Effect of Lyndiol, an Oral Contraceptive, on Breast Cancer

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Recent papers have reported small clinical trials of progestins in combination with oestrogens in the treatment of advanced breast cancer (Landau *et al.*, 1962 ; Stoll, 1965 ; Crowley and MacDonald, 1965). This form of combination therapy is based upon experimental observations in rats made by Huggins *et al.* (1962). The clinical reports to date suggest that a beneficial response may be expected in about 25% of cases where there has been either a failure of response or a loss of temporary response to oestrogens or androgens.

The most suitable progestin and the optimal relative proportion of oestrogen to progestin have yet to be worked out in the human. A previous pilot trial (Stoll, 1965) compared the effects of progestins alone at maximum tolerated doses, progestin–oestrogen combination as used in oral contraceptives, and progestins combined with relatively high doses of oestrogen.

The present report assesses the effect on female breast cancer of Lyndiol, a commercially available oral contraceptive containing lynoestrenol, a progestin of the 19-nor-steroid group, combined with the oestrogen mestranol. In all, 65 post-menopausal women with advanced breast cancer were given this drug combination. The therapeutic effects and side-effects of one tablet daily (the contraceptive dose) are compared with those of three and of six tablets daily. The effect of the progestin moiety alone is compared with that of the oestrogen moiety alone.

The correlation is examined between the likelihood of a response to Lyndiol and a previous response to other hormones ; also between the likelihood of a response to Lyndiol and the hormonal status of the patient, as reflected in the vaginal smear taken before treatment is begun.

Clinical Material and Results

All 65 patients were post-menopausal and the disease was beyond the control of local surgery or radiotherapy. Those selected for the trial had objective signs of progressing soft-tissue disease which could be measured, and also photographed, wherever possible. Simultaneous treatment of the part under observation was not permitted by any method except by local dressings. All patients who had been castrated either surgically or radiotherapeutically had been so treated at least six months previously. In the 22 cases where oestrogen or androgen therapy had been given previously it was at least two months since such therapy had been stopped. Treatment with Lyndiol was instituted only if the disease was progressing in activity.

Of the 65 patients in this trial 53 persisted with hormone therapy for two months or longer (Table I). Those discontinuing therapy before two months for whatever reason are excluded from statistical assessment as having had an insufficient trial. Of the 53 patients considered 11 received six tablets of Lyndiol daily, 10 received three tablets daily, and 21 were started on one tablet daily (where breakthrough uterine bleeding occurred this dose was increased to two tablets daily). A further seven patients received the progestin component of six tablets of Lyndiol—that is, 30 mg. of lynoestrenol or 17α-ethynyloestrenol daily. Also, four patients received the oestrogen component of six tablets of Lyndiol—that is, 0.9 mg. of mestranol or 17α-ethynyloestradiol daily.

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TABLE I.—*Analysis of 65 Cases in Present Study*

Treated for 2 months or more		53 cases
Lyndiol 6 tabs. daily	11 cases	
„ 3 tabs. daily	10 „	
„ 1–2 tabs. daily	21 „	
Lynoestrenol 30 mg. daily	7 „	
Mestranol 0·9 mg. daily	4 „	
Discontinued before 2 months		12 cases
Intolerance to drug	7 cases	
Rapidly advancing disease	5 „	

Details of each patient persisting with Lyndiol therapy for two months or longer are shown in Table II, and the clinical response rate according to hormone and dosage is summarized in Table III. Almost complete macroscopic regression of soft-tissue tumour occurred in 9 of the 42 patients taking Lyndiol. It was seen in 3 of 11 patients on six tablets daily, 2 of 10 patients on three tablets daily, and in 4 of 21 patients on one to two tablets daily. There was similar regression in one of the seven cases on lynoestrenol alone, but in none of the four cases on mestranol alone. The earliest measurable regression of the tumour was usually between six and eight weeks after instituting therapy. The duration of regression was between three and ten months, the average being five months.

Fig. 1 illustrates the response to therapy in one of the cases—a woman of 84. She had undergone a simple mastectomy in February 1960 and in November 1963 developed axillary-node

TABLE II.—*Details of 42 Cases Receiving Lyndiol for Two Months or Longer*

Age	Previous Response to: Androgens	Previous Response to: Oestrogens	Lyndiol: Daily Tablets	Lyndiol: Clinical Regression	Initial Vaginal Smear	Age	Previous Response to: Androgens	Previous Response to: Oestrogens	Lyndiol: Daily Tablets	Lyndiol: Clinical Regression	Initial Vaginal Smear
52			1	–	Atr.	67		+	3	–	Int.
71			1	–	„	71			3	–	Atr.
58	–	–	1	–	Int.	61			3	+	Int.
71			1	–	„	76		–	3	–	Atr.
68			1–2	–	Infl.	44			3	–	„
65		–	1	–	Int.	57		–	3	–	„
52			1	+	„	44			3	–	Int.
56	–	–	1–2	–	Atr.	64			3	–	Atr.
75		–	1–2	–	Infl.	69		+	3	–	Infl.
76		–	1	+	Int.	81		–	3	+	Int.
74			1	–	Atr.	55		–	6	+	„
88		–	1	–	„	34	+	–	6	–	„
39			1	–	„	80		–	6	–	„
33			1	+	Int.	51		–	6	–	„
60			1	–	„	50		–	6	–	Atr.
55			1	–	Infl.	57			6	+	Int.
43			1–2	–	Atr.	73			6	–	„
98		–	1–2	–	Infl.	84		–	6	+	„
67	–	–	1–2	+	Atr.	69	+	+	6	–	Infl.
57			1	–	Int.	66		–	6	–	Atr.
55			1	–	Atr.	40	–		6	–	Int.

Atr. = Atrophic. Int. = Intermediate. Infl. = Inflammatory.

The low incidence of oestrogen responders in this group reflects the selection of oestrogen failures for this investigation.

TABLE III.—*Clinical Response According to Administered Hormone and Dosage*

Hormone	Daily Dose	Proportion with Response
Lyndiol	6 tablets	3 of 11
Lyndiol	3 tablets	2 of 10
Lyndiol	1–2 tablets	4 of 21
Lynoestrenol	30 mg.	1 of 7
Mestranol	0·9 mg.	0 of 4

enlargement and recurrent metastatic nodules in the scar. She was given stilboestrol 15 mg. daily for three months with no benefit. By August 1964 the skin nodules were ulcerated, the supraclavicular nodes were enlarged, and an ulcerated tumour was present on the under surface of the opposite breast. She was given Lyndiol six tablets daily, and within three months the enlarged nodes had regressed and the ulcerating areas on the left chest wall and the right breast were healed (Fig. 2). Treatment was continued for 10 months, but after this period new nodular metastases appeared in the chest wall (Fig. 3). When Lyndiol was stopped there was a further regression of the "hormone withdrawal" type (Fig. 4), and this has persisted to date, 21 months after starting Lyndiol. Her liver-function tests showed a persistent rise in enzyme levels during treatment (see later), although she felt no ill effects.

Table II records the correlation between regression of tumour in this trial and a previous response to either oestrogen or androgen therapy. Of four cases previously responding to those hormones none responded to Lyndiol later. On the other hand, of five patients responding to Lyndiol who had received other hormones previously, *all* had failed to respond to oestrogen or androgen therapy. It seems likely, therefore, that the Lyndiol responders do not belong to the same group of patients as those who respond to oestrogen or androgen therapy. The same conclusion has been noted for progestin-treated cases in general (Stoll, 1966), where a proportion of patients failing to respond to oestrogen showed a response when progestins were added.

Side-effects

In the patients receiving Lyndiol, severe side-effects such as vomiting, depression, and lassitude caused cessation of treatment after one or two weeks in 7 out of 54 cases. Other side-effects included nausea, breast and pelvic discomfort, dizziness, constipation, and dyspepsia. "Breakthrough" uterine bleeding was noted in a few patients in the low-dosage group, but this was controlled by increasing the dosage to two tablets daily. Occasional patients receiving Lyndiol, lynoestrenol, or mestranol complained of nausea or vomiting while persisting with the drugs, but those symptoms could be in the main controlled by antiemetic drugs. There was no obvious difference in the proportion of these side-effects between patients on high and those on low dosage of Lyndiol.

Routine liver-function studies were carried out in all except the earliest cases in the series (Table IV). In addition, liver biopsy was carried out in seven cases where the serum transaminase level was grossly raised. Some of the results have already been described (Stoll *et al.*, 1965, 1966).

In the group receiving six tablets of Lyndiol daily all of the five patients tested showed a moderate or gross rise in serum glutamic oxaloacetic transaminase (S.G.O.T.) level well beyond normal (over 40 units, Reitman-Frankel method). The changes in liver function first appeared after two weeks' drug administration. In addition, clinical jaundice was noted in two of the patients, associated with a gross rise in the serum bilirubin level. The alkaline phosphatase and serum protein levels remained normal in all cases. Liver biopsy was carried out in four patients of this group. All cases showed evidence of parenchymal-cell necrosis, which was limited to the centrilobular zones with accumulation of lipofuscin. In addition, the two patients with jaundice showed cholestasis in the hepatic cells and biliary canaliculi (Stoll *et al.*, 1965, 1966).

Of the seven patients on 30 mg. of lynoestrenol daily (the progestin component of six tablets of Lyndiol), three

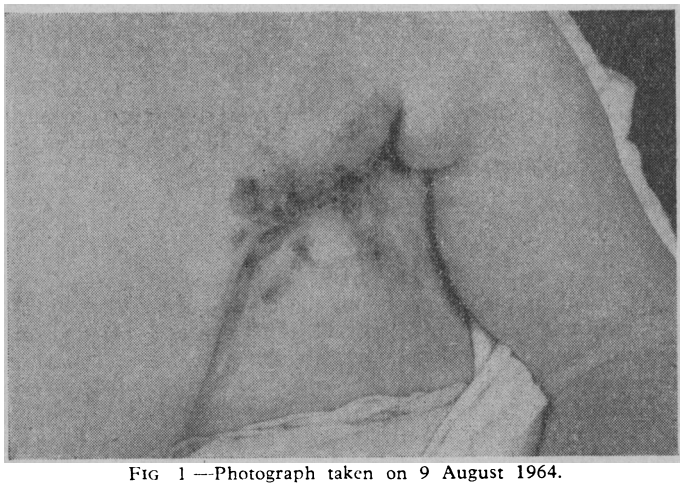

FIG 1.—Photograph taken on 9 August 1964.

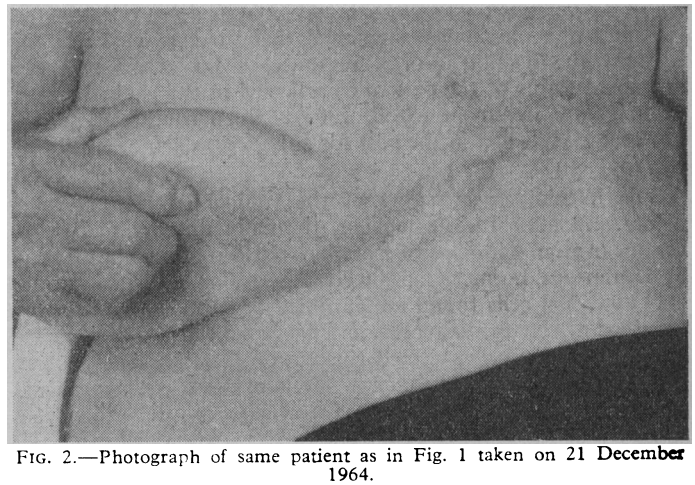

FIG. 2.—Photograph of same patient as in Fig. 1 taken on 21 December 1964.

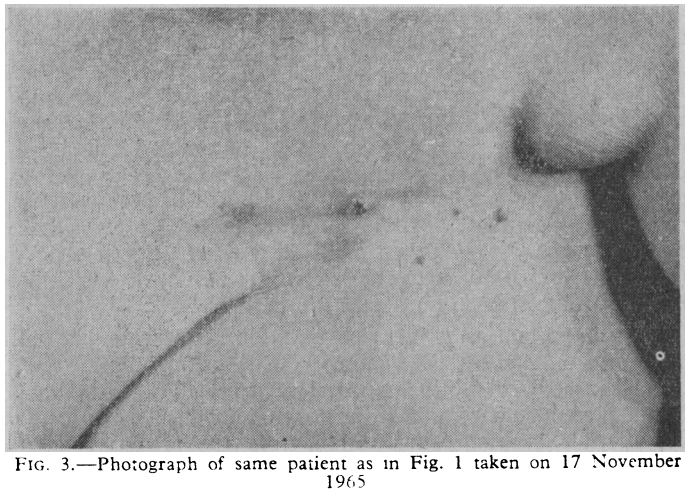

FIG. 3.—Photograph of same patient as in Fig. 1 taken on 17 November 1965

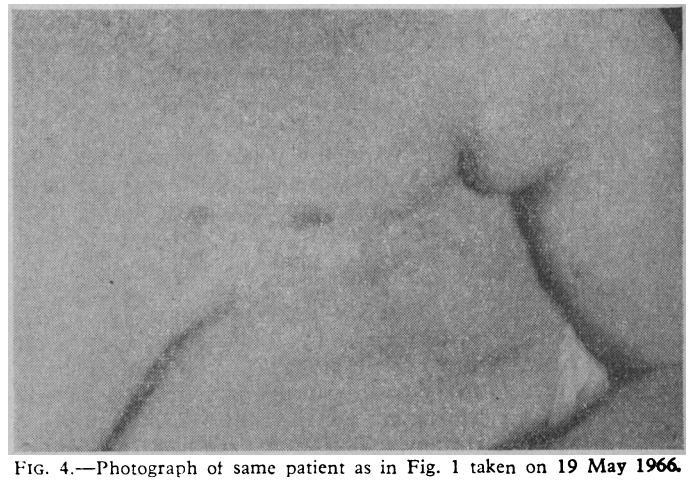

FIG. 4.—Photograph of same patient as in Fig. 1 taken on 19 May 1966.

developed a moderately raised S.G.O.T. level, but no abnormality in the serum bilirubin level. Liver biopsy taken in two cases revealed parenchymal-cell necrosis similar to that noted in the Lyndiol-treated cases, but of less degree. Of the four cases on 0.9 mg. of mestranol daily (the oestrogen component of six tablets of Lyndiol), none developed a rise in the S.G.O.T. level, nor any other biochemical evidence of liver damage.

In addition, 7 out of 13 patients receiving three tablets of Lyndiol daily and 3 out of 20 receiving one or two tablets daily developed an abnormal rise in S.G.O.T. levels, but none developed any abnormality in the serum bilirubin level. Liver biopsy in one case showed a similar picture to that noted above.

TABLE IV.—*Proportion with Elevated Serum Glutamic Oxaloacetic Transaminase, According to Administered Hormone and Dosage*

Hormone	Daily Dose	Proportion with Elevated S.G.O.T.
Lyndiol	6 tablets	5 of 5*
Lyndiol	3 tablets	7 of 13†
Lyndiol	1–2 tablets	3 of 20*
Lynoestrenol	30 mg.	3 of 7*
Mestranol	0·9 mg.	0 of 4

* Liver biopsy in 7 cases (see text).
† Includes some patients assessed at lower dose and subsequently dose level raised, to determine effect on transaminase level.

Overall, therefore, liver biopsy in patients with gross biochemical abnormality revealed parenchymal-cell necrosis in seven cases in this series, and associated cholestasis in two cases. Patients with the less gross biochemical abnormalities were not subjected to liver biopsy. Table IV demonstrates the increase in biochemical evidence of liver damage with increasing dosage of Lyndiol.

Assessment of Vaginal Smear

It has previously been suggested that there is a correlation between the likelihood of a response to progestins and the hormonal status of the patient as reflected in the vaginal smear taken *before* treatment (Stoll, 1965). Such a correlation has not been established in the past for either oestrogen or androgen therapy.

The histological structure of the vaginal epithelium, both before and after the menopause, normally mirrors the endogenous ovarian and adrenal secretion, but can also be influenced by extraneous hormone administration. The principal exfoliated epithelial cells found are cornified or superficial cells, precornified or intermediate cells, and parabasal cells. The percentage of cornified cells, termed the karyopyknotic index, reflects oestrogen concentration, but low levels of oestrogen concentration may cause a rise in the percentage of precornified or intermediate cells only.

After castration or after the natural menopause a proportion of women show a persistently raised karyopyknotic index suggesting persistent oestrogen secretion. It is important to note that the smear patterns of post-menopausal patients with breast cancer are no different from those of a normal control group of the same age distribution (Struthers, 1956; Finkbeiner, 1960).

In all the cases considered in this paper a vaginal smear to determine cytohormonal status was examined before treatment was started. This baseline smear was repeated more than once in some cases, because of fluctuations in oestrogen secretion said to occur after the menopause, but remarkably little variation was found. As stated above, in the case of patients who had received other forms of sex-hormone therapy previously, a therapy-free period of at least two months was insisted on before the patient entered this trial. This period of time allows the smear to return to the pre-therapeutic pattern in our experience, and our baseline figures are therefore not influenced by previous hormone therapy. This is evident also from study of Table II.

The smears are classified as predominantly atrophic if over 80% of the cells were parabasal in type, intermediate (non-atrophic, non-oestrogenic) if over 80% of the cells were of the intermediate type, and oestrogenized if over 20% of keratinized cells were present. Interpretation of the count is unreliable when the smear is too thin or in the presence of inflammatory changes.

Our observations in the past (Stoll, 1966) suggest that the patient with an intermediate vaginal smear is much more likely to respond to progestational agents than other post-menopausal patients. This observation is confirmed for the use of Lyndiol also (Table V). The parallel figures for our series treated with progestin, androgen, and oestrogen are also given for comparison. The persistence of an intermediate smear after the menopause is probably due to adrenocortical activity, but this is not proved. The interpretation of our observations is therefore a matter for speculation, but it is of great interest that in our experience the initial vaginal smear cannot be correlated with the likelihood of response to either oestrogens or androgens.

Repeated vaginal smears were also carried out throughout hormone therapy. It is interesting to note that the effect of Lyndiol is to induce an intermediate picture in patients with an initially atrophic smear. The karyopyknotic index is raised slightly at first, more so with higher dosage, but reverts to zero after four to eight weeks in practically all cases even while therapy continues.

TABLE V.—*Clinical Response to Lyndiol in Relation to Initial Vaginal Smear. Parallel Figures for Progestin, Oestrogen, and Androgen Series are Given for Comparison*

Hormone Therapy	Proportion of Cases Responding if Smear		Difference
	Atrophic	Intermediate	
Lyndiol series	1 of 16 (6%)	8 of 20 (40%)	Significant $P < 0.03$
Progestin series	2 of 32 (6%)	14 of 48 (29%)	Significant $P < 0.03$
Androgen series	11 of 36 (31%)	7 of 20 (35%)	Not significant
Oestrogen series ..	21 of 57 (37%)	14 of 45 (31%)	Not significant

Discussion

As noted in the introduction, the clinical use of combined progestin and oestrogen therapy in breast cancer is based upon carefully established experimental observations in animals. Clinically it is well known that oophorectomy, adrenalectomy, hypophysectomy, and androgen administration are often capable of causing regression in the growth of female breast cancer. Huggins *et al.* (1962) reported a hormone-sensitive spontaneous mammary cancer in female rats which will also regress after castration, adrenalectomy, hypophysectomy, and androgen administration. As this tumour can be induced at will by dimethylbenzanthracene-feeding, it is a most useful experimental model for obtaining information on the response of hormone-sensitive mammary cancer to other methods of hormonal regulation. Huggins *et al.* (1962) reported that the addition of small doses (20 μg. daily) of oestradiol to large doses (4 mg. daily) of progesterone is capable of completely extinguishing tumour growth in these animals in over half the cases. They emphasized that the relative doses of progesterone and oestrogen are important, but in a later clinical report (Landau *et al.*, 1962) suggest trials with different dosage combinations of oestrogen and synthetic progestins.

It is important to emphasize that Huggins's experimental work was on non-castrated animals, whereas our clinical trial is on castrated or post-menopausal patients. This is because in our present state of knowledge it seems unethical to withhold the possible benefits of castration from the pre-menopausal patient with advanced cancer. Our clinical results show that

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

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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,