estimated chemically, it was of a low order, particularly in the intermediate ranges. One may conclude that single occasional smears are not accurate enough to give a useful indication of oestrogenic activity in this group of women.

Even with sensitive chemical determinations, selection of those patients most likely to benefit from endocrine ablation is apparently not possible by means of OE, OD, and OT measurements alone. The trend shown by this small series suggests that the subjects with the larger amounts of the more active oestrogens, OE and OD, relative to the less active OT, may be the ones less likely to respond to castration. However, there is much overlapping, and the ratio OE plus OD:OT would not seem to have any practical predictive value.

In most cases the operations were carried out as therapeutic procedures when metastases had actually occurred, rather than as a prophylactic measure. It might be that by the time these women were considered for gonadectomy, tumours which were possibly once hormone-dependent had become autonomous. Another possibility is that tumour growth is dependent not on the absolute amounts of oestrogens secreted but on the balance between the various oestrogens, their metabolites, and other hormones (Bulbrook, Greenwood, and Hayward, 1960). It may be that where surgery is effective it succeeds by altering that balance.

Summary

Oestrone, oestradiol, and oestriol estimations were made pre- and post-operatively on patients with breast cancer who underwent oophorectomy or adrenalectomy, or both.

No difference was found in the pre-operative oestrogen levels of patients who improved and those who did not.

Clinical progress was not correlated with the decrease in oestrogens caused by operation.

No connexion was evident between the histology of the primary tumour and oestrogen levels or clinical response.

We are grateful to the radiotherapy department and surgical staff of University College Hospital for allowing us access to their patients, and we thank the sisters for collection of specimens.

REFERENCES

- Braunsberg, Hannelore, Osborn, S. B., and Stern, Margaret I. (1954). *J. Endocr.*, **11**, 177.
 — Stern, Margaret I., and Swyer, G. I. M. (1954). *Ibid.*, **11**, 189.
 Brown, J. B. (1955). *Biochem. J.*, **60**, 185.
 — Bulbrook, R. D., and Greenwood, F. C. (1957). *J. Endocr.*, **16**, 49.
 Bulbrook, R. D., and Greenwood, F. C. (1957). *Brit. med. J.*, **1**, 662.
 — Hadfield, G. J., and Scowen, E. F. (1958). *Ibid.*, **2**, 7.
 — and Hayward, J. L. (1960). *Lancet*, **1**, 1154.
 — and Williams, P. C. (1958). In *Endocrine Aspects of Breast Cancer*, edited by A. R. Currie, p. 181. Livingstone, Edinburgh.
 Dao, T. L.-Y. (1953). *Science*, **118**, 21.
 Diczfalussy, E., Birke, G., Franksson, C., Hellström, J., Hultberg, S., Plantin, L. O., and Westman, A. (1958). In *Endocrine Aspects of Breast Cancer*, p. 186.
 East, June (1959). *J. Endocr.*, **18**, vi.
 Greenwood, F. C., and Bulbrook, R. D. (1957). *Brit. med. J.*, **1**, 666.
 Jessiman, A. G. (1958). In *Endocrine Aspects of Breast Cancer*, p. 77.
 Johnsen, S. G. (1955). *Acta Endocr. (Kbh.)*, **20**, 101.
 Klinefelter, H. F., Albright, F., and Griswold, G. C. (1943). *J. clin. Endocr.*, **3**, 529.
 Smith, O. W., and Smith, G. V. (1952). *Recent Progr. Hormone Res.*, **7**, 209.

THIOTEPA IN CARCINOMA OF BREAST TREATED BY BILATERAL ADRENALECTOMY AND OOPHORECTOMY

BY

A. B. MILLER, M.B., B.Chir.

Medical Registrar, the Luton and Dunstable Hospital

Watson and Turner (1959) described a new approach to treatment of metastatic carcinoma of the breast by combining thiotepa with testosterone. It was claimed that the combination of the cytotoxic agent with testosterone proved more effective than either agent used alone. Tumour-inhibitory effects were seen in 88% (30 out of 34 cases). Encouraged by these results, it was decided at this hospital to try the effect of thiotepa on patients with advanced carcinoma of the breast who had previously been subjected to bilateral adrenalectomy and oophorectomy. The patients selected for treatment had either failed to improve after operation or had relapsed after a period of improvement.

Testosterone was given orally as methyltestosterone in doses of 20 to 30 mg. daily. This route of administration and the dosage were chosen as the method is the one used at this hospital. Nevertheless, the drug was poorly tolerated by many patients. Hirsuties, deepening of the voice, nausea, and vomiting often occurred, and sometimes hypertension and oedema developed in patients hitherto well controlled with adrenal substitution therapy. For these reasons testosterone treatment had often to be abandoned.

Thiotepa was given by intramuscular injection, starting with 15 mg. three times a week for two weeks, and thereafter 15 mg. weekly. This scheme was chosen because most cases were treated as out-patients. White-cell counts were initially performed twice weekly, and then weekly during maintenance therapy. Treatment was continued until leucopenia (defined as a total white-cell count of fewer than 4,000/c.mm.) rendered it hazardous or until deterioration was obvious. When patients developed leucopenia thiotepa was withheld until the white-cell count rose above 6,000/c.mm.; but usually there was a further fall in white cells, and eventually treatment with thiotepa had to be stopped.

Results

Of the 12 patients studied, five had had a period of improvement after bilateral adrenalectomy and oophorectomy varying from 11 to 30 months. In the remaining seven progression of the malignant disease had continued in spite of operation. Thiotepa produced temporary improvement in two patients (Cases 5 and 7). In the remainder no effect was seen. Details of the individual cases are summarized in the Table, and the case histories of the patients who improved are given below.

Case 5.—This patient underwent a radical mastectomy for carcinoma of the left breast in 1954, followed by a course of radiotherapy. She remained well until March, 1957, when she complained of a hoarse voice and dysphagia, and was found to have supraclavicular and cervical glandular secondaries, together with nodules in the scar of the radical mastectomy. Bilateral adrenalectomy and oophorectomy, performed in April, 1957, was followed by rapid relief of the dysphagia and hoarseness, and by partial regression of the glandular and skin secondaries. In September, 1959,

Clinical Findings and Progress of Patients

Case No.	Age	Duration when First Seen (Years)	Clinical Stage*	Radical Mastectomy	Histology	Secondaries in Axilla (Histologically)	Deep X-Ray	Time from Radical Mastectomy to Bilateral Adrenalectomy	Menopausal Status at Adrenalectomy	Type of Secondary	Palliation after Adrenalectomy and Oophorectomy	Time from Adrenalectomy and Oophorectomy to Thiotepa (Months)	Methyltestosterone	Dose of Thiotepa (mg.)	Leucopenia?	Palliation after Thiotepa	Total No. Years to Death (or Reporting)
1	73	9	T4 N3 M	No	Scirrhus	—	No	—	Post	Skin, Glands, Chest Skin	Nil	7	No	90	No	Nil	10
2	58	2/52	T3 N0 M0	Yes	Solid polygonal cell Adeno. (poorly diffn.)	Yes	Yes	6 months	—	Skin	—	5	Yes (intol.)	150	Yes	—	(2)
3	66	6/52	T3 N0 M0	—	Adeno. (poorly diffn.)	—	—	2 years	—	Skin, Glands, Skeletal	—	5	Yes	165	No	—	3
4	41	1	T3(a) N0 M0	—	Spheroidal Scirrhus	—	—	4 yr. 8 months	Post (irrad.)	Skin, Glands, Skeletal	Yes	18	Yes (intol.)	225	—	—	7
5	63	5	T3 N0 M0	—	Spheroidal Scirrhus	No	—	2 yr. 9 months	Post	Skin, Glands, Skeletal	—	30	Yes (intol.)	165 + 90	Yes	Yes	(11)
6	38	3	T3 N2 M	Yes (after oophorectomy)	Spheroidal	Yes	—	4 years	Post (operation)	Skin, Glands, Skeletal	—	12	Yes (intol.)	135	—	Nil	8
7	46	3/12	T4 N2 M0	Yes	Scirrhus Spheroidal	No (post D. X-R.)	Yes (pre-op.)	1 1/2	Pre	Skin	—	48	Yes	420 + 135	—	Yes	(5)
8	39	1	T2 N0 M0	—	Scirrhus Spheroidal	No	Yes	11	—	Skeletal Skin	Nil	3	No	90	—	Nil	12
9	49	1/52	T3 N0 M0	—	Scirrhus Spheroidal	Yes	—	14 months	—	Skin	—	5	Yes (intol.)	315	—	—	2
10	61	15	T4 N2 M0	No	—	—	No	—	Post	Skin, Gland, Skeletal, Lung	Yes	24	Yes (intol.)	150	No	—	(17)
11	42	1	T4 N0 M0	Yes	Adeno. (poorly diffn.)	No	Yes	18 months	Pre	Skeletal, Lung, Gland, Skeletal	Nil	3	No	105	—	—	2
12	51	3/12	T3 N2 M	No	Scirrhus	Yes	No	—	Post	Skeletal	Nil	8	Yes	150	Yes	—	(1)

* See British Medical Journal (1959).

dysphagia recurred, together with pain in the left side of the neck and chest from skeletal secondaries. She proved intolerant to methyltestosterone, but thiotepa was well tolerated, the dysphagia and pain being rapidly relieved. Despite the dramatic subjective improvement no objective improvement could be demonstrated either clinically or radiologically. Thiotepa was stopped because of leucopenia after 165 mg. had been given. In March, 1960, she had a recurrence of pain, without dysphagia, and on this occasion no relief followed thiotepa, which was stopped because of leucopenia after 90 mg. had been given. When last seen in July, 1960, she was slowly deteriorating.

Case 7.—This patient had a left radical mastectomy for carcinoma in 1953, followed by a course of radiotherapy, and a right radical mastectomy for a second carcinoma in 1955, preceded by radiotherapy. She remained well until April, 1956, when skin secondaries developed in the right radical mastectomy scar. In spite of methyltestosterone treatment they progressed, and bilateral adrenalectomy and oophorectomy was performed in December, 1956. After this operation the skin secondaries regressed slightly and then remained static until April, 1959, when further deterioration occurred. Methyltestosterone, 25 mg. twice daily, was well tolerated, but deterioration continued. In November thiotepa was given and in January, 1960, healing began at the edges of the ulcerated area. In February further deterioration occurred, and in April thiotepa had to be stopped because of leucopenia after 420 mg. had been given. A further course was given in June and July until leucopenia again occurred after 135 mg. had been given. No improvement resulted, and at the time of writing (August, 1960) massive oedema of the right arm and progressive ulceration of the skin was causing much distress.

Discussion

This trial was performed on out-patients in order to produce as little dislocation of patients' daily life as possible. The doses of thiotepa were therefore low in comparison with those of Watson and Turner (1959), who used 30 mg. intramuscularly on alternate days in most of their patients. Nevertheless, significant leucopenia occurred in over half of the present patients, suggesting that an adequate dose of thiotepa was being given. Leucopenia was readily detected, and in all cases the bone-marrow eventually recovered with no treatment other than stopping the drug. The longest period of bone-marrow depression encountered was two months. In the doses used thiotepa is a safe drug; in no case did irreversible pancytopenia occur as described by Rider (1960).

The disappointing finding of transient improvement in only two patients contrasts with the results of Watson and Turner (1959). Failure of thiotepa in the present cases might be explained by the difference in the type of patient treated, by the failure of the majority to tolerate methyltestosterone, or by the dosage of thiotepa used. All the patients in this study had had bilateral adrenalectomy and oophorectomy. It was considered unethical to withhold this operation (unless the patient was unfit for it) and substitute a relatively unproved form of treatment. This meant that treatment with thiotepa was being started in a more advanced stage of the disease and may explain the poor results in this series. That this cannot be the full answer, however, is suggested by the failure of patients who had initially responded to bilateral adrenalectomy and oophorectomy to respond to thiotepa. It remains a possibility that the results from bilateral adrenalectomy and oophorectomy could be improved if thiotepa was begun at the time of the operation. The patients tolerated methyltestosterone badly, probably partly because of their precarious

endocrine balance. Loeser's (1959) suggestion, that the good results of Watson and Turner (1959) were primarily due to the large doses of testosterone used, could go a long way towards explaining the poor results in the present series. Another reason for failure might be the relatively small doses of thiotepa used, though larger doses probably would have been hazardous. Hall *et al.* (1960) emphasized that cytotoxic agents should be tested not only in differing doses but by different routes of administration. It is probable that the future of chemotherapy in malignant disease lies with drugs with a greater cytotoxic action on tumour cells and bone-marrow cells (a higher "therapeutic index") than thiotepa; with regional transfusion (Abel, 1960); or with measures deliberately designed to produce severe bone-marrow depression followed by bone-marrow (Brit. med. J., 1960) or foetal cell (Kay and Constandoulakis, 1959) infusions. Bridges *et al.* (1960) report the case of a patient with disseminated breast carcinoma who received 225 mg. of thiotepa intramuscularly over 18 days. Severe pancytopenia ensued, but the patient recovered after infusion of foetal liver cells. A remarkable improvement in the patient's condition was reported, with a remission at that time lasting to five months.

One more factor deserves comment. The one benefit obtained in all patients by the use of thiotepa has been that on morale. Both the patients and their relatives feel that something is being done, and hope is retained.

Summary

Thiotepa has been used as a palliative measure in 12 patients with advanced carcinoma of the breast, who were deteriorating in spite of bilateral adrenalectomy and oophorectomy. In only two patients has a palliative effect been seen.

The possible reasons for the failure of thiotepa in these patients are discussed.

I thank Mr. Donald Barlow for permission to study his patients, and Dr. Thomas Parkinson for much help and encouragement and for advice in the preparation of this paper.

REFERENCES

- Abel, A. L. (1960). *Brit. med. J.*, **1**, 952.
 Bridges, J. B., Bridges, J. M., Edelstyn, G. J. A., Lyons, A. R., and Nelson, M. G. (1960). *Lancet*, **1**, 629.
Brit. med. J., 1959, **2**, 818.
 ——— (1960). **1**, 1189.
 Hall, B. E., Willett, F. M., and Hales, D. R. (1960). *Ann. intern. Med.*, **52**, 602.
 Kay, H. E. M., and Constandoulakis, M. (1959). *Brit. med. J.*, **1**, 575.
 Loeser, A. A. (1959). *Ibid.*, **1**, 1589.
 Rider, W. D. (1960). *Ibid.*, **1**, 1501.
 Watson, G. W., and Turner, R. L. (1959). *Ibid.*, **1**, 1315.

An exhibition of disposable hospital equipment, attended by nearly 1,100 visitors, and organized by the Salford Group Hospital Management Committee, was held recently at Hope Hospital. The idea of holding the exhibition arose partly because the Group are actively concerned with the development of a central sterile supply department, and partly because of the recommendations of the nursing advisory committee that certain items in the disposable field be introduced on a Group basis. Hospital management committees in the Manchester and Liverpool regions, the medical officers of health of the local and neighbouring districts, and the voluntary organizations were invited. Thirty-two exhibitors displayed their products during the two-day exhibition.

PROSTATECTOMY BY THE VESICO-CAPSULAR METHOD

BY

R. E. B. TAGART, M.Ch., F.R.C.S.
*Surgeon to the Newmarket and West Suffolk
 General Hospitals*

Freyer (1920) reported a series of 1,625 prostatectomies, with a mortality rate of 5.3%. At intervals since then reports have appeared showing that, while methods have varied, the mortality has remained in the region of 5% (Harris, 1934; Stewart, 1945; Hey, 1945; Galbraith, 1948; Millin *et al.*, 1949; Riches, 1949; Jacobs, 1951; Wells, 1953). From the published reports it is difficult to deduce the operability rates for the various series, since there are so many variable factors which influence this, but it is probably safe to say that over the past 40 years the operability rate has risen steadily. The result of this is that permanent suprapubic cystostomy is now a rare operation—a minor surgical revolution which, in terms of human well-being, is the equal of other more spectacular advances.

The situation in large centres, from which most of the published reports have come, is reasonably satisfactory, but doubts are often expressed in private, and occasionally in public (*Lancet*, 1956), about whether the picture in the country as a whole, and particularly in the smaller non-teaching hospitals, is quite so pleasing. The junior surgical staff in these places may be relatively inexperienced, and many suffer from a shortage of nurses. The patients in the present series were treated in the general surgical wards of non-teaching hospitals of about 200 beds each. They suffer from a shortage of nurses, and the surgical first assistants are of registrar or junior house officer grade. It has been my experience that, under these conditions, what is lost in quantity of care is more often than not made up by the quality of individual performance.

The vesico-capsular method of prostatectomy described by Ogier Ward (1948), and later by Bourque (1954) and Watts (1956), is simple to perform and has given excellent functional results. A slightly modified version of this operation was used in the present series. The method of post-operative care is as important as the type of operation. The present one is based on a closed bladder irrigation system, which has been found to be effective and easy to manage. In the 120 consecutive operations reported here the mortality rate was 4.2%.

Selection of Cases

The total number of patients referred as possible cases of prostatic obstruction in the relevant period was 188. Of these, 18 (10%) were diagnosed clinically as carcinoma and were treated with hormones with or without a transurethral resection. In 24 (12%) patients the symptoms were not severe enough to warrant surgery or were transient. In this latter group are included patients with a single episode of prostatic haematuria, those with temporary inflammatory swelling of the gland, and those in whom retention of urine was the result of confinement to bed during an illness, but who passed urine normally once they were ambulant. Five (3%) were ill with another disease, which was shortly to be fatal, and suffered from acute retention of urine as an incident in this illness. These conditions were myeloid leukaemia, carcinoma of a bronchus with