S. J. CREWS: POSTERIOR SUBCAPSULAR LENS OPACITIES

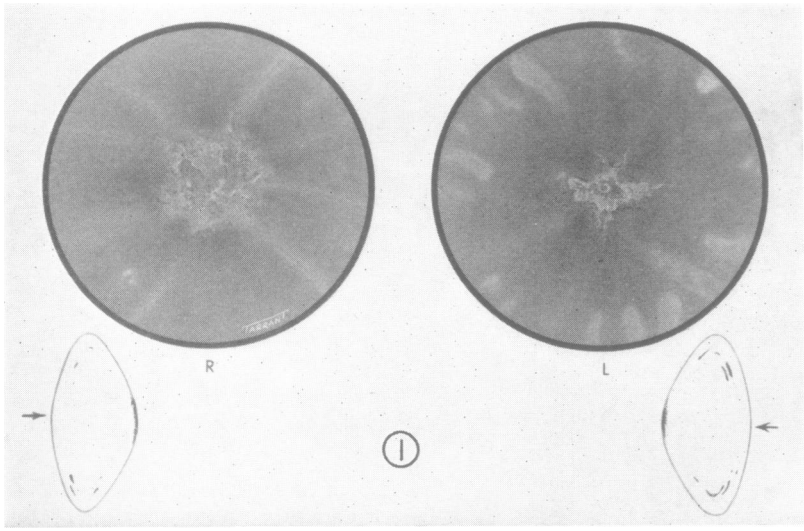
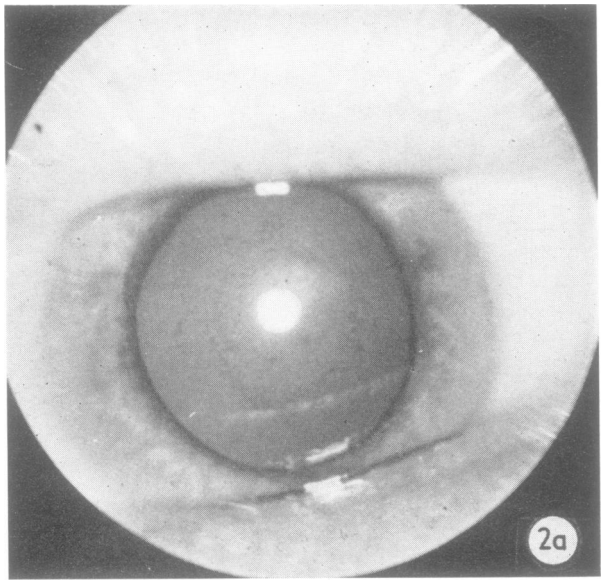


FIG. 1.—Early bilateral cataract; drawings of both eyes. Diagrams show site of opacities.



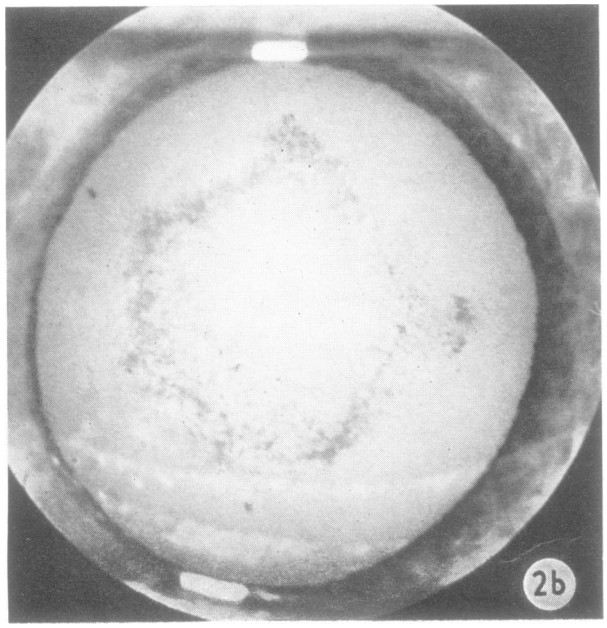


FIG. 2.—Patient with advanced cataract in both eyes. Photographs of right eye: (*a*) low power; (*b*) high power (histology of this right lens is reported in text).

S. ORAM *ET AL.*: RENAL CORTICAL CALCIFICATION AFTER SNAKE-BITE

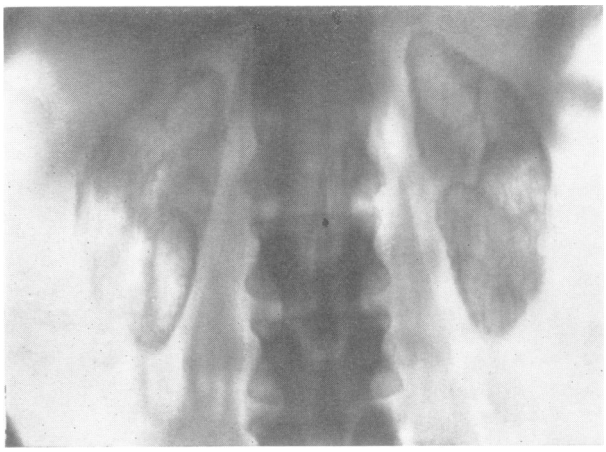


FIG. 1.—Kidneys are contracted. Dense marginal calcified bands, approximately 2 mm. wide, are seen in the cortex. Irregular strands of calcification extend inwards towards the renal pelves and enclose irregular translucent zones, which are presumably deformed renal pyramids.

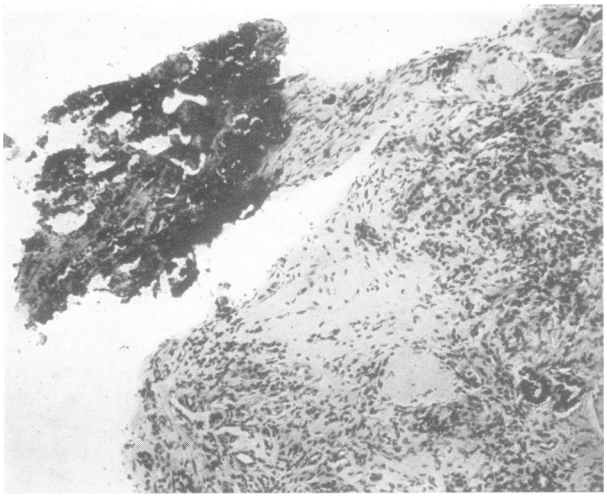


FIG. 2.—Photomicrograph of renal biopsy material (×150). The darkly stained area is necrotic calcified tissue. Two shrunken hyalinized glomeruli are seen, and between them is a dense infiltrate of mononuclear cells.

POSTERIOR SUBCAPSULAR LENS OPACITIES IN PATIENTS ON LONG-TERM CORTICOSTEROID THERAPY

BY

S. J. CREWS, B.A., M.B., F.R.C.S.Ed.
Consultant Ophthalmologist, Birmingham and Midland Eye Hospital

[WITH SPECIAL PLATE]

Posterior subcapsular lens opacities in patients on long-term corticosteroid therapy were first described by Black *et al.* (1960) in 17 out of 44 patients with rheumatoid arthritis. They suggested there was a direct relation between the dosage of steroids and the incidence of cataract formation. In subsequent papers (Ogelsby *et al.*, 1961a, 1961b) the series was increased to 30 out of 72 and included patients who were suffering from other rheumatic diseases—for example, psoriatic arthritis, dermatomyositis, and disseminated lupus erythematosus. Though other authors (Hart *et al.*, 1961; Pfahl *et al.*, 1961; Toogood *et al.*, 1962) have described isolated examples, there does not yet seem to have been any comparable group of cases to support this finding. Indeed, Gordon *et al.* (1961) have stated that there is no correlation between steroid therapy and the incidence of cataracts in rheumatoid arthritis.

It is thought that the present investigation is of interest in that it agrees substantially with the original American reports.

Material

A total of 250 patients have been examined, and these can be divided into two groups on the basis of whether they were being treated with corticosteroids or not.

1. "*Steroid Group.*"—There were 79 patients, comprising 52 with classical rheumatoid arthritis (American Rheumatism Association Committee, 1959), 20 with the nephrotic syndrome, 2 with disseminated lupus erythematosus, 2 with scleroderma, and 1 each with pemphigus, ankylosing spondylitis, and sarcoidosis.

2. "*Non-steroid Group.*"—These 171 patients comprised 34 with classical rheumatoid arthritis, 30 attending a special clinic for Sjögren's syndrome, 5 with nephrotic syndrome, 2 with discoid lupus erythematosus, and 100 consecutive patients attending an ophthalmic out-patient department.

It must be stressed that the series is a selected one, since patients were either referred by physicians because of visual disturbances or were examined because of availability of certain groups of patients being treated with or without corticosteroids. Details of general medical history, investigations, and treatment were obtained from hospital case records and where necessary from the referring physicians.

Methods

Ocular examination included refraction to determine maximal visual acuity; transillumination with ophthalmoscope and biomicroscopy with a modern slit-lamp were performed after mydriasis. In certain cases drawings were made of the opacities in the lens, and where possible they were photographed using a Zeiss fundus camera. Examination was made for any ocular disease likely to cause posterior cortical cataracts—for example, uveitis, retinitis pigmentosa.

Initially it was realized that there might be difficulty in deciding about very early changes, and so 100 random ophthalmic out-patients were examined to obtain a better idea of the normal variation in the posterior capsule and the minute opacities occurring in its vicinity. Only patients with definite vacuoles or granular opacities as seen by focal or retro-illumination were regarded as abnormal; the presence of polychromatic lustre or irregular specular reflex alone was felt to be too subjective.

The degree of opacity was classified into four groups: (1) occasional subcapsular opacities or vacuoles in central region with or without polychromatic lustre and distortion of specular reflex; (2) small clusters of subcapsular opacities remaining discrete; (3) multiple clusters of subcapsular opacities which had mainly coalesced; and (4) extensive subcapsular opacities forming a plaque on the back of the lens and extending forwards into the cortex (Special Plate, Fig. 1).

Retro-illumination with the slit-lamp was found the most valuable method for early diagnosis; a modern type with a lamp that can be rotated into the axis of viewing was found to be preferable—for example, Haag Streit 900 or Zeiss. With the ophthalmoscope it is likely that only grades 3 and 4 would be detected by a non-ophthalmologist using the method of transillumination with a +7 to 10D lens at 0.33 metre. Where there is only a small central opacity this is often obscured by the bright corneal reflex; the room should be darkened and the patient's pupil dilated.

Where possible, these patients were followed at three-monthly intervals.

Results in Steroid Group

Twenty-five patients on long-term corticosteroid therapy were found to have posterior subcapsular cataracts which in all cases were bilateral; only two showed a marked difference in the degree of opacity on the two sides. Repeated observation has revealed the presence of opacities in eyes that were originally considered normal in two patients with nephrotic syndrome after periods of three and six months respectively.

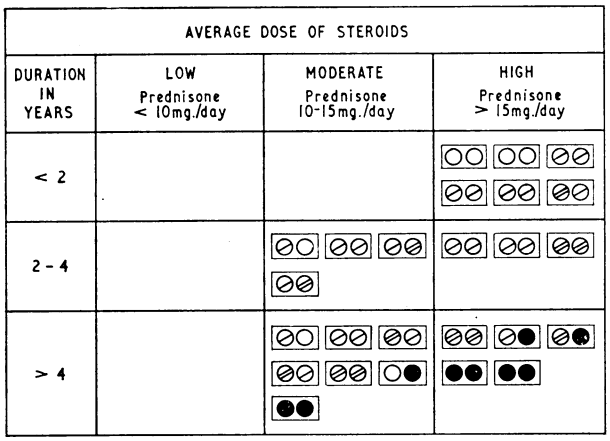
The general diagnosis was rheumatoid arthritis in 18, disseminated lupus erythematosus in 1, nephrotic syndrome (nephrosis) in 5, and sarcoidosis in 1. The duration of these diseases was rheumatoid arthritis 3–38 years, D.L.E. 4 years, nephrotic syndrome 1¼–6 years, and sarcoidosis 10 years. The sexes were equally distributed (13 females, 12 males) and the age incidence is shown in the Table.

The Chart demonstrates the relation between the degree of lens opacity and the dosage of steroid therapy. It would seem that there was no danger when a low maintenance dose was employed, but cataracts appeared when a moderate or high dose was prolonged for many years. Patients who developed opacities after less than two years' treatment had all received a very high dose indeed. There was also some relation between the steroid dosage and degree of opacity; advanced

cataracts occurred only when a moderate or high dose was prolonged for more than four years. All the usual preparations of corticosteroids were implicated, and one patient received only A.C.T.H. therapy.

Age Incidence

	Rheumatoid Arthritis	D.L.E.	Nephrotic Syndrome	Sarcoidosis
10–19 years ..	—	—	2	—
20–29 ,, ..	—	—	1	—
30–39 ,, ..	—	—	—	—
40–49 ,, ..	2	1	—	—
50–59 ,, ..	7	—	1	1
60–69 ,, ..	8	—	1	—
70–79 ,, ..	1	—	—	—



Relation between the dosage of steroid therapy and degree of cataract formation. (*A rectangle represents one patient and a circle represents each eye.*) ○ = Eye with earliest lens opacity grade 1 (occasional posterior subcapsular opacities (P.S.C.) with or without polychromatic lustre or distortion of specular reflex). ⊘ = Eye with grade 2 lens opacity (small clusters of P.S.C. opacities remaining discrete). ⊘ = Eye with grade 3 lens opacity (multiple P.S.C. clusters which have mainly coalesced). ● = Eye with grade 4 lens opacity (extensive P.S.C. opacities forming plaque on back of lens and extending forwards into cortex).

The visual impairment did not always run exactly parallel with the degree of cataract formation. Small opacities were often situated slightly off centre—that is, away from the visual axis—and even extensive ones allowed fairly good vision if they were not too dense centrally. Only 6 out of the 25 patients spontaneously complained of impaired vision, though others, when questioned, stated they had noticed some visual symptoms.

Visual acuity of individual eyes can be expressed in three groups: (1) poor<6/18, recorded in 7 eyes; (2) fair=6/9–6/18, recorded in 15 eyes; (3) good>6/9, recorded in 24 eyes.

Two patients were excluded as accurate refraction was not possible. Over half of the eyes retained good vision and only seven eyes had developed severely impaired sight. Three patients had poor enough vision in both eyes to warrant cataract extraction; one has had an intracapsular extraction (Special Plate, Fig. 2), and the lens was examined histologically by Professor Norman Ashton, who reported as follows:

"*Sections:* The lens has shrunken in preparation so that the anterior fibres are distorted and infolded. The lens capsule and epithelium are entirely normal and the nuclear bow at the equator is natural. There are early cortical cataractous changes anteriorly on one side, but the anterior half of the lens is otherwise normal, as also is the nucleus. Posteriorly there is a thin rim of cataractous change immediately beneath the capsule, which consists of oval and irregular aggregations of P.A.S.-positive material which may have arisen from the capsule and granular and vacuolated degeneration of the most superficial cortical fibres."

Corticosteroid Side-effects.—No attempt has been made to assess the true incidence of steroid side-effects, since the patients were referred from other clinics, but the impression gained from hospital notes is that there was a high incidence in patients with posterior subcapsular cataracts. Side-effects were noted in 18 out of the 25 patients with cataracts; nine patients showed excessive increase in weight sufficient to affect therapy, two developed peptic ulcers, three had persistent indigestion, and one needed transfusion for gastro-intestinal haemorrhage. Five patients showed marked bruising, four purpura, and five developed hypertension. Five were found to have spinal osteoporosis and three developed diabetes.

Results in Non-steroid Group

Of the 171 "non-steroid" patients examined none had typical posterior subcapsular lens opacities, though five showed posterior cortical cataracts of a different type (one unilateral and familial, two cataracta complicata, and two cupuliform).

Discussion

In the 25 patients on corticosteroid therapy the posterior subcapsular lens opacities followed a reasonably constant pattern though the degree of lustre varied in different patients.

Many causes are described for lens opacities in the posterior subcapsular region; some can be differentiated with ease from the type seen in this series on account of a specific appearance—for example, traumatic cataract—while others are more difficult to tell from the appearance alone.

Cataracts secondary to ocular disease (cataracta complicata) may have a similar appearance; though they usually have a more marked lustre and extend, with the formation of haloes, evidence of the ocular disease—for example, uveitis, myopia, retinal detachment, and retinitis pigmentosa—will be present.

Radiation cataract cannot be differentiated; however, in the series reported, though the number of diagnostic *x*-ray examinations was very variable, the total exposure was well below the cataractogenic dose.

Of the general causes, opacities associated with myotonic dystrophy, tetany, and atopic dermatitis can be differentiated by both the appearance and the absence of the general condition. Certain toxic cataracts may be of similar type, and it is of interest that the opacities associated with triparanol ("MER-29") are very similar.

There is one senile variety of cataract (cupuliform) which has a similar location though the anterior cortex is often affected at an early stage; the opacities tend to spread round in a dome-like manner and do not extend forwards into the cortex. This type of opacity occurring in a younger age-group often has a familial incidence, and it is stated that there is an increased incidence at an earlier age in association with diabetes mellitus.

A recent controversy has arisen over the incidence of idiopathic posterior subcapsular opacities in the normal population. No figures are available for a truly random population; those often quoted—for example, Kirby (1927) and Abrahamson and Abrahamson (1961)—were from ophthalmic out-patients. A difference of opinion is evident in the definition of abnormality of the

posterior cortex and capsular appearance; for example, Alvaro (1953) used the term cataract when referring only to a variation in iridescence of the posterior lenticular reflex. In some series of normal population opacities due to myopia are included. It has also been frequently asserted that there is an increased incidence of posterior subcapsular opacities in rheumatic diseases, but no figures are available on this subject. What is needed is a study on a truly random sample of population and in patients suffering from a variety of rheumatic diseases.

The high incidence of posterior subcapsular opacities in patients on corticosteroids and their virtual absence in the non-steroid group, coupled with the relation to dose and duration of treatment, would seem to implicate the therapy as a cause of the opacities. This is supported by the observation of these opacities in a variety of different diseases. As stated previously, it is impossible to assess the exact incidence of the opacities because of the methods of selection. It is also difficult to compare directly the steroid and non-steroid rheumatoid arthritis groups, as it may be argued that those receiving treatment are the more severe; however, patients were seen at many different centres where there was great contrast in the use of corticosteroids. It has been stated that steroid side-effects are more frequent in the rheumatic diseases though it may be that supervision is more difficult in these patients. There may equally be some special mechanism rendering certain individuals more susceptible to cataracts, as those cases with lens opacities had a high rate of other side-effects. A more precise study of the associated side-effects might throw some light on the causation of the cataracts, and this is under investigation.

Experimentally, von Sallmann *et al.* (1960) failed to show any changes in the lenses of rats treated with high doses of corticosteroids, but it may be of interest that hypophysectomy in rats alters the incidence of cataracts induced by galactose (Cotlier, 1962); it is possible that steroids unmask or accelerate incipient lens opacities just as they reveal latent diabetes. Harris and Gruber (1962) demonstrated a direct effect of many corticosteroid preparations on the isolated lens resulting in an increased permeability of the lens capsule to cations; however, it is difficult to explain a localized opacity on this basis.

None of these cases have been followed up longer than one year, but there has been a gradual progression of the opacities in four patients. Visual impairment is to be expected early as the cataract is central, but extraction is quite satisfactory on steroid therapy; the newer techniques allow for intracapsular removal of the lens even in younger age-groups.

In conclusion, it would seem reasonable to suggest that all patients receiving high doses of corticosteroids (equivalent to 15 or more mg. of prednisone) for many years should be routinely checked by an ophthalmologist.

Summary

A total of 250 patients were examined for posterior subcapsular lens opacities; these can be divided into two groups, depending on whether or not they were receiving corticosteroid therapy.

The steroid group of 79 patients comprised 52 suffering from rheumatoid arthritis, 20 from nephrotic syndrome, and 7 from miscellaneous conditions. Bilateral posterior subcapsular lens opacities were detected in 25 of these patients on long-term steroid therapy (18 with rheumatoid arthritis, 1 with disseminated lupus erythematosus, 5 with nephrotic syndrome, and 1 with sarcoidosis). Correlation with dosage of corticosteroids showed that cataracts occurred only in those patients where a moderate or high dosage was maintained for a long duration. The majority of cataracts occurred where therapy continued for more than two years; when opacities developed on a shorter duration of treatment those patients had received a very high dose indeed. There also appeared to be a relation between the corticosteroid dosage and the degree of lens opacity. Though the vision remained good in half of the eyes, seven eyes showed greatly impaired vision and three patients had poor enough sight on both sides to warrant cataract extraction; histology of one lens is reported. Of the 25 patients, 18 had marked corticosteroid side-effects.

The non-steroid group of 171 patients comprised 34 suffering from rheumatoid arthritis, 30 with Sjögren's syndrome, 5 with nephrotic syndrome, 2 with disseminated lupus erythematosus, and 100 consecutive ophthalmic out-patients. Five of this group were found to have posterior subcapsular opacities with differentiating features from those in the steroid group.

No exact figure can be given regarding the incidence of cataracts in the steroid group because the patients were, of necessity, selected.

The evidence presented supports the contention that a moderate or high dose of corticosteroid therapy over a prolonged time may cause posterior subcapsular lens opacities.

ADDENDUM.—Seven additional patients with similar posterior subcapsular cataracts have been seen by me since the paper was compiled. Three were in young patients (ages 14, 17, and 18 years) on high doses of corticosteroids for nephrotic syndrome and four receiving corticosteroid therapy for rheumatoid arthritis (three a medium dose for more than five years and one a very high dose for two years). Since the above was compiled Giles *et al.* (1962) have published a paper on cataract formation and systemic corticosteroid therapy.

I would like to thank my colleagues at the Birmingham and Midland Eye Hospital and the many physicians for kindly allowing me to see their patients; also Professor J. R. Squire, Dr. A. G. W. Whitfield, Dr. C. F. Hawkins, Dr. A. Paton, and Dr. D. Blainey for help and advice. My thanks are also due to Professor Norman Ashton for the histology report on Mr. M. Roper Hall's patient. I wish to thank Dr. Kanagasundaram and Mr. J. G. Williamson for valuable photographic help, and Mrs. M. K. Mason for illustrations and secretarial assistance. The excellent drawings of the lens opacities were done in the Department of Medical Illustration at the Institute of Ophthalmology.

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RENAL CORTICAL CALCIFICATION AFTER SNAKE-BITE

BY

SAMUEL ORAM, M.D., F.R.C.P. GORDON ROSS, M.B., B.S., M.R.C.P.
LIONEL PELL, M.B., B.S., M.R.C.P., D.M.R.D. JOHN WINTELER, M.D., M.R.C.P.

From King's College Hospital, London

[WITH SPECIAL PLATE]

Bilateral renal cortical necrosis is uncommon and even nowadays survival is rare. The clinical syndrome consists of the abrupt onset of oliguria which proceeds to anuria and uraemia, often with bilateral lumbar pain and sometimes with haematuria, but the blood-pressure remains normal or is only slightly raised as a rule. It is due to bilateral symmetrical patchy or diffuse ischaemic coagulative cortical necrosis with sparing of the medulla. A thin rim of cortical tissue 1–2 mm. wide immediately below the kidney capsule (cortex corticis) is also spared. Associated lesions which may be present include necrosis of the anterior pituitary gland and, more rarely, the adrenal (Sheldon and Hertig, 1942). According to Lauler and Schreiner (1958) the condition was first described by Juhel-Renoy in 1886.

The incidence of cortical necrosis is difficult to ascertain, since a definite diagnosis can be made in life only by renal biopsy. Fewer than 200 examples have been reported, though undoubtedly many more unpublished cases have occurred. Although the causes are numerous, as revealed in the excellent reviews of Duff and More (1941), Wahle and Muirhead (1953), and Lauler and Schreiner (1958), in fact they can be divided into three main groups. In women cortical necrosis is usually associated with accidental haemorrhage (abruptio placentae) or toxaemia in the last trimester—this group is the largest, accounting for more than half of the total cases; in men it is usually due to overwhelming infections or poisons causing bacterial shock; and in children vomiting and diarrhoea leading to dehydration is the commonest cause. Among other causes recorded are incompatible blood transfusions (Wahle and Muirhead, 1953), multiple fractures and internal haemorrhages (McFarlane, 1941), severe burns (Brown and Crane, 1943), peritonitis (McQueeney and Speed, 1952), streptococcal infection (DeGraeff and DeBaan, 1959), and phosphorus poisoning (Perry, 1953). Subsequent calcification of the renal cortices is extremely rare, and, so far as we can ascertain, it has been described during life in only five patients (Gormsen *et al.*, 1955; Moëll, 1957; DeGraeff and DeBaan, 1959; McAlister and Nedelman, 1961; Lloyd-Thomas *et al.*, 1962). The last-mentioned workers noted a double line or "tramline" pattern in the renal cortex radiologically.

In our patient severe bilateral renal cortical necrosis developed after snake-bite. She was treated by haemodialysis and made a partial recovery, but seven months later extensive bilateral radiological calcification of the kidneys was demonstrated. Survey of the literature has failed to reveal any other example of calcified renal cortical necrosis arising from this cause.

Clinical Features

A married woman of 50 was bitten on the right ankle by a snake at 10.30 p.m. on September 9, 1961, while she was in the vicinity of Lake Rudolph, Kenya. The snake was not positively identified, but was thought by the local experts to have been a saw-scaled sand viper (*Echis carinatus*). The patient immediately cut into the bite with a scalpel until the wound bled freely, and then rubbed in a mixture of potassium permanganate and iodine. After a few hours the right foot and ankle became painful and oedematous. During the next day she vomited blood several times and became anuric. Three days later she was flown to Kitale, by which time a haemorrhagic state had developed with epistaxis, haematemesis, melaena, and haemorrhages into both orbits. Four days later she was flown to Nairobi, where examination revealed fang marks and a large blister on the right ankle. Ecchymoses were present on the right arm, the left side of the neck, and the right groin. No clinical abnormality was detected in the respiratory, cardiovascular, or central nervous systems. The blood-pressure was 135/80 and the retinae were normal. At no time did clinical jaundice appear.

Investigations yielded the following results: blood urea 440 mg./100 ml.; serum electrolytes (mEq/l.)—sodium 136, potassium 7.5, chloride 85, alkali reserve 14, calcium 4.9, magnesium 3.0; *p*H (arterial blood) 7.3; haemoglobin 5.1 g./100 ml., W.B.C. 40,000/c.mm; P.C.V. 20%.

On September 19, under the direction of Dr. W. E. Lawes, dialysis was performed, using a Kolff double-coil machine, and by the next day the serum potassium had fallen to 5 mEq/l. and the blood urea to 330 mg./100 ml. Three weeks after being bitten the patient began to pass urine—at first in small amounts with much albumin, and later in increasing quantities. During her recovery the area of the wound sloughed and a skin graft was necessary. Her general condition slowly improved and she was able to leave hospital on December 9. The blood urea was then 117 mg./100 ml. and the haemoglobin 9 g./100 ml. Her weight, which was 47.5 kg. before being bitten, had fallen to 38 kg.

In April, 1962, she came to London. During the intervening months she had experienced malaise, anorexia, and occasional vomiting. She tired easily, was breathless on exertion, and her ankles tended to swell. On examination she looked sallow and unwell and was obviously anaemic. Apart from a trace of oedema at the ankles, however, there were no other abnormal physical signs; blood-pressure 140/70, retinae normal.

Investigations.—Blood count: haemoglobin 8.2 g./100 ml., red cells normochromic, heavy granulation of neutrophils, ample platelets. Urine: specific gravity 1005–1011; slight proteinuria, no casts, sterile, volume of night urine almost equal to volume of day urine. Plasma proteins: 7.2 g./100 ml., electrophoresis normal. Serum electrolytes (mEq/l.)—sodium 135, potassium 4.5, chloride 103, alkali reserve 20; blood urea 138 mg./100 ml. Liver-function tests normal. Chest *x*-ray picture normal. Electrocardiogram normal. *X*-ray examination of the abdomen (Special Plate, Fig. 1): plain films revealed contracted calcified kidneys with crenated wavy margins; the right kidney measured 10.4 by 4.8 cm. and the left 10.9 by 4.8 cm. (normal for women: right 12.4 ± 0.66 by 5.9 ± 0.37 cm., left 12.8 ± 0.77 by 6.1 ± 0.38 cm., Moëll, 1956). The calcification appeared to be distributed in a streaky fashion throughout the kidneys.