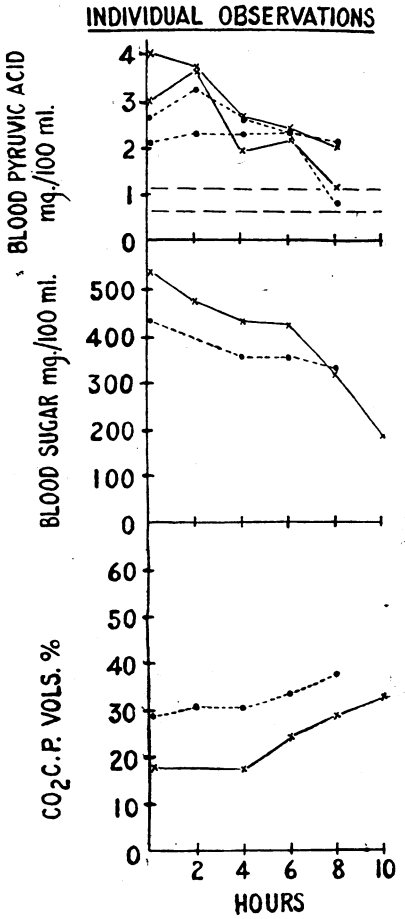

FIG. 2.—Fall in pyruvic acid levels in four patients and fall in blood sugar and rise in alkali reserve in two patients in which these were followed. ×——× = control patients; ●——● = cocarboxylase-treated patients.

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 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 B_1 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.

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ORAL PENICILLIN IN CHILDREN

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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.

The blood and penicillin serum levels were estimated by the capillary-tube method described by Fleming (1943), using whole blood inoculated with Richard's strain of *Streptococcus pyogenes*. The serum used for assay was from capillary blood collected in Wright's capsules. Blood was taken before the penicillin was given and three hours later. In many children blood was also taken at other intervals. A total of 208 test doses were given, involving 632 penicillin assays.

Results

The Table shows the number of children grouped according to the penicillin dosage and the use of antacid, with the numbers in each group having a serum penicillin level of 0.06 unit per ml. or over at various times after the ingestion of the drug.

Number of Children with Serum Penicillin Level of 0.06 unit/ml. or More at Various Times after Ingestion of the Drug

Dose; Units per lb. of Body Weight	Hours After Ingestion of Penicillin										
	Without Antacid							With Antacid			
	0	½	1	2	3	4	6	0	2	3	4
1,000–1,999..								0 of 18		**9 of 18**	
2,000–2,999..	0 of 20	7 of 7	11 of 12	10 of 12	**9 of 20**	0 of 12	0 of 12	0 of 20	9 of 9	**16 of 20**	0 of 9
3,000–3,999..	0 of 20	3 of 3	5 of 5	3 of 5	**13 of 20**	0 of 5	0 of 2	0 of 20	5 of 5	**19 of 20**	1 of 5
4,000–4,999..	0 of 20		6 of 6	5 of 6	**16 of 20**	0 of 6	0 of 4	0 of 20	6 of 6	**19 of 20**	1 of 6
5,000–5,999..	0 of 20		6 of 6	13 of 13	**16 of 20**	5 of 13	2 of 6	0 of 20	1 of 1	**19 of 20**	1 of 1
6,000–6,999..	0 of 30		7 of 7	7 of 7	**29 of 30**	7 of 7	2 of 7				

It can be seen that in the groups of children receiving less than 4,000 units per lb. of body weight without antacid, only 22 of 40 (55%) had an adequate bacteriostatic level at three hours. Of the 40 children receiving 4,000 to 5,999 units per lb. of body weight without antacid, 32 (80%) had a bacteriostatic level three hours after the administration of the drug. Finally, in the group without antacid, 29 of the 30 children (97%) who received 6,000 to 6,999 units per lb. of body weight had a level of 0.06 unit per ml. or over at three hours.

When antacid was given together with the penicillin, 9 of 18 children (50%) receiving 1,000 to 1,999 units per lb. of body weight, 35 of 40 children (87%) receiving 2,000 to 3,999 units per lb. of body weight, and 38 of 40 (95%) receiving 4,000 to 5,999 per lb. of body weight had a bacteriostatic level three hours after taking the penicillin tablets.

Fifty-seven children received the same dose of penicillin on two occasions, the first time without antacid and the second time some days later with antacid, all the other conditions of the test being exactly the same. In 42 children the bacteriostatic level at three hours was the same on both occasions—namely, either above or below 0.06 unit per ml. (in 3 below, in 39 above). Fourteen children had a level less than 0.06 unit per ml. at three hours without antacid and a level of 0.06 unit per ml. or more when antacid was given. One child had a level of 0.06 without antacid and a lower level with antacid.

Discussion

Although it has been suggested (Tompsett *et al.*, 1949) that the maintenance of bacteriostatic blood levels of penicillin for only a few hours every day may have therapeutic effects, the aim of most penicillin regimens in clinical practice is still the attainment and maintenance of a bacteriostatic blood level for the whole period of treatment. On this basis the results of the present work are discussed.

Hoffman *et al.* (1948) claimed satisfactory results with unbuffered penicillin with single doses as low as 1,400 units per lb. of body weight, and they recommend this dose at three-hourly intervals; but a study of their data reveals that of 137 children aged 1 to 12 years 41 had a blood level of less than 0.03 unit per ml. three hours after the oral dose. With a slightly higher dosage this level was found in 11 out of 85 children.

Similar results with unbuffered preparations and doses of approximately 1,500 to 3,000 units were obtained by Reisman *et al.* (1947), Cohlan *et al.* (1948), and Hildick-Smith *et al.* (1950).

In this investigation an attempt has been made to estimate the amount which had to be given in order to obtain a serum level of at least 0.06 unit per ml. three hours after penicillin was taken. The results show that even when the dose given by other investigators was doubled (4,000 to 5,999 units per lb. of body weight) 8 of 40 children (20%) had at the end of three hours a serum level of less than 0.06 unit per ml.

It was only when 6,000 to 6,999 units per lb. of body weight were given orally that the desired effect was achieved in all but one of 30 children (97%). It would seem that doses smaller than 6,000 units per lb. without antacid cannot be relied upon to maintain a bacteriostatic serum level of at least 0.06 unit per ml. over a period of three hours.

According to Reisman *et al.* (1947) and Cohlan *et al.* (1948) the addition of antacids did not improve the results when 50,000 to 100,000 units were given to children aged 2–12. Hildick-Smith *et al.* (1950), administering a dose of approximately 3,000 units per lb. of body weight with an antacid, obtained blood levels of 0.08 unit per ml. or over in all 10 children at the end of three hours.

The experience from the present series demonstrates the value of simultaneous administration of an antacid. With a dose of 2,000 to 5,999 units of penicillin per lb. of body weight a blood level of 0.06 unit per ml. or over was obtained in only 54 of 80 test doses (67%) without antacid, compared with 73 of 80 test doses (91%) when antacid was given.

The comparison in individual cases of the results with and without antacid, but on the same dose, further demonstrates this point. Of 57 children thus compared, 14 had a satisfactory level at three hours only when an antacid was given, but in one the effect was the opposite.

It is difficult to estimate the magnitude of the economy in penicillin achieved by the addition of an antacid. The results show that, when no antacid is given, at least 6,000 units of penicillin per lb. of body weight must be administered to ensure a level of 0.06 unit per ml. or over at three hours in more than 90% of the children. When an antacid is given the minimal dose likely to have a similar effect, as it appears from the table, is 3,000 units per lb. of body weight. On this basis, the addition of an antacid would permit a reduction of approximately 50% in the dosage of penicillin.

It is generally advised that if penicillin is given orally the dose should be three to five (Poncher and Unna, 1950; György and Lee, 1947) or four to eight (Herrell, 1949) times larger than the parenteral dose. As the recommended single dose for parenteral use in mild and moderate infections is 500 units per lb. of body weight (or 4,000 units per lb. per 24 hours in eight doses) even an eightfold increase in dose is inadequate for oral use. When no antacid is given nothing short of 12 times the parenteral dose can be trusted to produce satisfactory blood levels in most children. This would mean that a 10-year-old child would need more than 3,000,000 units of penicillin a day, or more than 1,500,000 units if an antacid were given at the same time. Another disadvantage is the three-hourly administration. This method of giving penicillin must therefore be weighed against the parenteral injection of a slowly absorbed preparation such as procaine penicillin in 2% aluminium monostearate, which is effective if given once every 24 or 48 hours (Emery *et al.*, 1949).

Summary

Blood levels of penicillin after oral administration of the drug with and without an antacid have been estimated in 76 children, who were given 208 test doses.

To attain a reliable bacteriostatic level of 0.06 unit per ml. three hours after the ingestion the single dose of penicillin should be not smaller than 6,000 units per lb. of body weight—that is, 48,000 units per lb. of body weight in 24 hours.

Simultaneous administration of an antacid may allow a reduction of this dose by approximately 50%.

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INSTILLATION OF STREPTOMYCIN INTO THE PERICARDIAL SAC IN TUBERCULOUS PERICARDITIS

BY

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Several cases of tuberculous pericarditis treated with streptomycin by the intramuscular route have been reported in the literature. Reference is made in a report of the Medical Research Council (1950) to one case of tuberculous pericardial effusion in which streptomycin was injected into the pericardial sac, but no details or dosage were given. Tapie *et al.* (1950) also report the case of a man of 44 with chronic pulmonary tuberculosis who developed a pericardial effusion. They gave five injections of streptomycin, totalling 1.15 g., into the pericardial sac without obvious improvement.

The following case is recorded because it shows that streptomycin injected into the pericardial sac, in conjunction with streptomycin by the intramuscular route, constitutes a safe and rational form of treatment in tuberculous pericarditis with effusion, and that it may be beneficial, especially in cases characterized by rapid reaccumulation of fluid after paracentesis.

Case Report

A Post Office electrician aged 20, whose brother was suffering from a pleural effusion, was found to have enlarged hilar glands on mass radiography in September, 1948. He was asked to attend for further radiological examination, but did not do so. On January 8, 1949, he developed substernal pain, malaise, fever, and vomiting, and two weeks later was admitted to hospital.

Examination on admission on January 22 revealed a well-built, pale, ill man, moderately dyspnoeic, and with a temperature of 103.2° F. (39.5° C.). There was pulsus paradoxus and moderate engorgement of the neck veins, the apex beat was just palpable in the fifth left space in the mid-clavicular line, and cardiac dullness extended from 1 in. (2.5 cm.) outside the right sternal border to the mid-axillary line. Pericardial friction was heard over a wide area of the praecordium. There was an area of dullness with bronchial breathing and increased vocal resonance over the left lower chest posteriorly near the midline. The blood pressure was 130/70.

Diagnostic pericardial paracentesis on January 26 yielded dark straw-coloured fluid which grew *Mycobacterium tuberculosis* on guinea-pig inoculation, but direct examination and Lowenstein culture were negative.

On January 30 he developed cardiac tamponade, and 32 oz. (907 ml.) of fluid was aspirated, with immediate relief of symptoms. Signs of tamponade returned, however, in 24 hours, and a further 22 oz. (624 ml.) was aspirated the following day. Within the next two months recurrent tamponade necessitated five further aspirations, and amounts varying from 14 to 32 oz. (397 to 907 ml.) were removed on each occasion.

Intramuscular streptomycin, 0.5 g. twice daily, was started on February 12, and, although this resulted in some lowering of the temperature, the pericardial effusion continued to accumulate at about the same rate as before. It was therefore decided to give streptomycin into the pericardial sac. On March 24 1 g. dissolved in 2 ml. of water was injected into the effusion. The procedure was repeated weekly for another five weeks. No adverse effects occurred and after the third injection there was a considerable drop in fever.