malaria. Sixteen thought that they had never had malaria and 11 that they might have had malaria. Three gave a more definite history of malaria, and of these patients one gave a history of tertian fever and one gave a history of quartan fever.

Blood Films.—Both the thick and the thin films from these patients were invariably negative. Not one parasite was found.

Serology.—The results of the malaria serology were also generally negative. With the *Pl. falciparum* antigen 23 patients had no detectable antibody. Five had minimal titres (20 to 80), and it is notable that these five patients had at some time lived in an area of recognized malaria transmission. The remaining two patients had significant titres—one of 320 and one of 1,280. Both of these patients, one a Luo and the other a M'luhya, had spent long periods in an endemic area. One of these two sera was positive at a titre of 20 when using the *Pl. malariae* antigen, but the other was negative, as were the remaining 19 sera tested with this antigen.

In the group of nephrotics the mean IgG level was 788 mg (range 320-1,920)/100 ml. The mean IgM level was 162 mg (range 62-320)/100 ml. The mean values for a control group of 42 Nairobi nurses were IgG 1,750 mg (range 1,140-3,300)/100 ml and IgM 146 mg (range 28-280)/100 ml. The β_{1C} globulin levels, with a mean of 178 mg (range 56-254)/100 ml, were similar to those of the control group of nurses, who had a mean of 156 mg (range 112-204)/100 ml.

Of the 18 patients with the nephrotic syndrome incompletely investigated none showed evidence of active malaria. No malaria parasites were found on any of the films made, and of the 16 sera that were examined all had negative or insignificant malaria antibody titres. The immunoglobulin patterns were similar to those of the group fully investigated.

Discussion

Historically the first suggestion that quartan malaria might cause a nephrotic syndrome was the demonstration of the co-existence of malaria parasitaemia with the syndrome (Manson-Bahr and Maybury, 1927).

More recently epidemiological and immunological evidence, reviewed by Edington and Gilles (1969), was put forward to support the concept that quartan malaria is causally related to many cases of the nephrotic syndrome in the tropics. In our series the findings were the reverse. Most of the patients came from the high central area of Kenya where quartan malaria is rarely, if ever, seen. Few gave a definite history of any previous illness resembling malaria.

The data from the blood slide examination suggest that malaria is not common in nephrotics in Nairobi. The serological tests also support this contention. The low rates of positive seroreactors contrast markedly with the findings of Kibukamusoke and Voller (1970) in quartan malaria nephrotic syndrome in Uganda.

Both IgG and IgM levels in the nephrotics were appreciably lower than other workers have found in the nephrotic syndrome in Uganda (Kibukamusoke and Voller, 1970) and in a malaria endemic area of Tanzania (Voller, Lelijveld, and Matola, 1971).

It can be concluded that the nephrotic syndrome commonly seen in Nairobi is not usually associated with malaria.

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Nephrotic Syndrome in Adult Africans in Nairobi

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Summary

The adult nephrotic syndrome as met with in Nairobi is predominantly encountered in young sophisticated African women, most of whom began to use skin-lightening creams containing mercury before the symptomatic onset of their illness. The particular form of mercury involved is well known to cause the nephrotic syndrome in other circumstances—for example, when applied to the skin in the treatment of psoriasis. In these circumstances the pathogenetic mechanism is thought to be of an idiosyncratic type. The use of mercury-containing skin-lightening creams in the patients studied seemed to be particularly associated with a "minimal-change" ("light-negative") renal glomerular lesion, this lesion being present in half of the patients. The prognosis in this group of patients seems remarkably good, with 50% entering remission, 77% of these doing so spontaneously on discontinuing the use of the creams.

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Introduction

It has been alleged that *Plasmodium malariae* has been shown to be the cause of the African nephrotic syndrome (Kibukamusoke and Voller, 1970). No association between malaria and the nephrotic syndrome has been demonstrable in Nairobi (Rees *et al.*, 1972). It therefore remained to define the various other aetiologies of this clinical entity in patients presenting to the Kenyatta National Hospital. We gained the impression that most of the adult nephrotics seen at this hospital were young, English-speaking, African women, and it was proposed that one factor which might distinguish this group from other patients was the use of cosmetics, and in particular skin-lightening creams. Subsequent inquiry showed that of the numerous products

in this range, two used by our patients contained, in a concentration of 5–10%, amino-mercuric chloride, a compound well known to cause the nephrotic syndrome (Turk and Baker, 1968).

Patients and Methods

All patients aged 15 and over with established nephrotic syndrome and a normal level of blood urea and blood pressure were admitted to the study. Sixty patients were seen in a period of about two years. Their ages ranged from 15 to 56 years.

English-speaking ability was determined and inquiry made about the use of skin-lightening creams, particular attention being paid to the nature of the cream and the duration of its use. The presence and degree of oedema was recorded and an estimate of the blood pressure made.

Quantification of urine protein, serum proteins, and serum cholesterol and serum protein electrophoresis were performed by standard techniques. Analysis of fasting blood sugar, antistreptolysin-0 titre, luetic serology, and an L.E. cell test were also carried out by standard methods. Urine mercury estimations were performed by the method of Wall and Rhodes (1966) as modified by Goldberg and Clarke (1970) except that instead of digestion at 56°C for 30 minutes, cold overnight digestion was used as recommended by Lindstedt (1970).

After intravenous pyelography and after exclusion of a major haemostatic defect a number of the patients were submitted to percutaneous renal biopsy, as described by Cameron (1966). The histological classification used was that of Sharpstone *et al.* (1969). Results of therapy were assessed only on those who had remained on follow-up for a minimum period of six months.

Results

(1) *Age, English-speaking Ability, and Sex Distribution.*—(*a*) Thirty-one (52%) of the patients were aged 15–20 years and 53 (88%) were aged 15–30 years. Analysis of females only gave corresponding figures of 59% and 89%. By comparison, of 1,400 patients admitted in one year to a 50-bed general medical unit, 27% were aged 15–20 years and 56% were aged 15–30 years. (*b*) Forty-one (68%) of the patients spoke English. Analysis of females only gave a corresponding figure of 73%. By comparison only 24% of general medical inpatients speak English, and for female general medical inpatients the corresponding figure is 16%. (*c*) Forty-four (73%) of the patients were female. By comparison only 38% of general medical inpatients were female. These figures show that the nephrotic patients as a group differ considerably from the general medical inpatient population in that they are much younger, many more of them speak English, and a notably greater proportion are women.

(2) *Use of Skin-lightening Creams containing Mercury.*—(*a*) Thirty-two (53%) of the patients were using (group A) or had used (group B) these creams. Analysis of females only gave a corresponding figure of 70%, for only one of the total of 16 males used skin-lightening creams at all. By contrast only 11% of female general medical inpatients use these creams. (*b*) The mean duration of use of these creams before the onset of swelling of the legs or face was 13 months (range 1–36 months). Only three women experienced onset of swelling of the legs or face before beginning to use these creams.

(3) All patients were oedematous and normotensive at presentation.

(4) *Biochemistry.*—(*a*) Urine protein concentration ranged from 1·5 to 20 g/litre, with a mean value of 5·7g/l. (*b*) Serum protein results are presented in Table I. Comparison with results obtained from a group of healthy, young, female African nurses showed that levels of serum albumen and alpha-1, beta, and gamma globulins were significantly lower in nephrotics while alpha-2 globulin was significantly higher, a pattern

TABLE I—*Serum Proteins. Results Expressed as Mean ± 2 Standard Deviations ing/100 ml*

	Albumen	Alpha-1 Globulin	Alpha-2 Globulin	Beta-Globulin	Gamma-Globulin
Normals	3·4 ± 0·5	0·33 ± 0·13	0·93 ± 0·18	1·16 ± 0·26	1·95 ± 0·48
Nephrotics	1·77 ± 1·16	0·20 ± 0·11*	1·19 ± 0·24	0·80 ± 0·51	0·93 ± 0·35*
Difference between means					
t-value	14·31	5·26	3·36	6·71	13·47
P value	< 0·001	< 0·001	< 0·002	< 0·001	< 0·001

*One standard deviation.

characteristic of the nephrotic syndrome (Kibukamusoke and Hutt, 1967). (*c*) Serum cholesterol concentration ranged from 114 to 950 mg/100 ml, with a mean value of 427 mg/100 ml.

(5) *Serology.*—(*a*) Antistreptolysin-0 titre was raised in six patients with values ranging from 500 to 2,500 Todd units per ml. (*b*) Luetic serology was positive in only one patient. Latent syphilis was confirmed by the finding of a strongly positive fluorescent treponemal antibody test in the absence of clinical stigmata of syphilis. (*c*) No patient had an abnormal fasting blood sugar or a positive L.E. cell test.

(6) *Urine Mercury.*—Levels of urine mercury were estimated in 53 patients and ranged from 0 to 250 ug/l. In those using mercury-containing skin-lightening creams at the time of study (group A) the range was 90–250 μg/l, with a mean value of 150 μg/l. In those who had discontinued the use of these creams before study (group B) the range was 0–90 μg/l, with a mean of 29 μg/l, while in those who had never used skin-lightening creams or had only used those not containing mercury (group C) the range was 0–45 μg/l, with a mean of 6 μg/l. There were six patients in group A, 22 in group B, and 25 in group C.

By the method used the upper limit of normal for urine mercury is 80 μg/l. All patients in group A therefore had excessive levels of mercury in the urine. The essentially normal results in group B patients reflect the fact that after the cessation of use of mercury-containing creams urine mercury levels rapidly fall to within the normal range (Barr *et al.*, 1972). No patient received a mercurial diuretic.

(7) *Histology.*—Percutaneous renal biopsy was performed in 36 patients. Material for histological examination was obtained in 34. Of these, 17 (50%) showed a minimal change lesion, 13 (38%) proliferative glomerulonephritis, and 4 (12%) membranous glomerulonephritis. Of the 17 patients with the minimal change lesion, 14 (82%) were in groups A and B, while of the remaining 17 only 4 (24%) were in groups A and B.

FOLLOW-UP STUDY

Twenty-six (43%) of the patients were suitable for inclusion in the follow-up study, the results of which are given in Table II. Patients have been followed for periods ranging from six months to two years. During this time 50% have entered a phase of complete remission, with complete regression of oedema, reduction in proteinuria to less than 200 mg/l, and restoration of a normal serum profile on protein electrophoresis. In all these patients therapy has been discontinued and only one has so far relapsed. Spontaneous remission was deemed to have occurred either when the patient had received only diuretic therapy or when remission had occurred more than three months after steroid therapy had been discontinued, as suggested by Miller

TABLE II—*Follow-up Study in 26 Patients*

Remission	Minimal Change Lesion	Proliferative Glomerulo-Nephritis	Membranous Glomerulo-Nephritis	No Biopsy	Total
Spontaneous	6	1	–	3	10
Steroid induced	1	1	–	–	2
Cyclo Phosphamide Induced	1	–	–	–	1
None	2	6	2	3	13

et al. (1969). The latter circumstance in fact accounted for only three patients. So far as could be determined all patients in groups A and B completely discontinued the use of skin-lightening creams after the first attendance at hospital. Of the patients in this category who entered remission, this remission occurred within 3 to 11 (mean 6) months after stopping self-administration of the creams.

Of the 13 (50%) who did not improve, six had used mercury-containing skin-lightening creams, 10 had received steroid therapy, and one of these had also been given cyclophosphamide. Unfortunately the criteria for administration of steroids and the regimens used were widely varied since many patients were referred for study after therapy had been started.

Discussion

It is well established that the nephrotic syndrome may occur as a result of the exposure to the heavy metals mercury (Kark *et al.*, 1958) and gold (Van den Broek and Han, 1966; Wilkinson and Eccleston, 1970). In relation to the former the nephrotic syndrome has been described in association with the use of ammoniated mercury (Becker *et al.*, 1962; Mandema *et al.*, 1963; Silverberg, *et al.*, 1967; Turk and Baker, 1968), the administration of mercurial diuretics (Derow and Wolff, 1947; Preedy and Russell, 1953; Munck and Nissen, 1956; Burston *et al.*, 1958; Clennar, 1958; Riddle *et al.*, 1958; Thayer *et al.*, 1961; Cameron and Trounce, 1965), and contact with a variety of other mercurial compounds (Fanconi *et al.*, 1947; Wilson *et al.*, 1952; Kazantsis *et al.*, 1962; Warren, 1965; Strunge, 1970). Since features of systemic mercurialism do not usually accompany this form of the nephrotic syndrome (Kazantsis *et al.*, 1963) it has been suggested that the latter results from idiosyncrasy (Kazantsis *et al.*, 1962) or an abnormal immune response to the metal (Cameron and Trounce, 1965). A similar pathogenetic mechanism has been proposed for acrodynia (Warkany and Hubbard, 1948). The fate of topically applied mercurials has been demonstrated and the subject recently reviewed by Barr *et al.*, (1972).

Skin-lightening creams containing mercury have been available to the Kenyan public for more than 15 years and it is unfortunate that records at the Kenyatta National Hospital do not allow a valid comparison of the prevalence of the nephrotic syndrome before and after the introduction of these preparations.

The sex distribution in the present series is at variance with previous experience in African (Kibukamusoke *et al.*, 1967), European (Sharpstone *et al.*, 1969), and North American patients (Miller *et al.*, 1969) as is the age distribution (Miller *et al.*, 1969; Fawcett *et al.*, 1971). These findings coupled with the disproportionate representation of those speaking English, suggest the operation of a different aetiological factor. In this regard it is of considerable interest that 4 of the 44 female nephrotics studied were nurses. In no other clinic in the hospital are 9–10% of the patients nurses. This statistic tends to support the opinion that in view of their almost uniform use of skin-lightening creams, female African nurses in Nairobi constitute a vulnerable population (Barr *et al.*, 1972). Indeed precisely the same proportion (70%) of these healthy nurses used skin-lightening creams containing mercury as did the female nephrotics (Barr *et al.*, 1972).

The frequency of raised antistreptolysin-O titres (10%) in the present series is similar to that reported by Ngu and Blackett (1970) in an unselected series of adult African nephrotics in Nigeria.

In relation to the single patient with latent syphilis it is of note that the nephrotic syndrome has been described in association with tertiary syphilis (Kark *et al.*, 1958). Only in patients actually using mercury-containing skin-lightening creams at the time of study (group A) were levels of mercury in the urine recorded which were above the acceptable upper limit of normal (Lane, 1954). A good correlation has previously been established between exposure to mercury and urine mercury levels in non-nephrotic subjects (Barr *et al.*, 1972).

Two patients developed the nephrotic syndrome during an episode of acute glomerulonephritis, the nephrotic features subsequently persisting as the nephritic ones regressed. Although Cameron *et al.* (1970) have described a combined nephritic/nephrotic illness in the majority of a series of adult European nephrotics with membrano-proliferative glomerulonephritis, the combination of acute glomerulonephritis and the nephrotic syndrome is said to be much commoner in Africa than elsewhere (Kibukamusoke and Hutt, 1967).

A remarkable finding was the number of patients (50%) with a minimal change renal glomerular lesion. In other series reporting the association of the nephrotic syndrome and exposure to mercury, the number of instances in which renal tissue has been obtained at biopsy or necropsy and examined histologically has been too few to allow of a meaningful comparison with the present series. Both minimal change lesions (Munck and Nissen, 1956; Kazantsis *et al.*, 1962; Mandema *et al.*, 1963) and features of membranous glomerulonephritis (Becker *et al.*, 1962; Cameron and Trounce, 1965) have, however, been described. An interesting parallel is the nephrotic syndrome related to the administration of gold in which minimal change lesions have also been reported (Van den Broek and Han, 1966; Wilkinson and Eccleston, 1970).

A possible explanation for the development of the nephrotic syndrome after exposure to mercury may stem from the demonstration on electronmicroscopy, in two such patients, of electron-dense material between the epithelial cells and the basement membrane of Bowman's capsule (Mandema *et al.*, 1963) for it is at this site that soluble immune complexes have been found in many patients with the nephrotic syndrome (*British Medical Journal*, 1970). Nevertheless, the finding of such a high proportion of adult nephrotic patients with the minimal change lesion sharply contrasts with experience not only in Europe (Blainey *et al.*, 1960; Cameron, 1966; Sharpstone *et al.*, 1969; Black *et al.*, 1970; Fawcett *et al.*, 1971) and North America (Miller *et al.*, 1969) but also elsewhere in Africa (Ngu and Blackett, 1970), for in each of these areas a figure of less than 25% is usual.

PROGNOSIS

With the exception of the patient with latent syphilis, no evidence for any underlying disease was obtained. Cameron (1966, 1970) reported that in 70–80% of adult European nephrotics no cause is identifiable.

Of the unusually high proportion (50%) of our patients who underwent complete remission, most (77%) did so spontaneously. All of this latter group on whom renal biopsy was performed had histological features which carry a good prognosis according to the experience of White (1967), who equates the minimal change lesion and mild proliferative glomerulonephritis in this respect.

In other reported cases of mercury-induced nephrotic syndrome complete remissions have occurred spontaneously on withdrawal of mercury or following administration of dimercaprol (Wilson *et al.*, 1952; Burston *et al.*, 1958; Clennar, 1958; Kazantsis *et al.*, 1962; Mandema *et al.*, 1963). Spontaneous complete remission has also occurred after cessation of gold therapy (Wilkinson and Eccleston, 1970). By comparison a spontaneous complete remission rate of 14% has been recorded in an unselected series of adult North American patients by Miller *et al.* (1969).

Responsiveness to steroid therapy was disappointing, for in only 2 (17%) of the 12 patients to whom these drugs were given was a complete remission achieved. Steroid-induced remissions have been achieved in other patients with the nephrotic syndrome after exposure to mercury (Becker *et al.*, 1962; Kazantsis *et al.*, 1962; Warren, 1965; Silverberg *et al.*, 1967) and gold (Van den Broek and Han, 1966).

No response could be induced in 50% of the patients in the present series despite the use of steroids and cyclophosphamide alone or in combination. Failure to respond to steroids in mercury-induced nephrotic syndrome has been recorded previously (Cameron and Trounce, 1965). Certainly in consideration of world-wide experience of the adult nephrotic syndrome the prognosis for most patients is poor (Miller *et al.*, 1969). Lack of response to therapy is believed by McIntosh *et al.* (1971) to relate to immune complex deposition in the glomeruli. In view of the known prevalence of this phenomenon in adult nephrotics (*British Medical Journal*, 1970), the poor prognosis in a significant proportion of patients can thereby be explained.

The group of patients presented are considered to represent a different spectrum of the adult nephrotic syndrome from that of common previous experience, in that most of them are thought to have developed as a result of exposure to self-administered mercury. This situation is believed to be entirely avoidable. We subscribe to the view expressed by Turk and Baker (1968) that "there remains no reason for ever prescribing mercury for topical use."

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Veno-arterial Difference in α_1-Antitrypsin Levels

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Summary

α_1-Antitrypsin levels, determined by radial immunodiffusion, were found to be higher in the venous than in the arterial blood of patients with pulmonary infections and in patients with obstructive airflow diseases. Large differences occurred in patients with both abnormalities. No difference was found in patients with other kinds of lung disease or in patients without lung disease. The veno-arterial difference probably occurs as blood passes through the lungs and probably results from alteration of the immunological properties of the α_1-antitrypsin, perhaps by attachment to proteases, rather than absorption into the lung tissue. Further studies are needed to define the diseases in which this antienzyme plays an active part and to determine the mechanisms causing the difference.

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Introduction

Laurell and Eriksson (1963) and Eriksson (1964) first described an association between low levels of serum α_1-antitrypsin and pulmonary emphysema. Eriksson pointed out that there are several sources of protease in the lung, including bacteria, leucocytes, and alveolar and peribronchiolar macrophages, and he postulated that α_1-antitrypsin protects the normal lung against the destructive action of proteolytic enzymes. Since then it has been shown that α_1-antitrypsin forms firm proteolytically inactive complexes with proteases and elastase from leucocytes (Ohlsson, 1971).

Alternatively, it has been proposed (Hunter *et al.*, 1968) that in normal ageing there is a metabolic turnover of connective tissue with a gradual enlargement of alveolar spaces and this is accelerated in the absence of α_1-antitrypsin. Both of these