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Immunosuppressive Treatment of Allergic Nephropathies

Efficiency and Problems

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Nine patients (three with subacute and six with chronic glomerulonephritis) have been treated with 6-mercaptopurine and azathioprine. The severity of the disease was determined on the evidence of protein excretion, the Addis count and the level of serum complement. The results justify not more than moderate optimism. Cytostatic drugs are applied only if corticosteroid therapy has no effect or is contraindicated. Peptic ulcer and amyloidosis are absolute, obesity and diabetes relative contraindications of steroid therapy. Epilepsy accompanying collagen disease is not a contraindication. Subcapsular cataract provoked by steroids makes no further progress if the steroid therapy has to be continued. Steroids, if administered after the 15th year of age, do not impede growth. A combination of cytostatic agents and corticosteroids seems to be beneficial and is perhaps less dangerous, although a patient developed agranulocytosis after having been treated with a combination of 6-mercaptopurine and prednisolone.

In the field of nephrology, immunosuppressive therapy is employed in lupus nephritis, in the nephrotic syndrome and in cases of progressive glomerulonephritis. Initially, treatment of this kind consisted of exposure to X-ray. Kay [16] postulated a two-stage mechanism for the genesis of Masugi nephritis. This theory was based on the experimental observation that X-ray irradiation prevented nephritis in rabbits injected with nephrotoxic duck serum. Irradiated animals do not produce antibodies against foreign proteins bound in the kidney or circulating in the blood. The employment of cytostatic agents preceded that of corticosteroids. Schwab et al. [25] demonstrated 20 years ago that mustard nitrogen prevented beef-gammaglobulin nephritis in rabbits. Mustard nitrogen was subsequently tested in clinical practice [4] but failed to gain wider acceptance owing to its undesirable side effects, and also to the fact that many authors had obtained satisfactory results with corticosteroids, especially in the treatment of nephrosis. This is why experiences on steroids are abundant the majority of our observations, too, having been made in connection with the employment of prednisolone. However, the purpose of the present paper was not to point out the advantages but to survey the drawbacks of steroid therapy, it being exactly on account of these drawbacks that the use of cytostatic drugs is now gaining ground.

There are comparatively few reports on the employment of cytostatics. In Hungary, Petrányi [23] described the favourable effect of 6-mercaptopurine, Boda et al. [7] that of chlorambucil (Leukeran). The material on which reports are

based is strikingly small: the number of cases in each material is rarely above twenty. Our material, too, is small: we treated four patients with 6-mercaptopurine and five with azathioprine (Imuran). Few in number as our cases are, they nevertheless illuminate the most significant problems of immunosuppressive therapy in the strictest sense of this term.

Our purpose was to study the effect of the treatment on the activity of the pathologic process. Activity in the lipoid nephrosis of children manifests itself through proteinuria. "Pure" nephrosis occurs rarely (or perhaps never) in adults but they suffer from subacute or chronic nephritis with or without nephrotic syndrome. Activity in these diseases is, according to our observations, most pregnantly characterized by the Addis count [1]. Accordingly, we adapted our method of treatment to the number of excreted red cells. We determined the immunological background by assessing the level of serum complement performed by the method of Lange et al. [18] (with 1.0 U as the lowest normal value). We administered 6-mercaptopurine (Leupurin – Chinoin Budapest) in daily doses of 50 mg, azathioprine (Imuran – Borroughs Wellcome et Co, London) in daily doses of 1.5 mg/kg.

Results

6-mercaptopurine had no effect in our first case; although it was effective in the second, the patient relapsed when the administration of the drug was discontinued. It was beneficial in the third case but the patient died of uraemia following infection of the upper air passages. It appeared that the infection and the immunosuppressive treatment did not have a causal relationship. The fourth patient developed agranulocytosis and grave anaemia.

Case-histories

L.B., male, 41, was admitted with acutely exacerbated chronic glomerulonephritis, nephrotic syndrome and pre-uraemia. In view of the patient's previous gastric haemorrhage we gave 6-mercaptopurine instead of prednisolone. It can be seen from Fig. 1 that, before the drug had time to take effect, i.e. before the marked diminution of clinical activity, the absolute neutrophil count had been reduced below 1000/mm^3 on July 15, 1968. The treatment was continued for another month during which the absolute neutrophil count varied between 690 and 1000/mm^3 which shows that the therapeutic and the toxic effects are in close relationship. As a result of the successful treatment, endogenous creatinine clearance rose from 27 to 54 ml/min. The patient was discharged.

Dehospitalized, the patient did not follow instructions, started working and suffered a relapse after a few months. The Addis count pointed to significant microscopic haematuria; endogenous creatinine clearance was 36 ml/min. The

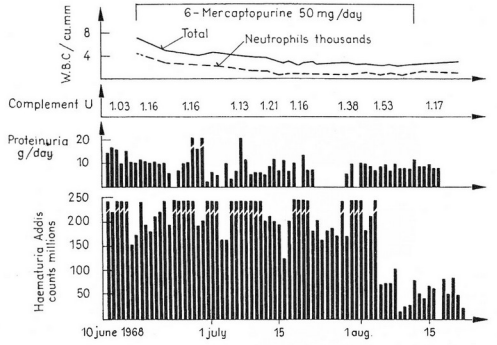

Fig. 1. L. B., 41-year-old male. Effect of 6-mercaptopurine on chronic glomerulonephritis and nephrotic syndrome

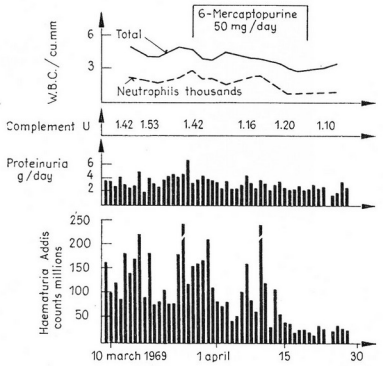

Fig. 2. L B. Effect of renewed 6-mercaptopurine treatment on chronic glomerulonephritis. The disease recurred after the cessation of the first cytostatic course

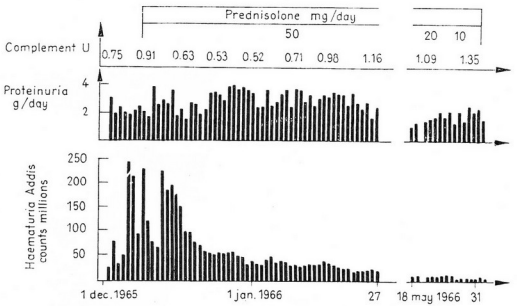

Fig. 3. J. G., 17-year-old male. Effect of prednisolone on subacute glomerulonephritis and nephrotic syndrome

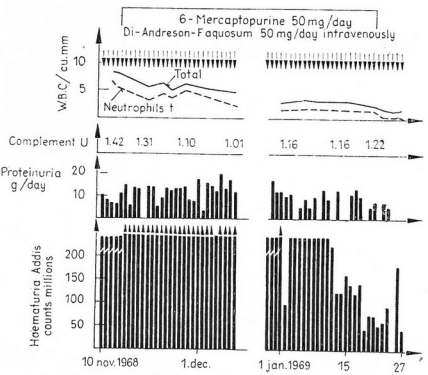

Fig. 4. J. G. Effect of combined treatment on subacute glomerulonephritis and nephrotic syndrome in the advanced phase of the disease

result of renewed mercaptopurine treatment was satisfactory (Fig. 2); at the second discharge, the value of endogenous creatinine clearance attained 41 ml/min.

This case is a good example to show that even in cases with a poor prognosis it is possible to control glomerulonephritis by means of immunosuppressive treatment.

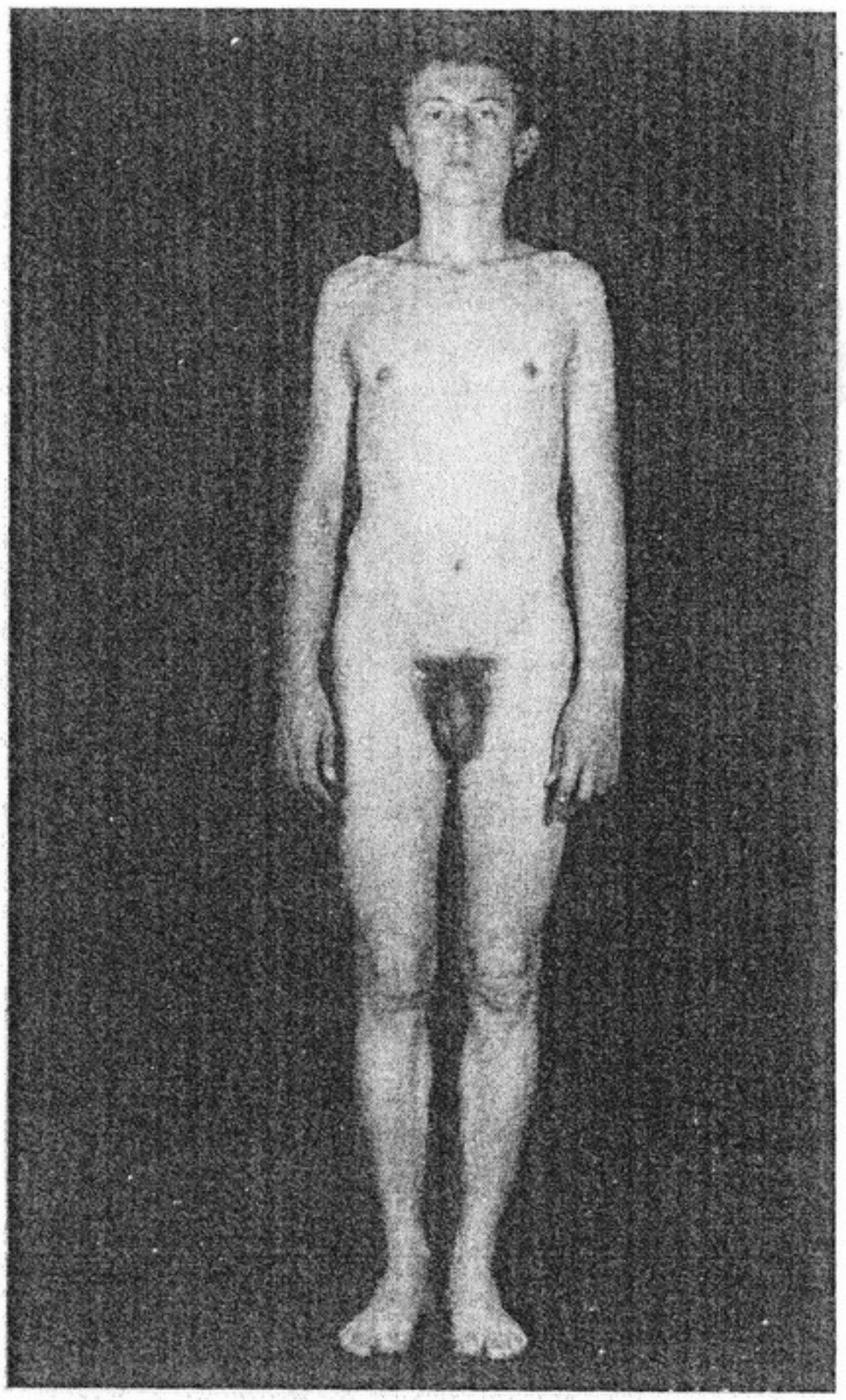

Fig. 5. J. G. During the reduction of the first vigorous prednisolone treatment

J.G., male. 17, was suffering from subacute glomerulonephritis with nephrotic syndrome. Treatment was commenced in 1965, and the administration of prednisolone started when clinical manifestations and immunological signs pointed to the disease having reached the progressive phase (increasing red-cell count in the urine, low level of serum complement). The treatment had a quick and highly satisfactory effect, microscopic haematuria practically subsiding after a few months (Fig. 3). The value of endogenous creatinine clearance rose from 73 to 119 ml/min. The boy was instructed to take daily two pills of prednisolone as a maintenance dose, and continued to be under the supervision of our outpatient department of nephrology.

The patient has not collaborated since February 1967 and also ceased to take prednisolone. After having developed oedema following infection of the upper respiratory tract, he was readmitted to our institute with an endogenous creatinine clearance of 56 ml/min. We administered prednisolone first orally then intravenously (Di-Adreson-F aquosum, Organon – Oss). Having achieved no

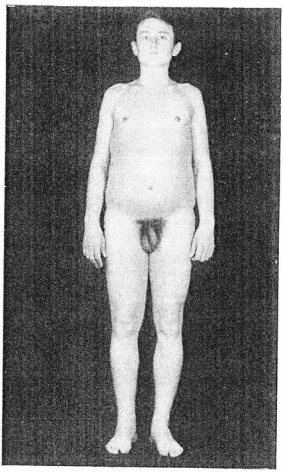

Fig. 6. J. G. Generalized renal oedema. The patient failed to collaborate and stopped taking the maintenance doses of prednisolone

improvement, we instituted a combined therapy by administering both Di-Adreson-F aquosum and 6-mercaptopurine. The result of combined treatment failed to come up to expectations, and while its therapeutic effect still was delayed, both the total white-cell count and the absolute neutrophil count began to diminish quite considerably. We stopped the administration of mercaptopurine when the absolute neutrophil count fell to 1500/mm^3, but it was apparently too late and the patient developed agranulocytosis. The concentration of serum creatinine was 5.82 mg/100 ml. The patient died on January 29, 1969. Although no sign of sepsis was observed at the time of death, there is no doubt that the suppression

of bone marrow function must have had a harmful effect on the patient's general condition. It is evident from Fig. 4 that the favourable effect of treatment and the grave toxic signs ensued approximately concomitantly.

Figs 5 through 8 illustrate the course of the disease with regard to oedema. It can be seen that the patient's condition was most satisfactory towards the end

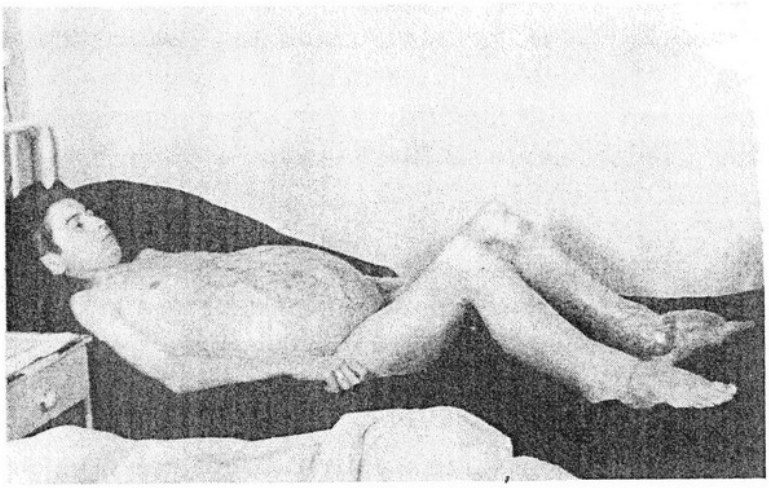

Fig. 7. J. G. Extremely grave generalized oedema at the outset of combined treatment with 6-mercaptopurine and Di-Adreson-F aquosum

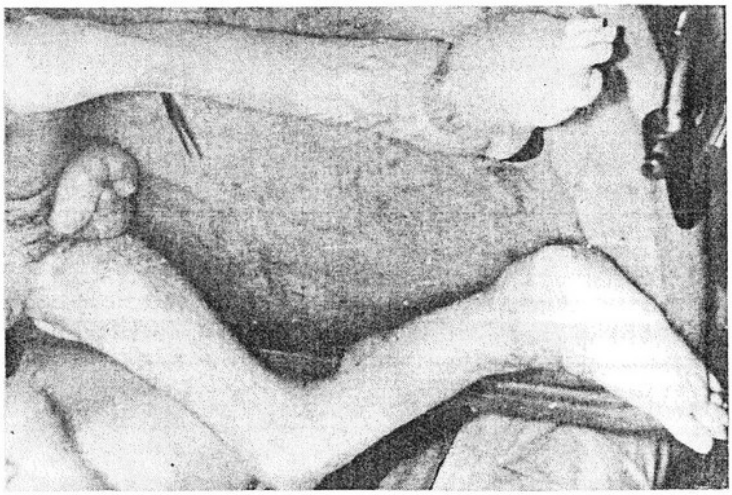

Fig. 8. J. G. Combined therapy has no effect on the oedema

of the first vigorous prednisolone therapy and that he developed generalized renal oedema after having, contrary to instructions, ceased to take prednisolone. Neither renewed prednisolone treatment nor combined therapy, instituted on account of the extremely grave oedema, yielded the expected improvement.

Dissection revealed a thickening of the basement membrane of the glomerular loops; the glomeruli were lobated owing to cellular proliferation; the tubular epithelium and stroma contained massive deposits of lipids. The zona fasciculata was atrophied, and the amount of active bone marrow seemed to be reduced.

Discussion

The doses of azathioprine employed by us have a less suppressive effect on the bone marrow, however, the therapeutic value was not convincing in any of our cases, and the drug proved to be useless in cases of leucopenia. One of our patients developed serious nephrotic syndrome during pregnancy which became still graver after delivery. Treatment with Lasix resulted in the escape of about 15 litres of oedematous fluid but the leucocyte count dropped meanwhile from 6000 to 4000/mm^3, the neutrophil count from 2520 to 1440/mm^3, remaining then at this level. We discontinued treatment with Lasix and started the administration of azathioprine (1.5 mg per day) despite the prevailing leucopenia. Cytostatic therapy had to be abandoned because the absolute neutrophil count fell to 1000/mm^3 after three days. The other patients received the drug for several months.

Correct choice of the drug is of prime importance. 6-mercaptopurine, azathioprine (Imuran), chlorambucil (Leukeran) and cyclophosphamide (Endoxane) are currently used by nephrologists. Owing to unsatisfactory results we do not intend to employ mercaptopurine frequently in the future. Correct dosage is likewise very important. This is not an easy problem, for the therapeutic and the toxic doses of all cytostatic drugs are but slightly different. The recommended daily dose of Imuran amounts to 1.5–3 mg/kg. A dose of 1.5 mg/kg was found by us to be insufficient for the control of progressive glomerulonephritis in adults. Cyclophosphamide (perhaps the least toxic compound), if administered in initial daily doses of 5 mg/kg and in maintenance doses of 2 to 3 mg/kg, results in leucopenia and causes baldness so that children so treated have to wear wigs. Although there follows a growth of new hair, it is thin and fair. Another side effect of the drug is toxic cystitis: though extremely unpleasant, it can be controlled by copious fluid uptake and frequent urination [21].

Likewise very important and perhaps decisive is the duration of treatment. We follow the principle that drugs should be administered until appreciable improvement or until the appearance of toxic signs. In this respect, a serious drop in the number of leucocytes is relevant. It is rather difficult to determine the limiting value: yet, relying on the principle of *nil nocere*, we think the administration of cytostatics should be interrupted when the absolute neutrophil count drops below 1000/mm^3. The case of our patient No. 1 shows that the treatment can be resumed after the subsidence of bone-marrow depression.

Prognosis is regarded as promising by the majority of authors. Cases of both complete and incomplete remissions have been reported [2, 5, 7, 8, 9, 21, 22, 23]. Our attitude is one of "modest optimism" [26, 28].

Petrányi [23, 24] found cytostatic drugs useful in cases of lupus nephritis, while corticosteroids seemed to be less efficient. Prednisolone resulted in marked improvement in some of our cases of lupus nephritis, but partial or total remission may take several years during which the administration of the drug must not be interrupted.

We think subacute glomerulonephritis is the most fruitful field for the application of cytostatic drugs. This rapidly progressive disease is mostly fatal despite vigorous prednisolone therapy. Besides, administration of prednisolone is not always possible in cases of acute exacerbation of chronic glomerulonephritis. Microscopic haematuria (as indicated by the Addis count) and/or low level of serum complement are the most decisive signs of the activity of the disease.

Cytostatic therapy may yield satisfactory results in the nephrotic syndrome, especially if biopsy reveals only minimal glomerular lesion under the light microscope [2, 8, 21], and if immunohistological examination indicates glomerular fixation of antibodies [10]. It is nevertheless generally agreed that, as a first measure, treatment with steroids should be attempted. It should be borne in mind that the nephrotic syndrome is curable without toxic symptoms in 40 per cent of the cases [3]. Steroid therapy has the following limitations.

(1) Contraindications of steroid treatment

(a) *Absolute contraindications:* acute peptic ulcer and amyloidosis [11, 15]. One of our patients, suffering from amyloidosis of the kidney, died of irreversible diarrhoea and exsiccosis shortly after the administration of prednisolone; another patient, who had received prednisolone prior to admission developed rapidly progressing azotaemia. There are several reports on similar observations [20, 27].

(b) *Relative contraindications:* obesity and diabetes.

(2) Steroid intolerance

First, mention should be made of the mental disorders among the undesirable side effects. A patient declared he would no longer eat because he had no stools, and refused to accept our explanation that he had no stools because he was taking no food. We hereupon declared him to be healed, stopped medication and left him a free choice of diet: the mental disorder stopped quite promptly.

Also epileptiform seizures have been described as undesirable side effects of corticosteroid preparations [6]. Systemic lupus erythematodes often manifests itself in the form of epilepsy [19]. Fits should be regarded as manifestations of the primary disease if epileptiform convulsions supervene during the steroid therapy of collagen disease. We observed a case of systemic lupus erythematodes and another of a not exactly definable collagen disease in which prednisolone treatment prevented the recurrence of fits.

It is beyond doubt that corticosteroids may exacerbate existing or induce fresh ulcers [12, 13]. Such ulcers are said by American authors to disappear

quickly on the administration of alkalies even if steroid therapy is being continued [17]. Fig. 9 shows a "true" prednisolone ulcer. Gastric roentgenogram was negative before the treatment, and the ulcer developed while the patient was being given alkalies. Gastric haemorrhage was so serious as to necessitate surgery. In another of our cases prednisolone ulcer developed in the presence of achlorhydria,

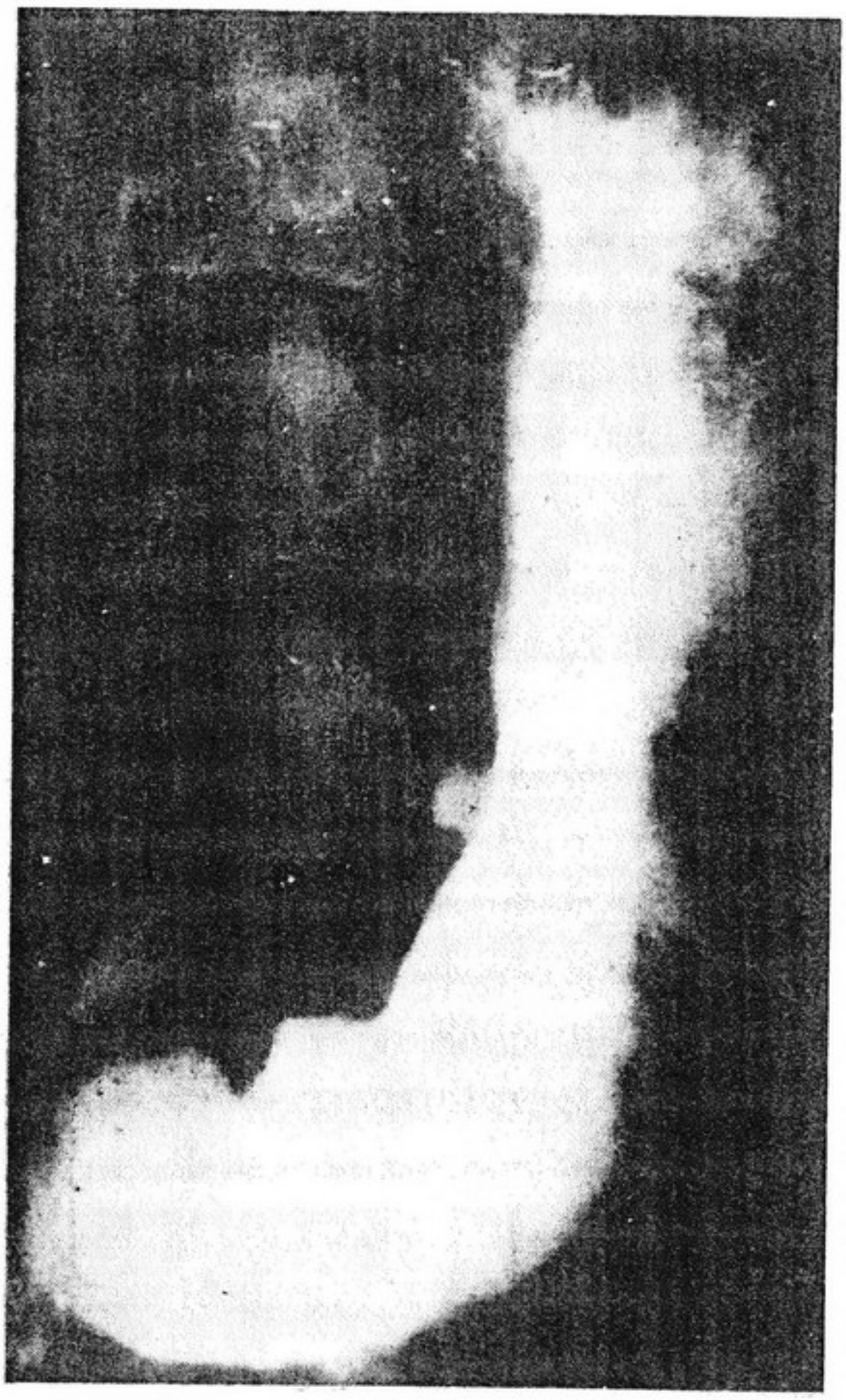

Fig. 9. "True" prednisolone ulcer. Early gastric roentgenogram. The ulcer penetrates steeply into the deeper layers as if made by a punch

but we succeeded in detecting it in due time by radiographic examination. The ulcer healed quickly after the discontinuation of prednisolone. Prednisolone gave rise to acute pancreatitis in another case so that corticosteroid therapy had to be discontinued.

Another grave toxic effect of corticosteroids is subcapsular cataract which occurred in three cases of our material. Of course, steroid treatment has to be interrupted in such cases; yet, subcapsular cataract means no absolute contra-indication so that a continuation of the steroid therapy may be attempted if the original disease recurs. A young female patient suffering from systemic lupus

erythematodes, who had been treated with prednisolone for several years, developed unilateral subcapsular cataract. To control her high fever she had to be given prednisolone in daily doses of 100 mg during the last serious relapse. The patient succumbed later to postpregnancy exacerbation. The subcapsular cataract made no progress during the forced prednisolone therapy.

(3) Resistance to steroids

Resistance may develop early, a phenomenon we repeatedly observed in connection with subacute nephritis, and it may appear also later.

(4) Dependence on steroids

Steroid therapy has to be applied without interruption even for many years as any break induces a recurrence of the disease. Dependence on steroids is, according to Moncrieff et al. [21], the main reason why cytostatic treatment is

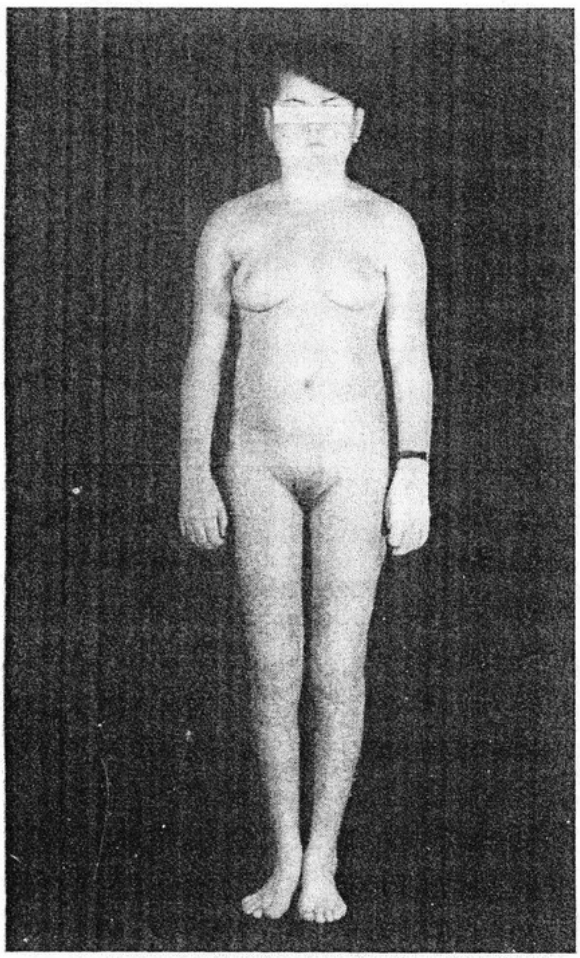

Fig. 10. M. K., female, 15, Cushing's syndrome caused by prednisolone

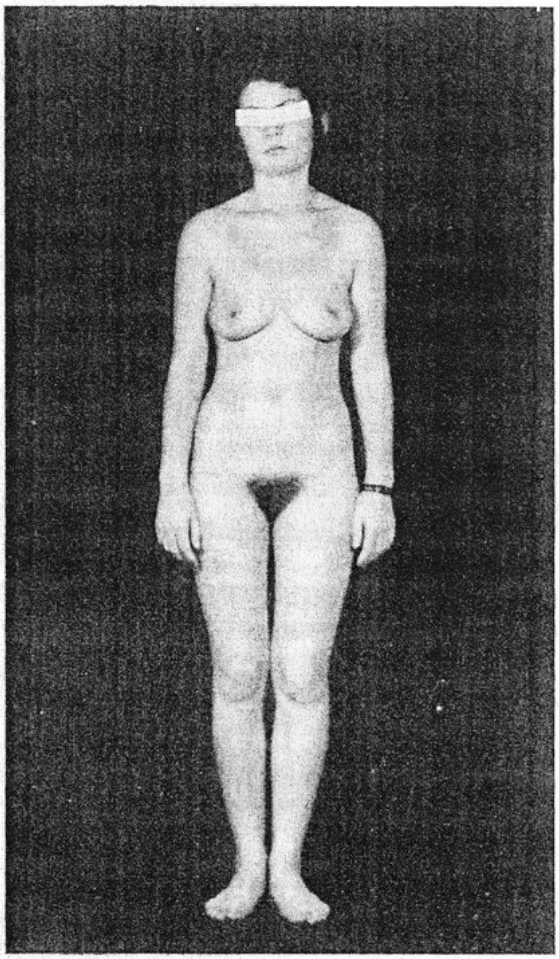

Fig. 11. M. K. Prolonged steroid therapy has not interfered with growth

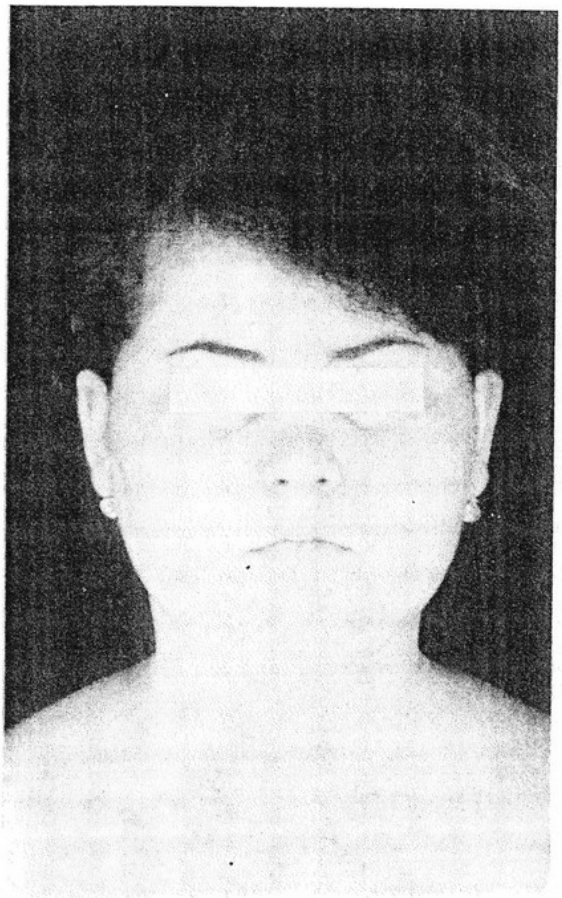

Fig. 12. M. K. "Moon-face" after prolonged prednisolone treatment

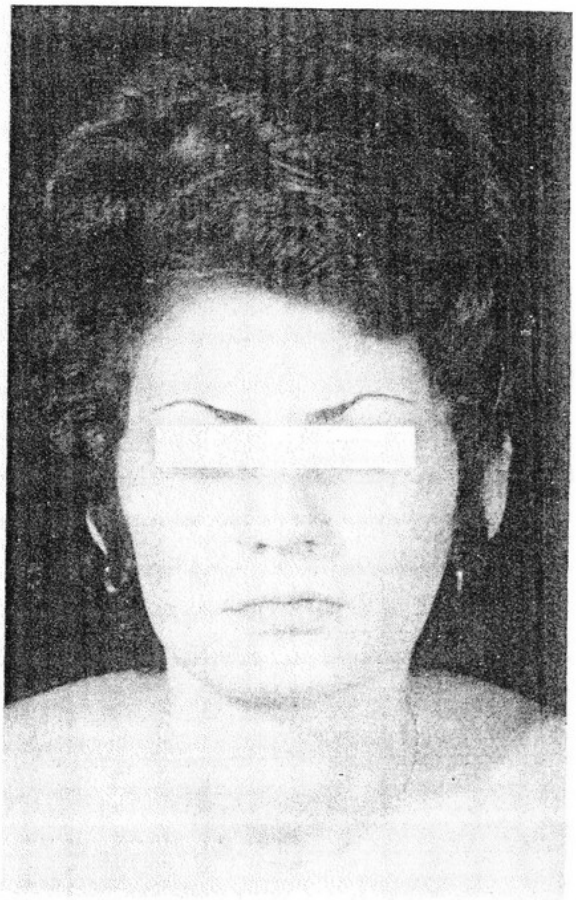

Fig. 13. M. K. Complete disappearance of "moon-face"

preferable for children with the nephrotic syndrome. As a result of prolonged steroid therapy, children become obese and stunted. Cushing's syndrome in adults means no great harm; we have found that the favourable effect usually appears about the time when the "moon-face" is formed. Iatrogenic Cushing's syndrome is reversible – except for the striae. Prednisolone does not retard growth above the age of 15 (3 cases). Let us quote the example of a girl of 15 who received prednisolone for seven months on account of acute glomerulonephritis. Although the patient developed Cushing's syndrome, follow-up examination made two years after termination of the steroid therapy showed undisturbed and normal growth of the girl (Figs 10, 11). The "moon-face" had disappeared (Figs 12, 13) but the striae remained (Fig. 14). This is why French women are reluctant to use corticosteroids.

Recently, the tendency has gained ground to apply combined immunosuppressive treatment, for example by administering cytostatic drugs together with small doses of prednisolone. Although the combined method is not invariably successful, it is theoretically promising since the mode of action of the two kinds of drugs is not the same. We pointed out at the Prague International

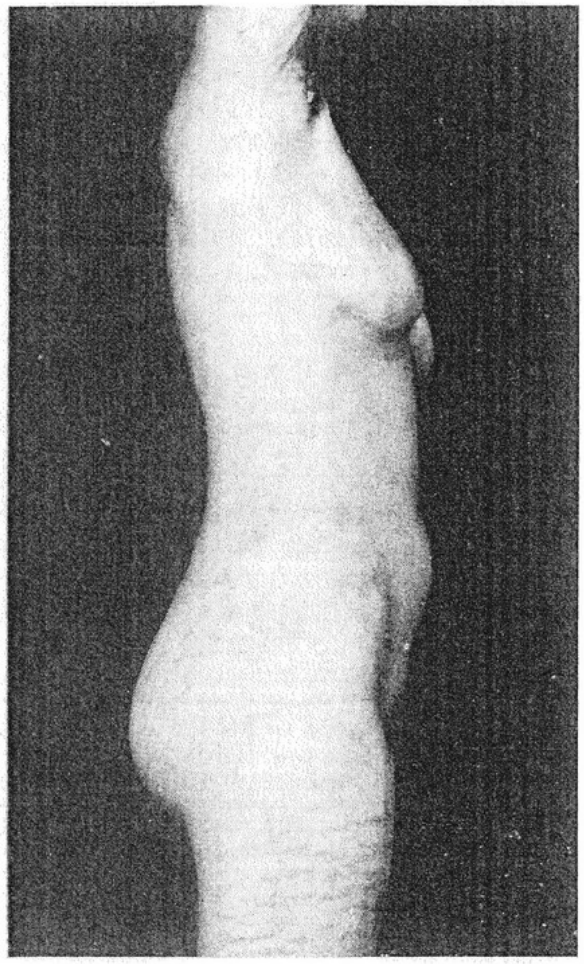

Fig. 14. M. K. Persistent striae

Congress of Nephrology in 1963 that the favourable effect of prednisolone on the Masugi nephritis was rather due to the antiphlogistic than to antiallergic action [14]. Combined treatment allows the administration of smaller doses. Besides, the difference in the toxic effects justifies the expectation that iatrogenic factors will no longer produce bald and obese dwarfs.

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