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.

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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 ¹³¹I uptake than other goitrous Congolese and little response to exogenous T.S.H. Other genetic and environ-

mental 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 epiphyseal dysgenesis of the capital femoral epiphyses.

Case 2.—A girl aged 3, sister of Case 1, was seen in the out-patient department of the American University Hospital because of decreased hearing of two years' duration. She was born at full term of a normal pregnancy. During the first year of life the parents thought she could hear, and she learned to say "mama" and "dada." Some time after her first birthday they noticed that her hearing decreased gradually and her speech did not develop beyond a few words acquired previously. She had no serious illness. Her physical development was slow, but the parents thought her mental development not too retarded. She had no constipation, dry skin, or intolerance to cold. On physical examination she had a hypothyroid facies. She was short (88 cm.) and overweight (16.4 kg.). The skin was dry. She had a protuberant abdomen and an umbilical hernia. The thyroid gland was diffusely enlarged, soft in consistency, and not nodular. The ear-drums appeared normal. The P.B.I. was 0.7 $\mu\text{g.}/100\text{ ml.}$ The bone age was retarded.

Family History.—The father and the mother were well and had no deaf-mutism. There was no history of consanguinity. No history of deaf-mutism or hypothyroidism on either side of the family could be elicited. The mother had a rather large diffuse non-nodular goitre, but she was euthyroid clinically. The father had no goitre. A sister aged 9½ had a palpable thyroid gland; a brother, 6½ years old, had a goitre. Both children were clinically euthyroid. An 8-months-old brother had no goitre and had a normal P.B.I. Dr. Ian Forbes tested the serum of the mother and found no thyroid cytotoxic antibodies or antibodies by the tanned-cell haemagglutination and complement-fixation tests.

Family B

Case 3.—A girl aged 5 was seen in the out-patient department of the American University Hospital because of deaf-mutism. She was born at full term of a normal pregnancy. At the age of 4 months her cry was noted to be poor. Her feeding became slow. She was cold to touch and was listless. Gradually her face became puffy and she slept most of the time, crying very little. At the age of 11 months a physician diagnosed hypothyroidism and started treatment with thyroid extract, which was followed by a remarkable improvement. The parents do not think that she ever was able to hear, and she only learned to say "mama" and "papa." The only serious illness she had had was a febrile episode at the age of 11 months diagnosed clinically as typhoid fever and treated successfully with chloramphenicol. The child, though slow for her age, was not regarded as mentally retarded by her parents. When first seen she was on 3 gr. (0.2 g.) of thyroid extract daily. On physical examination she was euthyroid and the thyroid gland was not palpable. The ear-drums appeared normal. She was slightly short (105 cm.) but of average weight (18 kg.). Three weeks after discontinuing thyroid therapy she became sluggish and anorexic. Her face became puffy and pale. When examined eight weeks after cessation of treatment she had gained 1.5 kg. in weight and looked puffy. The thyroid gland was definitely enlarged, soft in consistency, but not nodular. The P.B.I. was 2.2 $\mu\text{g.}/100\text{ ml.}$

Case 4.—A boy aged 3, brother of Case 3, was seen in the out-patient department of the American University Hospital because of a mass in the neck since birth. He was born at full term of a normal pregnancy. At birth a mass was noted in the midline of the neck. It had been growing proportionally to his general growth. The child was thought to be both physically and mentally retarded. He was described as highly strung and nervous, as prone to head-banging and easy irritability. He had no intolerance to cold, constipation, or lethargy. The parents thought he had some hearing. On physical examination he was slightly short (90 cm.) but of average weight (13.5 kg.). The thyroid gland was diffusely enlarged, soft in consistency, and not nodular. He had no stigmata of hypothyroidism. The ear-drums appeared normal. The bone age was not retarded. A skull x-ray showed nothing abnormal.

Family History.—The father and mother were well and had no deaf-mutism or goitre. They were first cousins. Two siblings were reported to be normal, but were not examined. The

paternal aunt, despite the absence of any evidence of consanguinity in her marriage, had a deaf-mute son and another son who had a goitre, decreased hearing, and slurred speech.

Investigation with Radioiodine

Cases 1, 2, 3, and 4, the two siblings of Cases 1 and 2, and 30 other goitrous children who formed part of an investigation of goitre in the Lebanon and who were clinically euthyroid and had no deaf-mutism, were each given between 15 and 30 $\mu\text{c.}$ of ^{131}I by mouth. Three to four hours* after the oral dose of ^{131}I counts were recorded over the thyroid area using a 1-in. (2.5 cm.) collimated NaI scintillation crystal at a distance of 40 cm. from the skin in front of the thyroid gland. Then 1.5 to 2 g. of potassium thiocyanate was given by mouth. Counts over the thyroid area were recorded again 15, 30, and/or 45 minutes, and in the four cases reported and their siblings 60 minutes, after the ingestion of the thiocyanate. These epithyroid counts were expressed as a percentage of the count over the thyroid recorded immediately before thiocyanate administration. The results are shown in Fig. 1.

FIG. 1.—Potassium thiocyanate test.

The four children with Pendred's syndrome discharged iodine, but their siblings and the other 30 goitrous children did not. This discharge of radioactivity is similar to the findings of Morgans and Trotter (1958) and of Fraser *et al.* (1960) in their study of Pendred's syndrome. Case 2, however, showed a relatively smaller discharge of radioactivity. It was definitely greater than that of her two siblings and similar to only one of the 30 goitrous children. This probably could be accounted for by the prolonged interval between giving the radioiodine and the potassium thiocyanate. In Pendred's syndrome the enzymatic defect is relative rather than absolute. Larger quantities of ^{131}I could have been oxidized in 72 hours, as compared with three to four hours after the oral dose was taken.

Other Investigations

Otology.—Audiograms of the four cases described showed severe impairment of hearing, especially in the higher frequencies. The siblings of Cases 1 and 2 who did not have a defect in iodine-binding as measured by thiocyanate administration had normal hearing (Fig. 2). As mentioned above, there was no evidence of middle-ear disease in any of the children. These otological findings are similar to those of Fraser *et al.* (1960) in persons with Pendred's syndrome.

Assessment of Mental Development.—No formal intelligence tests were done. All four children had slow motor development and all were mentally retarded. Case

*The same procedure was followed in Case 2 except for giving the potassium thiocyanate 72 hours after the dose of radioiodine.

4 was the most severely affected, while Case 3 was the least severely affected and could be regarded as a dull normal child.

FIG. 2.—Audiograms.

Discussion

Goitre is endemic in Lebanon (Matovinovic, 1961; Interdepartmental Committee on Nutrition for National Defense, 1962). Cases of goitre with deaf-mutism, retarded linear growth, and mental retardation in such a country would be regarded as "endemic cretins," a sequel of endemic goitre. The cases forming the subject of this report demonstrate that this assumption does not always hold true. On the basis of radioiodine, otological, and genetic studies, these cases belong to the well-defined entity of Pendred's syndrome (Fraser *et al.*, 1960), a syndrome consisting of perceptive deafness and goitre, with or without hypothyroidism and inherited as a simple recessive trait. The main feature of the thyroid abnormality is a decreased rate of oxidation of the trapped iodine. All four cases described had perceptive deafness, all had a defect in organic binding of iodine by the thyroid gland as demonstrated by thiocyanate administration, and the genetic distribution in the two families was suggestive of a simple recessive trait. The rest of the goitrous population examined did not belong to this entity; in fact, 30 goitrous children and, of greater interest, the two goitrous siblings of Cases 1 and 2 did not have the defect of Pendred's syndrome. Deaf-mutism is rare among this particular goitrous population (Matovinovic, 1961). Preliminary studies suggest environmental factors as the cause of goitre in this population, mainly iodine deficiency (Najjar *et al.*, unpublished observations).

Although the number of cases is small it is apparent that, at least in Lebanon, a country where goitre is endemic, deaf-mutism with hypothyroidism may not be aetiologically related to endemic goitre. Genetic factors rather than iodine deficiency may be responsible for the symptom-complex that has been referred to as "endemic cretinism."

Summary and Conclusion

Four children with Pendred's syndrome belonging to two families residing in an endemic-goitre area are described.

Persons with deaf-mutism, goitre, and hypothyroidism who reside in a goitrous area, classically "endemic cretins," need not be the victims of the same aetiological factors responsible for the endemicity of the goitre, but may have genetic defects in their iodine metabolism.

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Preliminary Communications

Potential Dangers of Morphine in Acute Diverticulitis of the Colon

Recent events have focused attention on the tragedies that may follow the use of newly discovered drugs whose properties are incompletely understood, but it should be remembered that other drugs which have been in widespread use for many years may have unsuspected side-effects. Morphine is the drug most often prescribed for the relief of severe pain, but it is possible that its beneficial analgesic action masks its other actions, some of which may be disadvantageous in certain circumstances.

During the course of investigations into the intraluminal pressures in the human sigmoid colon, both in health and in diverticulosis coli, the opportunity was taken to study the effect of morphine and other drugs on these pressures. The detailed results of these researches will be published elsewhere (Painter and Truelove, 1963; Painter *et al.*, 1963), but we feel that a brief résumé of certain of our findings is worth presentation in a general medical journal, as they appear to veto the use of morphine as an analgesic in acute diverticulitis.

METHOD OF INVESTIGATION

The intrasigmoid pressure patterns were recorded by means of water-filled open-ended "polythene" tubes introduced into the sigmoid colon through a sigmoidoscope, which was then withdrawn. The metal tips of these tubes were located radiologically. When patients with diverticulosis were being studied the relationship of these tips to the actual diverticula was ascertained, either by simultaneous cineradiography or by comparison with the relevant barium enema. The polythene tubes transmitted the intrasigmoid pressures to photoelectric pressure transducers. The resulting electrical signal was amplified by a Cambridge multi-channel recorder whose direct pen-writer registered the pressures on squared paper which moved at a set speed. Thus a permanent record of the intrasigmoid pressure patterns was obtained that could be studied at leisure. Patients were investigated for at least an hour under basal conditions—that is, at rest on a bed and abstaining from food and tobacco—and the resulting pressure tracing was called the "resting pattern of pressures." Morphine 1/6 gr. (11 mg.) was then given and the "post-morphine pattern of pressures" recorded for a further hour.