in four patients and fall in blood sugar and rise in alkali reserve in two patients in which these were followed. X—X—X—X = control patients; ●—●—●—● = cocarboxylase-treated patients.

comparisons are valid only when comparable cases are contrasted; this was more easily achieved with the rabbits than with the patients. Thus, while we have confirmed the evidence of defective pyruvic acid oxidation in diabetic acidosis, we found no evidence that this was due to a deficiency of cocarboxylase. Normal pyruvic acid metabolism requires not only cocarboxylase and other co-enzymes but also the integrity of the enzyme protein; it may be that in diabetic acidosis the protein component of the enzyme system is inhibited or partially inactivated as it is in sodium arsenite poisoning (Peters, Sinclair, and Thompson, 1946).

Summary

The blood pyruvic acid level was found raised during diabetic acidosis in 12 alloxan-diabetic rabbits and 4 acidotic diabetic patients.

Supplementing a standard treatment for diabetic acidosis by cocarboxylase (vitamin B₁ diphosphate) and riboflavin did not appear to accelerate further the recovery from diabetic acidosis, as measured by the rate of the fall of the raised blood pyruvic acid level, the fall of the blood sugar, the rise of the alkali reserve, or the observed clinical improvement.

We wish to express our thanks to Dr. Russell Fraser for his help and advice, to Dr. F. Wrigley for suggestions, and to Miss Shirley Looker for her assistance with the biochemical estimations. We are also indebted to the Diabetic Association for the grant of a Lund Research Fellowship to one of us. The cocarboxylase used in the investigation was kindly supplied by Roche Products Ltd.

cocarboxylase and riboflavin in the treatment of diabetic acidosis hastens the rate of clinical recovery and the return to normal level of the blood pyruvic acid and alkali reserve. We found the rate of improvement to be similar to that seen in paired controls given identical treatment with fluids and insulin without the addition of cocarboxylase and riboflavin; neither in the 12 alloxan-diabetic rabbits nor in the 4 acidotic diabetic patients was there any difference in the rate of clinical recovery, the fall in blood pyruvic acid and blood sugar, or the rise in alkali reserve.

The test of such a treatment in human patients is, of course, more difficult, since

REFERENCES

- Banga, I., Ochoa, S., and Peters, R. A. (1939). *Biochem. J.*, **33**, 1109.
 Boulton, R., Uhry, P., Meyer, F. W., and Bonfils, S. (1949). *Pr. méd.*, **57**, 689.
 Bueding, E., Wortis, H. I., Fein, H. D., and Esturonne, D. (1942). *Amer. J. med. Sci.*, **204**, 838.
 Duffy, E. (1945). *J. Path. Bact.*, **57**, 199.
 Friedemann, T. E., and Haugen, G. E. (1943). *J. biol. Chem.*, **147**, 415.
 Goodhart, R., and Sinclair, H. M. (1940). *Ibid.*, **132**, 11.
 Guest, G. M. (1942). *Amer. J. Dis. Child.*, **64**, 401.
 King, E. J. (1947). *Microanalysis in Medical Biochemistry*. Churchill, London.
 Markees, S. (1949). *Z. klin. Med.*, **145**, 354.
 — and Meyer, F. W. (1948). *Experientia*, **4**, 31, 195.
 — (1949). *Schweiz. med. Wschr.*, **79**, 931.
 Martin, H. E., and Wertman, M. (1947). *J. clin. Invest.*, **26**, 217.
 Peters, R. A., Sinclair, H. M., and Thompson, R. H. S. (1946). *Biochem. J.*, **40**, 516.
 Van Slyke, D. D., and Cullen, G. E. (1917). *J. biol. Chem.*, **30**, 289.

ORAL PENICILLIN IN CHILDREN

BY

S. A. DOXIADIS, M.D.

Senior Lecturer in Child Health, University of Sheffield

JOHN L. EMERY, M.D., D.C.H.

Clinical Pathologist; Lecturer in Pathology, University of Sheffield

AND

SHEILA M. STEWART, B.Sc.

Bacteriologist; Demonstrator in Bacteriology, University of Sheffield

(From the Children's Hospital, Sheffield)

It has been shown that satisfactory bacteriostatic blood levels are attained in infants by the oral administration of penicillin (Henderson and McAdam, 1946; Buchanan, 1946; Husson, 1947; Moseley, 1948). The oral use of penicillin in infants has therefore been widely adopted. In older children and adults the conditions for absorption of penicillin from the gastrointestinal tract are not equally favourable, probably because of the higher gastric acidity.

Charney *et al.* (1945) suggested the use of an antacid, and it was shown (György *et al.*, 1945; Burke *et al.*, 1945; Cohlan *et al.*, 1948; Hildick-Smith *et al.*, 1950) that the combination of penicillin with an antacid is effective in maintaining a bacteriostatic blood level. Hoffman *et al.* (1948) were unable to confirm this. They obtained satisfactory results by giving penicillin three-hourly in a dose of 1,400 units per lb. (450 g.) of body weight. All authors agree that penicillin should be given on an empty stomach to ensure maximal absorption.

Owing to the conflicting reports on the oral dose required and on the value of antacids it was felt that a study of these points was necessary before penicillin could be used by mouth for therapeutic purposes.

Methods

Seventy-six children aged 2–15 years were given penicillin two or more hours after a light breakfast. It was in tablet form, each containing 200,000 units. The dose given varied from 1,000 to 7,000 units per lb. of body weight. Sodium citrate, 3 g. in 1 oz. (30 ml.) of flavoured water, was used as antacid. It was given immediately before or after the penicillin.