Lyndiol at a dose of one to six tablets daily brought a clinical remission in 9 out of 42 patients when the drug was continued for two months or more. The smallest dose (the contraceptive dose) seems to produce a similar response to the larger dose, with the advantage of a much smaller incidence of liver damage, as judged by S.G.O.T. levels. The progestin component given alone caused a remission in one of the seven cases investigated. The oestrogen component given alone brought no remission in the four cases treated. This would suggest possible synergism between the components (as noted by Huggins in experimental animals), but these findings are not statistically significant.

The mode of action of such a progestin-oestrogen combination in the control of breast cancer growth is speculative. The oestrogen-dependent theory to explain hormonal control in breast cancer is outmoded, and it has been suggested that, once established, the tumour is pituitary-dependent. Oestrogen therapy and androgen therapy probably suppress the prolactin or gonadotrophin (luteinizing and/or follicle-stimulating hormone) secretion of the anterior pituitary (Stoll, 1958). The observation that oral contraceptives decrease the urinary excretion of luteinizing hormone (Brown *et al.*, 1964) suggests that these agents act as contraceptives by suppressing the synthesis or the release of pituitary luteinizing hormone (Diczfalusy, 1965). Their action in breast cancer may be similar.

It is essential that the incidence of breast and genital cancer developing in women receiving oestrogens and progestins be studied intensively. This applies more particularly now, because of the widespread use of oral contraceptives. If an analogy with experimental mammary cancer is permissible, then the incidence of breast cancer developing in pre-menopausal women may be reduced (Stoll, 1965). This present report, based as it is upon the treatment of post-menopausal females, provides no relevant information in this respect. However, this report supports the suggestion that the use of oestrogen-progestin mixtures, after the menopause, may well reduce the rate of development of breast cancer in some women (Wilson, 1962).

Summary

A series of 65 post-menopausal females with soft-tissue manifestations of advanced breast cancer were treated with Lyndiol, an oral contraceptive containing a synthetic progestin of the 19-norsteroid group, combined with the oestrogen mestranol. At the contraceptive dose level of one tablet daily, almost complete regression of tumour growth for some months was noted in 4 out of 21 cases, and with larger doses of three to six tablets daily, in 5 out of 21 other cases. The proportion of remissions is therefore similar at both dose levels, but the likelihood of liver damage is greatly increased at the higher dose levels. Liver damage seems more likely to be due to the progestin than to the oestrogen component.

There appears to be no correlation between the likelihood of response to Lyndiol and a history of previous response to oestrogen or androgen administration. Of nine patients responding to Lyndiol, five had previously received and failed to respond to oestrogen or androgen therapy.

However, the post-menopausal patient with a persistent intermediate picture in the vaginal smear shows a significantly greater likelihood of responding to Lyndiol than the patient with an atrophic smear. Such a relation has not been established by me either for oestrogen or for androgen therapy.

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Medical Memoranda

Thrombosis of the Pulmonary Arteries and the Nephrotic Syndrome

Brit. med. J., 1967, 1, 153-154

Gootman *et al.* (1964) reported thrombosis of the pulmonary arteries occurring in two patients with nephrosis who were treated with prednisone and chlorothiazide. This is the first time that such an association has been found. Subsequently, on reviewing 75 cases of primary renal disease in children, Symchych and Perrin (1965) found three instances of this association in children who had been treated with corticosteroids. We wish to record a further example of a child with the nephrotic syndrome who died as a result of extensive thrombosis of the pulmonary arteries while receiving corticosteroids and spironolactone.

CASE REPORT

A Bantu boy aged 3 years 9 months was admitted to hospital on 31 March 1964 with a history of swelling of the body and face, cough, and anorexia of two weeks' duration.

On examination his temperature was 101° F. (38.3° C.), pulse 140, and body weight 30½ lb. (13.8 kg.). There was oedema of the trunk, face, scrotum, and limbs. The blood pressure was 100/60 mm. Hg. A purulent nasal discharge was present. There was dullness to percussion with diminished air entry at both lung bases, and this was ascribed to the presence of pleural effusions. The liver was just palpable, and there was ascites. A specimen of urine contained albumin (+ +), hyaline and granular casts, and 18 white cells per high-power microscopical field. A clinical diagnosis of the nephrotic syndrome was made.

Investigations.—An electrocardiogram was within normal limits. The Mantoux test was negative; haemoglobin 11.5 g./100 ml.; leucocyte count 8,200/cu. mm. (normal differential count); platelets adequate and the sedimentation rate (Wintrobe) 48 mm. in one hour; total serum proteins 4 g./100 ml. (albumin 0.9 g., globulin 3.1 g.); serum cholesterol 440 mg./100 ml. A nasal swab was negative for *Corynebacterium diphtheriae*, and a rectal swab showed no pathogens. The blood urea and serum electrolyte levels were within normal limits. Intravenous pyelogram was normal. The protein content in the urine throughout his stay in hospital was assessed by Esbach's method.

The child was kept in bed without treatment for the first week. During this time his weight rose and the albuminuria persisted. Prednisone by mouth was started on 7 April in a dose of 10 mg. every eight hours (30 mg./day). A satisfactory diuresis occurred,

so that 10 days after the starting of corticosteroids his weight had fallen to 26½ lb. (11.9 kg.), and by the 17th day proteinuria was recorded as 0.25 to 1 g./l. There was a recurrence of the albuminuria, together with a rise in the body weight (30 lb.; 13.6 kg.), by the 22nd day. On 8 May (one month after treatment) the serum proteins had risen to 5.7 g./100 ml. (albumin 1.9 g.) but the cholesterol level remained high at 500 mg./100 ml.

After six weeks of continuous corticosteroid therapy the urine was almost free of albumin. Therefore intermittent corticosteroid therapy—given for three days in each week—was introduced. Within a fortnight a relapse had occurred, with an increase in proteinuria (4 to 6 g./l.), and a rise in body weight. Continuous prednisone therapy (30 mg. daily) was reinstituted. After a further fortnight (mid-June) his weight had fallen to 28 lb. (12.7 kg.) and the protein content in the urine was 0.5 to 1 g./l. Despite continuous corticosteroid therapy the child again became oedematous, and the degree of albuminuria had increased with a concomitant increase in weight to 34 lb. (15.4 kg.). Prednisone was stopped in the first week of July, and for the ensuing month there was no significant change in the clinical state. Oedema and marked proteinuria persisted. During this period an episode of purulent rhinitis was treated with phenoxymethyl penicillin by mouth.

On 10 August a different corticosteroid (triamcinolone) was given in the dose of 8 mg. every eight hours, together with potassium supplements. After 17 days on this regimen spironolactone 200 mg. daily was also prescribed. A week later the child's weight had fallen to 28½ lb. (12.9 kg.). Towards the beginning of September he developed mild intermittent fever associated with rhinitis and recurrent epistaxes. Penicillin was administered by intramuscular injection.

On 18 September he appeared well in the early morning, but suddenly collapsed at 11.30 a.m. with the passage of frequent loose stools. On examination he was stuporous and cyanosed, with a temperature of 99° F. (37.2° C.). The heart rate was 160, the jugular venous pressure was raised, while the liver was enlarged four fingerbreadths below the costal margin. A gallop rhythm was noted on auscultation. The blood pressure could not be determined. The lungs were clinically clear. A lumbar puncture was performed, the cerebrospinal fluid containing 1 lymphocyte with a protein content of 5 mg./100 ml. The electrocardiogram showed slow A-V nodal escape rhythm with late retrograde conduction to the atria. Shortly after this there was a cardiac arrest, and despite attempts at resuscitation the child died one and a half hours after the onset of clinical deterioration.

Necropsy Findings.—There was generalized oedema, most marked in the face, but there were no effusions in the serous cavities. Adherent antemortem thrombi were present in both main pulmonary arteries as well as in the right jugular vein. The heart showed generalized enlargement, weighing almost double the expected weight (110 g.). The right ventricle was dilated and two mural thrombi were present in the pulmonary outflow tract. The endocardium appeared normal. Both lungs were congested and showed two firm subpleural gritty areas 2 cm. in diameter in the right lower lobe and left upper lobe. The kidneys were enlarged and pale, while the suprarenal glands were reduced in size. Histological examination confirmed the presence of antemortem thrombi in the pulmonary arteries, jugular vein, and right ventricle. There was no significant underlying disease of these vessels. The thrombi were attached to the intima, which showed only slight hyperplasia in these areas, with some separation of elastic fibrils by histiocytes. The gritty areas in the lungs consisted of foci of calcification in the alveolar walls which had often elicited a foreign body reaction. The kidneys showed no glomerular changes by light microscopy. The basement membranes of the glomerular tufts were not thickened, and there was no evidence of proliferative glomerulonephritis. The tubular epithelial cells contained eosinophilic hyaline droplets and showed well-marked fatty change.

DISCUSSION

Pulmonary emboli and infarction are rarely observed in the paediatric age range (High, 1962; Haber and Bennington, 1962). Still rarer is the occurrence of pulmonary vascular thrombosis. Gootman *et al.* (1964), in their report of the two cases of nephrosis with pulmonary artery thrombosis, were able to trace only 18 patients under the age of 18 years in whom thrombosis occurred without previous embolic episodes. These

occurred in patients with congenital heart disease, severe pulmonary infection, or measles, or after an episode of dehydration. Thus to have two patients associated with the nephrotic syndrome was unique. The observation by us of yet another case where pulmonary artery thrombosis complicated childhood nephrosis suggests that this possibility should be considered if there is sudden collapse in such a patient who is receiving corticosteroid therapy.

Addis (1948) drew attention to the occurrence of venous thrombosis "in any part of the body, but most commonly in a leg," as a complication in the nephrotic syndrome, while Fishberg (1954) mentioned that venous and arterial thrombosis might occur. A number of reasons have been advanced (Seftel and Schewitz, 1957) to explain this thrombotic tendency—for example, (1) a decrease in circulating antithrombin (which is a serum albumin); (2) increased fibrinogen in the plasma; and (3) a relationship of fat metabolism to the thrombotic state. The disturbance of the lipoprotein pattern in the plasma is the same as in myocardial infarction and sometimes worse. In addition, the alpha-2 globulin which is raised in the nephrotic syndrome has been shown to have antifibrinolytic activity (Jacobsson, 1955). With the advent of corticosteroid therapy reports began to appear suggesting an increased incidence of thromboembolic episodes in patients on such therapy (Cosgriff *et al.*, 1950; Cosgriff, 1951; Fuzlullah, 1956). Furthermore, hypercoagulability of the blood has been noted during corticosteroid administration (Cosgriff *et al.*, 1950; Menczel and Dreyfus, 1960). Ozsoylu *et al.* (1962) studied the effects of corticosteroids on a number of blood-clotting factors. They found a rise in the level of antihæmophilic globulin and in addition some clot-promoting effect apart from this.

Thus the following factors were probably concerned in the production of the pulmonary thrombosis in our patient: (1) the nephrotic syndrome itself, with its predisposition to thrombosis (via mechanisms unknown); (2) the hypercoagulability of the blood produced by treatment with corticosteroids; (3) some degree of dehydration induced by the diuretic spironolactone, as well as by the terminal diarrhoea.

We wish to thank Dr. W. H. F. Kenny, superintendent, Baragwanath Hospital, for permission to publish this report, and Professor J. H. S. Gear, Director of the South African Institute for Medical Research, for facilities granted.

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