Papers and Originals

Treatment of Cystinuria

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[WITH SPECIAL PLATE]

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In an earlier study of cystinuria (Dent and Senior, 1955) general principles were laid down for the treatment of the disease, bearing in mind the then current concept that the mechanism of the increased cystine excretion was one of defective renal tubular reabsorption, and that efforts to reduce cystine output or to render the cystine more soluble in the urine would be unlikely to be helpful. *In vitro* studies then made of the solubility of cystine in urine showed that it should be possible to prevent crystallization of cystine, and therefore stone-formation, by increasing fluid intake. This had the object of ensuring a constantly dilute urine, especially at night-time, when it was thought that the stones usually form. The use of alkalis in ordinary doses, while theoretically beneficial as a means of slightly increasing cystine solubility, was not thought to be effective as sole treatment, and it required reassessment when combined with the high-fluid regime. The entire study was of a theoretical nature and used *in vitro* criteria only, it being realized that a very long follow-up study of such a chronic form of stone-formation would be required for final confirmation of the effectiveness of the treatment.

In this paper we report our first follow-up of 18 patients with cystinuria who have remained under our regular observation and treatment for between 4 and 14 years, a total of 166 patient-years. We think that some lessons can already be learned and that the treatment has been promising enough to recommend for further trial. It must be borne in mind that final opinions cannot be made for many more years, certainly not until we have also written for data from the much larger number of cystinurics about whom we have corresponded by post, but who have remained under the care of their own doctors on approximately the same regime as ours.

Crawhall *et al.* (1963) have suggested the use of D-penicillamine as an alternative treatment for cystinuria on the basis of the decreased cystine output its administration can induce. In view of the great cost of and known toxicity of penicillamine in large doses, it remains of some practical importance to assess the long-term results of a simple high-fluid intake on renal stone-formation and dissolution in patients with this disease.

Patients Studied

All our patients have in the first instance been examined clinically and have had routine blood and urine tests, including amino-acid chromatograph. All except one fit the criteria for cystinuria as defined by Dent and Senior (1955). The exception (Case 6) is one of the very rare subjects who have formed stones although they are only heterozygous for the incompletely recessive form of cystinuria. Her urine therefore contains an excess only of cystine and lysine, but the quantities (see Table III) are much greater than is usual in the heterozygotes, which explains her clinical mimicking of the homozygous state.

Most of the patients were admitted to hospital for a few days to train them in our water-drinking routine (Dent and Senior, 1955), which consists of sufficient fluid intake to produce 2 ml. of urine per minute throughout the 24-hour period, and which necessitates the patient waking once at night to drink some fluid and usually to pass urine. During admission we also made further measurements of cystine excretion and urine specific gravity. After this we have seen them at intervals (unless otherwise stated) of three to six months. Urine specific gravity is measured each time and the *p*H also if they are taking alkalis. Their urinary tract is usually *x*-rayed annually unless there is reason to do it more often. For convenience of description we have divided them into four groups, the main data of each group being given in Table I. We include three patients (Nos. 4, 5, and 7) whose data are inadequate for a variety of reasons, as we did not wish to allow any possible bias with regard to selection of patients for description here. The patients comprise all cystinurics under our regular care during the years 1948–60.

Alkali Therapy

Seven patients were treated with alkali in addition to the high-fluid intake. In two of these (Cases 1 and 7) sodium bicarbonate was given in low dosage only (4–6 g. daily). In another (Case 13) sodium bicarbonate was given in low dosage between 1948 and 1958, when alkalis were discontinued until 1962 as his stones had increased in size. He has since been given 15 g. daily with better results. One patient (Case 14) has been treated since 1961 with sodium bicarbonate 15 g. daily. Three other patients (Cases 2, 3, and 10) were given 30 g. daily for five years, 8 months, and four years, respectively. This treatment has now been discontinued in Cases 2 and 3. The urinary *p*H response is of interest in these cases. The two patients (Cases 2 and 10) in whom we determined the urinary *p*H while on high doses of sodium bicarbonate showed *p*H values above 7.6 each time it was measured, in some cases throughout the 24 hours. The urinary *p*H response of these individuals is in marked contrast to that of other patients who had low dosage only. For example, Case 1 often had urinary *p*H values below 7 while taking 4–6 g. daily of sodium or potassium bicarbonate.

X-ray films are reproduced in Figs. 1a–1e and 2a–2c (Special Plate) of the two patients (Cases 1 and 2) who show the most convincing stone-dissolution under treatment. We think that

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TABLE I.—*Summary of Cases*

Case No.	Sex	Age at, and Date of, First Attendance	History	Treatment	Urine S.G. at Follow-up	Remarks
			Group 1.—Cystinurics who have Shown Marked Stone-dissolution under Treatment			
1	F	38. 26/4/58	Renal colic and right ureterolithotomy at 4 yrs. Well till 1 yr. ago, when had right-renal colic and passed several stones. Well since then, but *x*-ray film showed several stones in right kidney	High-fluid regime and sod. bicarb. 6 g. daily changed to pot. bicarb. in Oct. 1962	1,002–1,012	Co-operative patient who finds the treatment no trouble
2	M	39. 19/2/58	Haematuria in 1944 and in late 1957. Low backache after exercise. Otherwise fit and well and leading active life. *X*-ray film showed enormous stones in both renal pelves. On admission plasma urea normal and 60% urea clearance. 30 g. sod. bicarb. a day produced only mild alkalosis (blood *p*H 7·47, total CO_2 30·2 mEq/l.). No hypertension or increase in body weight. His 24-hr. cystine output rose from 481 mg. before treatment to 751 and 823 mg. on high fluid and alkali. Remained symptom-free ever since	High-fluid regime. Sod. bicarb. 30 g. daily, which was discontinued in June 1962	1,003–1,010 (Urine *p*H averages 7·8 while on alkalis)	Intelligent man who co-operates fully. Complained only of mild thirst while on sod. bicarb.
3	M	26. 25/4/60	Repeated haematuria and right-loin pain over past 10 yrs. Stones passed over last 6 mths. thought to be of uric acid on analysis. Left nephrectomy 8 yrs. ago because of ureteric obstruction and hydronephrosis. *X*-ray film showed one large and several small stones in right kidney. On admission he tolerated well the high-fluid regime and sod. bicarb. 30 g./day, and was sent home on this. Gradual stone-dissolution occurred. No stones visible Sept. 1960. Remains well and stone-free	High-fluid regime. Sod. bicarb. 30 g. daily, which was discontinued in Dec. 1960	1,007–1,017	Patient is a laboratory technician with a full understanding of situation. Treatment causes only little inconvenience
			Group 2.—Cystinurics who came to us Stone-free and who have Remained Stone-free Under Treatment			
4	M	4. 29/3/56	Dysuria and frequency since 18 mths. age. Bladder stone found and removed at 3 yrs. Last *x*-ray Jan. 1959 showed no further stones	High-fluid regime. Alkalis tried but not accepted	Not done	Parents uncooperative and do not attend regularly
5	M	16. 24/10/56	4 attacks renal colic in previous 5 yrs. Each attack followed by passage of a small stone. Last *x*-ray Aug. 1962 showed no urinary stones	High-fluid regime	1,004–1,007	Apparently highly intelligent. Finds treatment no trouble. Annually measures at home his 4-hr. urine vol. over a 2-day period for check on regime
6	F	41. 27/11/57	Has passed stones regularly since 24 yrs. of age, often more than one at a time. Cannot remember how many altogether. Last *x*-ray Apr. 1964 showed no urinary stones	High-fluid regime	1,000–1,003	Co-operative patient who has become enthusiastic almost to point of obsession with fluid regime
7	M	4. 8/1/58	Gravel and small stones passed at age 18 mths. *X*-ray showed further stones. Removed and recurred. In all 4 operations done for removal of stones from kidneys and ureters. Last operation Nov. 1955; from then on had treatment as at present, and remained stone-free. Last *x*-ray May 1960. Returned to local doctor for follow-up, who reported (Feb. 1962) still stone-free	High-fluid regime. Sod. bicarb. 4 g. daily	1,007	Co-operative parents. He drinks well and has large diureses during day. One night specimen however, is usually too concentrated
8	M	24. 17/6/58	Left staghorn calculus discovered 1955, removed by nephrectomy. Has occasional right-loin pain not worsened by vigorous exercise. Last *x*-ray Apr. 1964 showed no urinary stones	High-fluid regime	1,003–1,020	Co-operative patient
9	M	46. 5/11/58	Left staghorn calculus 1943 removed by nephrectomy. No clear attacks renal colic since nor passage of stones. Partial gastrectomy for G.U. 1943. Last *x*-ray Feb. 1962 showed no urinary stones	High-fluid regime	1,002–1,008	Has depressive attacks. Meticulous about fluid intake
			Group 3.—Cystinurics Whose Stones at First Increased in Size but Later Began to Dissolve			
10	M	38. 30/9/50	First attack renal colic at age 17 yrs. Occasional colics and loin pain since. Right nephrectomy for multiple stones at 27 yrs. *X*-rays showed no stones till Apr. 1954, when 2 small ones appeared. These increased slowly till Dec. 1960, by which time he had a large staghorn calculus. We pointed out seriousness of situation to him, and the next *x*-ray taken on July 1961 showed several large foci of stone-dissolution. (Case S.L. of Dent and Rose, 1951.) Further annual *x*-rays (last July 1964) showed continued stone-dissolution	Sod. bicarb. 3 g. nightly till Dec. 1960, when dose raised to 20 g. daily. Mar. 1964 further increase to 30 g./day. High-fluid regime begun July 1954, and continued throughout	1,006–1,014 (Not measured before 1960)	Pleasant patient who at first did not follow our advice but recently has taken his treatment seriously
11	F	6. 21/10/59	Intermittent haematuria since 3 yrs. Large stones removed from both kidneys Apr. and July 1957. Slow regrowth of further stones on both sides. This continued under our treatment until Feb. 1961, by which time bilateral staghorn calculi were present. Importance of treatment impressed upon parents. Subsequent *x*-rays (last May 1963) showed slow but definite stone-dissolution	High-fluid regime. Pot. citr. 2 g. q.d.s.	1,001–1,016	Until recently the parents did not follow our advice
12	F	40. 2/11/55	Sister of Case 16 found to have cystinuria on routine testing of family. May have passed stone 17 yrs. ago, otherwise well and no renal or other symptoms. *X*-ray when first seen showed one small stone in each kidney. So far patient has remained symptom-free. Stones have varied in size, but over past 2 yrs. definite radiological evidence of stone-dissolution	High-fluid regime	1,010–1,012	Patient claims that she takes adequate fluid

(Continued on facing page)

TABLE I.—*Continued*

Case No.	Sex	Age at, and Date of, First Attendance	History	Treatment	Urine S.G. at Follow-up	Remarks
Group 4.—Cystinurics Whose Stones have not Dissolved and may have Recurred or Increased in Size while being followed at U.C.H.						
13	M	36. 9/11/48	3-week history of haematuria and pain in medial aspect of right thigh. *X*-ray showed large left staghorn calculus and smaller right-renal calculus. Have not changed in size. High-fluid regime begun in Mar. 1954. Alkalis given from first admission in 1948, but stopped in Oct. 1958 as he was becoming hypertensive. (Mr. G.S. of Dent and Rose, 1951.)	High-fluid regime. Sod. bicarb. 3–6 g. daily	1,009–1,016	Patient probably does not adhere to water-drinking regime. He is of low intelligence
14	F	15. 6/3/50	Attacks right renal colic for 2 years. Recently passed some small stones. (Miss I. W. of Dent and Rose, 1951.) On first admission passed many stones from right kidney. Finally required operative removal both sides. On follow-up had several more attacks of renal colic and four more operations for removal of stones and a right-sided partial nephrectomy spread over past 11 years	High-fluid regime	1,005–1,015	Patient uncooperative when pain-free. We do not think that she keeps to treatment
15	M	23. 3/3/50	Admitted with renal colic. 3 previous similar attacks. *X*-rays showed no urinary stones. Well till 1955, when further colic began. *X*-ray Feb. 1956 showed large right-renal stone. Removed surgically. No subsequent recurrence (Oct. 1963) (Mr. J. H. of Dent and Rose, 1951.)	Sod. bicarb. 3 g. daily till 1952, when high-fluid regime begun	1,006–1,013	Admitted he did not co-operate properly till 1956. Has done better since operation in that year
16	F	7. 2/1/52	Dysuria and frequency for at least 3 yrs. Large bladder stone found and removed. Thoroughly investigated (Case G. M. of Dent, Senior, and Walshe, 1954) and first patient to be treated with high-fluid regime. Stone-free till June 1958, when some left-loin pain and haematuria. *X*-rays then showed no stones. Routine *x*-ray Apr. 1959 showed large bladder stone. Removed after crushing. She has grown well and is fully active. Her B.P. tends to be about 140/95. She has formed a further left-sided stone	High-fluid regime	1,008–1,011	Infrequent follow-up
17	F	19. 15/6/55	Since age 2 years, has had 9 operations for removal of renal stones. Good general health. *X*-ray showed small left-renal stone when first seen at U.C.H. This stone has become gradually larger	High-fluid regime	1,010–1,015	Tries hard to keep to fluid regime but admits does not always take night drink as she has difficulty in waking
18	M	17. 28/9/53	Bilateral renal pain with haematuria and passage of a stone 1 year ago. Recent recurrence of left colic. *X*-rays showed no stones. During next 10 years stones have formed on both sides and in 1963 he had large bilateral renal calculi. Has had occasional colics but lives an active life otherwise	High-fluid regime	1,002–1,014	Claims that he keeps to treatment, but we suspect that he is not co-operating

the response in Case 1 was almost entirely due to her fluid-drinking regime, which she kept to scrupulously. The small dose of alkali she also received was of the quantity which previously we found quite inadequate as sole treatment. The change from sodium to potassium bicarbonate was made as the sodium salt seemed to make her mildly hypertensive.

Cystine Analysis

All analyses were by the previously described polarographic method (Dent and Senior, 1955). We were anxious to repeat the two experiments previously described by the same authors in which an acute diuresis was shown to increase cystine output quite markedly in a cystinuric with stones, presumably owing to stone-dissolution, but not to increase it in a cystinuric without stones as would be required on our present theory of pathogenesis. Our further results are shown in Tables II and III. It will be seen that in only one instance has the diuresis increased cystine output to a similar extent to that found in the single previously published experiment. Our present results are more in accord with our current clinical study, since stone-dissolution has been shown to be very slow even in our best patients.

TABLE II.—*Effect of Water Diuresis on Cystine Output in Urine of Six Cystinurics with Stones*

Case 18		Case 1		Case 10		Case 13		Case 2		Case 16*	
M.V.	C.O.	M.V.	C.O.	M.V.	C.O.	M.V.	C.O.	M.V.	C.O.	M.V.	C.O.
2·2	788	2·2	882	4·3	603	1·5	842	3·1	846	0·5	774
3·6	904	6·1	985	5·5	676	10·2	928	4·7	1,110	3·9	609
9·3	1,640	12·7	1,040	9·8	800	16·5	995	13·3	1,312	10·8	786
12·3	2,150	16·0	840	9·3	1,046	16·6	986	9·3	1,020	11·8	742
12·5	2,480	17·6	1,590	10·0	798	21·8	944	7·3	961	16·7	754
11·6	2,260			7·1	760	20·6	886			8·2	670
13·4	2,420					22·4	952			10·8	885

M.V. = Minute-volume of urine in ml. C.O. = Cystine output in μg./min.
* Case 16 had had a bladder stone, which was removed between the first and second diuresis experiments.

Discussion

We are suggesting here that our results so far show that the water-drinking routine, alone or combined with alkalis, can deal adequately with the problem of stone-formation in cystinurics, which is indeed the only disease to which they are predisposed. There are already reports of further cases which present indisputable evidence of stone-dissolution following similar measures (MacDougall, 1961; MacGregor, 1965). Rather to our surprise there has been no evidence yet of any discomfort or trouble from the passage of small particles of stone during the process of dissolution. Although most of our patients found the regime acceptable we are still worried that

TABLE III.—*Effect of Water Diuresis on Cystine Output in the Urine of Two Cystinurics Without Stones*

Case 16*		Case 6	
Minute-Volume of Urine (ml.)	Cystine Output (μg./min.)	Minute-Volume of Urine (ml.)	Cystine Output (μg./min.)
4·7	1,230	4·0	345
6·7	971	5·5	431
15·5	1,184	12·6	494
11·4	1,092	13·7	627
13·1	955	16·7	469
12·1	1,078	15·3	681
12·6	1,175	15·4	584

* Case 16 had had a bladder stone, which was removed between the first and second diuresis experiments.

so high a proportion (33%) were unable to keep to the treatment, finding the constant drinking, especially the one night drink, too much of a nuisance. Our success or otherwise with a patient seems to depend largely on the enthusiasm with which the whole project is put to him. At first, when we had had fewer good results, we did not press patients too hard when we felt they were not co-operating. As we accumulated more evidence we tried much harder, and later we prepared a simple typewritten sheet which explains the facts of the disease and its treatment (see Appendix) and which we now always distribute to the patients and their doctors.

Our recent success with the three patients in group 3, whose stones increased under early follow-up but are now dissolving satisfactorily, can be directly related to this factor. Likewise it is, unfortunately, rather painfully obvious that our best results (Table I, groups 1 and 2) have all been achieved on patients more recently treated by us and with whom we have had good success in training them early on to our high-fluid regime. Our oldest patients are shown in Table I (group 4). We started badly with them and have failed dismally to make them change their ways subsequently. One patient (Case 15), however, was badly shaken when his further stone required operation in 1956. He has been more co-operative in consequence, and has since done so well that he might now be considered to be classed as a patient for group 2. We stress the importance of regular out-patient measurement of the specific gravity of the patient's urine as a rough check on what is going on. Pressure is put on the patient if he produces a concentrated urine for us on out-patient attendance.

In the previous paper from this department (Dent and Senior, 1955) we showed that an acute diuresis in a patient with cystine stones could cause a measurable increase in cystine output which we argued could only be due to stone-dissolution. A simple calculation on the basis of the quantities in question would lead one to believe that our ordinary drinking routine could lead to stone-dissolution at the rate of at least 100 mg. a day. As most cystine stones weigh only a few grammes we should be able to dissolve the stones much faster than actually occurred in our best patients in group 1. The further diuresis experiments carried out (Tables II and III) have not, however, shown that all stones can dissolve as quickly as this in an acute experiment. Moreover, careful study of the *x*-ray films of the larger dissolving stones in our patients has shown clearly that dissolution begins at a few points only on the surface of the stone, after which the surface is quickly undermined and eroded until sometimes another hard layer is encountered, when the process repeats itself. The conclusion seems inescapable that occasional layers of less-soluble material are laid down as the cystine stones grow and that these are responsible for the phenomena noted above. Clearly we must try to determine the exact nature of this insoluble layer.

Two further practical issues arise from this line of thought. The first is that there may still be a place for surgical removal of a symptomless stone should it have long resisted our usual measures for dissolution. The patient could reasonably be led to expect that prevention of further stone-formation may still be attained after the operation. The second concerns a hypothetical but likely situation in which a very large stone is present that would be difficult to remove surgically and that may be showing itself to be slow to dissolve on medical treatment. If for such a patient a simple surgical procedure could be devised by which a number of holes could be bored through the mass of the stone, then medical measures would surely be very successful in subsequently completing the dissolution. This assumes, of course, that intravenous pyelography has shown good secretion of urine from that kidney.

The place of alkalis now seems clearer. We have confirmed our previous view that low dosages (5–10 g. of sodium bicarbonate daily) are of no use in the treatment of cystinuria. With very large doses of the order of 30 g. a day it is, however, possible to ensure a constantly alkaline urine of *p*H above 7.6. Although this does increase cystine solubility in urine we have insufficient evidence as yet that it has directly contributed to quicken stone-dissolution *in vivo*. It must be recalled here that maximal rate of stone-dissolution (as calculated from its known solubility) has never been attained, so the urine passed on water drinking alone is constantly undersaturated with cystine. This weakens the theoretical argument that alkalis should be of much additional value. On the other hand, such large doses of alkalis certainly make the patient thirstier and thus help to encourage the necessary fluid intake. We stress, however, that there are potential dangers in long-term, high-alkali treatment. One patient has had symptoms suggestive of alkalosis on the high dosage. We avoid alkalis when there is renal damage, hypertension, or any history of oedema or of conditions predisposing to oedema. Probably the main place for alkalis is with children or with adults who find the full regime of high-fluid intake alone difficult.

In cystinuria we can see that Nature has provided us with a simple model experiment, a form of chronic stone-formation due to the operation of one factor only—namely, the formation of a urine that tends constantly to be oversaturated with a rather insoluble substance. Cystinurics rarely develop urinary infections, and rarely have abnormalities of the urinary tract, nor have we found that dietary or most other environmental factors play any conspicuous part in the immediate cause of their stone-formation. This contrasts with the situation, for instance, with calcium-containing stones where the degree of calcium excretion is only vaguely related to stone-formation, the immediate cause of the stone presumably requiring the simultaneous presence of many other factors concerned in preventing or promoting calcium-salt precipitation. We, nevertheless, feel that our moderate success in treating cystinuria by the high-fluid regime may well have a wider significance in the treatment of other renal stones, especially when cause and treatment are not already known. A similar long-term follow-up of such patients on the round-the-clock, high-fluid regime may be worth while.

Crawhall *et al.* (1964) have shown that when D-penicillamine is administered the quantity of cystine in the urine is reduced, the amount of reduction varying with the dose of penicillamine administered. During penicillamine administration the urine was found to contain penicillamine-cystine disulphide and penicillamine disulphide, both of which are much more soluble in water than cystine. They treated seven patients with D-penicillamine, with a total follow-up of three patient-years at the time of their latest publication. The doses of penicillamine administered varied between 1,050 and 1,800 mg. a day, given in divided doses. A diffuse morbilliform rash was observed in three of the patients soon after beginning the treatment. In two patients this was controlled by the administration of corticosteroids, but in a third the rash progressed to a mild exfoliative stage and the penicillamine was discontinued. Goldberg *et al.* (1963) have reported the occurrence of renal damage after the administration of D-penicillamine. There is at present no long-term follow-up showing stone-dissolution on this treatment. The cost of penicillamine in the dosage required varies between £400 and £740 per patient per annum. We have calculated that if we had treated all of the patients in the present series throughout the last year with penicillamine, this alone would have increased the annual cost of drugs at this hospital by some £10,000, which is about 10% of the year's expenditure on drugs. We therefore consider that the use of D-penicillamine in such large doses for the long-term treatment of cystinuria is still in the experimental stage and should not be generally adopted at present.

Summary

A further study is reported of the medical treatment of cystinuria based mainly on a round-the-clock, high-fluid-intake routine.

FIG. 1*a*

FIG. 1*b*

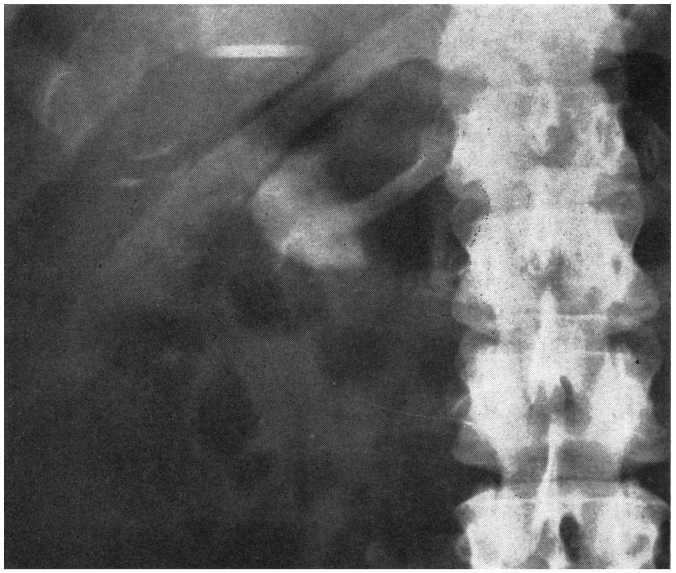


FIG. 1*c*

FIG. 1*d*

FIG. 1*e*

FIGS. 1*a*–1*e*.—Case 1. A series of straight *x*-ray films of the right renal area. Note the gradual decrease in size of the cystine stones between July 1958 and October 1963. The surface of the stone appears to be eroding away at a few points, then undermining and becoming irregular. This is best seen in the *x*-ray films of January and July 1959 (Figs. 1*b* and 1*c* respectively).

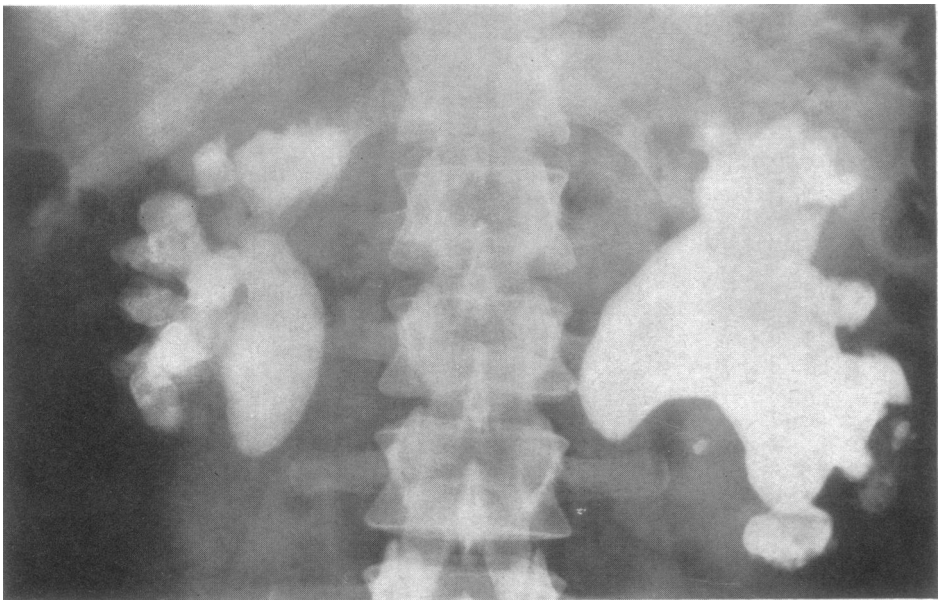
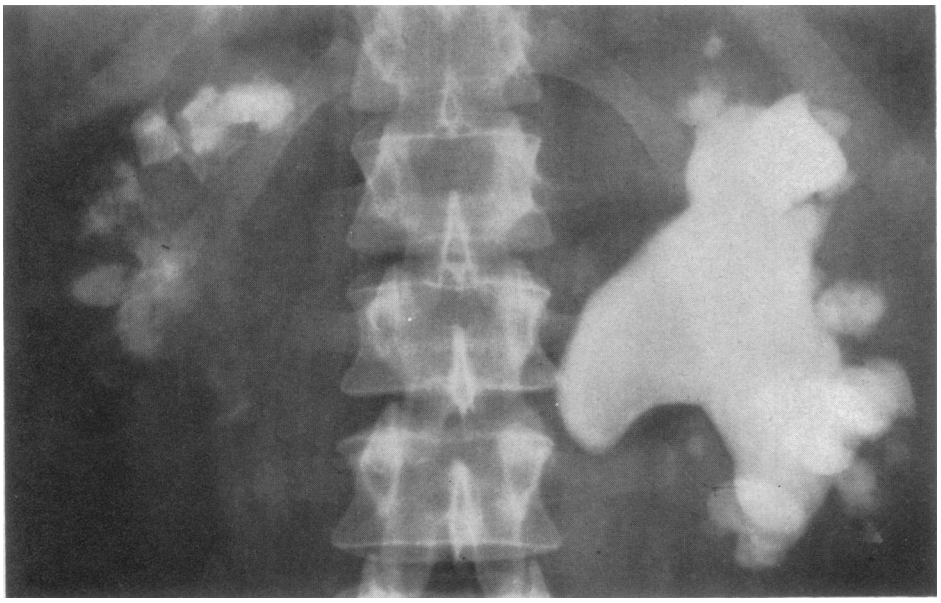


FIG. 2*a*



FIGS. 2*a*–2*c*.—Case 2. A series of straight *x*-ray films of the renal areas. The film taken on 18 March 1958 (Fig. 2*a*) shows bilateral staghorn calculi. At that time an I.V.P. showed that the left kidney excreted very little dye, whereas on the right the excretion was normal. Subsequent films, taken after prolonged water drinking in November 1960 (Fig. 2*b*) and February 1964 (Fig. 2*c*), showed marked dissolution of the stone on the right. The stone on the left has remained virtually unchanged, and this we think is due to the fact that the left kidney is non-functioning.

FIG. 2*b*

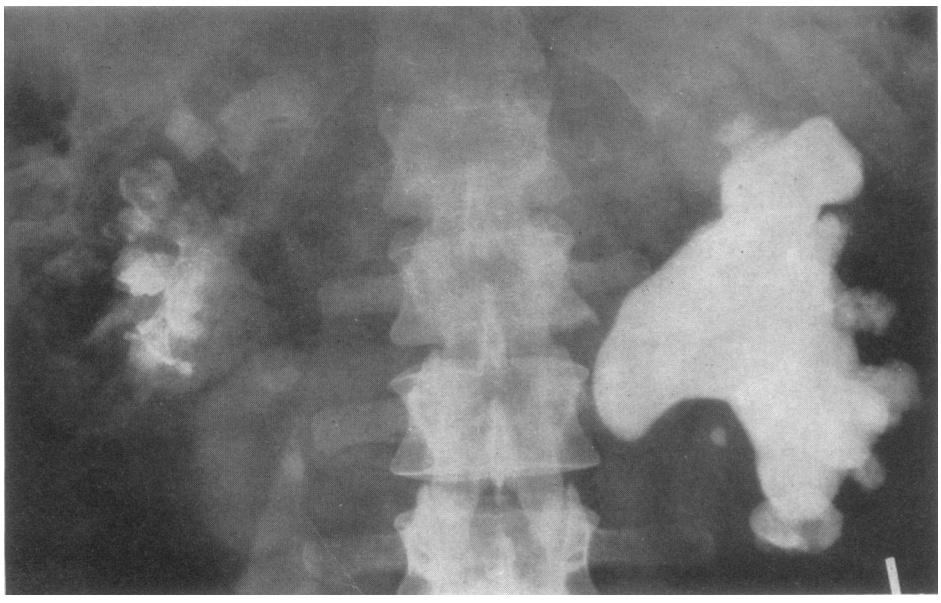


FIG. 2*c*

Of 18 patients on whom we have adequate data only 12 are at present keeping to the desired routine.

Those who have failed to keep to the treatment have shown recurrent stone-formation or an increasing size of stones already present.

Those who have kept to the treatment have shown no recurrence of stone when they began in a stone-free state. When they had stones to begin with, clear signs of stone-dissolution have appeared, results being sometimes spectacular. Dissolution was slower than theoretically expected, and we are obtaining evidence that cystine stones, as they grow, may from time to time lay down a coating of much less soluble material.

The effect of treatment by alkalis, in addition to the fluid-drinking routine, is also reassessed. Doses of the order of 10 g. a day of sodium bicarbonate have very little effect. Very large doses, of the order of 30 g. a day, probably cause stone-dissolution to occur a little faster, but cannot yet be recommended for general use in view of possible long-term dangers.

We are grateful to our numerous colleagues who referred cases to us for investigation and treatment.

Appendix (Instruction Sheet for Cystinuric Patients)

What to Do if You Have Cystinuria

General Facts

Cystinuria is not a disease in the ordinary sense. It is a permanent state of affairs due to your having inherited something from both your mother and your father, through no fault of theirs (or yours). As a result, you all your life pass in your water a lot of cystine, which is a rather insoluble substance. This tends to form a muddy deposit, which sometimes causes pain while being passed, or to collect inside you and form little stones which slowly enlarge (if you do nothing about it) and damage your kidneys. There is no known way, by diet or medicine, of curing this by lessening the amount of cystine passed in your water. Fortunately, we know that by drinking a lot of water, and sometimes by also taking sodium bicarbonate tablets, we can keep the cystine in dissolved form. When this is done stones cannot form; indeed, if already present they slowly dissolve away. Once this happens, and so long as it continues, the only known disadvantage you have disappears and you can consider yourself cured. May we stress that if mud- and stone-formation are prevented you become quite normal and in no way different (except to a doctor who does special tests) from anybody else. Your kidneys will remain undamaged, you will get no more pain, and you will be as long-lived and healthy as anybody else. We know now how this condition is inherited. It is only likely to occur in children of the same family, and the chances of it occurring in any of your brothers and sisters are one in four. We usually like to ask them for urine specimens so as to see how they stand. People who have cystinuria and their near relatives have a greater chance than others of having children with cystinuria, but the odds are very remote (1 in 400 or so) and are not worth worrying about.

Treatment by Water-drinking

Because of the way your kidney is made you are constantly putting out these large amounts of cystine in your urine. We know, further, that the excretion continues at exactly the same rate night and day. In order, therefore, to keep it dissolved you have to make sure that you pass throughout the 24 hours a large-enough volume of urine. Normal kidneys, however—and yours are normal from this and every other point of view—make a much smaller volume of urine at night than in the day, a happy arrangement which enables us to sleep through the night without having to empty our bladders. This means that while many people with cystinuria do pass a large-enough volume during the day to dissolve the cystine, hardly anybody ever does this at night. In other words, we have good scientific evidence that cystine stones mainly form at night-time and that it is then that we have to be especially careful with regard to the treatment.

This, then, is what you have to do:

1. Roughly every four hours throughout the day or night you must ensure an intake of 600 ml. (about 1 pint) of any kind of fluid. We suggest that you roughly divide the day into four-hour periods for this purpose, beginning at 8 a.m., say, and continuing for the four-hour periods beginning 12 noon, 4 p.m., 8 p.m., 12 midnight, 4 a.m., and so on. (Any other time to begin will do, however.) At any time during these periods ensure that you take the fluid, which can be in any form whatever, from tap-water to tea or beer. (If you find that milk drinks do not make you pass as much urine as more watery ones you should not include their volume in the fluid calculations.) The kidney reacts to this fluid load by rapidly getting rid of the extra fluid, and will do it fairly constantly throughout the 24 hours. The tendency to pass less urine at night, however, will still remain, but will be much less than before, and usually this routine ensures adequate treatment. If you are doing things properly your urine should look pale and never deep yellow in colour.

2. As noted above, special care needs to be taken about the night drinking. As most people sleep about eight hours, this period can usually be easily fitted into the four-hour routine. It will be necessary, however, to have a large drink (about a pint) immediately before going to bed and another in the middle of the night. Your full bladder will usually wake you for this. Otherwise you must train yourself to wake or else use an alarm clock. Most people can get easily into this routine with practice and go to sleep again straight after, as parents with young children have usually already discovered. On rising, another large drink begins the next four-hour period. This routine of drinking does entail a definite sacrifice on your part; you must see it as the price you have to pay in order to become otherwise normal. Remember that the treatment has to be lifelong, so it is well that it is as harmless as it is. Whenever you stop the treatment you are at once again in danger from stone-formation and its possible serious consequences.

3. In hot weather you will lose a lot of fluid by sweating, leaving less to do its good work in the kidneys. You must then drink correspondingly more, and be especially sure your urine looks always pale and watery and not of a strong yellow colour. On the whole, going to a hot country or sweating a lot for any other reason, such as violent exercise, introduces a further danger, and you must take especial care about the treatment.

4. It is most advisable every year or so to check that your urine flow is adequate under the conditions you have imposed on yourself. This means merely collecting all your urine over a trial two-day period, keeping each four-hour collection together and measuring its volume before discarding. Ideally each four-hour specimen should measure more than 500 ml. (just under a pint). If it does not then you have not drunk enough in that four-hour period. However, if one of the six daily specimens is a little short it does not usually matter; indeed, it is very difficult to avoid one short specimen during one of the night periods because of the natural behaviour of one's kidneys. Be especially careful to do this test if you have hot weather or any other cause of sweating. We will sometimes ask you to show us the results of such a test, and if you have any difficulties with this we may ask you to come to hospital to do it under supervision for a few days.

5. Do not forget that we have a lot of experience now with this treatment and we know that it means all the difference between a normal life and considerable misery for some people. If you have been lucky enough to escape forming a stone until, say, you are 40 years old, and then have had it removed surgically, this does not mean you will take 40 years to make another. It means only that you should be thankful you were so lucky. Moreover, once a stone has formed, and especially when you have had to have it out by operation, further ones form much more easily. We can speak to you with much conviction here, as we know that, so far as the quantity of cystine excretion is concerned, all you cystinurics are all exactly the same. We are puzzled why some people begin to form stones at 1 year of age and others not till much later. This may be something to do with their natural habit of fluid intake, but there are other factors concerned. These latter factors are the only things we are unsure of in this condition, and we are actively trying to uncover them.

6. Small children are treated on exactly the same principles as adults, but the volumes of fluid concerned are of course less. We will advise here as necessary.

7. If you like medical details we will show you on *x*-ray films what happens to stones made of cystine when their owners do and don't do what they are told.

Treatment by Tablets of Sodium Bicarbonate

We sometimes advise people to take these tablets in addition to doing the water-drinking routine, never instead of it. The tablets plus water-drinking probably work a little better than the water alone. However, they are more trouble, and there is always the possibility that they are not good for you if taken for a long time. We therefore reserve their use for special situations and will not give you any without explaining this further.

REFERENCES

Crawhall, J. C., Scowen, E. F., and Watts, R. W. E. (1963). *Brit. med. J.*, **1**, 588.
—— —— —— (1964). Ibid., **1**, 1411.
Dent, C. E., and Rose, G. A. (1951). *Quart. J. Med.*, **20**, 205.
—— and Senior, B. (1955). *Brit. J. Urol.*, **27**, 317.
—— —— and Walshe, J. M. (1954). *J. clin. Invest.*, **33**, 1216.
Goldberg, A., Smith, J. A., and Lockhead, A. C. (1963). *Brit. med. J.*, **1**, 1270.
MacDougall, J. A. (1961). Ibid., **2**, 819.
MacGregor, M. E. (1965). *Proc. roy. Soc. Med.* In press.

Use of Disinfectants in Hospitals

A Report by the Public Health Laboratory Service Committee on the Testing and Evaluation of Disinfectants*

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1. Introduction

This committee was set up in May 1961 to consider the evaluation of liquid antiseptics and disinfectants for hospital use. In particular three questions were thought to require answers: To what uses were these agents put? Into what categories could these uses be divided? What tests were proper for each category?

This task is not an easy one. It is probable that there will always be disagreement over matters of detail, and indeed rigid standardization may limit progress, but meanwhile disinfection policies for hospitals must be planned, and this communication is an attempt to give some guidance to those responsible.

2. Present Usage

A questionary was prepared in which 166 hospitals in England and Wales were asked about 53 possible uses for disinfectants. The replies were not easy to analyse, but two points emerged quite clearly. (*a*) In most hospitals no policy existed. A number of different disinfectants were used at many different strengths and often particular disinfectants were used for quite unsuitable purposes. (*b*) In a significant minority of hospitals a clear, if empirical, policy had succeeded in reducing the number of disinfectants to a very few. Some examples will illustrate these points.

Sluices.—At least 25 different disinfectants were used. The most popular were phenolics, which included lysol at dilutions between 1/20 and 1/500 and white fluids between 1/80 and 1/600. The next most popular were quaternary ammonium compounds, which were used at dilutions between 1/200 and 1/6,000, and chlorhexidine: both of these are quite unsuitable for this purpose (see Section 5).

Handwashing in Operating-theatres.—At least 20 different preparations were listed. In most replies no strength was given, but chlorhexidine 5% concentrate was used in dilutions between 1/20 and 1/200. Two hospitals stated that they used only "physical methods" but did not elucidate further.

More generally, quaternaries and chlorhexidine were commonly used in situations where they could be rapidly inactivated by organic matter or in which their ineffectiveness against the tubercle bacillus could be a serious disadvantage.

The total number of agents reported as being used varied greatly between hospitals, for example:

	No. of Agents Used		
	Mode		Range
For general use on inanimate objects ...	8	...	3–23
For use on skin or mucous membranes ...	6	...	0–14

Appendix 1 gives the disinfectants which were most popular for various purposes.

This survey thus showed that in many hospitals disinfectants were used in an irrational way; this is undesirable for two reasons. First, the disinfectant may be ineffective, and therefore unsafe, either because it is inherently unsuitable or because it is used at too low a concentration. Secondly, very large sums of money may be wasted if an unnecessarily expensive disinfectant or an unnecessarily high concentration is used. From the information available it was not possible to calculate the actual cost to the Health Service of these misuses of disinfectants. In one group known to us the total annual cost of disinfectants was cut from 22s. 4d. to 12s. 2d. per bed by a relatively conservative rationalization. If this annual saving of 10s. per bed were applied to all non-mental beds in England and Wales at least £125,000 would be available for other purposes; this figure could easily be raised by more radical measures.

3. Limitations and Scope of Liquid Chemical Antimicrobial Agents

It is now generally accepted that only certain physical methods, such as heat or ionizing irradiation, can be relied on to kill all microbes with absolute certainty. Few liquid disinfectants will kill spores within a reasonable time or will kill viruses with certainty, and the efficacy of all is apt to be impaired by the presence of organic matter. Thus they should be used only when physical methods are impossible or impracticable.

Some of the uses to which disinfectants are commonly put are now examined.

* The members of the committee were: Sir Graham Wilson (chairman 1961–3), Dr. J. W. Howie (chairman 1963–4), Mr. H. Davis, C.B.E., Ph.D., F.R.I.C., Professor L. P. Garrod, Dr. R. J. Henderson, Mr. G. Sykes, M.Sc., F.R.I.C., Mr. A. H. Tomlinson, D.Phil., Dr. J. C. Kelsey (secretary), Central Public Health Laboratory, Colindale Avenue, London N.W.9.