the practice to return patients from the operating suite to a cool bed in order to avoid peripheral vasodilatation and consequent hypotension. We have found that a little warmth is a useful adjunct to the treatment of hypertension post-operatively.

Much attention is given, and rightly so, to urinary output in the post-partum period, especially in patients who present with an accidental haemorrhage. One is led to wonder how great or significant an effect the administration of ergometrine exerts on the renal blood-vessels of such patients. Byrom and Pratt (1952) state that "as long as the causation of renal cortical necrosis in pregnancy remains obscure, all vasoconstrictors . . . must be suspect."

The choice of anaesthesia exerts considerable influence on the pressor response to ergometrine. One severely toxæmic patient who was delivered of twins and was deeply sedated with tribromethanol showed no elevation of pressure following ergometrine. A study being conducted in this department at the moment shows that the hypertensive response to ergometrine in pre-eclamptic women is modified greatly by ether or halothane anaesthesia.

Summary

A study was made of 266 pregnant patients requiring general anaesthesia for caesarean section or instrumental delivery who were given 0.5 mg. of ergometrine maleate intravenously as an oxytocic following delivery of the child.

A marked rise in both systolic and diastolic pressures exceeding in many cases 20 mm. Hg was noted in patients suffering from hypertensive toxæmia.

No significant vasopressor response was elicited by ergometrine in normotensive patients. Similarly, patients with chronic hypertension showed little or no response.

Attention is drawn to the possible dangers of this effect of ergometrine under modern conditions, where little use is made of depressant anaesthetics which tend to counteract this response.

The intense interest of my obstetric colleagues in this investigation has been a constant encouragement. I am particularly grateful to Dr. A. D. Telford Govan, Director of Research, Glasgow Royal Maternity Hospital, for helpful discussion and criticism of this paper.

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EFFECT OF PENICILLAMINE ON CYSTINURIA

BY

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The diagnosis of cystinuria in this report refers to the classical condition of cystinuria with recurrent urinary calculus formation, now known to be characterized by the urinary excretion of abnormal quantities of cystine, lysine, arginine, and ornithine.

The loss of these amino-acids does not produce any known harmful effects. The only clinical features arise from the recurrent formation of stones in the renal tract, the main cause of this feature being the high excretion and urinary concentration of the insoluble disulphide amino-acid cystine.

Disulphides undergo exchange reactions with thiols and with other disulphides, and these reactions may be simply represented by the equations: $R-S-S-R + 2 R_1-S-H \rightleftharpoons 2 R-S-S-R_1$ and $R-S-S-R + R_1-S-S-R \rightleftharpoons 2 R-S-S-R_1$. The active molecular species are the ions $R-S^-$ and R_1-S^- (Kolthoff *et al.*, 1955; Ryle and Sanger, 1955; Pihl *et al.*, 1958).

The mixed disulphides $R-S-S-R_1$ have different properties from the corresponding symmetrical disulphides $R-S-S-R$ and $R_1-S-S-R_1$.

This reaction offered a possible means of converting cystine into a more soluble derivative by an exchange reaction, if a suitable thiol or disulphide could be administered. Preliminary experiments showed that the cystine which readily crystallized from the urine of cystinurics could not be crystallized from the same urines at pH 7.2 after the addition of D(-)penicillamine (D(-) β - β_1 -dimethylcysteine) *in vitro*. This report shows the effect of oral administration of D(-)penicillamine on the urine cystine excretion in two patients with cystinuria.

Case 1

The first investigation was carried out on a man aged 37 who had suffered from recurrent cystine calculi over 15 years. At the time of investigation several small calculi were situated in the left renal pelvis and there was a mild low-grade urinary infection with *Pseudomonas pyocyanea* and *Escherichia coli*. The blood-pressure was normal and there was no evidence of impairment of renal function.

The urine was collected and acidified to pH 2 with concentrated hydrochloric acid immediately. The gross urine cystine excretion was estimated by weighing the cystine isolated from a 500-ml. aliquot of each 24-hour urine collection. Isotope dilution analysis performed on 7 of the 14 urine specimens collected confirmed the results of this finding.

D(-)penicillamine (1.05 g. six-hourly) was administered orally for four days and showed a marked reduction or disappearance of cystine from the urine. The result is shown

in detail in Fig. 1. The excretion of cystine returned to its former level the day after the administration of penicillamine ceased.

Paper chromatographic analysis of the urine confirmed the reduction or absence of cystine excretion when penicillamine was administered. Two new spots appeared on the chromatogram during this time, which we believe on the evidence of chromatographic identification to be the mixed

Fig. 1.—Case 1. Chart of daily excretion of cystine in mg./day. 1.05 g. of D(–) penicillamine was administered six-hourly from the 8th to the 11th day inclusive.

disulphide of D(–)penicillamine and cysteine (Tabachnick *et al.*, 1954) and the symmetrical disulphide of D(–) penicillamine.

Case 2

The second investigation was undertaken on a girl aged 11 who had developed cystine calculi three years previously. These had been removed surgically. No calculi were demonstrable at the time of the investigations. The urine was sterile and there was no evidence of impairment of renal function.

Complete 24-hour specimens of urine were collected into "polythene" bottles containing concentrated hydrochloric acid (10 ml.). A known volume (5 ml.) of standard (^{35}S) L-cystine was added to 500-ml. portions. These were evaporated to a slurry in a rotary evaporator at reduced pressure at 38° C. The residue was quantitatively transferred to a centrifuge tube in hydrochloric acid (1N, 50 ml.). Any insoluble residue was removed by centrifugation. The supernatant was then made alkaline (pH > 10) by the addition of concentrated ammonia solution (specific gravity 0.880). Any insoluble material was again removed by centrifugation. The pH was then adjusted to 4.5 with glacial acetic acid. Acetone equal to four-fifths of the total aqueous volume was then added and the mixture maintained at 4° C. for 24 hours. The precipitated cystine was collected by filtration. The precipitate after drying and weighing was redissolved in a minimum volume of a 50% solution of concentrated ammonia (specific gravity 0.880). Any precipitate was removed by filtration and the alkaline solution brought to pH 4.5 with glacial acetic acid. The mixture was maintained at 4° C. for 24 hours and the recrystallized cystine collected by filtration.

Preliminary experiments had shown that the cystine was now pure as judged by the constancy of its radioactivity on further recrystallization and by its optical rotation. The total quantity of cystine present in the urine could also be obtained from the radioactivity of the precipitated cystine, and it was found that the gravimetric values were 15–20% lower than the isotopically obtained values.

D(–)penicillamine (1.05 g. six-hourly) was now administered and led to the virtual disappearance of cystine from the urine. There was evidence in this patient of the continuation of penicillamine action during the first 24 hours after its administration had been stopped. The effect of

smaller doses (0.3 g. 12-hourly, 0.3 g. six-hourly, and 0.6 g. six-hourly) of D(–)penicillamine were also studied, and these results are depicted in Fig. 2.

Fig. 2.—Case 2. Chart of daily excretion of cystine in mg./day. The black areas indicate gravimetric measurements and the shaded areas measure isotope dilution. D(–) penicillamine was administered orally for four periods in the doses indicated.

The isotopically determined values of cystine excretion may have a different significance during penicillamine administration, as the (^{35}S)-cystine also exchanged with cystine bound in the penicillamine-cysteine mixed disulphide, and these results have therefore been omitted from Fig. 2.

For the chromatographic analysis of the urinary amino-acids, urine (2 ml.) was passed through an ion-exchange column containing "zeo-karb 225" (0.9 by 10 cm.) in the H⁺ ion form. The column was washed with water (20 ml.) and the washings were discarded. The amino-acids were eluted with diluted ammonia (4N, 20 ml.). The ammonia eluate was dried by evaporation in a vacuum desiccator using P₂O₅ as desiccant. The residue was dissolved in water (0.4 ml.) and 10 microlitres of this applied as a spot to a paper chromatogram. The chromatograms were developed by the ascending technique, using the Dent and Datta frame (Aimer Ltd.) with a mixture of butanol-isopropanol-formic acid-water (solvent 2) (64:96:20:20) in one direction, followed by a mixture of butanol-isopropanol-methyl ethyl ketone-dicyclohexylamine-water (solvent 1) (32:48:80:16:32) in the other. The amino-acids were revealed by dipping the chromatograms in a solution of ninhydrin in acetone (0.2%) containing acetic acid (5%). By this method the various amino-acids formed colours of varying shades of blue and purple and could be characterized by their distinctive colours as well as by their positions (Fig. 3).

Fig. 3.—A. Diagram of urinary chromatogram of untreated cystinuria. B. Diagram of urinary chromatogram to show the effect of the administration of penicillamine in cystinuria. (1) Lysine; arginine: ornithine. (2) Cystine. (3) Penicillamine cysteine disulphide. (4) Penicillamine disulphide. (5) Cysteine.

Comment

These investigations show that the oral administration of D(-)penicillamine can reduce or abolish the excretion of cystine in cystinuric patients. The cysteine residues are excreted, as is the D(-)penicillamine cysteine mixed disulphide, which is more soluble in water.

These observations suggest that the use of D(-)penicillamine may have therapeutic value in the management of patients with cystinuria who are prone to the development of urolithiasis. We are investigating further the long-term effects of the use of D(-)penicillamine in cystinuria, and further studies on this, and on the mechanisms of action, will be reported later in greater detail.

Summary

Disulphide exchange reactions with thiols and other disulphides suggested that the excessive excretion of the insoluble disulphide amino-acid cystine might be modified by the administration of a suitable thiol.

Penicillamine has been administered to two patients with cystinuria.

The daily urinary cystine excretion was measured both gravimetrically and by isotope dilution.

The cystine excretion was shown to be abolished or reduced according to the dose of penicillamine administered.

During penicillamine administration two new substances appeared in the urine which on chromatographic evidence are penicillamine-cysteine disulphide and penicillamine disulphide.

The greater solubility of these compounds in water offers a new therapeutic approach to the prophylaxis of urolithiasis in cystinuria.

We are pleased to acknowledge the collaboration of Dr. H. E. Archer in the exploratory experiments, and the technical assistance of Miss E. D. Bell, Miss D. R. Gibbs, and Mr. L. Rawlings. We are indebted to Dr. C. A. Lewis for information on the chromatographic solvent systems employed.

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The Scottish Home and Health Department, in consultation with the medical profession in Scotland and the Scottish Association of Executive Councils, is to introduce experimentally in the counties of Renfrew, Perth, and Kinross a revised type of medical card. It is designed with a pouch to carry a personal medical record card. It has space for entries by the patient's family doctor, hospital or clinic doctors, and (in the case of schoolchildren) school doctors. In it can go data which should be available to any doctor into whose care a patient might come, for example, in emergency. The revised type of card will be issued only as and when a new medical card would have been required in normal course—that is, for infants, new patients coming into the area, on change of doctor, etc. Under the present arrangements patients are required to show their medical card to their doctor if he asks to see it, and there is evidence of many cases where medical cards are mislaid or lost. It is hoped the experiment will help the efficient care of patients and also encourage safer custody by patients of their medical card.

**STATURE AND NUTRITION IN
CYSTINURIA AND HARTNUP DISEASE**

BY

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Andrews (1952), in a review of cystinuria, stated: "Cystinurics are in general persons of somewhat less than average stature. While not to be described as dwarfs in any sense of the word, cystinurics have always been of somewhat slight build." He did not, however, publish any figures confirming this impression. In a recent metabolic study of cystinuria (Asatoor *et al.*, 1962), one of us (J.E.C.) independently noticed that many of the patients were below the average height for age and sex. As cystinuria is an important disease of amino-acid metabolism, with possible effects on general nutrition, it was thought worth while to make a more detailed survey of the heights of cystinuric patients. Similar studies were made in the closely allied but much more rare condition, Hartnup disease (Baron *et al.*, 1956).

Methods

Heights were measured in 44 cystinuric patients. All of them, except two children, gave a history of urinary calculus disease and were thus presumably homozygotes (Dent and Harris, 1951; Harris and Warren, 1953; Harris *et al.*, 1955). The two exceptions were shown by paper chromatography to be excreting large quantities of cystine, lysine, arginine, and ornithine, and were therefore homozygotes who had not yet developed clinical symptoms of the disease. Twenty-one of the patients were personally observed by us, and the heights of the other 23 were kindly supplied by physicians and surgeons known to be in clinical charge of cystinuric patients.

Only 15 cases of Hartnup disease have been described to date, and only eight of these could be traced by postal inquiry. Heights of these patients were obtained either from the patients themselves or from their parents. The data in Hartnup disease are neither as complete nor as accurate as those in cystinuria, but are thought worth reporting.

Control heights of the normal population were obtained from the paper by Clements and Pickett (1957), which reports data from 25,000 males, and from a publication, *Women's Measurements and Sizes* (1957), reporting data obtained from 5,000 women. Normal heights of children were obtained from Stuart and Stevenson (1959). The observed heights were expressed as deviations from the expected mean for age and sex, but have been graphed (see Chart) as corrected heights for normal adult males with a mean height of 170.3 cm. ± 6.5 cm. (Clements and Pickett, 1957).

Results

The data are shown in the Chart. The mean height of the cystinuric patients is 2.5 cm. less than the mean of normal subjects, and that of the patients with Hartnup disease 5.3 cm. less. The standard deviations in both