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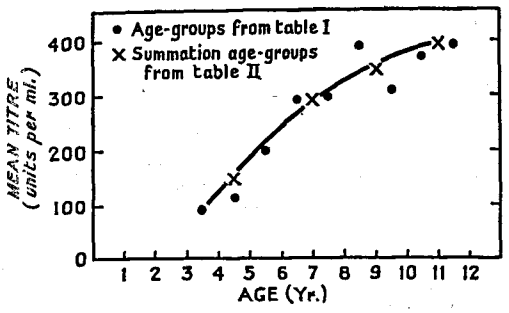

Fig. 3—Age and mean A.S.O. titre.

localised indolent streptococcal infections of infants are gradually replaced (by about the age of 5) by a more acute, and clinically well-defined, pharyngitis. This altered response, they suggest, is related to sensitisation to streptococci through repeated infections. Rantz et al. (1951) have shown that such repeated streptococcal infections in young children lead to a striking enhancement of the antibody response; their findings therefore support the idea that sensitisation (i.e., increased antibody response) to streptococci tends to develop in childhood. It is known that repeated infections with group-A hæmolytic streptococci commonly precede attacks and recurrences of rheumatic fever and this, together with the well-established increase in antibody response which most rheumatic subjects show, has supported the concept that rheumatic fever itself is a phenomenon of sensitisation. The results reported here suggest, on the contrary, that in young children with acute rheumatism this state of sensitisation is not uncommonly poorly developed and should therefore probably be regarded as dissociated from the mechanism by which streptococci induce rheumatic fever.

Summary

107 children with acute rheumatic fever, aged 3–12 years, showed no age differences in the frequency of preceding upper-respiratory-tract infection, or of positive throat or nose swabs for group-A β-hæmolytic streptococci.

20 children included in this study were under the age of 6 years; these showed a significantly lower frequency of raised antistreptolysin-O titres, and a significantly lower mean titre, than those over 6 years of age.

This result suggests that, contrary to the current concept, the pathogenesis of rheumatic fever is not primarily related to the sensitisation to streptococci or their products that commonly occurs in childhood.

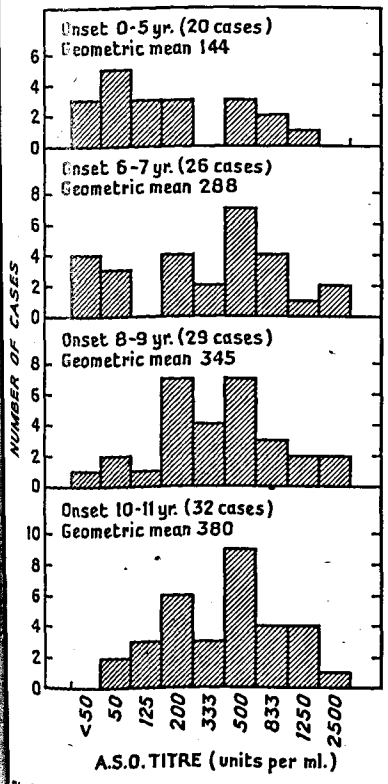

Fig. 4—Distribution of actual A.S.O. titres in the four age-groups.

The standard globulin preparation obtained in July, 1953, was kindly sent by Dr. B. F. Massell, the House of the Good Samaritan, Boston, Mass., U.S.A.

REFERENCES

Anderson, H. C., Kunkel, H. G., McCarty, M. (1948) *J. clin. Invest.* **27**, 425.
Coburn, A. F., Pauli, R. (1935) *Ibid*, **14**, 769.
Harris, S., Harris, T. N. (1950) *Ibid*, **29**, 351.
Hodge, B. E., Swift, H. F. (1933) *J. exp. Med.* **58**, 277.
Johnson, G. D. (1955) *J. clin. Path.* **8**, 296.
Jones, T. D. (1944) *J. Amer. med. Ass.* **126**, 481.
Lancefield, R. C. (1933) *J. exp. Med.* **57**, 571.
McCarty, M. (1952) *In* Rheumatic Fever. Edited by L. Thomas. Minneapolis; p. 136.
Powers, G. F., Boisvert, P. L. (1944) *J. Pediat.* **25**, 481.
Rantz, L. A., Maroney, M., Di Caprio, J. M. (1951) *Arch. intern. Med.* **87**, 360.
— Randall, E., Rantz, H. (1948) *Amer. J. Med.* **5**, 3.

PALLIATIVE HORMONE THERAPY OF ADVANCED MAMMARY CANCER

REVIEW OF 106 PATIENTS STUDIED IN SEVEN YEARS

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It has long been known that the ovaries influence the growth of the breasts, and that oöphorectomy sometimes causes breast cancer to regress (Schinzinger 1889, Beatson 1896, Boyd 1900, Morris 1902, Thompson 1902, Lett 1905a and b).

Haddow (1935) found that certain carcinogenic hydrocarbons retarded experimental malignant growths in laboratory animals, and some of these substances had an œstrogenic effect. This discovery led to a trial of synthetic œstrogens for carcinoma of the breast. Most workers agreed on the value of œstrogens in postmenopausal women and that the best responses were obtained in soft-tissue metastases, with little benefit in skeletal metastases.

Androgens were given to patients with breast cancer to inhibit œstrogens which might be stimulating the growth (Loeser 1938, 1939, 1940, McWhirter et al. 1944, Adair and Herrmann 1946, Herrmann and Adair 1946, Cutler and Schlemenson 1948, Prudente 1948, Lowenhaupt and Steinbach 1949, Douglas 1952, Hallberg et al. 1953).

It is now considered that some breast cancers are dependent on œstrogens, whose removal will improve the prognosis. This view is emphasised by Cade (1955) and Dodds (1955).

The insufficiency of oöphorectomy and/or androgen therapy gradually became evident. Œstrogens secreted by the adrenal cortex are increased after oöphorectomy because the adrenal glands then hypertrophy. With the advent of cortisone to control patients during and after operation it was logical to remove the adrenal glands. Since Huggins and Dao (1952) and Huggins and Bergenstal (1952) reported a series of cases so treated, adrenalectomy and oöphorectomy have been widely practised for the young patient with advanced metastases. If extirpation is complete, only those cases which presumably depend on œstrogens show a rapid and dramatic improvement and a recession of tumour growth which may last several months.

All workers are agreed that there is no means of determining which case depends on œstrogens, and can then be expected to improve under treatment, except trial of hormone therapy. This takes several weeks, but there is a dramatic response one to six days after adrenalectomy if the tumour is œstrogen-dependent.

Old postmenopausal patients often show a spectacular temporary remission, particularly of soft-tissue lesions, after large doses of œstrogens—possibly owing to a

local effect as well as to inhibition of the anterior lobe of the pituitary gland.

Material

This paper is an analysis of 106 cases of breast cancer treated with either œstrogen or androgen in women who died in a period of seven years, and the following data relate to the patients' state when accepted for hormone therapy.

All the patients had advanced stage-IV cancer of the breast and had already received all possible benefit from either X-irradiation or surgery or both, or else the lesion was too far advanced for anything except palliative hormone therapy.

Previous treatment.—Of the 106 women 3 had had surgery alone, 10 X-irradiation alone, 82 surgery and irradiation, and 11 no treatment.

Histology.—78 patients had histologically proved carcinoma, but Broders's grading was not stated in many of the pathological reports. Records of histology were missing in 7. There were no pathological reports in 21 cases which were much too advanced for surgery and in which the diagnosis was obvious on clinical findings.

The *duration of disease* before the start of hormone treatment was as follows: 94·5% of the women had had the cancer for 6 months, 86·0% for 1 year, 68·0% for 2 years, 48·0% for 3 years, 34·0% for 4 years, 21·0% for 5 years, 10·4% for 7 years, and 4·0% for 10–15 years.

Connubiality.—24·6% of the patients were single and 75·4% married.

Age-distribution.—9 patients (8·5%) were aged less than 40, 61 (57·5%) were aged 41–60, and 36 (34%) were aged 61 or more.

The menopause had occurred in 81%, and of these it had followed either irradiation or oöphorectomy in 12·6%.

Pregnancy or miscarriage was recorded in 55·6%.

Distribution of metastases was as follows:

Axillary, supraclavicular, or other lymph-nodes	74·5%
Skin nodules, ulceration, or infiltration	70·0%
Bones	52·8%
Lungs or pleura	33·0%
Other breast	21·7%
Other sites	14·3%

Some patients had metastases in several or all of these sites.

General condition.—Advanced cardiovascular disease was found in 8·5%. The general nutrition was good in 37·8%, but 56·5% had lost weight up to 2 st. and 5·7% more than that.

Methods

All the patients were interviewed and examined monthly or every two months according to their condition and response to treatment. Serial records of weight, hæmoglobin, erythrocyte-sedimentation rate (E.S.R.) (Westergren), and blood alkaline and acid phosphatase were kept. Changes in lesions were recorded photographically or followed on serial radiographs.

Œstrogen Therapy

Originally the British Empire Cancer Campaign wished to compare the effect of low dosage (0·3 mg. q.i.d.) with that of high dosage (5 mg. q.i.d.) of stilbœstrol. Printed forms were received, and patients were allocated at random to the dosage printed on these; by this means no individual selection of high or low dosage was made by each investigator. Patients were, if possible, kept on their allotted dosage until death. A change to high dosage was made only if it was obvious that no effect was being obtained from low dosage. Similarly, on occasions the dosage had to be lowered if symptoms of toxicity were intolerable.

Much individual variation was noted in tolerance within the dosage range 0·3–5·0 mg. q.i.d. After preliminary nausea, anorexia, flatulence, or giddiness most patients became gradually tolerant, but a few remained unable to take stilbœstrol. In my experience small doses of this hormone are practically valueless; hence early doses of 5 mg. q.i.d. are advocated, with increase of this amount to as much as 50 mg. q.i.d. if required.

Although the œstrogen was usually stilbœstrol, occasionally ethinyl œstradiol was substituted because of intolerance or sometimes when large dosage was required.

Androgen Therapy

57 patients were treated with androgens—of these, 6 were aged less than 40, 38 were aged 41–60, and 13 were aged 61 or more; 35 of these (61·4%) had bone secondaries when first seen.

To determine whether androgen therapy was of benefit or not, it was decided to give the largest possible tolerated dosage and to maintain this until there was some clinical or radiographic improvement, or until it was obvious that the patient was rapidly deteriorating. When this trial started, it was necessary to collect as many cases as possible for inclusion in the British Empire Cancer Campaign trial of low and high dosages of œstrogen, and some of the early cases were so treated although bone secondaries were present, when better judgment would have indicated treatment with androgens. However, after some experience, the younger patients and those with osseous metastases were given only androgens.

The high dosage chosen, 300 mg. daily, was not limited at first by expense, because adequate material was freely available through the generosity of several firms.

Most patients treated with androgens were given daily injections, but some, too thin to tolerate repeated treatment by this route, or to give them a brief rest, were given oral therapy with either methyl androstenediol or methyltestosterone. A few were also treated with implants of testosterone or of testosterone propionate for various reasons—e.g., difficulty of regular attendance and supervision.

Large dosages of androgens were usually continued indefinitely, even when patients were in a quiescent stage in reasonable health, though often the frequency of dosage was lessened, only to be restored with signs of further deterioration or spread.

For example, in a patient who survived for 360 weeks, the following enormous doses were given: 60·7 g. of testosterone propionate, 84·0 g. of testosterone isobutyrate, 10·5 g. of methyl androstenediol by injection and 8·4 g. by mouth, and 6·72 g. of methyltestosterone by mouth up to about a month before death.

In the patients who had been menstruating until the start of treatment amenorrhœa persisted.

Toxic Effects

Œstrogens

The well-recognised toxic effects of stilbœstrol and ethinyl œstradiol are common even with minimal dosage for endocrine dyscrasias, but (as already stated) a much bigger dosage was believed to be necessary and was given. Hence it is not surprising that 40·3% of the patients so treated complained of toxic effects. It was necessary to encourage these patients to persevere with the prescribed dosage, and usually tolerance improved. Some patients assimilated 160–200 mg. of stilbœstrol daily.

Toxic symptoms noted were anorexia, flatulence, nausea, retching, sometimes vomiting, dizziness, and general malaise. These symptoms developed either early or late in treatment; in the latter case they were possibly due to hepatic metastases impairing detoxication. Often these patients were lethargic, dehydrated, and wasted, with dry inelastic sallow skin.

Androgens

Only 29·8% of the patients treated with androgen complained of nausea or vomiting. Sometimes it was necessary to reduce the daily dosage, and potassium citrate and a powder of magnesium trisilicate and bismuth carbonate were of value. In view of the suggestion that the toxic effect in the earlier cases in this series treated with massive therapy was due to hypercalcæmia, the

serum-calcium level was investigated on many occasions but was never found significantly raised.

Side-effects

Œstrogens

Postmenopausal bleeding was not uncommon in patients taking a small ineffective dosage of 0·3–1·0 mg. q.i.d. for a month or so; treatment had then been stopped by either the patient or the doctor. The correct procedure is to increase the dosage to 5 mg. q.i.d. and to impress on the patient the importance of not interrupting regular therapy. With 5 mg. q.i.d. interval bleeding takes place only rarely, and then perhaps after the tablets have been omitted for a day; if patients were given continuous therapy with 20 mg. q.i.d. or more for many months, there was no bleeding. Withdrawal of œstrogen caused bleeding in 31·2% of 61 menopausal cases: 10 of them bled on a dosage of stilbœstrol from 0·3 mg. q.i.d. to 5 mg. q.i.d., and 9 on one of 5·0 mg. q.i.d.; of the 42 remaining patients 2 on 0·3 mg. q.i.d. had not bled in seven and eleven weeks before death, and no report was available for 1 patient who discontinued attendance. In 30 patients who received 5·0–50 mg. q.i.d. there was no bleeding during their treated lifetime—sometimes for as long as 125 weeks. There was no bleeding in 3 patients while having ethinyl œstradiol 0·05 mg. q.i.d. or more, in 1 patient while having œstradiol benzoate 10 mg. on alternate days, and in 5 patients while having stilbœstrol 1·5 mg. q.i.d. in addition to a daily dose of 100–300 mg. of testosterone propionate by injection.

Pigmentation was striking in some patients, particularly the older group and in those who were normally darkly pigmented, and in this series it developed in 32·8%. It was very intense around the nipples and areolæ, the linea nigra, and the perineum, and in senile keratoses. The colour varied from dark brown to almost black. The nipple of an irradiated breast was often less pigmented than that of the other breast. After months of therapy the pigmentation often disappeared, even though big doses were continued. In association with this there was sometimes sufficient keratinisation of the nipples to give them a greyish black tinge which, like the pigmentation, ultimately disappeared, leaving a paler smooth nipple.

Œdema of the ankles and lower legs was not unusual with continued large dosage, and sometimes the œdematous arm on the side of the radical mastectomy was still further enlarged. Rarely in some of these old patients congestive failure was precipitated, but it was usually only necessary to restrict the intake of salt and to give an oral diuretic—e.g., 'Mercloran' and acetazolamide.

Androgens

Side-effects with androgens naturally depend on the duration of treatment and the dosage, but there was also an individual susceptibility. The most powerful known action of androgens is anabolic, with retention of nitrogen and sodium, increasing the weight of many patients, and making their muscles noticeably larger and firmer though the patients had advanced cancer. Much of the benefit of androgen therapy is probably due to this effect, with subjective improvement of appetite and sometimes an increase in well-being and energy, enabling patients to continue their work or their domestic duties. There was often pronounced plethora.

The unpleasant side-effects are those of virilisation. This varied from one patient to another: some were rapidly affected, whereas others, who survived only a short time, showed very little virilisation. The distribution of signs of virilisation, expressed as a percentage of patients treated with androgens, was as follows:

Sign of virilisation	*No. of patients*
Hirsutism	33 (*58·0%*)
Voice change	26 (*45·5%*)
Enlarged clitoris	15 (*26·3%*)
Acne	11 (*19·3%*)

Hirsutism was the most embarrassing and unpleasant side-effect for the patient and was often very considerable. Not only was there an intense growth of long coarse hair on the cheeks, upper lip, chin, and general beard area but also the excess hair on the body, arms, and legs was considerable. It is the former, however, to which the patient naturally objects. Patients developing hypertrichosis were all recommended to shave daily, preferably with an electric razor, and not to resort to depilatory agents such as wax, pumice, emery paper, electrolysis, and plucking, all of which methods tend to cause infection of the skin follicles and unsightliness noticed by all, whereas, with a well-kept shaven face, the fact that the patient shaves is known only to herself and her husband. One patient with particularly heavy hirsuties controlled her appearance extremely well by rubbing off the hair from time to time with the pith side of lemon peel.

Voice changes probably depend on the normal pitch of the patient's voice. They developed early in some and very late in others. The voice may be very deep and gruff or husky, or may crack and change like that of a pubescent boy. Patients sometimes commented on their inability to sing in the same register, which may drop an octave or so. This was rarely a source of dismay but is irreversible.

Enlargement of the clitoris was sometimes considerable although not invariable. The glans was often enlarged to 0·8–1·0 cm. in diameter, appeared congested, and protruded from the enlarged prepuce, whose sulcus contained smegma. The body of the clitoris was often 2–3 cm. long. Concomitant with this overgrowth of the clitoris there was increased vaginal secretion.

Acne developed only occasionally. The skin was more greasy in most of the patients in whom acne developed, and the acne then usually affected the face, chin, back, chest, and shoulders and probably depended partly on personal cleanliness.

All the above-mentioned virilising side-effects were seen with all the androgens used, occurring almost as much with methyl androstenediol as with testosterone and its esters. Although methyl androstenediol is said to be not so virilising, it certainly was so in the dosage of 100 mg. daily for a long time.

Increase of libido was an important side-effect (cf. Foss 1951); 14 patients (24·6%) admitted to a considerable increase of libido, but the actual incidence was probably higher. It may be associated with hypertrophy of the clitoris. Patients commented on constant irritability and sensitivity, but in some cases where examination revealed an enlarged clitoris an increase in libido was denied.

Results

Survival.—55·5% of the 106 patients were still alive 6 months after starting hormone treatment, 31·2% after 1 year, 11·6% after 2 years, 4·7% after 3 years and after 4 years, and 0·94% after 5 years. The average age of these 106 women at the beginning of therapy was 55 years and the mean survival for the group 48 weeks. The mean number of weeks lived in 5 years was 18·6% of the expected survival (Foss 1955). After the percentage expectancy of life in 5 years had been calculated for each case, statistical analysis gave the following results:

Group	*Age (yr.)*	*No. of patients*	*% expectancy*	*S.D.*
1	40 or less	9	9·42	±3·6
2	41–60	61	16·3	±2·1
3	61 or more	36	24·5	±4·45

The differences between groups 1 and 2, and between groups 2 and 3 were not significant, but between groups 1 and 3 the expectancy of life was so increased as to be outside the range of random chance. If the survival figures from the onset of symptoms are used instead of from the start of hormone treatment, we find that the average age at onset of symptoms was 51·2 (range 26–76), and the average survival 58·5 months (range 10 months–27 years. Dividing the patients into age-groups we get:

Group	*Age (yr.)*	*No. of patients*	*Average age at onset (yr.)*	*Survival (wk.)*	*5 yr. % expected survival*
1	Up to 40	18	35·5	230	88·8%
2	41–60	66	50·5	255	98·8%
3	61 +	22	66·5	173	68·6%

These figures indicate that the prognosis in women aged more than 60 at onset was worse than in younger women: 97·3% of the patients were still alive after 6 months from the onset of symptoms, 87·8% after 1 year, 62·2% after 2 years, 46·0% after 3 years, 34·0% after 4 years, 26·4% after 5 years, 5·6% after 10 years, and 2·8% after 15 years.

Improvement was observed in 31 patients (29%): 1 aged less than 40, 19 aged 41–60, and 11 aged 61 or more. In 13 of the 14 women treated with œstrogen the first symptom had started after the menopause. Œstrogen therapy was started 4–27 years (mean 15 years) after the onset of the menopause. 7 of these patients had not undergone operation, because the cancer was too advanced when they were first seen. The average age of the 14 women was 63, and their average survival was 32 months: a woman on 0·3 mg. q.i.d. survived 59 months with quiescent bone metastases; another on 0·3 mg. q.i.d. survived 29½ months with temporary regression of soft-tissue metastases; a woman on 5·0 mg. q.i.d. or more survived 17 months with quiescent bone metastases; and 11 women on 5·0 mg. q.i.d. or more survived 31·7 months (mean) with good regression of soft-tissue metastases.

Only 17 patients (30%) of those treated with androgens showed some improvement; their average age was 49 and average survival 17·25 months. Of these 17 women 14 (82%) had their first symptom before the menopause (1 underwent hysterectomy 11 years before the first symptom), and 4 had had neither surgery nor radiotherapy. The results of treatment were as follows:

	No. of patients
Skin deposits regressed	7
Lymph-nodes regressed	6
Bone healing and recalcification	4
Abdominal secondaries regressed	2
Lung metastases regressed	2
Loss of pain and subjective improvement but no change in secondaries	3

The different types of metastases responded as follows:

Type	*No. of patients*	*No. improved*	*With œstrogen*	*With androgen*
Skin	74	17	10	7
Lymph-glands	79	13	7	6
Bone	55	4	..	4
Lungs and pleura	35	3	1	2

Of the 55 patients with bone metastases 35 were treated with androgens, and of 31 complaining of severe pain 11 were relieved, including the 4 showing improvement radiographically. 6 patients had pathological fractures (4 during treatment) in which there had been no clinical improvement. In one the fractures were present on starting androgen treatment and subsequently healed: in another a fracture occurred during the early phase of treatment but later healed, together with radiographic improvement in the other bone metastases. After œstrogen treatment none of the remaining 20 patients who had bone metastases showed clinical or radiographic improvement, and pathological fractures occurred in 4 during the course of therapy.

In addition, less objective evidence of improvement was obtained by assessing the effect of treatment on the following:

(1) Pain or distress, which occurred in 80 patients, 20 of whom obtained relief.

(2) Serial hæmoglobin levels. Before the start of treatment anæmia was found in 49 patients, 24 of whom had radiographically proved bone metastases. There was virtually no improvement with treatment.

(3) The E.S.R. was raised initially in 68 patients and fell during treatment in 17.

(4) The body-weight increased in 23 (13 given androgen, 10 given œstrogen), decreased in 53, and did not change in 30.

(5) Blood-alkaline phosphatase: no definite correlation was found between clinical improvement or extension or regression of bone metastases judged by radiographic appearances. In one or two cases with bone secondaries which improved with testosterone, where the initial pre-treatment levels were high, subsequent values were much reduced. On the other hand, some cases treated with œstrogen showed similar changes in phosphatase with progressive deterioration in osseous metastases.

Discussion

A therapeutic trial of this kind can only help to assess the effect of alteration of the steroid hormone balance of the host and makes no allowance for the specific malignancy of the cancer. Unfortunately the complete Broders's grading of each case was unknown. In a few cases no details of the histology were available and many years had elapsed since the original operation.

In the preliminary trials it soon became apparent that only the old postmenopausal women with soft-tissue metastases might benefit.

The survival of any one patient with breast cancer of this advanced stage of severity must obviously depend on numerous factors—the patient's age, the distribution and type of metastases, the grade of malignancy, the hormone dependence (whether of œstrogens or possibly of pituitary hormone), and other general health factors.

Spontaneous regression has been reported by Gordon Taylor, but malignancy may lie dormant for years. In the present series, however, the 106 patients had very advanced stage-IV metastases. Even so, some patients were in reasonable general condition, whereas others were almost moribund. No cases were selected except that those with clinical evidence of considerable liver metastases were excluded.

Comparison is necessary with the survival of patients with untreated advanced mammary cancer:

Wade (1946) reported 27 untreated patients with breast cancer of whom 24 were in stage III. The average duration of life was 8 months from first being seen, and all were dead in 2 years.

Greenwood (1926) found a mean survival of 38·3 months from the onset of symptoms in 651 cases; Wyard (1925) found the mean duration of life to be 37 months in 311 cases; and Daland (1927) quotes 40·5 months in 100 cases. Wade has collected these numbers together and found that the average duration of life in untreated cases was 38·55 months in 777 patients, and that the duration of life increased from the age-group 25–34 to that of 65–74 and then decreased again.

According to Wade (1946) X-irradiation alone or together with surgery raised the survival time by 21·5% at one year, 22·5% at 2 years, 10% at 3 years, 10·5% at 4 years, and 9·5% at 5 years over the survival-rates of untreated cases. In her series the mean survival of 27 patients with advanced stage-III untreated cancer when first seen was only 8 months; hence 12 months' survival in the present series of advanced stage-IV cancer after treatment with hormones is possibly significant. All her patients had died in 2 years, whereas 11·6% of the present series were alive at 2 years and 4·7% at 4 years.

As regards surgical treatment alone, Lewison et al. (1953) claim a 5-year survival-rate of 43·2%, regardless of the type of operation. These were presumably selected cases, inoperable stage-IV cancer being almost certainly excluded.

In the present series most of the patients had received standard surgical and X-ray treatment in addition to hormones, and the mean duration of life was 58·5 months from the first symptom. There was a 5-year survival-rate of 26·4% from onset. Although superficially this compares unfavourably, it must be remembered that my series consists solely of stage-IV advanced cancer.

The age at onset seems to influence duration of life. In patients who developed cancer of the breast when over 60 the percentage expected survival in 5 years was 20% less than in patients aged less than 40, and 30% less than in patients aged 41–60. A similar prognosis was reported by Burdick and Chanatry (1954).

In the present series of advanced stage-IV cancer the percentage expectancy of life in 5 years was significantly greater after hormone treatment in the patients aged

more than 60 than in the younger patients. Although breast cancer is more rapidly fatal if it begins at the age of more than 60, there is more chance of prolonging survival in this age-group by hormone therapy when metastases are widespread.

Assessment of improvement was made as objective as possible. Temporary regression of metastases in glands, photographically recorded improvement in skin lesions, and radiographic evidence of bone healing were accepted as beneficial effects of hormone therapy. 5 cases were regarded as improved, because pain of bone secondaries was diminished, although no radiographic improvement was seen during long periods of survival in moderate health. Only 4 of 35 patients with bone secondaries treated with androgen showed radiographic evidence of bone healing. This figure of 11% compares unfavourably with 30% claimed by Hallberg et al. (1953), who also claim improvement in general condition and palliation in 85%. In the present series objective improvement was seen in 30% of those treated with androgen—a very similar figure to 27% found in a shorter observation period by Segaloff et al. (1951) in 48 cases treated with testosterone propionate 100 mg. thrice weekly.

Subjective improvement was noted in a few other patients in this series treated with androgens, but it was doubtless partly due to the anabolic effect—increased appetite and temporary euphoria.

For some old patients who present with fungating lesions too advanced for surgery or X-irradiation œstrogens are a useful means of palliation. Healing of ulceration in some cases may last months.

Huseby (1954), who treated with œstrogens 100 patients with advanced mammary cancer, reported that those in whom the response was favourable had an average survival of 29 months from the start of therapy, and that 24 of these were more than 5 years past the menopause (natural or therapeutic). The response of those with bone lesions was poor. Only 1 of his 5 patients who had not reached the menopause improved. There was major regression of pulmonary metastases in 11. These figures are similar to my finding in 14 patients who improved with œstrogens. Their average age was 63 (range 53–76) and average survival 32 months from the start of therapy.

The considerable virilisation caused by big dosages of androgens is perhaps not so very important. Shaving with an electric razor will maintain a presentable appearance. Methyl androstenediol, which is claimed to be less virilising, has nothing to recommend it over testosterone. Patients treated with 100 mg. of methyl androstenediol daily for some months developed almost as much hirsutism as those given testosterone esters; moreover methyl androstenediol causes pain when it is given in crystalline suspension, and in several cases it caused an abscess at the site of injection. Segaloff et al. (1952) observed similar results and achieved regression of the lesions in only 2 of 24 cases treated solely with methyl androstenediol.

The choice of therapy was not dictated at first by a knowledge of œstrogen dependence of a particular cancer. Usually old postmenopausal women with soft-tissue metastases were treated with œstrogens, and the younger patients or those with widespread bone metastases were given androgens. Subsequent analysis of the 17 patients who responded to androgens, however, showed that 82% had had their first symptom of cancer before the menopause, whereas of the 14 who improved with œstrogens 93% had had their first symptom after the menopause. This may possibly be a guide to selection for hormone therapy, and in the androgen-treated group with premenopausal onset this may indirectly indicate œstrogen dependence; or, conversely, the postmenopausal onset suggests that not even stroma-cell œstrogens were responsible stimulants to their cancer (Sommers et al. 1953). In these old patients, in whom pituitary activity is not inhibited by endogenous œstrogens, there may be excessive production of somatotrophin and prolactin as well as gonadotrophin, and the beneficial effect of œstrogen therapy may be due to inhibition of these hormones.

It is quite clear that there is a type of patient with breast carcinoma which is temporarily responsive to treatment with androgens or by oöphorectomy or by adrenalectomy, and that the essential common factor is œstrogen dependence (Pearson et al. 1954). Unfortunately there is no way of detecting œstrogen dependence, and only recently have chemical methods of estimating œstrogens in urine been elaborated, but the method is laborious (Brown 1955) and is not yet readily adaptable to clinical use.

In the present series the patients were so widely riddled with metastases that one could not hope for much benefit; hence an improvement-rate of about 30% for both œstrogens and androgens is possibly satisfactory.

As Asher (1955) aptly remarked: "Prolongation of life is not the only aim of treatment; it should be a tolerable life. It is better to be wholly alive for one month than half alive for two." The latter part of his statement referred to cases after endocrine surgery, which, like hormone therapy at present, suffers from an inability to discriminate between cancer cases with and without hormone dependence.

In the present series the side-effects and possible upsets and the prolonged course of oft repeated intramuscular injections were a high price to pay by patients for no improvement; perhaps it would have been better if they had been allowed to spend their remaining life under increasing doses of morphine. So much, however, depends on each patient's temperament. One can only remember the gratitude and faith of those who were fortunate in their response to treatment, some of whom enjoyed many months' freedom from pain and freedom from odour, and lived reasonably normal lives. Such results, even though restricted to about a third of those treated, are worth while.

Summary

106 women with stage-IV mammary carcinoma were treated with either androgen or œstrogen and kept under observation until death.

Improvement was observed in only 29% of cases. Of the 17 women who improved with androgen 14 had had their first symptom before the menopause; and of 14 patients who improved with œstrogen 13 had had their first symptom after the menopause.

The average age of those patients who received benefit from œstrogen was 63 and from androgen 49. The prognosis was better for the older patients treated with œstrogen, the average survival for these being 32 months, compared with 17·25 months for those who improved with androgen.

The possible significance of œstrogen dependence in the younger group and pituitary-hormone dependence in the older postmenopausal patients is discussed.

My thanks are due to Sir Charles Dodds, who persuaded me to join in the British Empire Cancer Campaign œstrogen trial; the British Empire Cancer Campaign for a grant for three years for laboratory assistance; Prof. Milnes Walker for permission to treat patients in the department of radiotherapy at the Bristol General Hospital; the physicians and surgeons who allowed me to treat their patients; Miss G. M. Jeffree, my technician; Dr. C. H. G. Price and Dr. A. L. Taylor for advice and help; and Miss J. E. Nixon, of the records department of the department of radiotherapy, for much secretarial help. The androgens were provided by Ciba Laboratories, Organon Laboratories Ltd., and British Drug Houses Ltd.

References overleaf

SERUM-CHOLINESTERASE LEVELS IN DIABETES MELLITUS

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IN 1937 Antopol et al. briefly reported that the plasma-cholinesterase level was raised in diabetes mellitus—an observation which was confirmed by Faber (1943) and by Cristol et al. (1946). Each of these reports, however, described only a small series of diabetic patients, and no details were given of the age of the patients, or the type or severity of the diabetes.

Saviano et al. (1948) reported raised plasma-cholinesterase levels in dogs with alloxan diabetes. Berry et al. (1954), however, found a strong correlation between the amount of surface fat and the plasma-cholinesterase level in a group of 345 men from three districts in England, and suggested that the high cholinesterase values found in diabetes mellitus might be related, not to the diabetic state per se, but to the obesity which often accompanies it.

We therefore determined the serum-cholinesterase levels in a series of diabetic patients and recorded whether these patients were "obese" or "non-obese." The severity of the diabetes and the adequacy of the control by insulin were assessed. Serum-cholinesterase levels were also determined in a series of obese non-diabetic patients attending hospital for other reasons.

Method

Blood was drawn from the antecubital veins of 50 adult patients with diabetes mellitus (25 of them obese and 25 non-obese), 25 adult obese non-diabetic patients, and 33 non-obese healthy adults.

In most cases, blood was taken in the afternoon; a study of 2 healthy subjects showed that there was no significant difference between the fasting serum-cholinesterase level and the levels at one, two, three, and four hours after a meal containing 60 g. of fat.

The diabetics were all outpatients under treatment, and the diagnosis had been confirmed by blood-sugar estimations. The degree of control of the diabetes was assessed by the amount of glycosuria, determined by daily urine-testing ('Clinitest') and interpreted as follows:

Degree of control	*Results of urine tests*
Good	Never more than blue or green throughout the twenty-four hours.
Fair	Usually green, occasionally tan colour.
Bad	Frequently tan colour.

The severity of the diabetes was assessed by the dose of insulin required to establish control, but we realised that this was only a very limited method of assessment.

The presence of obesity was established on clinical grounds, bearing in mind the patient's height, weight, build, and amount of subcutaneous fat.

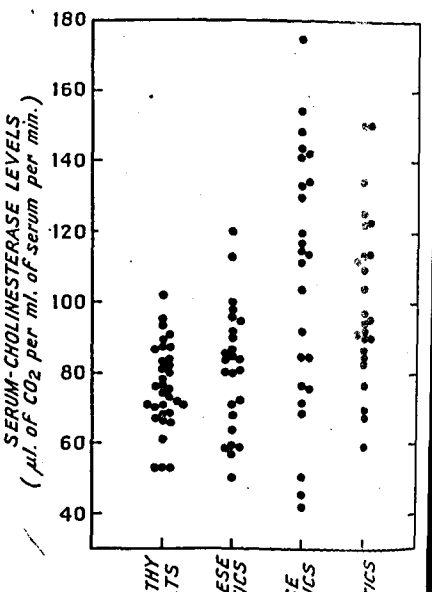
As it was not our aim to discover a precise correlation between plasma-cholinesterase levels and small variations in the degree of obesity, we decided that this classification was adequate for the purpose of the investigation, and we did not attempt a more accurate assessment of the amount of subcutaneous fat, such as measuring the thickness of the subcutaneous tissue fold (Edwards 1950).

All but 4 of the obese non-diabetic patients were attending hospital on account of their obesity. In the remaining 4, the obesity was coincidental.

Estimation of Cholinesterase

Cholinesterase activity was estimated manometrically on a sample of the separated serum by a modification of the method of Ammon (1933).

The free acid released from the choline ester by the action of the cholinesterase liberates carbon dioxide from the 0·025 *M* sodium bicarbonate medium; acetylcholine perchlorate (0·015 *M*) was used as substrate. Measurements were done in duplicate and were corrected for non-enzymic hydrolysis of the substrate. These enzyme measurements were made by one of us (R. H. S. T.), who at the time was unaware of the patient's clinical state, but in every case serum either from a healthy person or from a non-obese diabetic, and serum from an obese diabetic or an obese non-diabetic patient, were assayed simultaneously. Cholinesterase activity was expressed as µl. of carbon dioxide per ml. of serum per minute.



Serum-cholinesterase levels in four groups of adults.

Results

The serum-cholinesterase levels found in these 4 groups of subjects are shown in the accompanying figure, and the mean values and the standard errors of the means are listed in the accompanying table. The levels in the healthy adults varied from 53 to 102 µl. of carbon dioxide per ml. of serum per minute. Of the 25 obese

DR. FOSS: REFERENCES

Adair, F. E., Herrmann, J. B. (1946) *Ann. Surg.* **123**, 1023.
Asher, R. (1955) *Proc. R. Soc. Med.* **48**, 376.
Beatson, G. T. (1896) *Lancet*, ii, 162.
Boyd, S. (1900) *Brit. med. J.* ii, 1161.
Brown, J. B. (1955) *Lancet*, i, 320.
Burdick, D., Chanatry, F. (1954) *Cancer*, **7**, 47.
Cade, S. (1955) *Proc. R. Soc. Med.* **48**, 549.
Cutler, M., Schlemenson, M. (1948) *J. Amer. med. Ass.* **138**, 187.
Daland, E. M. (1927) *Surg. Gynec. Obstet.* **44**, 264.
Dodds, E. C. (1955) *Proc. R. Soc. Med.* **48**, 550.
Douglas, M. (1952) *Brit. J. Cancer*, **6**, 32.
Foss, G. L. (1951) *Lancet*, i, 667.
— (1955) *Proc. R. Soc. Med.* **48**, 551.
Greenwood, M. (1926) *Rep. publ. Hlth med. Subj., Lond.* no. 33.
Haddow, A. (1935) *Nature, Lond.* **136**, 868.
Hallberg, O., Nohrman, B., Sylven, B. (1953) *Acta radiol., Stockh.* **39**, 161.
Herrmann, J. B., Adair, F. E. (1946) *J. clin. Endocrin.* **6**, 769.
Huggins, C., Bergenstal, D. M. (1952) *Cancer Res.* **12**, 134.
— Dao, T. L. Y. (1952) *Ann. Surg.* **136**, 595.
Huseby, R. A. (1954) *Amer. Surg.* **20**, 112.
Lett, H. (1905a) *Med.-Chir. Trans.* **88**, 147.
— (1905b) See *Lancet*, i, 227.
Lewison, E. F., Trimble, F. H., Griffith, P. C. (1953) *J. Amer. med. Ass.* **153**, 905.
Loeser, A. A. (1938) *Brit. med. J.* ii, 319.
— (1939) *C.R. Soc. franç. Gynéc.* **9**, 77.
— (1940) *Brit. med. J.* i, 479.
Lowenhaupt, E., Steinbach, H. L. (1949) *Surg. Gynec. Obstet.* **88**, 291.
McWhirter, R., Paterson, E., Thurgar, C. J. L., Walker, J. Z., Windeyer, B. W., et al. (1944) *Proc. R. Soc. Med.* **37**, 731.
Morris, H. (1902) *Brit. med. J.* ii, 1293.
Pearson, O. H., West, C. D., Hollander, V. P. (1954) *J. Amer. med. Ass.* **154**, 234.
Prudente, A. (1948) *Surg. Gynec. Obstet.* **80**, 575.
Schinzinger (1889) *Verh. dtsch. Ges. Chir.* **18**, 28, quoted by Halberstaedter, L., Hochman, A. (1946) *J. Amer. med. Ass.* **131**, 810.
Segaloff, A., Gordon, D., Horwitt, B. N., Schlosser, J. V., Murison, P. J. (1951) *Cancer*, **4**, 319.
— — — — — (1952) *Ibid.* **5**, 271.
Sommers, S. C., Teloh, H. A., Goldman, G. (1953) *Arch. Surg.* **67**, 916.
Thompson, A. (1902) *Brit. med. J.* ii, 1538.
Wade, P. (1946) *Brit. J. Radiol.* **19**, 272.
Wyard, S. (1925) *Brit. med. J.* i, 206.