FIG. 1A

FIG. 1B

FIG. 1A.—General condition of patient with multiple skeletal and intrathoracic metastases from adenocarcinoma of the kidney.

FIG. 1B.—After receiving testosterone for 18 months. Considerable gain in weight, free from symptoms, and working full-time: this condition maintained for three years.

FIG. 2A.—Large osteolytic deposit involving anterior aspect of tibia. Second small deposit present at lower end of this bone close to posterior cortex.

FIG. 2B.—Upper tibial deposit treated by irradiation, curettage, bone graft, and insertion of a Hodgkinson nail. Note increase in lower tibial deposit and new lesion in middle third of shaft during treatment with a progestational agent.

FIG. 2C.—Pathological fracture at site of previous large osteolytic deposit but position of fragments well maintained and callus present. During treatment with testosterone metastasis in mid-shaft disappeared and deposit at lower end of tibia recalcified with reconstitution of destroyed cortex. Radiograph 38 months after beginning testosterone and three months before death with widespread deposits confined to soft tissues.

FIG. 2A

FIG. 2B

FIG. 2C

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FIG. 3A.—Left hilar mass and multiple small deposits in lateral part of left upper zone prior to hormone therapy.

FIG. 3B.—Increase in hilar mass during treatment with a progestational agent.

FIG. 3C.—Complete regression of hilar mass during treatment with testosterone. Radiograph seven months after beginning this hormone: small lesions in left upper zone show no change.

FIG. 4A.—Small osteolytic deposit in cranial vault prior to hormone therapy.

FIG. 4B.—Rapid extension of skull deposit during treatment with a progestational agent for two months.

FIG. 4C.—Skull deposit became stationary one month after changing to testosterone and by three months was smaller. Complete healing occurred and lasted until death. Radiograph 38 months after beginning testosterone.

FIG. 4D.—Section of skull (post-mortem specimen) shows fibrous tissue bridging bone defect produced by previous deposit. No microscopical evidence of residual tumour.

FIG. 5.—Moderately differentiated renal adenocarcinoma (nephrectomy specimen).

FIG. 6.—Section of basilar portion of pons (post-mortem specimen) showing junction of viable tumour deposit with area of cystic gliosis. Is the latter the result of changes produced by hormone therapy in a metastasis which caused the first episode of hemiplegia 42 months previously and from which the patient recovered rapidly during treatment with testosterone?

Cystic gliosis

Viable tumour

Hormones and the Kidney: Possible Therapeutic Role of Testosterone in a Patient with Regression of Metastases from Renal Adenocarcinoma

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[WITH SPECIAL PLATE]

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The relationship between the kidney and the endocrine system is perhaps greater than is generally appreciated. In experimental animals hypophysectomy results in a decrease in kidney weight, prevents compensatory hypertrophy, and reduces renal function (McQueen-Williams and Thompson, 1940 ; Winternitz and Waters, 1940 ; White *et al.*, 1949). Administration of anterior pituitary extract causes renal hypertrophy (Selye *et al.*, 1945). Thyroid hormone produces slight hypertrophy of the kidney with an increase in renal function, while thyroidectomy is followed by depression of function (Heinbecker *et al.*, 1943 ; Korenchevsky and Hall, 1944). The principal effects of pituitary antidiuretic hormone and of adrenocortical steroids on the kidney are well known.

In recent years the kidney has come to play a more direct part in the complex story of parathyroid physiology. Parathormone has a direct action on the normal kidney, increasing phosphate excretion probably by reducing tubular reabsorption (Bartter, 1961 ; Lavender *et al.*, 1961). Copp *et al.* (1962) have described a new parathyroid hormone, calcitonin, which lowers blood calcium, and its site of action is likely to be the renal tubules (Stanbury, 1963). A relationship between the gonads and the kidney in experimental animals has been known for nearly 25 years. Thus castration and the administration of gonadal hormones, especially androgens, influence renal structure in the mouse and rat (Korenchevsky and Ross, 1940 ; Selye, 1941 ; Ludden *et al.*, 1941 ; Lattimer, 1942).

In addition to being a target organ for various hormones the kidney itself appears to fulfil the role of an endocrine gland by producing angiotensin (Page and Bumpus, 1960), erythropoietin (Jacobson *et al.*, 1957 ; Naets, 1958), and an "aldosterone-stimulating hormone" which may be renin (Davis *et al.*, 1961 ; Davis, 1963).

In view of the many endocrine factors influencing normal renal structure and function, certain well-known features in the natural history and pathology of renal cancer, and the effect of hormones and of endocrine ablation procedures on the growth of an experimental hormone-induced kidney tumour, it was tempting to consider the possibility of a hormonal background to renal adenocarcinoma in man (Bloom *et al.*, 1963a, 1963b). This concept led to a trial of gonadal and corticosteroid hormones in patients with advanced cancer of the kidney, and between May 1959 and December 1963 20 such patients were treated in this way at the Royal Marsden Hospital and followed to the time of death (Bloom, 1964). Marked signs of tumour regression occurred in four cases, and in one of these the changes were so striking as to warrant this separate report. In a further three patients objective signs of tumour regression were noted, but no special claim is made for these cases because of the limited or doubtful response.

This paper is primarily concerned with the possible therapeutic action of testosterone in a patient showing regression of pulmonary and skeletal metastases from adenocarcinoma of the kidney. Attention is also directed to the influence of this hormone on the normal kidney and upon the oestrogen-induced renal tumour of the Syrian hamster.

Action of Testosterone on the Normal Kidney

It has long been known that androgens have a renotropic action in certain experimental animals. In male rats gonadectomy reduces kidney weight, while androgen administration induces renal hypertrophy in castrated males and in normal and ovariectomized females (Korenchevsky and Ross, 1940). Androgens were found to cause hypertrophy of the convoluted tubules and of the parietal cells of Bowman's capsule in both intact and castrated mice of both sexes (Selye, 1939). Renal function in dogs (Welsh *et al.*, 1942) and the degree of normal tubular hypertrophy in the remaining kidney following unilateral nephrectomy in rats (MacKay, 1940) are increased by testosterone. This hormone also appears to increase the remaining renal function in male patients in whom one kidney has recently been removed (Lattimer, 1942).

In male mice castration brings about a fall in kidney size and testosterone an increase. These procedures also lead to changes in the concentration of alkaline and acid phosphatase in the kidney (Kochakian and Fox, 1944). The concentration of glucuronidase in the mouse kidney is also selectively increased by testosterone administration, and this action is neutralized by stilboestrol treatment (Fishman and Farmelant, 1953). The renotropic action of testosterone appears to be a direct one, since this hormone can induce hypertrophy of the kidney in the absence of the pituitary gland (Selye, 1941).

Treatment with testosterone protects mice and rats against renal damage associated with mercuric chloride poisoning (Selye, 1940 ; Longley, 1942) and prevents nephrosclerotic changes induced by deoxycortone acetate (Selye and Rowley, 1944). Several authors have suggested the possibility of using testosterone to improve renal function in patients with kidney disease (Korenchevsky and Ross, 1940 ; Ludden *et al.*, 1941 ; Selye and Rowley, 1944). Some degree of improvement has been reported in cases of renal failure treated with androgens (Pasqualini and Imbriano, 1947), but this may be explained by a reduction in protein catabolism rather than by a direct effect on the kidney.

Effect of Testosterone on an Experimental Oestrogen-induced Renal Tumour

Matthews *et al.* (1947) described an adenomatous tumour of the kidney in a Syrian golden hamster after prolonged administration of stilboestrol. This observation was confirmed and

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extended by Kirkman and his colleagues at Stanford University (Kirkman and Bacon, 1949, 1952a, 1952b; Kirkman, 1959) and in this country at the Chester Beatty Research Institute by Horning (1952, 1954, 1956a, 1956b; Horning and Whittick, 1954). This subject has been reviewed by Bloom *et al.* (1963b), who report further experiments dealing with the influence of various hormonal preparations and also of endocrine ablation procedures (Bloom *et al.*, 1963a) on the growth rate of renal tumour transplants.

The kidney tumour in the hamster appears as multiple bilateral small pale nodules in the renal cortex following continuous stilboestrol treatment for approximately seven months. The tumours become palpable in the flank in 70 to 80% of animals treated for nine to twelve months. They spread by direct implantation and also by metastases via the blood-stream and lymphatics. Tumour production by oestrogen can be almost completely inhibited by the simultaneous administration of testosterone. Kirkman (1959) obtained renal tumours in 97 out of 100 male hamsters treated with stilboestrol for 250 to 599 days, compared with only 2 out of 56 animals receiving stilboestrol with the addition of testosterone propionate for 228 to 543 days: in both these animals the tumours were only of microscopic size. Comparable results were obtained by Horning (1956a) in a smaller number of animals.

Testosterone had no inhibitory effect on the *established* primary renal tumour, nor on the *transplanted* tumour (Kirkman, 1959; Bloom *et al.*, 1963b). Bilateral orchidectomy prevented the grafted renal tumour from growing and inhibited further increase in size in well-established transplants. The effects of orchidectomy were completely nullified by the simultaneous administration of oestradiol or testosterone (Bloom *et al.*, 1963a). It would appear that the transplanted tumour, although *independent* of administered stilboestrol, is still *dependent* upon endogenous oestrogen derived from the adrenals and testes. In these circumstances the action of testosterone may be explained on the basis of its conversion in the body to oestrogen (West *et al.*, 1956).

The features of the hamster renal tumour clearly indicate that it should be classified as a hormone-dependent growth, comparable to other dependent neoplasms in laboratory animals, such as those arising in the thyroid, adrenal cortex, testis, and ovary.

Androgens are antagonistic to certain other tumours in experimental animals whose development is dependent on or assisted by oestrogen administration, such as mammary and testicular tumours in mice (Hooker and Pfeiffer, 1942; Gardner, 1946), pituitary tumours in rats (Albert and Selye, 1942), and uterine and abdominal fibroids in the guinea-pig (Lipschütz and Vargas, 1941).

Observations concerning the influence of hormones on experimental tumours should be of special interest to the clinician because the principal actions of individual hormones are generally alike in all species. It is therefore worth trying to apply knowledge gained from the behaviour of hormone-dependent tumours in animals to the treatment of what appear to be analogous tumours in man. It must be pointed out, however, that the susceptibility of the hamster's kidney to undergo neoplasia with prolonged oestrogen treatment appears to be peculiar to this animal, although Richardson (1957) has reported renal tumours in a small proportion of male mice treated with stilboestrol.

Possible Endocrine Factors in Human Renal Adenocarcinoma

A number of clinical and pathological observations support the idea of a hormonal background to the development and progress of renal carcinoma in man. For example, small renal cortical adenomas may represent latent or pre-invasive malignant foci, a position comparable to that found in cancer of

the prostate (Franks, 1954, 1956). Bartley and Hultquist (1950) and Zak (1957) have described regressive changes in adenomatous foci in the renal cortex which they claim to represent different stages in the spontaneous healing of potential adenocarcinomas.

The slow progress of the primary tumour or of metastases in some cases of renal cancer, the long interval between nephrectomy and the appearance of distant metastases, and those examples of spontaneous regression or of prolonged survival following removal of an apparently solitary deposit, all suggest that renal carcinoma in such cases is not fully autonomous. This implies some degree of tumour restraint by the host. The causes of latency and of host resistance in such cases are unknown, but a hormonal background is a possible explanation. Bartley and Hultquist (1950) claim to have found a higher proportion of strongly regressive hypernephromas among patients with endocrine disturbances. Whisenand *et al.* (1962) have reported a higher incidence of cellular hyperplasia in certain endocrine glands in patients with renal adenocarcinoma compared with non-cancer control cases.

Polycythaemia may occasionally occur in patients with renal adenoma or adenocarcinoma, and such cases provide a direct link between hormonal activity and renal adenocarcinoma in man. Thus removal of a renal tumour may bring about remission of polycythaemia which recurs with the appearance of metastases. Hewlett *et al.* (1960) have found increased amounts of erythropoietin in extracts of renal adenocarcinoma from polycythaemic patients. As Riches (1963) points out, some renal tumours resemble those of the thyroid, parathyroid, and suprarenals in the ability of both the primary tumour and its metastases to produce a specific hormonal effect.

Male Predominance in Renal Cancer.—Small renal cortical adenomas are rather common lesions found more often in males than in females. Adenocarcinoma occurs twice as often in men as in women. Spontaneous regression of renal cancer occurs predominantly in the male sex: of a total of 16 cases found in the literature only two were in women (Buehler *et al.*, 1960; Prentiss *et al.*, 1962). The experimental hamster renal tumour is produced by oestrogens normally only in males. In relation to this sex predominance it was interesting to note that when tritium-labelled stilboestrol was administered to hamsters the concentration of this hormone in the kidney was significantly greater in male than in female animals (Ghaleb, 1961). The sex factor in renal neoplasia, together with the known effects of androgens and other sex hormones on the kidney, suggests that if there is a hormonal background to the development and progress of renal cancer, it may be of gonadal origin.

Testosterone Treatment in Human Renal Cancer

Case Report

In January 1960 a dock labourer aged 58 presented at his local hospital complaining of a painful swelling of the right leg. A fixed soft mass 8 cm. in diameter was present over the anterior aspect of the tibia. X-ray examination showed a large underlying osteolytic lesion (Special Plate, Fig. 2A), biopsy of which revealed secondary adenocarcinoma typical of renal cell origin. The patient was anaemic and had recently lost over 20 lb. (9 kg.) in weight. There were no clinical signs to suggest the presence of a renal tumour. Subsequent radiological investigations, however, at the Royal Marsden Hospital revealed a mass in the left kidney and further metastases in the cranial vault (Special Plate, Fig. 4A), the upper zone of the left lung, and the left hilar region (Special Plate Fig. 3A). Nephrectomy was performed on 11 February 1960.

Pathological Report (Dr. N. F. C. Gowing).—Left kidney weighs 900 g., the lower half of which is replaced by a lobulated tumour mass 11.5 by 10 by 9.5 cm. The renal vein is filled with a cylindrical mass of growth. In the upper half of the kidney there are four discrete cortical nodules up to 1 cm. in diameter. *Histology:* Sections show a primary carcinoma of the renal parenchyma (hypernephroma) (Special Plate, Fig. 5). There are areas of both

"clear" and "granular" cells. In some fields differentiation is poor. There is a considerable amount of necrosis and fibrosis. Invasion of the renal vein is confirmed. Separate nodules of similar tumour are present in the cortex of the upper half of the kidney.

Because of pain and risk of fracture irradiation was given to the deposit in the upper tibia beginning on 18 February (250 kV x rays; H.V.L. 3.5 mm. Cu; tumour dose 4,500 r in four weeks). At the end of this time it was evident that the intrathoracic and also the skull metastases were increasing in size and that new osteolytic areas were developing in the right tibia below the recently irradiated zone. Treatment with the synthetic progestational agent Provera (medroxyprogesterone acetate), 100 mg. by mouth three times daily, was begun on 19 March. On 31 March curettage of the tibial deposit was carried out with insertion of a Hodgkinson intramedullary nail, the bone defect being replaced by fragments from the iliac crest (Mr. G. R. Fisk).

X-ray examination on 17 April showed that there had been a further increase in the skull and hilar metastases (Special Plate, Fig. 3B). The dose of Provera was therefore raised to 500 mg. daily. During the next four weeks the patient's general condition greatly deteriorated. He lost more weight, became apathetic, with bouts of aggressive behaviour, and developed a left hemiparesis. Considerable extension of the skull metastasis occurred (Special Plate, Fig. 4B). A small deposit appeared in the upper zone of the right lung and new osteolytic lesions were seen in the tibia below the previously irradiated area (Special Plate, Fig. 2B). In view of these signs of tumour advancement Provera therapy was abandoned on 17 May and injections of testosterone propionate were begun, 100 mg. intramuscularly daily, five days a week. Four weeks later his general condition had improved greatly and after eight weeks he was described as "a new man." In September androgen therapy was continued, using a maintenance dose of 50 mg. of methyltestosterone daily. The improvement in general health following the change from Provera to testosterone was almost immediate and the metastases, which had previously been advancing rapidly, became stationary, as judged from films taken eight weeks later. Seven months after beginning testosterone treatment there were well-marked radiological signs of tumour regression in the tibia, skull, and chest (Special Plate, Fig. 3C).

Eighteen months after starting testosterone the patient had gained some 50 lb. (22.7 kg.) in weight and was enjoying good health and working full-time on security duties at the London Docks (Special Plate, Figs. 1A and 1B). There were no signs of hemiparesis and the metastases in the skull and in the middle and lower end of the tibia (not irradiated) had disappeared; the upper end of the tibia (irradiated) showed considerable recalcification. The right lung was clear and the left hilar mass was no longer evident. Several small discrete lesions remained in the upper zone of the left lung.

The patient enjoyed excellent health with no clinical or radiological evidence of active disease for 35 months from the time testosterone was started. One morning in April 1963 he suddenly collapsed and was admitted to his local hospital with a left hemiplegia. A mass of lymph nodes appeared in the left supraclavicular fossa and increased rapidly.

In July he was transferred to the Royal Marsden Hospital. There were no new skeletal lesions and the sites of the previous deposits in the tibia and skull showed no signs of renewed activity (Special Plate, Figs. 2C and 4C). Chest x-ray film, however, now revealed metastases in the right lung. A fixed mass of glands, 7 by 5 cm., was present in the left supraclavicular fossa. Stilboestrol (15 mg. daily), prednisone (20 mg. daily), and testosterone propionate (100 mg. intramuscularly daily) were all tried in turn, but without signs of tumour regression. His general condition continued to deteriorate and he died on 4 October 1963.

Necropsy by Dr. A. Levene revealed widespread metastases of renal adenocarcinoma in both lungs, the myocardium, thyroid, right adrenal, and the mediastinal and supraclavicular lymph nodes. The histological appearances were comparable with those of the primary tumour removed over three years previously. A haemorrhagic area, 1.5 cm. in diameter, of recent onset was present in the rostral end of the left corpus striatum in the centre of which was a metastasis. A further tumour deposit, 1 cm. in diameter, was found in the basilar portion of the pons on the right. The pontine tumour was immediately adjacent to a circumscribed area of cystic gliosis (Special Plate, Fig. 6). These appearances in the pons were consistent with past tumour regression and recent recrudescence of growth. Such events were compatible with the history of a left-sided weakness in May 1960, signs of which promptly

disappeared with the introduction of testosterone treatment, and the second episode of left hemiplegia five months before death, which failed to respond to various hormones. It was of great interest to find that the previous large skull defect at the bregma had been completely bridged over by a dense fibrous membrane, approximately 5 cm. in diameter, histological examination of which revealed no evidence of residual tumour (Special Plate, Fig. 4D).

Discussion

This patient is one of four cases showing well-marked radiological signs of regression in a series of 20 consecutive cases of progressive metastatic renal adenocarcinoma treated with various hormones (Bloom, 1964). Regression in the three other cases was noted during treatment with Provera (6 α -methyl-17 α -hydroxyprogesterone acetate), a powerful synthetic progestational agent, practically devoid of androgenic and oestrogenic properties (Babcock *et al.*, 1958) and of low toxicity (Bloom *et al.*, 1963b). In these three patients the objective improvement was confined to pulmonary metastases and limited to periods of 3, 9, and 20 months. In a fifth patient, a woman aged 63, there was slight reduction in the size of multiple subcutaneous metastases during treatment with testosterone propionate, but no claim is made for this case since the response was limited and lasted for only one month. All 20 patients had multiple metastases and in 15 of them more than one organ was involved. Eight cases were considered "terminal" when hormone therapy was started.

Regression in 4 out of 20 patients with renal carcinoma is in keeping with the response obtained by hormone therapy in such well-established dependent tumours as carcinoma of the breast and carcinoma of the endometrium. As with dependent tumours in general, so in the case reported here, there was recrudescence of tumour activity after a period of control. It was of interest that the response during testosterone treatment was maintained for practically three years, and that the skeletal lesions were radiologically healed at the time of death; in the case of the skull this was confirmed by histological examination.

The growth of prostatic cancer can be accelerated by the administration of testosterone, and, occasionally, of breast cancer by oestrogens or androgens. Such an event appeared to be a complication of Provera treatment in our patient with carcinoma of the kidney. As soon as this hormone was changed for testosterone there was a dramatic improvement in general health associated with inhibition of further growth of renal cancer metastases, followed later by tumour regression.

Other aspects of treatment have been discussed elsewhere (Bloom, 1964). Until a lead can be obtained from additional clinical experience, from biochemical studies, or from the effect of various hormones on the patient's own tumour grown in tissue culture (work in progress at the Royal Marsden Hospital and at the Chester Beatty Research Institute), the choice of endocrine treatment for a particular case of disseminated renal cancer must remain largely empirical.

Spontaneous Regression of Renal Carcinoma

Was the regression of metastases observed in the case reported here and in three other cases referred to the result of hormone therapy or due to a spontaneous event? Partial or complete natural regression of metastases in renal cancer is a well-recognized but rare phenomenon. No examples were seen by Riches (1963) in a personal series of 130 cases. Everson and Cole (1959) were able to find only 112 authentic cases of natural regression of various cancers in the world literature since 1900, and 11 of these had carcinoma of the kidney. In a more recent review Everson (1964) considered that of a total of 1,000 cases of tumour regression reported in the literature or by personal communication only 130 could be accepted as probable examples of true spontaneous regression, and of these 21 had renal carcinoma.

Spontaneous disappearance of renal cancer appears nearly always to involve pulmonary metastases. Smithers (1962) lists 10 such cases from the literature, which was reviewed by Sakula (1963). This last author refers to 11 reported cases and adds one of his own. Further cases are reported by Buehler *et al.* (1960), Miller *et al.* (1962), and Prentiss *et al.* (1962), making a total of 16 published cases. Everson (1964), in discussing his 21 collected cases of regression of renal cancer, mentions that in two calcification of the primary tumour occurred, while in a third a local recurrence disappeared after development of an abscess: in all the remaining 18 cases regression was confined to pulmonary lesions.

In 15 of Everson's renal cases showing regression of pulmonary metastases this event followed nephrectomy. In our case this operation has been carried out when metastases were known to be present. The patient's general condition did not improve until four months after nephrectomy, and radiological signs of regression of skeletal metastases were not evident until 10 months after the operation. This interval, however, does not exclude a spontaneous event, perhaps related to nephrectomy, as being the underlying cause of improvement in our patient, since intervals of three months to two years between operation and signs of tumour regression have been quoted in many of the reported cases. Immediately after the nephrectomy in our case there was a further increase in skeletal and pulmonary metastases, and during treatment with Provera these changes appeared to be accelerated with marked deterioration in general health and the onset of a left hemiparesis. The rapid improvement in general condition within four weeks, the decrease in hemiparesis within six weeks, and the halt of metastatic growth seen in x-ray films taken eight weeks after changing to testosterone encourage us to suggest that these events were related to the change in hormone treatment. Furthermore, to the best of our knowledge, spontaneous regression of skeletal metastases in renal carcinoma has yet to be reported, although bone involvement in this disease is common.

In view of the rare occurrence of spontaneous regression in renal carcinoma we feel that the objective signs of improvement observed in a patient receiving testosterone and in three others treated with Provera in a consecutive series of 20 cases, all with progressive metastatic renal cancer, may be due to the hormone therapy and not the result of natural regression. This concept is supported by the short interval in these cases between the administration or change of hormone preparation and clinical improvement.

Conclusion

In presenting this communication it is hoped that other workers will test for hormone-responsiveness in patients with metastases from cancer of the renal parenchyma for whom no other treatment is feasible. Hormone administration is not advocated at present for patients with limited or apparently quiescent metastatic disease. Thus a deposit in the spine or pelvis or a lymph-node mass is treated by irradiation and solitary lesions in the lung or brain are considered for surgical excision. If the primary tumour is present and operable, a nephrectomy is performed and the metastases are observed for signs of spontaneous regression. Only when metastases are clearly advancing is hormone treatment introduced. In order not to lose the opportunity of studying possible endocrine changes in such patients before hormonal treatment is undertaken, it would seem preferable at this stage for cases to be investigated in centres with endocrine laboratory facilities, where, for example, gonadotrophin, androgen, and oestrogen estimations can be carried out.

It would be of considerable interest if further observations confirm that a hormone-dependent tumour may arise from the human kidney, an organ which is not a secondary sex structure nor generally thought to be a member of the endocrine system. It is of additional interest that the hormones concerned with

induction and inhibition of renal tumours in the hamster and associated with regression of metastases in four patients with renal cancer are of gonadal origin.

Summary

Attention is directed to the many endocrine factors, including gonadal hormones, which influence renal structure and function, and to the possible role of the kidney itself as an endocrine organ.

Reference is made to renal cortical tumours which can be induced in male hamsters by prolonged oestrogen treatment and prevented by the simultaneous administration of testosterone or of progesterone. Sex is an important factor in cancer of the human kidney. The disease occurs twice as often in men as in women, and spontaneous regression is seen predominantly in males.

A man aged 58 whose general condition was deteriorating with skeletal and intrathoracic metastases after nephrectomy for renal carcinoma was treated with hormones. Tumour growth appeared to be accelerated during the administration of a progestational agent, Provera (medroxyprogesterone acetate; 6 α -methyl-17 α -hydroxyprogesterone acetate). With a change to testosterone propionate there was rapid improvement in general health with subsequent regression of metastases for almost three years. Death occurred with widespread soft-tissue deposits, the skeletal lesions remaining radiologically healed. Histological examination of a previous large osteolytic deposit in the skull showed no residual tumour.

The case described here is one of four cases showing well-marked objective signs of tumour regression in a consecutive series of 20 patients with progressive metastatic renal cancer treated with hormones: the three other patients received Provera. Reasons are given for suggesting that the regression of metastases observed in these cases may be the result of hormone treatment.

Attention has been given to the subject of spontaneous regression of renal cancer. At this stage it is impossible to rule out this phenomenon as the explanation for the observed response in the hormone-treated cases, but, if so, the incidence of natural regression in this disease must be greater than is at present generally appreciated.

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Figs. 1A and 1B have been reproduced by kind permission of the Editor of the *British Journal of Cancer*.

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Relief of Post-operative Pain: Comparison of a 25% Nitrous-oxide and Oxygen Mixture with Morphine

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Nitrous oxide has had a wide use as an analgesic in midwifery and in dental surgery, but its use does not appear to have been investigated for the relief of post-operative wound pain.

We describe here a study designed to compare the relative potency of nitrous oxide and morphine for relief of pain in patients during the first 48 hours after upper abdominal operations. Post-operative pain in such patients restricts breathing to a marked degree, and the relief by analgesics of this restriction can be assessed by simple tests of vital capacity in the manner described by Overholt (1930), Bromage (1955), and Masson (1962). Previous work on volunteers (Chapman *et al.*, 1943; Sonnenschein *et al.*, 1948; Delisle Burns *et al.*, 1960; Dundee and Moore, 1960; Parkhouse *et al.*, 1960; Robson *et al.*, 1960; Dundee *et al.*, 1962) suggested that 25% nitrous oxide in oxygen was the most suitable concentration for this study.

Material and Methods

The investigation was limited to patients under the age of 60 who had operation wounds in or extending to the upper abdomen. Prior to operation the patients were seen, the nature of the trial was explained, and their co-operation obtained; vital capacity and peak expiratory flow readings were then

measured and the nitrous oxide and oxygen breathing apparatus was demonstrated.

If vital capacity is measured before operation and again after operation, when the patient is fully recovered from the anaesthetic, its diminution gives some measure of the impairment of respiratory movement. This can be taken as some measure of the degree of pain. If this pain is then relieved by an analgesic the vital capacity increases in proportion to the efficacy of the drug. A perfect analgesic will restore the vital capacity to virtually the pre-operative value, whereas a drug having no effect will make no difference to the vital capacity. We therefore used changes in vital capacity, and, to a less extent, those in peak expiratory flow rate, as a way of assessing the analgesic effects of nitrous oxide and morphine.

Vital Capacity.—This was measured by the Wright respirometer used with a mouth-piece and Ruben valve, and with a nose-clip applied. After practice readings the mean of three readings was noted. Although the Wright respirometer is less accurate than bulkier apparatus for vital capacity measurement, it was thought to give satisfactory comparative readings since the same respirometer was used in every case.

Peak Expiratory Flow Rate.—The Wright peak flow meter was used and the mean of three readings taken after practice "puffs."

25% Nitrous Oxide in Oxygen Mixture.—The mixture was delivered to the patient from a specially calibrated Walton 5 machine using a reservoir bag and a non-rebreathing circuit with a Ruben valve. The "pressure" control was adjusted so that the reservoir bag did not collapse during inspiration while

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