MEDROXYPROGESTERONE ACETATE IN THE TREATMENT OF RENAL CELL CARCINOMA (HYPERNEPHROMA)

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Medroxyprogesterone acetate, a potent synthetic progestational steroid, was administered to 23 patients with metastatic renal cell carcinoma. Seven patients received 300 mg/d orally. Six patients received 100 mg/d intramuscularly of the commercial preparation Provera. Ten patients were given 400 mg/w intramuscularly of an investigational preparation. Twenty-one patients completed a minimum treatment period of 6 weeks and were considered evaluable. There were one complete and two partial objective remissions to the parenteral preparations. No responses were observed with the oral preparation. The dose to response varied from 5.2 to 9.0 Gm and the duration of response from 4 to 30+ months. There did not appear to be a correlation of response with age, duration of disease, or histologic grade or cell type. A "symptom status" indicating severe disability from disease did adversely affect response. Minimal side effects were weakness in two patients, loss of libido in one male patient and minimal signs of virilism in one female patient. Eleven patients who showed progressive disease after an adequate trial of medroxyprogesterone acetate received further treatment with testosterone. There was one partial objective response of 5 months' duration. These results are superior to those obtained with chemotherapy.

THE INCIDENCE OF RENAL CELL CARCINOMA is 2% of all human cancer and appears to be increasing.[6, 19, 40] Seventy-two per cent of patients with inoperable or metastatic tumor are dead within 1 year and 93% within 2 years.[45] In the operable group, Riches' review of the literature reveals 50% 3-year survival, 40% 5-year survival and 20% 10-year survival.[41] As death from intercurrent disease varies from approximately 5 to 20%,[2, 42, 45] it is apparent that most of these patients will present for some type of additional therapy. While radiotherapy is of great value in the palliation of metastatic bone lesions and in reducing the pain from an inoperable primary lesion, chemotherapy has proven of questionable value in achieving worthwhile palliation.[55]

In 1964 Bloom[4] reported objective partial regressions in advanced metastatic disease in four of 20 patients treated with hormones. Regressions were seen with the progestational agent, medroxyprogesterone acetate, as well as with testosterone proprionate. Corticosteroids were apparently ineffective. By 1967 he had expanded his series to 38 patients and reported eight partial responses ranging in duration from 2 to 35 months.[3] Ten of these patients were terminal and died before completing 6 weeks of treatment; they are considered unevaluable; therefore, the overall response rate is 28%. Subsequent confirmation has not appeared in the literature, except for an isolated response noted by Woodruff.[55] For this reason, we wish to report our experience with a series of 23 patients with disseminated renal carcinoma treated with medroxyprogesterone acetate. Testosterone was administered to those patients who failed to show improvement on medroxyprogesterone acetate therapy when possible. Four objective remissions were obtained, thus confirming Bloom's observations. In addition, we note the effect of histologic grading and dosage schedule on response.

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MATERIALS AND METHODS

Twenty-three patients with a diagnosis of metastatic renal carcinoma who were re-

TABLE 1. Patient Status

No. patients	Median age (range)	Sex M/F	Symptom status* 1	2 & 3	4	Median duration of disease† (mo)	(range)	Prior treatment* Nephrectomy	Radiotherapy	None
23	57	15/8	7	8	8	6	<1–72	20	3	3

* See text.
† From diagnosis to hormone therapy.

ferred to the medical service of The University of Texas M.D. Anderson Hospital and Tumor Institute between June 1, 1965 and August 1, 1967 are included in this report. The pertinent clinical data are summarized in Table 1. All patients were accepted for treatment regardless of the extent of disease. The pathologic findings were reviewed and the diagnosis confirmed in each patient before initiation of therapy.

A second review of the pathologic findings was conducted at the end of the study with the aim of further classification into low, moderate, and high degree of malignancy, or grades, I, II and III according to the criteria of Griffith and Thackray.[14] Grade I consists of well-developed tubule formation or papillary cystic structures. Grade III shows marked disorganization with variability in size and shape of individual cells and increased mitotic activity. Grade II shows cells that are of uniform size and shape but are not organized into any discrete arrangement. Cell type was further classified into clear, grandular, mixed and spindle, as it is felt by some that prognosis is improved when clear cells are predominant.[9, 12, 35, 37] While many authors feel that cell typing is of doubtful value because of the diversity of cell types found in about half of the tumors,[36, 53, 54] grade does clearly correlate with prognosis.[17, 40, 41, 53]

Symptom status was evaluated as follows: 0 = no symptoms and fully active; 1 = symptoms, fully ambulatory but incapable of full time work; 2 = bed rest less than 50% of the time but requires nursing assistance; 3 = bed rest more than 50% of the time; and 4 = bedfast.

Tumor response was graded as follows: Complete regression constituted disappearance of all palpable or radiologically distinct nodules. Partial regression constituted a greater than 50% decrease in the product of the greatest diameters of any measurable tumor. No response included either no change in the size of tumor masses or increase in their size.

Medroxyprogesterone acetate (MPA) was administered in 3 dosage regimes:

1. Seven patients were initially treated using Bloom's procedure of 300 mg/d orally in three divided doses of ten tablets each.

2. Six patients received 100 mg/d in 2 cc intramuscularly of the commercial preparation Provera.*

3. Ten patients received 400 mg of the investigational depot preparation in 1 cc intramuscularly once weekly.† Two patients were subsequently treated with 500 mg once weekly of the commercially available preparation because of a supply shortage.

Therapy was continued for 6 consecutive weeks and, if there was no evidence of tumor progression, an additional 6 weeks of therapy was prescribed. Four patients receiving 400 mg per week showed tumor progression at the 6- and 12-week periods and therapy was changed to large dose depot MPA, 1.0 Gm twice weekly, for a minimum period of 6 weeks.

Testosterone, in either the proprionate or aqueous form, 100 mg daily intramuscularly, was administered to 11 patients who failed to respond to treatment with MPA for a minimum of 6 weeks. If there was minimal or no change in tumor status, therapy was continued. The only precautions taken with both drugs was to limit sodium chloride intake in three patients with manifest pedal edema.

RESPONSE

Two patients died of their disease before completing 6 weeks of treatment and are considered unevaluable. There were no re-

* Medroxyprogesterone acetate, The Upjohn Co., Kalamazoo, Mich.

† We are indebted to The Upjohn Company and to Samuel S. Stubbs, MD, Department of Medical Development, for supplying the investigational depot preparation of medroxyprogesterone acetate.

TABLE 2. Patients Showing Objective Response

Initials	Age	Sex	Symptom status*	Dose†	Dose to response (Gm)	Rapidity to response‡	Quality of response	Duration of response (mo)
				Medroxyprogesterone Acetate				
JP	62	M	1	100 mg/day	9.0	90	Partial regression of pulmonary metastases	4
IP	56	F	3	400 mg/week	6.0	107	Complete regression of mass in right flank, regression of edema right lower extremity	30+
MD	69	M	1	400 mg/week	5.2	93	Partial regression of pulmonary metastases	6
				Testosterone				
GB	51	M	1	100 mg/day	6.7	67	Partial regression of pulmonary metastases	5

* See text.
† Intramuscular route.
‡ Number of days from start of therapy to >50% regression.

sponses in the oral MPA group. Three objective remissions were noted in the parenteral MPA groups (Table 2). Fig. 1 illustrates one of these remissions. One patient (IP) continues in complete remission, receiving 400 mg intramuscularly once weekly. The remaining two patients relapsed and were started on testosterone, without further

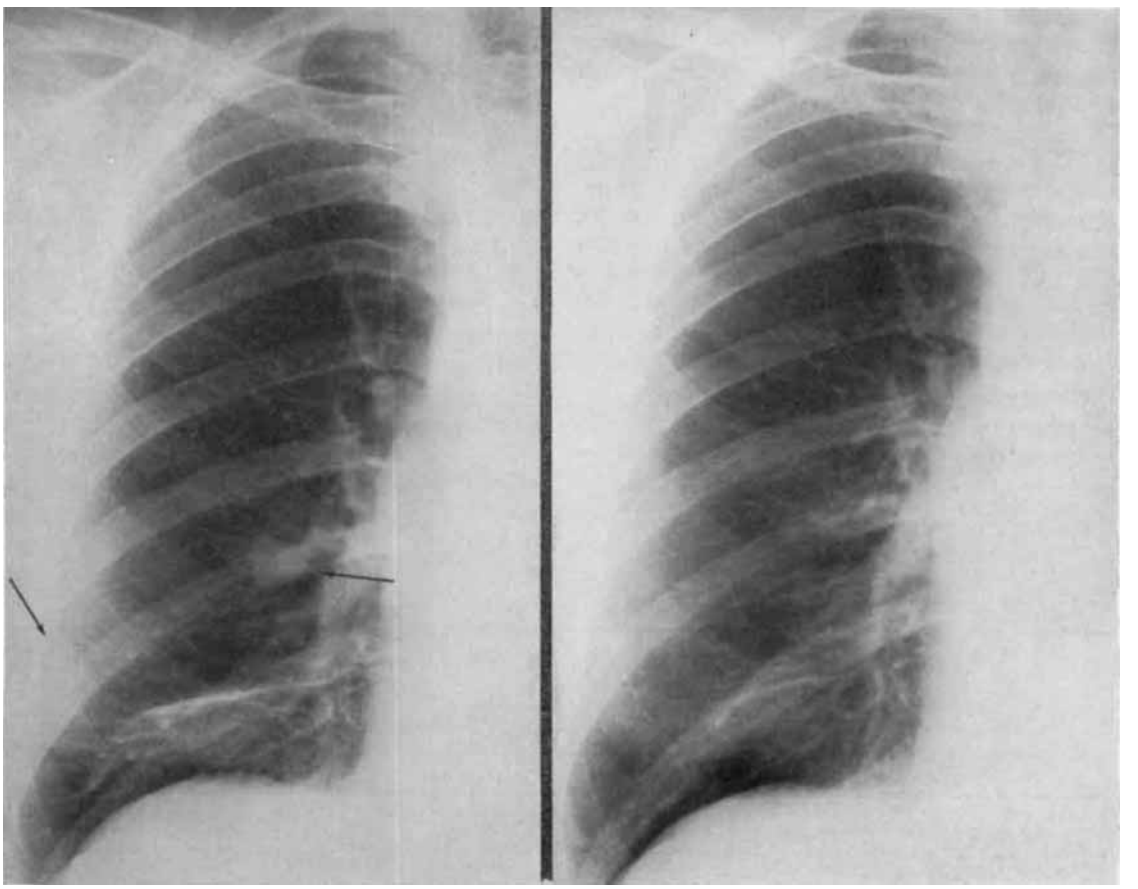

FIG. 1. A (left), Pretreatment roentgenogram of right lung of patient JP, showing two metastatic nodules. B (right), After 3 months of intramuscular medroxyprogesterone acetate therapy.

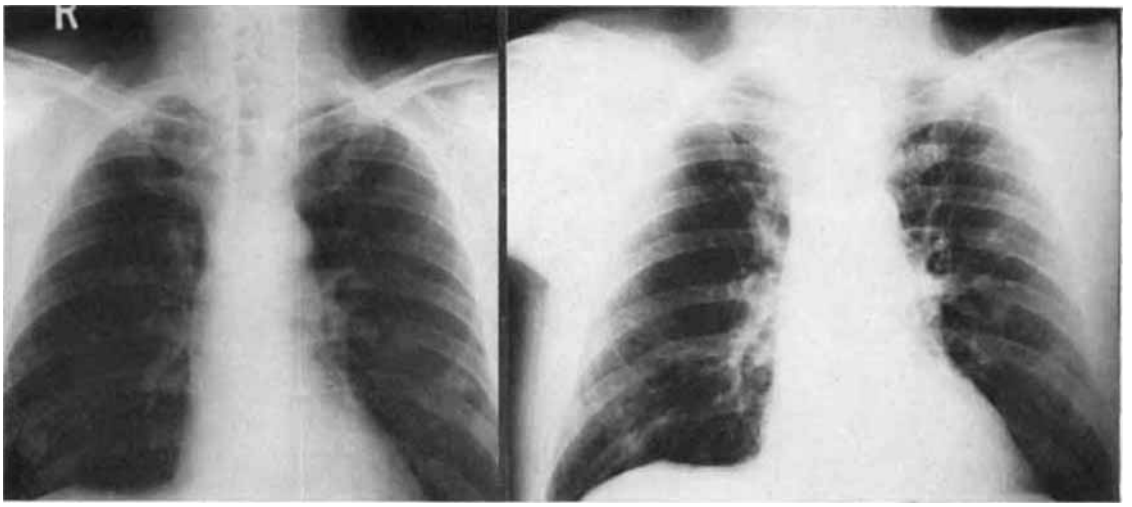

FIG. 2. A (left), Chest roentgenogram of patient GB after 3 months of no response to medroxyprogesterone acetate. B (right), Almost complete response to testosterone proprionate.

response to this drug. A fourth patient demonstrated a striking decrease of pleural effusion on oral MPA but intrapulmonary metastatic deposits did not change and this patient is not considered a responder. A fifth patient showed a greater than 50% decrease in one of three pulmonary lesions on 400 mg MPA per week but this is not regarded a significant response. The four patients who received the large dose of depot MPA continued to show progressive disease. Only one of the 11 patients who received testosterone showed a response (Table 2, Fig. 2). This was maintained for 5 months with continuous testosterone therapy.

Comparison of the responders with the nonresponders (Table 3) shows no significant difference in age, duration of disease prior to therapy or mean dose of MPA during the first 60 days. The difference in symptom status is considered significant, indicating that the nonresponders were more disabled from their illness. The mean survival of the responders is 18+ months with two living and two dead; the mean survival of the nonresponders is 7.7+ month with 8 living and 11 dead.

Fig. 3 shows the distribution of the pathologic findings of the four responders and 16 of the nonresponders who were available for restudy. Although the longest responder (IP) is a well differentiated (grade I) clear cell type, it can be seen that there is little correlation between cell type, grades I and II, and response. The small number of entries in grade III does not allow for a more encompassing statement.

MPA was well tolerated with no serious side effects. One patient complained of loss of libido and two complained of weakness.

TABLE 3. A Comparison of Medroxyprogesterone Acetate Responders with Nonresponders

	No. patients	Mean age (years)	Mean symptom status*	Presenting metastatic sites			Median duration of disease** (mos.)	Mean dose (Gm) first 60 days			
								Oral		Depot	
				lung	skeletal	other		No. pts.	Dose	No. pts.	Dose
Responders	3	62	1.6	2	0	1†	6	0	0	3	4.4
Nonresponders††	18	55	2.4	8	1	10‡	6	6	18	12	4.6

* See text.
† Locally recurrent disease within renal bed and abdomen.
‡ Includes three patients with metastases to lung and skeleton and seven with metastases to lung and liver.
** Diagnosis to hormone therapy.
†† Two unevaluable patients are not included.

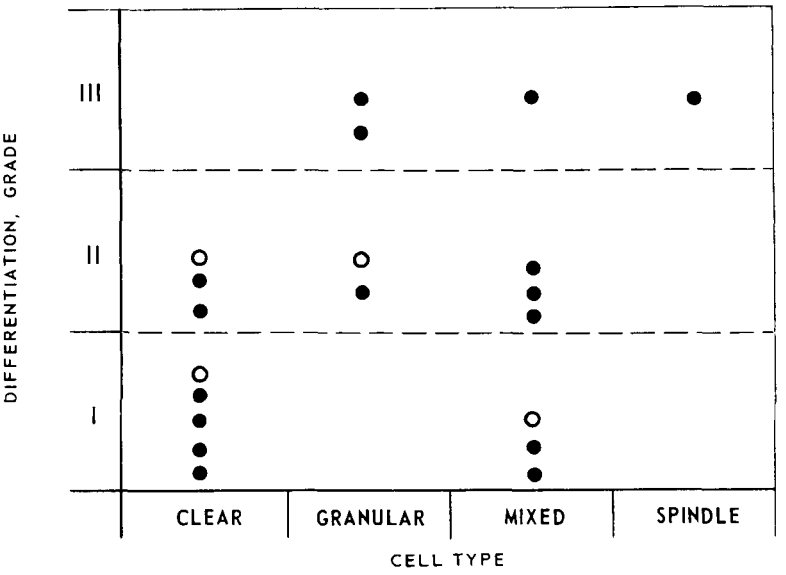

FIG. 3. Histological classification of 20 primary renal tumors. Each symbol represents one patient, o=responder, ●=nonresponder. See text for criteria.

A mild acneiform eruption with minimal facial hirsutism was observed in one female patient on 400 mg MPA intramuscularly per week. Hypercalcemia was encountered in one patient while receiving oral MPA. The dosage was increased to 1.0 Gm daily intramuscularly for 7 days with no effect. Corticosteroids were then started but the patient died after 1 week from a perforated gastric ulcer. A second patient in the unevaluable group presented with hypercalcemia and was treated with oral MPA and oral phosphate mixture (Neutra-Phos®). Calcium levels remained stationary (6.5 mEq/l) until death 1 month later.

DISCUSSION

An endocrine background to renal cell carcinoma in man is suggested by the predominance in males[14, 40, 44] and the glandular pattern of the well-differentiated or grade I tumors.[53] Mostofi has observed that many renal cell carcinomas show a distinctly endocrine pattern[36] and Bloom[3] has commented on the similarity of the response rate to other endocrine-sensitive tumors.

Experimental observations in the golden hamster have demonstrated that renal tumors can be readily induced in the male in response to chronic estrogen administration.[26, 34] The histologic pattern of the estrogen-induced neoplasm is very similar to its human counterpart[23]; a common origin is believed to be the epithelium of the proximal convoluted tubules and possibly also the distal tubules.[28, 39]

If testosterone is administered concomitantly with estrogen, tumor induction is inhibited.[21] This effect is also obtained with progesterone.[29] Attempts to transplant the estrogen-induced tumor to male hamsters are successful only if the host has been pretreated with estrogen.[22] Thus, estrogen is required not only for tumor induction but also for continued growth of the transplant. However, after repeated transplantation over a 5-year period, the latent period for clinically detectable tumor becomes progressively shortened and the transplant finally acquires autonomy.[27]

Renal tumors cannot be induced in the female hamster by estrogens, except under circumstances of low progesterone secretion, as for example following ovariectomy.[29] The mechanism of tumor induction by estrogen is not clear. Since tumor cells from the estrogen-dependent neoplasm can be made to grow in vitro in a hormone-free environment, Algard[1] has suggested that the hormone acts by destroying controls normally operating in the regulation of growth. However, culture of "organ" fragments does necessitate the addition of estrogen to the medium, suggesting that hormone action is effective at the tissue level, possibly acting on the stroma.

Kirkman[26] noted that, while progesterone and testosterone proprionate do inhibit tu-

mor induction by estrogen, they do not prevent transplant growth in a stilbesterol-prepared male host. However, progesterone does markedly inhibit the growth rate of the transplant when compared to testosterone proprionate or the control, thus suggesting possible use in man.

Bloom,[5] working with the transplanted estrogen-independent tumor, found that MPA and testosterone proprionate have no effect on tumor growth, whereas cortisone produces tumor necrosis with a reduction in growth rate. Further, the combination of cortisone and MPA produced almost complete inhibition of tumor growth. Bloom[4] then used this combination in three patients and corticosteroid therapy alone in seven patients with no response. A somewhat different action of cortisone has been reported by Kirkman.[26] Administration of cortisone to the stilbesterol-treated transplant-bearing male hamster resulted in a significant increase in primary renal tumors, as well as metastases. In further experiments cortisone alone would not maintain transplant growth.

MPA is well known as a potent progestational agent but has many additional actions which may be of importance in explaining antitumor activity. It will cause gonadal atrophy in the experimental animal[11, 13] and gonadal suppression in man.[16, 31, 48] This effect is the result of suppression of pituitary gonadotrophin rather than of a direct effect on the gonad.[30] It will also cause a marked reduction of the hypoglycemia-induced growth hormone response to insulin and inhibits the effect of arginine infusion on growth hormone release.[49] Extreme atrophy of the adrenal gland follows administration to the male and female rat and this is associated with decreased pituitary ACTH content.[20, 30] However, Kupperman[31] and Segaloff[46] report no depression of 17-ketosteroid and 17-hydroxycorticoid excretion in patients treated with MPA. Rather, this synthetic hormone has been demonstrated to have a significant glucocorticoid action and will sustain an adrenalectomized patient without supplementary mineralocorticoid therapy for brief periods.[8]

Of further interest is the prolonged duration of action of parenterally-administered MPA as evidenced by protracted adrenal hypofunction,[32] azospermia in experimental animals[11] and amenorrhea of 4 to 7 months' duration following cessation of treatment.[15] These observations are best explained by the very slow metabolic turnover as shown by the recovery of 98% of the tritiated drug in urine and stool of dogs over a 40-day period following intramuscular injection or 180 days following subcutaneous administration.[15]

In addition to these known actions MPA may exert a direct action on proliferating neoplastic cells, as Heckman[18] has demonstrated with endometrial carcinoma in tissue culture. Stone[52] has reported that progesterone suppresses HeLa cells in culture and Rivera[43] noted that progesterone was extremely toxic in organ cultures of mouse mammary tumors. There have been few clinical trials of progestational agents in nonendocrine tumors, but Jolles[24] has recently reported objective regressions in leiomyosarcoma of the uterus and carcinoma of the cervix, suggesting direct action on the tumor. Smith[50] has reported disappearance of perineal metastases from endometrial carcinoma following direct injection of MPA, despite failure to respond to systemic treatment.

Of further importance may be the metabolic effects of sex steroids which are essentially unrelated to their primary actions on the genital tract. Thus, progesterone in a dose of 50 mg/d is catabolic in man, causing a significant rise in urinary nitrogen in association with a fall in most plasma amino acids.[33]

Progestational agents produce about a 20–30% remission rate in mammary and endometrial cancer[25, 38, 51] and large doses are usually required. High dosage also appears desirable in the treatment of renal cell carcinoma, as there may be a spectrum of tumor sensitivity suggested by results with progestational therapy of endometrial carcinoma.[47] It is apparent that a dosage of 400 mg once weekly intramuscularly is capable of producing complete remission and it has now become our practice to initiate therapy at this dosage. Our results show that a further increase in dosage will not improve the remission rate.

While MPA is apparently well absorbed from the gastrointestinal tract in most patients with non-neoplastic disease, we believe there are several reasons to use the depot preparation preferentially. The oral preparation in the dosage recommended is much more expensive. Further, a malabsorption syndrome has recently been described in a high percentage of patients with neoplastic disease not involving the gastrointestinal

tract.[10] The characteristic abnormal biochemical parameters are also associated with jejunal biopsy findings of partial villous atrophy. It seems prudent that, in evaluating any new therapy in the cancer patient, the parenteral route be initially used. Lastly, in constitutional sexual precocity, MPA has been used with success and significantly reduces the pituitary gonadotrophin level.[31] However, the drug is ineffective when given by the oral route.

Brenner[7] has shown through graphic analysis of metastatic lesions in the lungs that renal cell carcinoma may be slow growing with a boubling time of 8 months or rapidly growing with a doubling time of about 1.3 months. Therefore, brief trials of several weeks' duration may represent inadequate therapy in the slowly growing lesions, even though Bloom states that regressions are usually in evidence by 4 to 6 weeks.[3] In our experience the time to come to a full partial response is about 3 months, although regressions are measurable at 60 days. Since the combined mean survival of the responders of Bloom's series and our own is 16+ months and since the expected mean survival of patients with pulmonary metastases is about 7 months,[45] it appears that objective response is accompanied by prolongation of survival.

REFERENCES

1. Algard, F. T.: Hormone-induced tumours—I. Hamster flank organ and kidney tumors in vitro. *J. Nat. Cancer Inst.* 25:557-572, 1960.

2. Arner, O., and Von Schreeb, T.: Renal adenocarcinoma prognosis. *Acta Chir. Scand.* 132:370-376, 1966.

3. Bloom, H. J. G.: Treatment of renal cell carcinoma with steroid hormones—Observations with transplanted tumors in the hamster and incurable cancer in man. *In* Renal Neoplasia. Boston, Little, Brown and Company, 1967; pp. 605-633.

4. ———: Hormone treatment of renal tumors—Experimental and clinical observations. *In* Tumours of the Kidney and Ureter. Baltimore, Williams and Wilkins Company, 1964; pp. 311-338.

5. ———, Dukes, E. C., and Mitcheley, B. C. V.: Hormone-dependent tumours of the kidney—I. The oestrogen-induced renal tumour of the Syrian Hamster. Hormone treatment and possible relationship to carcinoma of the kidney in man. *Brit. J. Cancer* 17: 611-645, 1963.

6. Boyland, E.: Causes of cancer of the kidney. *In* Renal Neoplasia. Boston, Little, Brown and Company, 1967; pp. 195-217.

7. Brenner, M. W., Holsti, L. R., and Perttala, Y.: The study by graphical analysis of the growth of human tumours and metastases of the lung. *Brit. J. Cancer* 21:1-13, 1967.

8. Camanni, F., Massara, F., and Molinatti, G. M.: The cortisone-like effect of 6α-methyl-17α-acetoxyprogesterone in the adrenalectomized man. *Acta Endocr.* 43:477-483, 1963.

9. Claes, G.: Concerning the relationship between the morphology and the symptomatology of hypernephroma. *Urol. Int.* 15:265-279, 1963.

10. Dymock, I. W., MacKay, N., Miller, V., Thomson, T. J., Gray, B., Kennedy, E. H., and Adams, J. F.: Small intestinal function in neoplastic disease. *Brit. J. Cancer* 21:505-511, 1967.

11. Ericsson, R. J., and Dutt, R. H.: Progesterone and 6α-methyl-17α-hydroxyprogesterone acetate as inhibitors of spermatogenesis and accessory gland function in the ram. *Endocrinology* 77:203-208, 1965.

12. Foot, N. C., Humphreys, G. A., and Whitmore, W. F.: Renal tumors—Pathology and prognosis in 295 cases. *J. Urol.* 66:190-200, 1951.

13. Glenn, E. M., Richardson, S. L., and Bowman, B. J.: Biologic activity of 6α-methyl compounds corresponding to progesterone, 17α-hydroxyprogesterone acetate and compound S. *Endocrinology* 8:265-285, 1959.

14. Griffith, I. H., and Thackray, A. C.: Parenchymal carcinoma of the kidney. *Brit. J. Urol.* 21:128-151, 1949.

15. Gunning, J. E., and Molyer, D.: The effect of medroxyprogesterone acetate on endometriosis in the human female. *Fertil. Steril.* 18:759-774, 1967.

16. Hahn, H. B., Hayles, A. B., and Alexander, A.: Medroxyprogesterone and constitutional precocious puberty. *Proc. Mayo Clin.* 38:182-189, 1964.

17. Hand, J. R., and Broders, A. C.: Carcinoma of the kidney—The degree of malignancy in relation to factors bearing on prognosis. *J. Urol.* 28:199-216, 1932.

18. Heckman, V.: The action of norhydroxyprogesterone caproate on endometrial cancer in tissue culture. *German Med. Monthly* 11(2):48-49, 1966.

19. Hewitt, C. E.: 1. Renal carcinoma—A clinical challenge. *In* Renal Neoplasia. Boston, Little, Brown and Company, 1967; pp. 3-12.

20. Holub, D. A., Kratz, F. H., and Jailer, J. W.: Inhibition by 6-methyl-17-acetoxyprogesterone of ACTH synthesis and release in the rat. *Endocrinology* 68:173-176, 1961.

21. Horning, E. S.: Endocrine carcinogenesis. *Rep. Brit. Emp. Cancer Camp.* 32:65-67, 1954.

22. ———: Observations on hormone-dependent renal tumours in the golden hamster. *Brit. J. Cancer* 10:678-687, 1956.

23. ———, and Whittick, J. W.: The histogenesis of stilbesterol-induced renal tumours in the male golden hamster. *Ibid.* 8:451-457, 1954.

24. Jolles, B.: Progesterone in the treatment of advanced malignant tumours of breast, ovary, and uterus. *Ibid.* 16:209-221, 1962.

25. Kelley, R. M., and Baker, W. H.: Progestational agents in the treatment of carcinoma of the endometrium. *New Eng. J. Med.* 264:216-222, 1961.

26. Kirkman, H.: Estrogen-induced tumors of the kidney—III. Growth characteristics in the Syrian hamster. *Nat. Cancer Inst. Monogr.* 1:1-57, 1959.

27. Kirkman, H., and Horning, E. S.: Endocrine carcinogenesis. *Rep. Brit. Emp. Cancer Camp.* 35:66-67.

28. Kirkman, H., and Robbins, M.: Estrogen-induced tumors of the kidney—V. Histology and histogenesis of the Syrian hamster. *Nat. Cancer Inst. Monogr.* 1:93-139, 1959.

29. Kirkman, H., and Wurster, D. H.: Estrogen-

induced kidney tumors in female Syrian hamsters. *Proc. Am. Assn. Cancer Res.* 2:221, 1957.

30. Kraicer, J., and Logothetopoulos, J.: Correlation of anterior pituitary morphology with thyroid function after 6α-methyl-17α-hydroxyprogesterone acetate. *Endocrinology* 71:660-662, 1962.

31. Kupperman, H. S., and Epstein, J. A.: Medroxyprogesterone acetate in the treatment of constitutional sexual precocity. *J. Clin. Endocr.* 22:456-458, 1962.

32. Logothetopoulos, J., Sharma, B. B., and Kraicer, J.: Effects produced in rats by the administration of 6α-methyl-17α-hydroxyprogesterone acetate. *Endocrinology* 71:660-662, 1962.

33. Landau, R. L., and Lugibihl, K.: The effect of progesterone on the concentration of plasma amino acids in man. *Metabolism* 12:1114-1122, 1968.

34. Matthews, U. S., Kirkman, H., and Bacon, R. L.: Kidney damage in the golden hamster following chronic administration of diethyl-stilbestrol and sesame oil. *Proc. Soc. Exp. Biol. Med.* 66:195-196, 1947.

35. Melicow, M. M.: Classification of renal neoplasms—A clinical and pathological study based on 199 cases. *J. Urol.* 51:333-385, 1944.

36. Mostofi, F. K.: Pathology and spread of renal cell carcinoma. *In* Renal Neoplasia. Boston, Little, Brown and Company, 1967; pp. 41-85.

37. Murphy, G. P., and Mostofi, F. K.: The significance of cytoplasmic granularity in prognosis of renal cell carcinoma. *J. Urol.* 94:48-54, 1965.

38. Mussey, E., and Malkasian, G. D., Jr.: Progesterone treatment of recurrent carcinoma of the endometrium. *Am. J. Obstet. Gynec.* 94:78-85, 1966.

39. Oberling, C., Riviere, M., and Haguenau, F.: Ultrastructure of the clear cells in renal carcinomas and its importance for the demonstration of their renal origin. *Nature* 186:402-403, 1960.

40. Riches, E.: On carcinoma of the kidney. *Ann. Royal Coll. Surg. Eng.* 32:201-218, 1963.

41. Riches, E.: Factors in the prognosis of carcinoma of the kidney. *J. Urol.* 79:190-195, 1958.

42. ———: Analysis of patients with adenocarcinoma in a personal series. *In* Tumors of Kidney and Ureter. Baltimore, Williams and Wilkins Company, 1964; pp. 357-368.

43. Rivera, E. M., Elias, J. J., Bern, H. A., Napalkov, N. P., and Pitelka, D. R.: Toxic effects of steroid hormones on organ cultures of mouse mammary tumors, with a comment on the occurrence of viral inclusion bodies. *J. Nat. Cancer Inst.* 31:671-687, 1963.

44. Robson, C. J.: Radical nephrectomy for renal cell carcinoma. *J. Urol.* 89:37-42, 1963.

45. Royce, R., and Tormey, A.: Malignant tumors of the renal parenchyma in adults. *J. Urol.* 74:23-35, 1955.

46. Segaloff, A., Cunningham, M., Rice, B. F., and Weeth, J. B.: Hormonal therapy in cancer of the breast, XXIV—Effect of corticosterone and medroxyprogesterone acetate on clinical course and hormonal excretion. *Cancer* 20:1673-1678, 1967.

47. Sherman, A. I.: Progesterone caproate in the treatment of endometrial cancer. *Obstet. Gynec.* 28:309-314, 1966.

48. Shoen, E. J.: Treatment of idiopathic precocious puberty in boys. *J. Clin. Endocr.* 26:363-370, 1966.

49. Simon, S., Schiffer, M., Glick, S. M., and Schwartz, E.: Effect of medroxyprogesterone acetate upon stimulated release of growth hormone in men. *J. Clin. Endocr. Met.* 27:1633-1636, 1967.

50. Smith, J. P., Rutledge, F., and Soffar, S. W.: Progestins in the treatment of patients with endometrial adenocarcinoma. *Am. J. Obstet. Gynec.* 94: 977-984, 1966.

51. Stoll, B. A.: Therapy by progestational agents in advanced breast cancer. *Med. J. Aust.* 1(9):331-334, 1966.

52. Stone, D.: Selection of HeLa cells sub-lines resistant to steroids from a HeLa cell strain sensitive to the growth inhibitory influences of desoxycorticosterone, progesterone and testosterone. *Endocrinology* 71: 233-237, 1962.

53. Thackray, A. C.: The pathology and spread of renal adenocarcinoma. *In* Tumours of the Kidney and Ureter. Baltimore, Williams and Wilkins Company, 1964; pp. 72-86.

54. Throckmorton, M. R.: Prognosis in hypernephroma—Review of literature and report of 42 cases. *J. Urol.* 73:773-782, 1955.

55. Woodruff, M. W., Wagle, D., Gailani, S. D., and Jones, R., Jr.: The current status of chemotherapy for advanced renal carcinoma. *Ibid.* 97:611-618, 1967.