Discussion

The nephrotic syndrome in children is a fluctuating condition. It is characterized by episodes of exacerbation of proteinuria and oedema. Some children remit spontaneously, losing oedema and proteinuria permanently. Others continue to pass protein, without impairment of renal function, for long periods. A small proportion die of renal and cardiac failure or other causes. Absence of proteinuria for many months does not preclude a relapse. This makes it impossible to evaluate the results of treatment over short periods.

In two of our cases moderate doses of cortisone and prednisone did not affect the proteinuria, while a course of prednisolone produced a marked reduction. As Arneil (1956) and Lennard-Jones (1957) have also shown, prednisolone is the only form of treatment that consistently reduces or abolishes proteinuria in children. Proteinuria may recur many months after successful prednisolone treatment—as occurred in two of our children; however, these children responded to a further course. It is suggested that prolonged treatment with small doses of prednisolone—for example, 5 mg. on alternate days—may prevent relapse.

Summary

Six cases of the nephrotic syndrome in children have been treated with large doses of prednisolone and followed for periods of up to 18 months. Five cases lost their proteinuria, and three of these are protein-free at 6, 15, and 18 months after treatment. Two developed proteinuria and oedema after 3 and 15 months. Both were treated again with a course of prednisolone, with disappearance of oedema and reduction in proteinuria. One further case has continued to pass a decreased amount of protein, which was further decreased after another course of prednisolone.

ADDENDUM, August, 1958.—Since October, 1957, three of ten children—D. C., S. T., and T. J.—have had no relapses. P. M. and L. L., when last seen, some months ago, were also well. K. G. has had two more relapses; each has responded to further short courses of prednisolone (0.5 g. in two weeks). Two other cases have been treated and followed up for nine and six months respectively. Each responded to the initial course, and was kept on a maintenance dose. One of these had to be readmitted six months after his initial course, but responded to a short course of prednisolone (0.5 g. in two weeks). The latter remains well, but continues to have proteinuria, despite maintenance therapy.

Our thanks are due to Dr. J. Forest Smith, Dr. H. K. Goadby, and Dr. B. D. R. Wilson for allowing us access to their cases and for their encouragement, and to Dr. W. J. Griffiths for chemical studies. We are grateful to the sisters and nursing staff of the children's wards of St. Thomas's Hospital, St. Peter's Hospital, Chertsey, and St. Andrew's Hospital, Bow, for their help.

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The Public Health (Preservatives, etc., in Food) Regulations, 1925–1953, permit the importation of citrus fruit in wrappers impregnated with diphenyl to the extent of not more than 40 mg. per 100 sq. in. Exporting countries now employ other methods of preservation—for example, the impregnation of the container with diphenyl or the inclusion of impregnated pads or spacers in the container—and the regulations have been amended to permit the importation and sale of citrus fruit which contains diphenyl or orthophenylphenol or admixtures of the two substances within prescribed limits.

D

EXOPHTHALMOS IN CUSHING'S SYNDROME

BY

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Cushing (1932), in his original description of the syndrome that now bears his name, recorded several instances of mild-to-moderate exophthalmos. Subsequent reports have confirmed this finding. Although there does not appear to be any example of severe exophthalmos, some degree of proptosis was found in 8% of 189 patients with Cushing's syndrome reviewed by Plotz *et al.* (1952).

The following case appears worthy of record because of the unusual course of the disease in which the appearance of malignant exophthalmos preceded the evolution of severe Cushing's syndrome.

Case History

A woman of 39 was admitted to the London Hospital on July 11, 1956. She had been agitated and depressed for the six weeks before admission, and for the previous three days had been very excitable, unable to converse intelligently, and was quoting odd phrases from the Bible.

Her ankles had been swollen four weeks before admission, the oedema being dispersed by acetazolamide. Her eyes had been slightly prominent for as long as her relatives could remember, but for the previous 18 months they had been sore and watering, although no increase in prominence had been noted.

On examination she was found to be obviously psychotic. Bilateral proptosis was present in marked degree, with severe conjunctivitis and slight ptosis on the right. Thyrotoxicosis was looked for particularly, but no sign other than her exophthalmos was found. A provisional diagnosis of an intracranial tumour was made.

During the first night in hospital she made an attempt at suicide by cutting her wrists with pieces of a broken spectacle lens. Consequently on July 13 she was transferred to Warley Hospital, where she was found to be mentally inaccessible, with delusions and hallucinations. Physical examination revealed obesity and male distribution of body hair, together with a severe proptosis. Her blood pressure was 120/90.

By July 16 her exophthalmos had increased to such an extent that orbital decompression was considered. Two days later electric convulsion therapy was started and a course of seven electroplexies completed on July 27. A considerable improvement in her mental condition had occurred and her exophthalmos had diminished.

On August 16 her mental condition relapsed, her eyes became more prominent, but a further course of seven electroplexies improved her condition. Up to this time menstruation had been normal, but she then developed amenorrhoea, which persisted until December. On September 3 her blood pressure was 180/130. Another relapse necessitated a further course of electric convulsion therapy, but by October 21 she had so improved that she could be discharged. She was then referred to one of us (A. S. M.), and on this occasion volunteered the fact that she thought her face was changing and that some fat was

collecting over her shoulder girdle. On examination her face was fat and heavy, with a faint hairy down over her chin. Her scalp hair was thin. Bilateral severe exophthalmos was present. There was no ophthalmoplegia. Her skin was rather dry, and her blood pressure was 170/125.

At that time she did not exhibit the habitus of Cushing's syndrome, and her general appearance and skin texture were suggestive of myxoedema. Thyroid extract, in a dose

FIG. 1

of 3 gr. (0.2 g.) daily, was therefore started on September 20. On the 26th her exophthalmos was thought to be rather worse, but did not progress subsequently.

However, by November 1 a rounded face, fat around the neck, and a decrease in the bulk of the limb muscles became apparent. Stilboestrol in a dose of 2 mg. daily was started. At that time the 17-ketosteroid excretion was 14.1 mg./24 hours, and the skull did not show any radiological abnormality.

On January 30, 1957, she was admitted to New End Hospital for further investigation. Gross bilateral exophthalmos was still present with chemosis and conjunctivitis, though the retro-orbital

FIG. 2

tension was not unduly raised (Figs. 1 and 2). Eye movements were full. She remained obese, with a rounded face, supraclavicular pads of fat, and a "buffalo hump." Her extremities were relatively thin (Fig. 3). Pitting oedema of the ankles was present.

Her blood pressure was 175/120 at rest in bed. Two months previously the diagnosis had been problematic, but the subsequent rapid change in her appearance left no doubt that the diagnosis was Cushing's syndrome.

Investigations.—Hb, 103%; total W.B.C. 14,000/c.mm.; E.S.R., 12 mm. in one hour (Westergren); total serum proteins, 5.8 g./100 ml. (albumin 3.9 g., globulin 1.9 g.); serum sodium 156 mEq/l.; potassium, 5 mEq/l.; bicarbonate, 29 mEq/l.; chlorides, 95 mEq/l.; cholesterol, 225 mg./100 ml.; 17-ketosteroids (Medical Research Council, 1951), 7.7 mg./24 hours; 17-hydroxycorticoids (Appleby *et al.*, 1955), 38.2 mg./24 hours, and by the method of Reddy (1954) 21.4 mg./24 hours. Glucose-tolerance test (50 g. of glucose given orally): fasting blood sugar, 95 mg./

100 ml.; 30 minutes, 123 mg.; 60 minutes, 180 mg.; 90 minutes, 200 mg.; 120 minutes, 205 mg.; 150 minutes, 198 mg. X-ray examination of lumbar spine showed moderate osteoporosis and multiple disk lesions.

On February 6 she began menstruating. Nine days later, crops of petechiae appeared over her right breast, right arm, and right side of her back. Her blood pressure in bed and at rest was constantly in the region of 180/130.

Further Investigations.—Hess test positive. Platelets, 204,000/c.mm.; clotting-time (Lee-White), 3½ minutes; bleeding-time, 4½ minutes; 17-ketosteroids (M.R.C., 1951), 12.9 mg./24 hours; 17-hydroxycorticoids (Appleby *et al.*, 1955), 66.1 mg./24 hours, and by the method of Reddy (1954) 34.9 mg./24 hours.

While these investigations were being completed her mental state did not give rise to anxiety, and she appeared to be a calm and composed patient. On February 16, during the early hours of the morning, she jumped from a bathroom window to the street, two stories below. She died a few minutes later.

The cause of death was found at necropsy (Dr. F. Camps) to be due to a ruptured aorta. The endocrine glands all appeared to be of normal size. Dr. A. B. Bratton gave the following histological report. "Hyaline changes in numerous basophil cells in the anterior lobe of the pituitary correspond to those described by Crooke (1935). Slight hyperplasia of the adrenal cortex is present. There are numerous corpora fibrosa and a few cystic follicles in a slightly fibrotic ovary. One small microfollicular adenoma of the thyroid, otherwise normal thyroid tissue. The myocardium of the left ventricle is hypertrophied."

Discussion

The salient point in the natural history of this patient was the rapid progression of the signs of Cushing's syndrome after a period of 30 weeks in which the picture was that of a malignant exophthalmos and an episodic mental state consisting of an agitated depression. There was no evidence of thyroid dysfunction. The exophthalmos varied *pari passu* with the psychotic episodes, but did not become pronounced again as the adrenal disorder became obvious and progressive. The tragic end to this case again emphasizes the great care needed although mental disturbance is not obvious.

The occurrence of mental changes as a part of Cushing's syndrome is well known (Schlezinger and Horwitz, 1940; Spillane, 1951; Plotz *et al.*, 1952; Trethowan and Cobb, 1952). Starr (1952), in a series of 53 cases, observed that depression was the most frequent finding. The suicide rate of the series was 1,000 times that of the general population.

The pathological physiology of exophthalmos has been discussed extensively (Greene, 1955), but as yet there is no full explanation. All the evidence points to a pituitary-thyroid relationship. Apparent exophthalmos has been produced in the experimental animal by the administration of cortisone (Aterman, 1952; Aterman and Greenberg, 1953, 1954), and it might be possible to extrapolate such work to explain the findings in our case. However, another

FIG. 3

explanation has been offered by Boas and Scow (1954) for these results. They considered that the apparent exophthalmos was due to retarded body growth induced by cortisone. Essex (1955) also held the view that body growth is retarded by cortisone, while the eye, as an ectodermal structure, was little affected. Wyn Williams (1955) found that this cortisone-induced exophthalmos could be produced only in the growing animal. Moreover, it has been suggested that systemic cortisone might improve exophthalmos, and, although this was not borne out in a trial carried out under the auspices of the Medical Research Council (1955), no case was made worse by such treatment.

Although no definite mechanism can be implicated, the natural history of this case, with exophthalmos preceding the other signs of Cushing's syndrome, would suggest that the primary disturbance was hypothalamic or pituitary rather than adrenal.

Summary

A case of Cushing's syndrome with mental disturbance and malignant exophthalmos is described. A possible mechanism of the exophthalmos is discussed. It is suggested that the primary lesion of Cushing's syndrome was in the hypothalamus or pituitary rather than the adrenal glands.

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RENAL FAILURE DUE TO PARA-AMINOSALICYLIC ACID

BY

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Drug allergy has been said to have ousted syphilis in recent years as "the great imitator." Florid cases of allergic reactions to para-aminosalicylic acid (P.A.S.) have often been reported, but associated renal involvement has been uncommon and usually confined to patients who also had hepatitis. Accounts of allergic reactions to P.A.S. with renal failure and jaundice are given by Cuthbert (1950), Livingstone and Street (1950), Jeffrey *et al.* (1952), and Mann (1953). Two papers have also described renal failure in patients having allergic reactions to P.A.S. without jaundice, but in the earlier case (Le Melletier and Gerphagnon, 1950), the patient was already almost moribund with tuberculosis. In the other paper, Silverman *et al.* (1956) report a case of "toxic nephritis" without clinical but with biochemical evidence of hepatic damage. The following account is therefore the first authentic report of a case of renal failure due to P.A.S. without hepatitis.

Case Report

An Irishman of 31 was first found to be suffering from pulmonary tuberculosis, with a positive sputum, in April, 1956. In August, he was admitted to hospital, where he was given 1 g. of streptomycin daily with calcium B-P.A.S., 3.5 g. t.i.d., and isoniazid, 100 mg. t.i.d., for 83 days.

He was transferred to Colindale Hospital on October 30. On admission he was a healthy-looking man with a symptomless goitre. There was no clinical evidence of thyrotoxicosis. His temperature was 98.4° F. (36.9° C.), pulse 84, blood pressure 130/80. No abnormal physical signs were found in the chest or any other system. X-ray examination revealed bilateral apical pulmonary tuberculosis without cavitation. Sputum was negative for acid-fast bacilli on smear and culture. The E.S.R. (Westergren) was 3 mm. in one hour. The urine was found to contain sugar. Fasting blood sugar was 110 mg./100 ml. The glucose-tolerance curve was within normal limits. The blood count was normal; Hb, 106%.

There was no family history of asthma or other allergic conditions. His mother had a goitre. The patient did not remember ever having had a drug reaction. He had never had asthma or other manifestations of allergy.

On November 3 the patient started streptomycin, 1 g. three times a week, with daily sodium P.A.S. 12 g., and isoniazid 300 mg. by mouth. He made satisfactory progress until December 8 and 9, when the evening temperature was 99° F. (37.2° C.), and on December 10 it rose to 101.6° F. (38.7° C.). An injection of penicillin was given. Next morning a pink macular rash was noticed. The posterior cervical glands were enlarged, firm, and discrete, but not painful or tender. The patient was thought to be suffering from rubella. The evening temperature on December 11 was 103° F. (39.4° C.). Although no complaint of sore throat had been made the fauces were reddened. P.A.S. and isoniazid were continued, and streptomycin, P.A.S., and isoniazid were given the next day, December 12, as usual. That evening the temperature rose to 103.2° F. (39.5° C.) with enlargement of glands in the anterior triangles of the neck. Another injection of penicillin was given.

On December 13 the possibility of drug hypersensitivity was considered, and penicillin, streptomycin, P.A.S., and isoniazid were discontinued. A course of diphenhydramine hydrochloride was started. The same evening the temperature fell to 100° F. (37.8° C.), and by the evening of the 14th it was normal and remained so for over 36 hours, but the rash had become red and blotchy with considerable pruritus, and glands could be felt in the axillae and groins. The conjunctivae were suffused. The blood count remained normal. The Wassermann reaction was negative. No glandular fever cells were seen in the blood then or at any time. The Paul-Bunnell test and all other agglutination reactions were negative.

On December 16 and 17, while he was still on diphenhydramine hydrochloride, the temperature rose again to 99° and 102.2° F. (37.2 and 39° C.) respectively, and the drug was therefore discontinued.

On December 19 there was an evening pyrexia of 105° F. (40.6° C.) with a fresh crop of glands in the post-auricular regions, and the spleen was found to be palpable. One dose of chlortetracycline was given that night, but the drug was discontinued owing to vomiting. Although the rash gradually faded without desquamation, the urine became scanty and highly coloured. It contained sugar and a trace of albumin.

Another spike of pyrexia—101.4° F. (38.6° C.)—occurred on December 23 with a transient erythematous rash on the trunk. The general condition remained good, but the patient was still vomiting, and only 2 oz. (57 ml.) of urine had been passed in the previous 24 hours. This was solid with albumin and contained leucocytes, erythrocytes, and hyaline and granular casts. Culture was sterile. The blood urea was