- Brit. med. J.*, 1966, 1, 1433.
 Carstairs, K. C., Breckenridge, A., Dollery, C. T., and Worlledge, S. M. (1966). *Lancet*, 2, 133.
 Chaplin, H., jun., and Mollison, P. L. (1952). *Blood*, 7, 1227.
 — (1953). *Clin. Sci.*, 12, 351.
 Comty, C. M., Bailod, R. A., and Shaldon, S. (1965). *Proc. Europ. Dialysis Transplant. Ass.*, 2, 88.
 Desforges, J. F., and Dawson, J. P. (1958). *Arch. intern. Med.*, 101, 326.
 Giovannetti, S., Balestri, P. L., and Cioni, L. (1965). *Clin. Sci.*, 29, 407.
 — *et al.* (1963). *Minerva nefrol.*, 10, 226.
 Gomori, G. (1942). *J. Lab. clin. Med.*, 27, 955.
 Hulme, B., and Hardwicke, J. (1966). *Proc. roy. Soc. Med.*, 59, 509.
 Joske, R. A., McAlister, J. M., and Pranker, T. A. J. (1956). *Clin. Sci.*, 15, 511.
 Loge, J. P., Lange, R. D., and Moore, C. V. (1958). *Amer. J. Med.*, 24, 4.
 Muirhead, E. E., and Jones, F. (1963). *Blood*, 22, 272.
 Ragen, P. A., Hagedorn, A. B., and Owen, C. A. (1960). *Arch. intern. Med.*, 105, 518.
 Turnbull, A., Hope, A., and Verel, D. (1957). *Clin. Sci.*, 16, 389.
 Veall, N., and Vetter, H. (1958). *Radioisotope Techniques in Clinical Research and Diagnosis*, p. 233. London.
 Verel, D., Turnbull, A., Tudhope, G. R., and Ross, J. H. (1959). *Quart. J. Med.*, 28, 491.

Dissolution of Cystine Stones During D-Penicillamine Treatment of a Pregnant Patient with Cystinuria

J. C. CRAWHALL,* PH.D., M.B., B.S.; E. F. SCOWEN,* M.D., D.SC., F.R.C.P., F.R.C.P.ED., F.R.C.S., F.C.PATH.
 C. J. THOMPSON,* M.A.; R. W. E. WATTS,* M.D., PH.D., M.R.C.P.

[WITH SPECIAL PLATE]

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Crawhall, Scowen, and Watts (1963) reported that D-penicillamine reduced the excretion of cystine in cystinuria, and that the more soluble cysteine-penicillamine disulphide was excreted in the urine. The use of D-penicillamine to prevent urolithiasis in cystinuria was suggested on the basis of these results (Crawhall *et al.*, 1963), which have now been confirmed in several laboratories (Crawhall, Scowen, and Watts, 1964; Lotz and Potts, 1964; King and Boyce, 1965; Crawhall and Thompson, 1965). The relative merits of D-penicillamine treatment and of the regimen which consists of promotion of a vigorous water diuresis throughout the 24 hours, recommended by Dent and Senior (1955) and Dent, Friedman, Green, and Watson (1965), requires long-term evaluation. There have already been reports of encouraging results in short-term studies with D-penicillamine (Crawhall, Scowen, and Watts, 1964; Lotz and Bartter, 1965; Bartter, Lotz, Thier, Rosenberg, and Potts, 1965; McDonald and Henneman, 1965).

The present paper records briefly the case of a patient whose stones had disappeared completely and asymptotically after 18 months' continuous D-penicillamine treatment, during which time she became pregnant and gave birth to a normal child.

Case Report

The patient's first urinary symptoms were an attack of right loin pain and increased frequency of micturition when she was 12 years old. These symptoms subsided spontaneously after a few days, and she remained well until August 1963, when, at the age of 18, she had a sudden attack of severe pain in the right loin, associated with increased frequency of micturition and macroscopic haematuria, which lasted for about one day. Attacks of similar pain recurred, and she was referred to St. Bartholomew's Hospital in September 1963. She also gave a history that her only sib (a brother aged 21) had had an attack of pain similar to renal colic, and he has been shown to be a homozygous cystinuric (Patient No. 5, Crawhall, Saunders, and Thompson, 1966).

There were no abnormal findings on physical examination; blood-pressure was 105/85, height 59 in. (150 cm.), weight 7 stone 12 lb. (50 kg.). The urinary centrifuged deposit contained erythrocytes, pus cells, and cystine crystals; urine culture gave a scanty growth of *Escherichia coli*. The cyanide-nitroprusside test (Lewis, 1933) for excessive urinary cystine was positive, and increased amounts of lysine, ornithine, and arginine were also present. The right kidney contained multiple radio-opaque calculi (Special Plate, Fig. 1), it

was hydronephrotic, and its ability to excrete sodium diatrizoate was impaired.

The patient was admitted for further study in December 1963, when the following additional observations were made: haemoglobin 13 g./100 ml.; leucocyte count 4,000/c.mm., with normal differential count; blood urea 34 mg./100 ml.; quantitative urine culture 100,000 organisms/ml. Mean urinary cystine excretion determined gravimetrically (Crawhall *et al.*, 1963) 719 mg. (S.D.=120; 8 observations)/24 hr. or 664 mg. (S.D.=156; 8 observations)/g. creatinine; and 733 mg. (S.D.=113; 9 observations)/24 hr. or 666 mg. (S.D.=108; 9 observations)/g. creatinine when determined by the 5,5'-dithiobis-(2-nitrobenzoic acid) (Ellman's reagent) colour reaction (Crawhall, Saunders, and Thompson, 1964, 1966). The validity of the results obtained on representative specimens was also confirmed by quantitative ion-exchange chromatography with the Technicon automatic amino-acid analyser.

D-Penicillamine hydrochloride (450 mg. eight-hourly) lowered the cystine excretion to less than 100 mg./24 hr., determined gravimetrically (the colorimetric method of Crawhall, Saunders, and Thompson (1964, 1966) cannot be used during treatment with D-penicillamine). A diffuse morbilliform rash developed acutely on the eighth day of treatment; this was accompanied by fever (101.2° F.; 38.4° C.) and tachycardia, but there was no lymphadenopathy or splenomegaly. The drug was stopped and prednisolone was given orally (an initial dose of 15 mg. followed by 10 mg. every eight hours for two days and then 5 mg. eight-hourly for two days). D-Penicillamine was resumed after a total lapse of 10 days, and the dose increased in increments of 300 mg./24 hr. on successive days. The rash recurred on the third day after prednisolone was stopped. It involved the face and feet only, and was accompanied by a tachycardia but no fever. The administration of D-penicillamine was continued 300 mg. every 12 hours, and prednisolone, 10 mg. every eight hours, suppressed the rash in 24 hours; the dose of the steroid was gradually diminished and stopped completely after seven days. The rash again recurred on the forearms on the third day after the cessation of prednisolone therapy; when this was reinstituted for a further five days the eruption disappeared within 12 hours. The rash recurred for the third time after two days without steroid cover, and disappeared within 24 hours; pyridoxine (200 mg. stat. and two 50-mg. doses at eight-hourly intervals) was given on this occasion. The patient was discharged from hospital taking 300 mg. of D-penicillamine hydrochloride every 12 hours. She was not given any more steroids or pyridoxine, and the rash did not recur. The dose of D-penicillamine was gradually increased to 1,050 mg./24 hr. over the course of one month.

The patient conceived in September 1964. Except for some vomiting in the early months the pregnancy proceeded normally to term; delivery was complicated by transverse arrest of the head, but was effected without undue difficulty. The puerperium was normal. D-Penicillamine (1,050 mg./24 hr.) was continued for the whole

* Medical Professorial Unit (Dunn Laboratories), St. Bartholomew's Hospital, London.

period of pregnancy and subsequently, but no attempt was made to increase it further. The urinary excretion of cystine, cysteine-penicillamine disulphide, and penicillamine disulphide was measured by ion-exchange chromatography with the Technicon automatic amino-acid analyser, before, during, and after the pregnancy (Table I). The patient's blood urea was 44 mg./100 ml. nine days after delivery. Radiological studies performed at this time showed that the calculi were no longer present (Special Plate, Fig. 2), and that the right kidney was small and hydronephrotic.

TABLE I.—*Urinary Excretion of Cystine, Cysteine-penicillamine Disulphide, and Penicillamine Disulphide by a Cystinuric Patient Taking 1,050 mg. D-Penicillamine Hydrochloride (=843 mg. D-Penicillamine Base/24 hr.) Before and During Pregnancy. Representative Values Before Treatment were 840 mg. and 684 mg. Cystine/24 hr. in December 1963*

Date	Approximate Duration of Pregnancy	Urinary Excretion (mg./24 hr.)		
		Cystine	Cysteine-penicillamine Disulphide	Penicillamine Disulphide
7-8 June 1964		362	405	74
9-10 Aug. 1964		392	178	30
30 Nov.-1 Dec. 1964	8 weeks	460	258	—
15-16 Mar. 1965	26 "	498	246	24
10-11 May 1965	36 "	370	246	47
30-31 May 1965	38 "	304	304	46
9-10 June 1965	40 "	298	307	47

The baby, a normal boy, weighed 5 lb. 13 oz. (2.64 kg.) at birth and 5 lb. 15 oz. (2.70 kg.) when 9 days old, and was never breast-fed. Physical and mental development were normal when he was last seen at the age of 3 months. Specimens of urine passed during the first days of life contained cysteine-penicillamine disulphide and penicillamine disulphide as well as cystine. The results of quantitative amino-acid analyses of the baby's urine with respect to these sulphur-containing amino-acids and the "basic" amino-acids are presented in Table II. Thin-layer chromatograms (Crawhall, Saunders, and Thompson, 1964, 1966) confirmed the presence of cysteine-penicillamine disulphide and penicillamine disulphide in the urine passed during the first days of life; all the specimens studied showed prominent "spots" in the positions of cystine, lysine, and ornithine. Arginine was not detected in any of the specimens by this technique. The later specimens also showed a prominent proline spot, the concentrations of this amino-acid in the urine being 7.84, 6.52, and 4.78 mg./100 ml. on 7 June 1965, 7 September 1965, and 20 September 1965, respectively.

TABLE II.—*Concentrations of Cystine, Cysteine-penicillamine, Penicillamine Disulphide and the "Basic" Amino-acids in the Urine of an Infant whose Mother was Treated with D-Penicillamine Hydrochloride (1,050 mg./24 hr.) Throughout Pregnancy*

Age of Infant	Amino-acid Concentration (mg./100 ml.)					
	< 1 day	2 days	4 days	3 months		
				Specimen 1	Specimen 2	Specimen 3
Cystine..	1.37	3.67	1.372	3.75	3.54	2.62
Cysteine-penicillamine	1.69	1.53	0.575	0	0	0
Penicillamine disulphide..	0.486	Trace	0.419	0	0	0
Ornithine..	0.801	1.85	1.11	1.397	1.26	0.92
Lysine..	9.73	18.7	6.15	27.55	23.5	19.2
Arginine..	0.552	0.44	Trace	1.00	1.36	0.986
Total volume (ml.)	1.3	12	31	96	585	515
Length of collection (hr.)	—	—	—	9	23	20

Discussion

We consider it very unlikely that stones as large as some of those shown in Fig. 1 would have been passed asymptotically even though the ureters dilate during pregnancy. The patient had no treatment except D-penicillamine. No alteration occurred in the fluid intake, she maintained a normal diet (cf. Brand, Cahill, and Harris, 1935; Lotz and Bartter, 1965), and no alkali was given. The conclusion that D-penicillamine caused stone dissolution in this patient therefore seems inescapable.

The presence of cysteine-penicillamine and penicillamine disulphide in the infant's urine establishes that D-penicillamine

and/or these disulphides cross the placental barrier, and the fact that they were still present four days after birth suggests that these "unphysiological" amino-acids may have been present in forms other than simple solution in the tissue fluids. It is of particular interest that foetal development proceeded normally in spite of this alteration in the foetal internal environment throughout gestation.

The pattern of basic amino-acid excretion seen on the thin-layer chromatograms—namely, prominent lysine and ornithine "spots" with no apparent increase in arginine—is compatible with the child being heterozygous for the abnormal gene which causes cystinuria. This is in agreement with our knowledge that the mother is homozygous for the abnormal gene and the father showed no chemical abnormality (Crawhall *et al.*, 1966).

The dose of D-penicillamine was less than that used by McDonald and Henneman (1965), who have also reported cystine stone dissolution during D-penicillamine therapy. We were initially rather cautious about increasing the dose because of the ease with which skin rashes had developed during the earlier stages of treatment. The patient then became pregnant, and, in spite of reports that patients with Wilson's disease had given birth to normal children while taking D-penicillamine (Sherwin, Beck, and McKenna, 1960; Boulding, 1961), it was thought prudent to increase the dose no further until after delivery.

The urinary cystine excretion was reduced to about 400 mg./24 hr. (=270 mg./l. or 330 mg./g. creatinine) on most of the occasions that it was measured (Table I). This concentration of cystine (270 mg./l.) is only just below the solubility limit of cystine in urine at pH values between 5 and 6.5 (Dent and Senior, 1955), and our practice is to try to keep the cystine excretion below 200 mg./24 hr. in adults or in the range 100–150 mg./g. creatinine in children. Lotz and Bartter (1965) recommended keeping the urinary cystine excretion below 100 mg./g. creatinine and have described the use of simple qualitative tests for this purpose. Thus the present patient received barely adequate treatment according to these chemical criteria, and these considerations make the radiological findings (Special Plate, Figs. 1 and 2) even more striking. It is apparent that her right kidney, although diseased, still excretes radio-opaque dyes, and therefore has a useful degree of residual functional capacity. This may explain why the stone dissolved so rapidly in response to treatment. Conversely, another cystinuric patient under our care (Scowen and Watts, unpublished) has a stone in a very poorly functioning kidney, and this has not dissolved during D-penicillamine therapy. These considerations suggest that D-penicillamine should be used before renal function has become impaired by calculus formation and its complications.

Summary

A case of cystinuria in which renal calculi had disappeared after 18 months' continuous treatment with D-penicillamine is described. The treatment (approximately 1 g. D-penicillamine hydrochloride per 24 hours) was continued throughout pregnancy without any untoward effect on the mother or foetus.

The results of urinary amino-acid analyses on the mother during pregnancy and on the baby are reported. Cysteine-penicillamine disulphide and penicillamine disulphide were present during the first eight days of life but not when the child was approximately 3 months old.

The control of D-penicillamine therapy by measuring the urinary cystine is briefly discussed, as well as the possible relationship between renal function and the therapeutic efficacy of D-penicillamine in promoting the dissolution of renal calculi.

NOTE.—The child was seen when 1 year old and had continued to progress normally.

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REFERENCES

- Bartter, F. C., Lotz, M., Thier, S., Rosenberg, L. E., and Potts, J. T. (1965). *Ann. intern. Med.*, **62**, 796.
 Boulding, J. E. (1961). In *Wilson's Disease: Some Current Concepts*, edited by J. M. Walshe and J. N. Cumings. Oxford.
 Brand, E., Cahill, G. F., and Harris, M. M. (1935). *J. biol. Chem.*, **109**, 69.
 Crawhall, J. C., Saunders, E. P., Thompson, C. J. (1964). First Meeting of Federation of European Biochemical Societies. Abstract A 117.
 ——— (1966). *Ann. hum. Genet.*, **29**, 257.
 ——— Scowen, E. F., and Watts, R. W. E. (1963). *Brit. med. J.*, **1**, 588.
 ——— (1964). *Ibid.*, **1**, 1411.
 ——— and Thompson, C. J. (1965). *Science*, **147**, 1459.
 Dent, C. E., Friedman, M., Green, H., and Watson, L. A. C. (1965). *Brit. med. J.*, **1**, 403.
 ——— and Senior, B. (1955). *Brit. J. Urol.*, **27**, 317.
 King, J. S. and Boyce, W. H. (1965). *Invest. Urol.*, **2**, 595.
 Lewis, H. B. (1933). *Ann. intern. Med.*, **6**, 183.
 Lotz, M., and Bartter, F. C. (1965). *Brit. med. J.*, **1**, 855.
 ——— and Potts, J. T. (1964). *J. clin. Invest.*, **43**, 1293.
 McDonald, J. E., and Henneman, P. H. (1965). *New Engl. J. Med.*, **273**, 578.
 Sherwin, A. L., Beck, I. T., and McKenna, R. D. (1960). *Canad. med. Ass. J.*, **83**, 160.

Artifact Ulcers and Bone Lesions Produced by Elastic Bands

IAN D. KITCHIN,* M.B., F.R.C.S.ED.; C. MCGIBBON,† M.D.; R. H. SEVILLE,‡ M.D., M.R.C.P.

[WITH SPECIAL PLATE]

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It must be uncommon for ulcers to follow the deliberate use of an elastic band, but for the band to have been lost and recovered at operation must be rare indeed. An extensive search of the literature has revealed no such case, so the two described should be of interest.

Case 1

The patient was a married woman aged 69. The family and the past history were positive for varicose veins, and she developed a white leg (left) in 1922 after pregnancy. It was not until 1947 that she produced some ulcers. She was first seen as an outpatient in 1954, when a diagram of irregular-shaped ulcers was made. She defaulted after being told by one of us (R. H. S.) that she would get better only if she would leave them alone. In 1962 a band of ulcers developed fairly suddenly on the lower part of the left leg, and a consultation was sought because of the severity of her pain. During this examination she was asked if an elastic band had been put round the leg, but she resented the question and changed the subject, mentioning the chronic invalidism of her husband and her own inability to work because of the ulcer.

She was subsequently admitted to hospital with three linear ulcers measuring $\frac{1}{2}$ in (0.8 cm.) wide and about 1 in. (2.5 cm.) long, placed horizontally round the distal third of the lower part of the left leg. There was pigmentation of the surrounding skin, which was also oedematous, indurated, eczematous, and slightly moist. Secondary eczematous spread was observed on the thighs, forearms, and, to a lesser extent, on the back.

Healing was uneventful, but she still complained of excessive pain on walking, so an x-ray examination was arranged, and the opinion of an orthopaedic surgeon (I. D. K.) requested. When seen by him all the ulcers had healed, but the skin over most of the lower third of the leg was of poor quality, thin, and shiny. The foot was oedematous. During the examination it was noted that a very shallow depression in the skin encircled the leg through the healed ulcer area. This was difficult to see, and then only when the light threw a shadow upon it. The groove coincided with the level of the peculiar radiological changes (Special Plate, Figs. 1 and 2). When these were studied it was noted that the depression in and the new bone formation on the tibia and fibula involved certain surfaces only, and these corresponded to the surfaces which would be in contact with an encircling band, like a belt round two pulleys.

In spite of the patient's protests that no encircling band could possibly be present it was decided to explore. This was done through

a postero-lateral approach through the only area of reasonably sound skin. The fibula was exposed and no foreign material was found, but as the bone was thick and rough some was chiselled away, disclosing an elastic band. This was divided and removed without difficulty. Healing of the wound was uneventful, and the patient was discharged from hospital.

Within 10 days a triangular-shaped ulcer had developed just below the original site with scarring, suggestive of a phenol type of burn. On her readmission marked dressings were always altered and coloured ointments removed. The area was then occluded, but further artifact lesions appeared at the edge of the dressing, and when this was extended she attacked her wedding-ring finger with a tight elastic band hidden under the ring. Her attitude was always one of amazement, but the innuendoes showed the underlying resentment. She still has her ulcers.

Case 2

The patient, a man aged 51, presented first in 1948 with an ulcer almost encircling the lower third of his right leg. He was a mild diabetic, in poor circumstances, and very dirty. It was thought then that the ulcer had been aggravated to gain admission to hospital, where it healed spontaneously in a month. He was next seen in 1958, again with an ulcer of his right leg, which this time completely encircled the limb just above the ankle. The leg had been much constricted but the circulation was good. In 1960 a loop of rubber appeared in the ulcer. It was divided, one end pulled upon, and a rubber band removed. A week later another band was removed under similar circumstances, and yet a third and final one was similarly dealt with at the end of another week. After this the ulcer healed completely in a few weeks, and has remained so. X-ray films of this case (Special Plate, Figs. 3 and 4) show clearly the grooves in the bone caused by the three bands.

Comment

Patients with self-inflicted lesions usually hope to gain something from their presence, deny any knowledge of their origin, and cannot be tricked into admission. It is thought that the motivation behind this may well be subconscious. Briefly it may be stated that the lesions are bizarre-shaped and their site is important, as usually the injury is inflicted with the right hand (in right-handed individuals) and so must be within its reach. The appearance of fresh lesions above an occlusive dressing is diagnostic. In Case 1 it transpired that the patient avoided keeping summer visitors, which she resented, by means of the ulcers. Chronicity here is probably due to the very long

* Consultant Orthopaedic Surgeon, Lancaster.

† Consultant Dermatologist, Liverpool.

‡ Consultant Dermatologist, Lancaster.

J. C. CRAWHALL *ET AL.*: DISSOLUTION OF CYSTINE STONES DURING D-PENICILLAMINE TREATMENT

FIG. 1.—Plain abdominal radiograph and intravenous pyelogram before treatment with D-penicillamine.

FIG. 2.—Plain abdominal radiograph and intravenous pyelogram after 18 months' treatment with D-penicillamine.

A. EBRINGER AND P. COLVILLE: CHLOROQUINE NEUROMYOPATHY

FIG. 2.—Biopsy from the weak left tibialis anterior muscle: there is replacement of a large proportion of the sarcoplasm by vacuoles and only occasional myofibrils are intact. (H. and E. $\times 75$.)

FIG. 3.—Biopsy from the left tibialis anterior muscle three months after stopping chloroquine, when strength had returned: there is almost complete disappearance of vacuoles and there are more intact muscle fibres than in the previous biopsy. (H. and E. $\times 75$.)