- Short, R. V. (1960). In *The Biosynthesis and Secretion of Adrenocortical Steroids*, Biochemical Society Symposia No. 18, p. 59. Cambridge Univ. Press, London.
- (1964). *Recent Progr. Hormone Res.*, 20, 303.
- (1965). *Proceedings of the 2nd International Congress of Endocrinology*, p. 940. Excerpta Medica Foundation, Amsterdam.
- Siiteri, P. K., Vande Wiele, R. L., and Lieberman, S. (1963). *J. clin. Endocr.*, 23, 588.
- Simmer, H. H. (1964). *Recent Progr. Hormone Res.*, 20, 391.
- Steen, O., de Moor, P., and Lauweryns, J. (1966). *Proceedings of the 2nd Symposium on Steroid Hormones* (Ghent, June 1965), p. 186. Excerpta Medica Foundation, Amsterdam.
- Surace, M., Luisi, M., Monetta, E., Marescotti, V., and Polvani, F. (1966). *Ibid.*, p. 16.
- Tait, J. F., and Horton, R. (1964). *Steroids*, 4, 365.
- Tamm, J., Schmidt, H., Starcevic, Z., and Klosterhalfen, H. (1966). *Proceedings of the 2nd Symposium on Steroid Hormones* (Ghent, June 1965), p. 77. Excerpta Medica Foundation, Amsterdam.
- Van den Molen, H. J., Groen, D., and Peterse, A. (1965). *Ibid.*, p. 1.
- Vande Wiele, R. L., and Lieberman, S. (1960). In *Biological Activities of Steroids in Relation to Cancer*, edited by G. Pincus and E. Vollmer, p. 93. Academic Press, New York.
- MacDonald, P. C., Gurpide, E., and Lieberman, S. (1963). *Recent Progr. Hormone Res.*, 19, 275.
- Vermuelen, A. (1966). *Proceedings of the 2nd Symposium on Steroid Hormones* (Ghent, June 1965), p. 71. Excerpta Medica Foundation, Amsterdam.
- Warren, J. C., and French, A. P. (1965). *J. clin. Endocr.*, 25, 278.
- Wieland, R. G., de Courcy, C., Levy, R. P., Zala, A. P., and Hirschmann, H. (1965). *J. clin. Invest.*, 44, 159.
- Zimmermann, W. (1935). *Hoppe-Seyler's Z. physiol. Chem.*, 233, 257.

Adrenalectomy for Disseminated Breast Cancer

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The incidence of breast cancer in women in England and Wales has risen progressively for the past 40 years, and during 1964 9,860 women died of it. The cause of death in these cases is metastatic spread of the disease.

Huggins and Bergenstal (1952) showed that control of metastases from breast cancer can be achieved in a proportion of patients by adrenalectomy. This report is based on a personal series of 348 patients (including three males) with a disseminated breast cancer, submitted to bilateral adrenalectomy and gonadectomy during the past 14 years.

The operation is effective in about half of those submitted to it, and the results in hormone-dependent tumours are unsurpassed by any other form of treatment as regards degree of response and length of period of remission, and only equalled by the results of hypophysectomy.

Clinical Material

The ages of the patients varied from 24 to 76 years, but the majority were in the fourth and fifth decades. The series included 24 patients with bilateral mammary cancer and nine with pregnancy or lactational cancer. There is no evidence that the younger age group responded differently from the older; neither was success or failure in any way related to the pre- or post-menopausal state of the patient.

The operative mortality, defined as death within one month of the operation, was 4.3% in the overall series and 1% in the last 100 patients. The technique of the operation in all cases was by the posterior route through the bed of the 11th and 12th ribs. In almost all patients the operation was done in two stages: left adrenalectomy and bilateral oophorectomy followed one week later by right adrenalectomy. No correlation was observed between the histological variety of breast cancer and the response to adrenalectomy.

Site of Metastases.—The commonest site of metastases was the skeleton; in many patients both skeletal and visceral metastases were present, in others lymph nodes were involved, and in some there were cutaneous recurrences. The distribution of metastases is shown in Table I. The histological examination of the ovaries and adrenals showed that 40% of the adrenal glands and nearly 30% of the ovaries were found to be involved by metastases (Lumb and Mackenzie, 1959).

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TABLE I.—Metastases in 348 Patients

Bone	212 (61%)	Brain	12 (3%)
Bone and viscera	172 (50%)	Heart	4 (1%)
Lung and pleura	108 (31%)	Local recurrences of primary tumour	90 (26%)
Liver	59 (17%)		
Eye	14 (4%)		

Choice of Patients for Adrenalectomy

Only half of those submitted to adrenalectomy are likely to benefit from it. The choice of patients for bilateral adrenalectomy therefore presents some difficulty, as there is today no simple, reliable, and generally applicable test to predetermine "hormone-dependence." The response to adrenalectomy is not solely determined by the biological factor of hormone-dependence, and other factors should be taken into consideration.

Extent, Type, and Site of Metastases

The extent of metastatic involvement and the interference with vital functions increase the operative hazard and influence the response to treatment.

The size of the metastases and the type of invasion and spread are more important than the site. Thus hepatic metastases have been reported as less likely to respond than skeletal metastases, but a study of patients with hepatic metastases indicates that a large number of small metastatic nodules may regress completely, whereas one or two large massive deposits will not be affected.

Similarly, pulmonary metastases revealed radiologically as multiple, discrete, spherical shadows may regress completely after adrenalectomy, whereas infiltration of the pulmonary lymphatics (lymphangitis carcinomatosa) invariably fails to respond. Similarly, intracranial metastases at the base of the skull or cerebral or cerebellar metastases may respond if small although multiple, whereas large tumours may kill the patient from a sudden haemorrhage and raised intracranial pressure. These observations indicate that adrenalectomy should be undertaken as soon as metastases are diagnosed and not as a last resort.

Confusion of thought between failure to respond, owing to hormone-independence of the cancer and functional failure of

the organ the seat of metastases, led to the belief that visceral metastases are less hormone-dependent than skeletal metastases.

"Free Period"

The best-known factor in the assessment of the likely response or lack of response to adrenalectomy is the length of the so-called "free period"—the interval between the first treatment (mastectomy) and the occurrence of metastases.

If this free period is short, 12 to 18 months or less, adrenalectomy is not likely to benefit the patient. After a free period of four years or more a favourable response to adrenalectomy occurs in almost 50% of patients.

Personal experience over 14 years indicates that if adrenalectomy proves to be effective it is so irrespective of the site of metastases. In this series several patients with involvement of the liver have shown regression of the hepatic metastases with remission for periods up to three years.

Previous Hormone Treatment

A review of 165 patients in this series previously treated by oestrogens, androgens, or cortisone and subsequently submitted to adrenalectomy shows that (1) lack of response to androgens, oestrogens, or oophorectomy does not mean that adrenalectomy will not control the metastasis; (2) aggravation of symptoms by oestrogens indicates hormone-dependence and so does improvement after oophorectomy; (3) the periods of remission after the administration of androgens or oestrogens, with or without cortisone, are shorter than periods of remission following adrenalectomy; (4) the incidence or frequency of regression is higher after adrenalectomy than after androgens, oestrogens, and steroids; (5) adrenalectomy following prolonged hormone treatment is less frequently effective than adrenalectomy performed as the initial treatment. This is especially the case in pulmonary metastases, as the response to androgens and steroids in these patients is of short duration and is often followed by widespread recrudescence and rapid deterioration of the patient's state, which precludes adrenalectomy.

Many patients submitted to this "medical" trial with a favourable initial response survive a few months only. Dao and Nemoto (1965), in a critical evaluation of adrenalectomy and androgen therapy in disseminated breast cancer, conclude that adrenalectomy should be "performed at the onset, when metastases first become demonstrable, as a primary therapy." The present series confirms their experience, especially as regards pulmonary metastases. They conclude that "the data from this study provide evidence that patients with pulmonary metastases, unless they receive immediate effective treatment, die within a few months. Treatment of such patients with hormonal therapy is equivalent to procrastination."

Critical observation of this series of patients adrenalectomized for disseminated breast cancer indicates that not infrequently the preliminary trial of "simpler" hormonal treatment by androgens, oestrogens, or steroids has proved detrimental to the patient and has rendered "inoperable" a previously "operable" patient. If the chances of a favourable response to adrenalectomy in the previously untreated patient are 50%, this chance is reduced in those previously submitted to medicinal hormone therapy who prove resistant to it and in whom the metastases continue to grow in number and size. Study of these patients makes clear the fallacy of the argument: "there is no harm in trying hormone therapy, and if or when it fails there is still adrenalectomy to turn to."

Many metastases remain for a time clinically silent and undetectable, as shown by the considerable number of ovaries and adrenals found to be involved on histological examination and the discovery at laparotomy of hepatic metastases previously unsuspected. Bilateral adrenalectomy has proved of greater

value when undertaken early, both by the number of remissions and by prolonged periods of control.

Remission and Regression

Objective evidence of a favourable response to adrenalectomy is the regression or disappearance of visible and palpable lesions, healing of ulceration and radiological evidence of regression of pulmonary metastases, healing of pathological fractures, recalcification of osteolytic metastases, and restoration of function—for instance, vision after regression of intraocular metastases.

Regression of lesions can be complete or partial, lasting or temporary. The length of remission varies from a few months to several years. Reactivation of the disease is shown by the appearance of fresh lesions, although no recurrences may develop at the actual site of previous lesions which have regressed following adrenalectomy. The periods of remission achieved in this series are shown in Table II.

TABLE II.—Duration of Remission Following Adrenalectomy

Duration of Remission	Patients		Patients Assessed
	No.	%	
Nil (failures)	109	32	337
Up to 6 months	45	13	320
1 year	61	19	313
2 years	35	11	309
3 "	20	6.5	297
4 "	10	3.4	272
5 to 12½ years	19	7	

Prolonged survival—for periods of 5 to 12½ years—in patients submitted to adrenalectomy between 1952 and 1959 is shown in Table III.

TABLE III.—Prolonged Survival Among 272 Patients Submitted to Adrenalectomy (1952-9)

Years	5	6	7	8	9	10	12	12½	Total
No. of patients	8	4	1	3	1	1	1	2	19 (7%)

This series of 348 patients with disseminated breast cancer includes three with involvement of the heart and pericardium, necessitating aspiration of blood-stained pericardial effusion prior to adrenalectomy; one patient who submitted to oesophagectomy for an oesophageal metastasis from breast cancer, before cortisone became available and adrenalectomy could be undertaken, subsequently developed skeletal metastases, for which adrenalectomy was done. Two patients required post-adrenalectomy gastric resection, and one patient vagotomy and gastro-enterostomy for haematemesis; all three gave a history of previous peptic ulceration, and this was aggravated when cortisone had to be given. Hypercalcaemia in the presence of extensive osteolytic skeletal metastases required pre-adrenalectomy treatment by steroids to render the patient fit for surgery. Primary carcinoma of the breast of *en cuirasse* type proved hormone-independent.

Illustrative Cases of Prolonged Remission and Regression

The clinical histories of eight patients with prolonged survival following bilateral adrenalectomy and oophorectomy are summarized.

Case 1.—Married woman aged 43. Nullipara, pre-menopausal. This case has been described and illustrated (Cade, 1955). The patient developed a local recurrence two years after radical mastectomy for carcinoma of the left breast. The lesion was not controlled by radiotherapy. Bilateral adrenalectomy and oophorectomy in 1953, with rapid and total regression of the lesion. Well and free from recurrence to date, 12½ years later.

Case 2.—Married woman aged 47. Multipara, pre-menopausal. Radical mastectomy in August 1950 for stage I carcinoma of the

right breast. Two years and two months later pain developed in right buttock and leg, which continued for 18 months. Bilateral adrenalectomy and oophorectomy in November 1953 for osteolytic metastases in the left humerus, right ischium, and ninth rib. All the lesions recalcified. Well and free from disease to date, 12½ years later.

Case 3.—Married woman aged 56. Multipara, six years post-menopausal. Radical mastectomy in May 1948 for stage II carcinoma of right breast. Post-operative radiotherapy given. In January 1952 paralysis of left vocal cord developed. In July 1952 x-ray examination showed bilateral pulmonary metastases and paralysis of right diaphragm. Treated by radiotherapy and androgens. Four months later the supraclavicular nodes were enlarged. In February 1954 there were bilateral pulmonary metastases and a mediastinal mass, with paralysis of left vocal cord and of right leaf of diaphragm. Metastases in right supraclavicular lymph nodes and choroidal metastasis in left eye. Bilateral adrenalectomy and oophorectomy in February 1954. Choroidal metastasis regressed completely, with recovery of vision; supraclavicular lymph nodes could no longer be felt. X-ray examination of chest showed complete regression of pulmonary metastases, but paralysis of vocal cord and diaphragm persisted. Well and free from active disease, with complete regression of all metastases to date, 12 years after adrenalectomy.

Case 4.—Spinster aged 48. In July 1950 radical mastectomy for a stage III carcinoma of right breast, previously treated by radiotherapy. In October 1953 a right pleural effusion and paralysis of the right vocal cord developed. Bilateral adrenalectomy and oophorectomy in October 1954. At laparotomy liver contained metastases. Histological examination showed metastases in left adrenal and left ovary. Following adrenalectomy complete remission of all lesions till June 1961—that is six years and eight months—when skeletal metastases appeared in the left pubic ramus and left femur. These were treated by radiotherapy and androgens. Death occurred on 10 June 1963. Following adrenalectomy the patient survived nine years, with complete remission for six years and eight months, although at the time of adrenalectomy there were metastases in the mediastinum, pleura, liver, ovary, and adrenal.

Case 5.—Married woman aged 35. Multipara, pre-menopausal. Radical mastectomy in June 1946 for a stage II carcinoma of left breast. Post-operative radiotherapy given. In December 1957, 10 years after mastectomy, the patient then aged 45 became pregnant but aborted spontaneously in 10th week. During pregnancy local recurrences developed in scar, and metastases were found in the supraclavicular lymph nodes on biopsy. Bilateral adrenalectomy and oophorectomy in December 1957 resulted in complete regression of enlarged lymph nodes and of local recurrence. In January 1964, 17 years after the mastectomy and seven years after adrenalectomy, patient developed carcinoma of the opposite (right) breast and underwent a radical mastectomy. Well to date, nine years after adrenalectomy. No other case where mammary cancer developed several years after adrenalectomy and oophorectomy has been recorded.

Case 6.—Married woman aged 49. Nullipara, pre-menopausal. Radical mastectomy for stage II carcinoma of right breast in December 1954. In March 1957 laparotomy revealed extensive carcinomatous involvement of parietal and visceral peritoneum, omentum, mesentery, and liver. Bilateral adrenalectomy and oophorectomy was done; both ovaries and adrenals contained metastases. All the lesions regressed and patient is alive and clinically free from disease to date, nine years after adrenalectomy.

Case 7.—Married woman aged 56. Nullipara, post-menopausal. Radical mastectomy for carcinoma of right breast in 1947 and

post-operative radiotherapy. In August 1954, seven years after mastectomy, metastases developed in both humeri with pathological fractures. Within four months there was widespread blood-borne dissemination; the skeleton was extensively involved by metastases in skull, both humeri, both femora, left scapula, left clavicle, and several ribs. Liver grossly enlarged to level of umbilicus by multiple metastases proved by biopsy at laparotomy for oophorectomy. Bilateral adrenalectomy and oophorectomy on 4 January 1955. Ovaries and adrenals free from metastases. The response to adrenalectomy was rapid, with healing of pathological fracture, recalcification of all skeletal metastases, and regression of hepatic metastases. Patient returned to full work as school-teacher and led a normal life. Remission lasted for over seven years, when skeletal metastases became active. Post-adrenalectomy survival: seven years eight months.

Case 8.—Married woman aged 43. Hysterectomy for fibroids in 1954. Radical mastectomy for carcinoma of right breast in 1956. In 1959 metastases in right lung and skeletal metastases in skull, ribs, pelvic bones, and both femora. At that time a large duodenal ulcer was shown on barium-meal examination. Bilateral adrenalectomy and oophorectomy in March 1960. Metastases found in one right adrenal and in one of two accessory adrenal glands. Two years later, in 1962, vagotomy and gastrojejunostomy for activation of duodenal ulcer. At that time there was no longer any radiological evidence of pulmonary metastases, and all skeletal metastases had recalcified. Remains well and free from recurrence to date, six years after adrenalectomy.

Summary and Conclusions

The paramount indication for adrenalectomy is disseminated breast cancer, and the natural history of the disease shows clearly that a "solitary" metastasis is evidence of dissemination and that a metastasis remains "solitary" for a short time only.

Pre- and post-adrenalectomy management by cortisone is now fully understood and easily achieved. The operation presents no special difficulty in the hands of a surgeon of average skill; the operation mortality is now 1%. Life on cortisone is almost normal. The earlier adrenalectomy is undertaken the greater the chances of prolonged remission. The response to previous hormonal treatment is not a reliable indication of hormone-dependence, and preliminary hormone therapy often precludes a favourable response from adrenalectomy.

Restoration of function, such as recovery of vision following regression of intraocular metastasis and recovery from various cranial-nerve paralyses from metastatic involvement of the base of the skull, has been achieved following adrenalectomy.

In hormone-dependent tumours relief of pain is achieved almost immediately after adrenalectomy.

Survival for periods of up to twelve and a half years has been achieved with complete regression of skeletal and visceral metastases.

REFERENCES

- Cade, S. (1955). *Brit. med. J.*, 1, 1.
 Dao, T. L., and Nemoto, T. (1965). *Surg. Gynec. Obstet.*, 121, 1257.
 Huggins, C., and Bergenstal, D. M. (1952). *Cancer Res.*, 12, 134.
 Lumb, G., and Mackenzie, D. H. (1959). *Cancer (Philad.)*, 12, 521.