NEPHROSIS IN NIGERIAN CHILDREN

ROLE OF PLASMODIUM MALARIAE, AND EFFECT OF ANTIMALARIAL TREATMENT

BY

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Watson (1905), reviewing the clinical features of *Plasmodium malariae* infections, remarked on the presence of oedema and albuminuria in several of his patients. In 1912 Clarke wrote: "I believe that the occurrence of oedema in the tropics, of such a nature as to make one think of parenchymatous nephritis, is a reason for making a search for quartan malaria parasites imperative." McFie and Ingram (1917) reported nine cases of the nephrotic syndrome from the Gold Coast; all the patients were under 10 years of age and all had *P. malariae* in the peripheral blood. Giglioli (1930) made a survey of kidney disease and its relation to malaria in British Guiana during 1923–9, and noted the close relationship between *P. malariae* and the nephrotic syndrome. Subsequent reports from Sumatra, Kenya, New Guinea, and India all supported Giglioli's hypothesis (Surbek, 1931; Lambers, 1932; Maegraith (1948), after critically reviewing the literature, Carrothers, 1934; *Indian Medical Gazette,* 1942). accepted the association between *P. malariae* and the nephrotic syndrome. Despite all the above reports, in recent years the whole question seems to have been reopened and a notable tone of incredulity is manifested in some of the modern textbooks dealing with medicine in the tropics. Luder (1958) concluded that the association is still unproved, and Trowell (1960) suggested that the time was ripe for the reassessment of the whole problem.

The "nephrotic syndrome" is common in Ibadan, and *P. malariae* infection is prevalent. We have reinvestigated the epidemiological relationship between these two conditions. This paper reports the results of this investigation and includes only such clinical and pathological findings as are necessary to establish the diagnosis of the nephrotic syndrome. We have in addition tried to assess the short-term effect of antimalarial therapy in our patients.

For the purpose of this study the criteria for diagnosing the nephrotic syndrome were: oedema, massive albuminuria, severe hypoproteinaemia, no azotaemia, and normal blood-pressure. We did not demand hypercholesterolaemia as a criterion, although in fact it was present in almost all the patients.

Materials and Methods

Between March, 1959, and June, 1961, 113 patients (aged 2–10 years) were seen who satisfied the criteria laid down in our definition of the nephrotic syndrome.

Of the 113 patients, 101 were referred to us from the general practice clinic of University College Hospital, where, thanks to the co-operation of Dr. K. Cobban, the head of the department, we could be almost certain that no antimalarial treatment had been given. This requirement was vital if the role of *P. malariae* was to be assessed. The remaining 12 patients were sent either from other hospitals or from general practitioners; these were accepted despite the difficulty in ascertaining if antimalarials had been given. Five of the patients in this group showed no malaria parasites in the peripheral blood.

After blood films were taken, the first 89 patients seen were allotted at random to one of two groups, A or B. The 44 children in group A received no antimalarial therapy, while the 45 in group B received chloroquine 0.2 g. twice daily for two days and pyrimethamine 25 mg. weekly. This therapy eliminates only the erythrocytic phase of the parasite. A third group of 24 patients (group C) were given, in addition to chloroquine and pyrimethamine in the same dosage as above, primaquine diphosphate 3.75 or 7.5 mg. (according to body weight) for 14 days. This regimen produces a radical cure of *P. malariae* infection. Group C had necessarily to be selected since primaquine at the above dosage may cause haemolysis in patients deficient in glucose-6-phosphate dehydrogenase. It therefore consisted of consecutive patients whose erythrocytes had been shown not to be deficient in the enzyme.

Thick blood films were taken on admission and stained by Field's rapid method. Under a magnification of $\times 600$, 100 consecutive fields were examined microscopically for plasmodia. Thin films were stained by Giemsa's method and used to confirm species-identification of parasites detected in thick films.

Biochemical and bacteriological examinations were performed in the departments of chemical pathology and bacteriology, utilizing standard techniques.

Renal biopsy specimens were taken by the technique of Kark *et al.* (1955). Specimens were fixed in Carnoy's fluid in the first 25 biopsies in order that the presence or absence of malaria pigment might be determined. No malarial pigment was seen, and in subsequent biopsies 10% neutral formol-saline was used as fixative.

Clinical Findings

Except in rare instances, the history was relatively short (two to four weeks), and it was the appearance of swelling in the face and feet that led the parents to seek medical advice for the children. Only in two patients (8 and 6 years old) was there a history of former swelling, two and three years previously. Oedema was noted in all patients at their first attendance. Ascites was present in 98% of all patients. The comparatively cheerful appearance of the nephrotic child with ascites and gross proteinuria contrasts markedly with the miserable attitude of the oedematous kwashiorkor child, in whom ascites and proteinuria are rare. Pleural transudates were present in 15 patients.

The clinical appearance of a typical patient is shown in Fig. 1; Fig. 2 shows the same child a year later; he was then free from oedema, but still had gross proteinuria. Antimalarials were not given.

Laboratory Findings

The salient biochemical findings are given in Table I, together with values for normal Nigerian children in the same age-group.

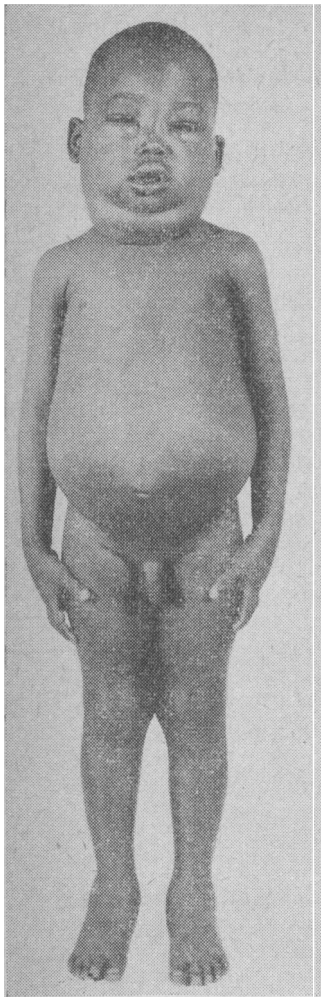

FIG. 1

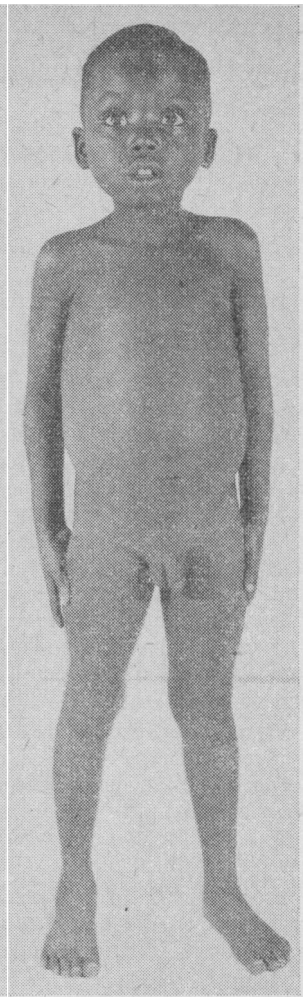

FIG. 2

FIGS. 1 and 2.—Clinical appearance of nephrotic child on admission and a year later.

It will be noted that the total serum protein levels are reduced mainly at the expense of the serum albumin; the α_2 fraction is increased, but the gamma-globulin fraction has remained relatively high despite losses in the urine. The mean serum cholesterol is high and the blood urea, although within normal limits, is slightly higher than in "normal" Nigerian children. Urinary protein was found on electrophoresis to contain 60% of albumin. The remainder was globulin, of which the α_2 fraction was present in the smallest quantity.

Throat swabs were taken from 103 patients; of these, three grew *Streptococcus pyogenes*. This incidence is similar to the carrier rate in the general population (Collard, 1961).

Urinalysis revealed albuminuria in all patients (2–17 g./l.). A few red cells and leucocytes were usually present. In 10 patients sufficient pus cells were present to suggest a complicating infection of the urinary tract. In four of them pathogens were cultured from the urine (*Escherichia coli* in three and *Str. pyogenes* in one). Four patients showed evidence of pyelonephritis on renal biopsy, and in two culture of renal biopsy specimens yielded a growth of *E. coli*. The urinary infection responded to appropriate antibiotics in all these patients.

Histological Findings

The renal biopsies were reported on by Professor G. E. Edington, who summarized his findings as follows.

The findings by light microscopy in 43 renal biopsies indicated that the renal pathology of the nephrotic syndrome associated with *P. malariae* was that of a non-specific membranous glomerulonephritis with progressive glomerular sclerosis and secondary tubular changes reflecting the degree of glomerular damage. The glomerular lesions developed in a patchy fashion varying in severity from glomerulus to glomerulus and even varying within the glomerulus. There was no direct evidence of malarial aetiology in the tissue examined.

Of the 43 biopsies which showed membranous glomerulonephritis, mild lesions were seen in only four; in these the majority of the glomeruli appeared normal, a few showing tufting and thickening of the basement membrane of the capillary loops. Tubular changes were absent or slight (Fig. 3). In the remaining biopsies all gradations of glomerular damage was noted. Sclerosis of the tuft occurred, and in these glomeruli both capsular epithelium and space were prominent. Mild proliferation of the capsular epithelium was occasionally noted, but true crescent formation was never seen. Occasionally glomeruli were completely hyalinized. Periglomerular fibrosis was noted in six instances, in which there was a coincident pyelonephritis. Tubular degenerative changes (including eosinophilic granular degeneration of the proximal tubules) were marked features of the severe cases.

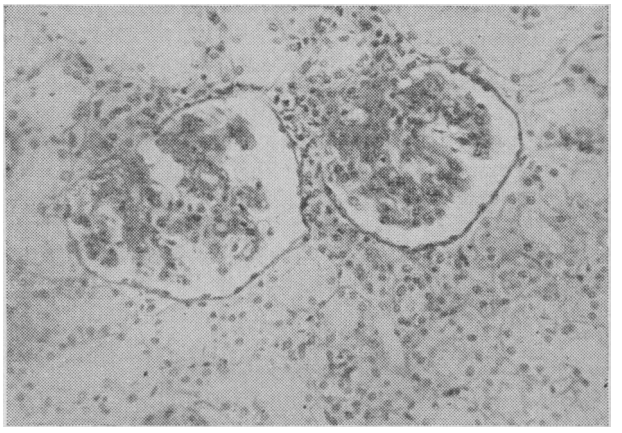

FIG. 3.—Renal biopsy. Showing tufting and thickening of the basement membrane of the capillary loops. (Periodic-acid-Schiff stain. ×160.)

TABLE I.—*Mean Biochemical Values in Nephrotic and "Normal" Nigerian Children*

Nephrotic Children	Total Serum Protein (g./100 ml.)		Serum Albumin (g./100 ml.)		Serum Globulins (g./100 ml.)								Serum Cholesterol mg./100 ml.		Blood Urea mg./100 ml.	
					α_1		α_2		β		γ					
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Group A (44)	4·46	0·60	0·64	0·30	0·34	0·03	1·00	0·14	0·73	0·11	1·71	0·34	302	15·4	18	2·14
„ B (45)	4·60	0·54	0·70	0·31	0·29	0·03	0·03	0·12	0·76	0·16	1·69	0·42	327	13·6	18	3·02
„ C (24)	4·59	0·48	0·71	0·32	0·28	0·08	1·16	0·14	0·67	0·19	1·80	0·39	302	14·2	19	2·08
"Normal" children*	6·90	—	3·20		0·30		0·80		0·90		1·70		101		13	

* J. Edozien, personal communication.

Epidemiology

In order to assess the significance of the incidence of *P. malariae* in our patients with nephrosis, the incidence of this parasite in two other groups of children in the same age range was also studied. The first group consisted of 920 children seen at University College Hospital with various illnesses other than nephrosis, none of whom had had antimalarial therapy before examination. The second was composed of 340 unselected children living in their own environment in villages close to Ibadan.

The incidence of malaria in our patients with nephrosis and in the other two groups studied is given in Table II. The high incidence of *P. malariae* in nephrotic children will be noted. (*P. ovale* was encountered in a few instances in all three groups of children as a mixed infection with *P. falciparum*. These patients are included in the *P. falciparum* column in Table II.)

TABLE II.—*Incidence of Malaria in Nephrotic and Non-nephrotic Nigerian Children (Aged 2–10 Years)*

Group	No. Examined	*P. falciparum* + *P. malariae*	*P. malariae*	Overall *P. malariae* Infection Rate	*P. falciparum*	Overall *P. falciparum* Infection Rate	No Parasites Seen
Nephrotic children ..	113	60%	28%	88%	2%	62%	10%
Non-nephrotic ill children	920	18%	6%	24%	52%	70%	24%
Unselected village children	340	12%	6%	18%	44%	56%	38%

Overall *P. malariae* infection rate:
Nephrotic/non-nephrotic ill children $\chi^2=138{\cdot}3$; n=1; P<0·001
Nephrotic/unselected village children $\chi^2=177{\cdot}1$; n=1; P<0·001
Overall *P. falciparum* infection rate:
Nephrotic/non-nephrotic ill children $\chi^2=2{\cdot}3$; n=1; P<0·1
Nephrotic/unselected village children $\chi^2=1{\cdot}03$; n=1; P<0·3

The age at onset of nephrosis in Ibadan is different from that encountered in Europe and America. A histogram (Fig. 4) illustrates the distribution on the basis of age and sex in the series of nephrotic children; it is apparent that no sex different exists. The peak age at onset, however, occurs betwen 5 and 7 years. This is in contrast to findings in Europe and America, where the peak incidence of the nephrotic syndrome occurs between 6 months and 2 years (Barnett *et al.*, 1952; Lawson *et al.*, 1960; Arneil, 1961). Three of our 113 patients were 2 years of age; none of them were younger.

This is made even clearer in Fig. 5, which illustrates the age at onset of the nephrotic syndrome in a composite American series of 425 cases (Barnett *et al.*, 1952) compared with the age of onset in Ibadan.

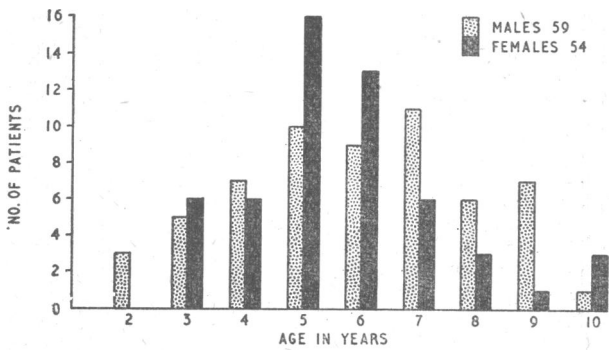

FIG. 4.—Age and sex distribution of 113 cases of nephrotic syndrome (2–10 years).

The natural history of *P. malariae* was studied during a malaria survey carried out in village communities a few miles from Ibadan. It will be seen from Fig. 6 that *P. malariae* infection is encountered very early in life; it reaches its maximum intensity between the ages of 3 and

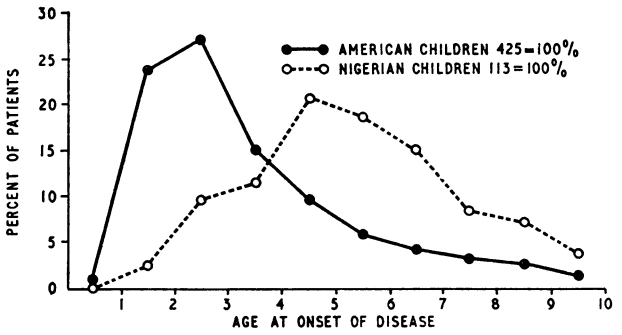

FIG. 5.—Age at onset of the nephrotic syndrome in Nigerian and American children.

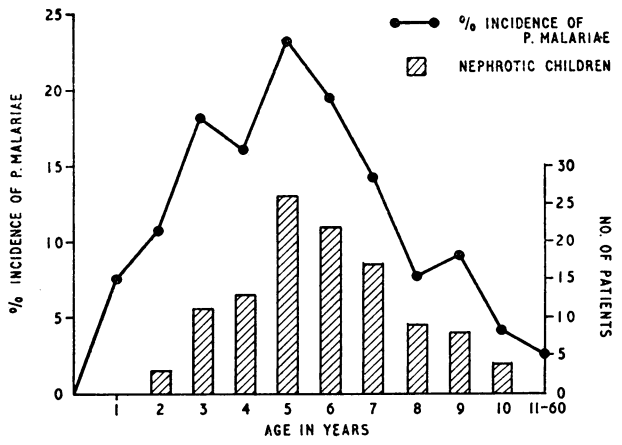

FIG. 6.—Natural history of *P. malariae* in the Ibadan area contrasted with number of cases of the nephrotic syndrome per age group in our series.

7 years, and then virtually fades out in adult life (incidence 2 to 3%). These results are similar to those obtained by Bruce-Chwatt *et al.* (1953) at Ilaro, in the forest belt of the Western Region of Nigeria. It will be noted that the age distribution of the nephrotic syndrome in Ibadan corresponds closely to the peak incidence of *P. malariae*.

Effects of Antimalarial Treatment

Ninety per cent. of the children were treated as out-patients. Children who had renal biopsies were admitted for a period of three or four days only. Irrespective of their groups all children received the following standard treatment: (1) advice on low-salt high-protein diet; (2) diuretics—chlorothiazide or hydroflumethiazide; (3) potassium supplement if indicated; (4) protein supplement of "casilan" if serum albumin level was below 1 g./100 ml.; and (5) antibiotics for the treatment of superimposed infections were used as and when indicated.

All patients were assessed at the end of a six-months period and placed into one of two categories. Those with no albumin or with less than 50 mg./100 ml. of urine were classified as "inactive." Those with persistent albuminuria were classified as "active." It was considered that a period of six months would be adequate to detect any immediate response to antimalarial therapy.

Fig. 7 shows the number of active and inactive cases in the three groups of children at the end of six months. It will be seen that we have not been able to show any immediate beneficial effect of antimalarial therapy in our groups of children. The number of inactive cases was three in group A, three in group B, and two in group C.

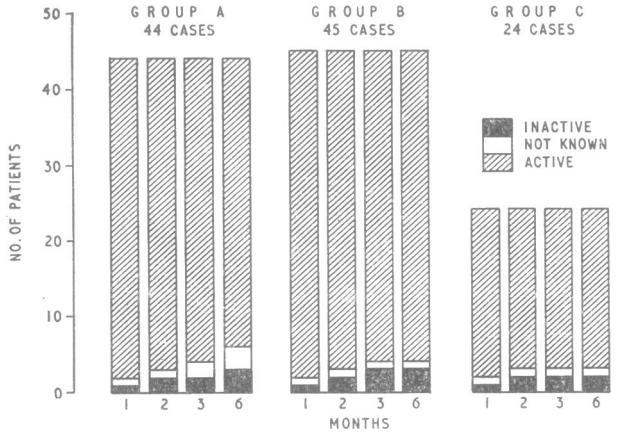

FIG. 7.—Comparative short-term effect of antimalarial and no antimalarial treatment on the course of the nephrotic syndrome.

Discussion

It is clear from the clinical and laboratory data given that we are dealing with the nephrotic syndrome in childhood as classically described (*British Medical Journal,* 1962).

There are, however, two important differences. The age at onset is much later than in Europe or America, and the condition is closely associated with infection by *P. malariae.* Moreover, the peak incidence of *P. malariae* and the peak age at onset in our patients with nephrotic syndrome are the same.

Few will disagree with Leather (1960) when he remarks that it is not surprising that malaria and "nephritis" should coexist in tropical countries. What is surprising and noteworthy, however, is that *P. malariae* as a particular species should be so closely associated with the nephrotic syndrome when it is not the predominant malaria parasite. Thus in Western Nigeria the incidence of *P. falciparum* in unselected village children of 2–10 years of age varies from 64% to 85%, and that of *P. malariae* from 15% to 25% (Bruce-Chwatt *et al.,* 1953). Yet in our series of nephrotic children the incidence of *P. falciparum* was unchanged while that of *P. malariae* was four times higher than normal.

A second point of interest emerges from a comparison of the number of children with the nephrotic syndrome in Ibadan and elsewhere. We encounter 50 cases of the nephrotic syndrome yearly in one of the two hospitals in the city. In Durban, where *P. malariae* does not exist, fewer than 12 cases were observed over an 18-months period among all children attending the three largest general hospitals, one of which has a turnover of African children thrice that of University College Hospital, Ibadan (F. Walt, 1960, personal communication; P. Klenerman, 1960, personal communication). Similarly in a series from Glasgow, where there are about 500,000 children at risk, the average yearly number of admissions with nephrosis was 10 (Arneil, 1961). In Uganda the data available are at present conflicting. Trowell (1960) states that his colleagues at Mulago Hospital are doubtful of the existence of "malarial nephritis," and that there is little quartan malaria in children around Kampala. Musoke (1961), in an analysis of admissions to the paediatric division of the same hospital in 1959, reviews 181 cases of clinical malaria and states that in his series malignant tertian has been almost the only parasite recorded; moreover, very few cases of nephrosis are included in his yearly analysis. Recently, however, Patricia Jelliffe and Price (1962) reported a high incidence of quartan malaria in Uganda children, found both in a rural survey and in the wards of Mulago Hospital. If these results are substantiated a reason must be sought for the apparent different in the incidence of the nephrotic syndrome in children in Kampala compared with Ibadan.

Perhaps the most convincing epidemiological evidence in favour of the aetiological role of *P. malariae* in the nephrotic syndrome in children comes from British Guiana. Giglioli (1962a) demonstrated that since the eradication of malaria the nephrotic syndrome, previously common, had become a rare condition. Moreover, he has been able to follow patients presenting with an uncomplicated and mild quartan malaria attack to quartan malaria with intermittent albuminuria, to quartan malaria with persistent albuminuria, and thence to established nephrosis (Giglioli, 1962b). In Freetown, Sierra Leone, where malaria has been brought under control, the nephrotic syndrome is rare, although in other respects the paediatric problems resemble those of Ibadan (Carter, 1961).

It has been claimed by several authors that antimalarial therapy produces a dramatic effect in the nephrotic syndrome associated with *P. malariae* (Manson-Bahr and Maybury, 1927; James, 1939; Sarrouy-Portier, 1939; Boyd, 1940; Keitel *et al.,* 1956). We have been unable to confirm these claims.

There are two mechanisms that might explain this association between the nephrotic syndrome and *P. malariae. P. malariae* may cause the nephrotic lesion by direct action; against this hypothesis is the absence of malaria parasites in biopsy material and the poor response to antimalarial therapy. An alternative hypothesis, and the most likely one in our view, is that in some individuals repeated untreated attacks of infection with *P. malariae* sensitize the kidney, which produces an auto-antibody. Thus it is possible that some children in their attempt to suppress the infection overact and produce, as well as normal gamma-globulin, an antigen/gamma-globulin complex which has an affinity for the glomerular basement membrane (Lovell Becker, 1961). When antibody titres to *P. malariae* can be measured it may well be found that they are significantly higher in nephrotic children with *P. malariae* than in children equally parasitized but not suffering from nephrosis. The late age at onset of the nephrotic syndrome in Ibadan could be explained by the relatively poor antigenicity of the malaria parasite (Cohen *et al.,* 1961). A therapeutic trial under the direction of one of us (R. G. H.) is now in progress on a new series of patients to assess the relative merits of prolonged steroid administration together with radical cure of quartan malaria.

Summary

A high incidence of the "nephrotic syndrome" has been observed in children attending University College Hospital, Ibadan.

We investigated the possible aetiological role of *P. malariae* by examining three groups of Nigerian children. One group consisted of children with the nephrotic syndrome, another group consisted of children with various illnesses other than nephrosis, and the third group were unselected village children. The incidence of *P. malariae* in the nephrotic children was four times higher than in the

other two groups. These epidemiological findings indicate a definite relationship between the nephrotic syndrome in Nigerian children and infection with *P. malariae*.

The clinical, biochemical, and histological features are similar to those classically described in childhood, with two important differences: (1) the age at onset is much later than in Europe or America, and (2) the condition is closely associated with infection by *P. malariae*.

We have been unable to confirm the dramatic results with antimalarial treatment reported by others.

The possible mechanisms of production of "malarial nephrosis" are discussed.

We should like to express our thanks to Dr. K. Cobban, Professor J. Edozien, and Professor P. Collard for their help. We are grateful to Professor B. G. Maegraith for advice and encouragement, and to Professor A. Brown for his interest in the investigation.

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PENDRED'S SYNDROME IN TWO FAMILIES LIVING IN ENDEMIC GOITRE AREA

BY

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The aetiological relationship between endemic cretinism and endemic goitre is still greatly debated. The main features of endemic cretinism are retarded physical growth, retarded mental development, severe deafness leading to mutism, usually a goitre bearing no relationship to the severity of the condition, and various degrees of hypothyroidism, in persons living in an endemic goitre area. The hypothyroidism has been challenged by some—for example, Costa (1957). On the one hand, there are those who hold the view of a causal relationship between the two entities, while others doubt the existence of such a relationship.

In recent reviews of the subject, Trotter (1960) favours the view that "endemic cretinism (and the deafness which often accompanies it) is in the main the result of environmental rather than genetic factors," while Clements (1960) doubts "the possibility that persons suffering from endemic goitre are more likely to produce cretins, deaf-mutes and mental defectives than persons living in a goitre-free area." Clements suggests the possibility of a genetic basis for endemic cretinism. Both authors, along with others, have urged the use of modern diagnostic evaluations of thyroid function in the hope of elucidating some, if not all, of the problems of this controversy. Bastenie *et al.* (1962), studying the endemic cretins of the Uele region of the Congo, were of the opinion that severe iodine deficiency plays a major part in the pathogenesis of those cretins who had clinical and biological evidence of hypothyroidism without thyroid antibodies or evidence of a major enzymatic defect in thyroid hormone synthesis. They had a lower ^{131}I uptake than other goitrous Congolese and little response to exogenous T.S.H. Other genetic and environmental factors that may play a part in the thyroid lesions were not dismissed.

Taking the lead from Stanbury and Querido (1957) that "even though endemic cretinism may have been completely defined in one locale, the situation may be completely different in the next valley," we studied the children of two families living in an endemic area who were deaf-mute, hypothyroid, and goitrous—typical findings in endemic cretinism—in order to investigate the relationship between the two conditions of endemic goitre and endemic cretinism.

Family A

Case 1.—A boy aged 5 was seen in the out-patient department of the American University Hospital because of deaf-mutism. He was born at full term after a normal pregnancy. At birth a swelling was noted in the neck—in the midline and to the left. A physician prescribed drops of undetermined nature. The swelling gradually became smaller and localized to the midline, but it never disappeared. The parents think that when very young he probably could hear, but he never developed any speech and at present he hears very little. He was slow in developing physically and to a lesser degree mentally. His mother noted that his skin was dry and scaly, that he was sensitive to cold, and that he was not constipated. He had had no major illness. On physical examination he had the typical hypothyroid facies with myxoedema. He was short (96 cm.) but of average weight (19 kg.). The skin was cool, particularly over the extremities, dry, and scaly. The abdomen was protuberant, and he had an umbilical as well as an inguinal hernia. The thyroid gland was diffusely enlarged, soft in consistency, and had no nodules. The ear-drums appeared normal. The P.B.I. was 1.5 μg./100 ml. *X*-ray studies revealed a delayed bone age and epiphysial dysgenesis of the capital femoral epiphyses.