At a meeting recently a friend of mine produced the following quotation from J. J. Rousseau. "Si quelquefois les savants ont moins de préjugés que les autres hommes, ils tiennent en revanche, encore plus fortement à ceux qu'ils ont." This is applicable to our vaccination policies. If I may translate "savants" as "doctors and scientists" the quotation could read: "If doctors and scientists have fewer prejudices than other men, they hold all the more strongly to the few they have."

REFERENCES

- Apostolov, K., Flewett, T. H., and Thompson, K. S. (1961). *J. clin. Path.*, **14**, 196.
 Dane, D. S., Dick, G. W. A., Simpson, D. I. H., Briggs, E. Moya, McAlister, J., Nelson, R., and Field, C. M. B. (1962). *Lancet*, **1**, 939.
 de Vries, E. (1961). In *Encephalitides*. Proceedings of a Symposium on the Neuropathology, Electroencephalography, and Biochemistry of Encephalitides, Antwerp, 1959, edited by L. Van Bogaert *et al.*, p. 96. Elsevier Publishing Co., Amsterdam and London.
 Dixon, C. W. (1962). *Smallpox*. Churchill, London.
 Downie, A. W. (1961). *Smallpox, in Virus and Rickettsial Diseases of Man*, 3rd ed., p. 99. Arnold, London.
 Griffith, G. W. (1962). In *Smallpox*, by C. W. Dixon, p. 356. Churchill, London.
 Koster, L., and van Tilburg, J. Q. (1953). *Ned. T. Geneesk.*, **97**, 17.
Lancet, 1962, **1**, 954.
 Meindersma, T. E., and de Vries, S. I. (1962). *Brit. med. J.*, **1**, 226.
 Ministry of Health (1956). Quoted by C. W. Dixon, *Med. Offr.*, 1956, **96**, 39.
 — (1962). *Brit. med. J.*, **2**, 250.
 Wilson, G. S. (1947). *Brit. med. J.*, **2**, 855.

THIOTEPA IN TREATMENT OF ADVANCED BREAST CANCER

BY

ARNOLD LYONS, M.D., M.R.C.P., F.F.R.C.S.I., D.M.R.T.

Consultant

GEORGE EDELSTYN, M.D., D.M.R.T.

Senior Registrar

The Northern Ireland Radiotherapy Centre

The problem of how to deal with an individual case of advanced carcinoma of the breast is one that confronts every clinician working on malignant disease. We feel that such patients should always be treated initially by simple hormone administration for a trial period to determine whether they can be controlled in this way. If this is not possible they should then be considered for endocrine surgery or chemotherapy. The results of chemotherapy with thiotepa (triethylene thiophosphoramide) in a group of 46 such patients are reviewed below.

Watson and Turner (1959) reported the use of thiotepa and testosterone given concurrently in breast cancer, having obtained the remarkable objective remission rate of 85%. Seven out of 34 of their patients were stage 2 cases; but, even if these are excluded, 23 of the remaining 27 patients with metastatic disease were said to show some measure of control. Cree (1960), using the same technique, had similar results in 17 patients.

We were anxious to see if we could repeat these results and so develop the treatment as an alternative to endocrine surgery. We also hoped to find points in the patients' history and in their general pattern of disease which might guide us in assessing the chances of response.

Material and Methods of Treatment

All the patients considered for the treatment were suffering from progressive metastasizing breast cancer. All had had a trial of hormone therapy and had either responded initially and subsequently relapsed or had failed to respond. If there was clinical or biochemical evidence of liver involvement or the general condition of the patient was very poor, thiotepa therapy was withheld. All deaths occurring in less than one month from the end of treatment were regarded as being caused by the drug.

A patient classified as receiving benefit from treatment had to show evidence of objective remission on radiological, photographic, or clinical findings. Before a positive result was claimed such improvement had to be maintained for at least three months after the last dose of thiotepa had been given. Subjective remissions were not considered significant, as the large doses of testosterone produced feelings of wellbeing in almost all

the patients, even in those in whom the disease was obviously advancing. Before starting treatment relevant photographs and radiographs were taken and liver-function tests and a full blood count were performed.

The doses of thiotepa and testosterone followed closely those suggested by Watson and Turner, though in our experience it was not possible to give some of the larger quantities they used. The scheme was as follows:

1. Testosterone propionate. 100–200 mg. daily five days a week by intramuscular injection. This substance was continued until the patient's discharge from hospital.
2. Thiotepa. After the first five injections of testosterone 15 mg. of thiotepa was given by intramuscular injection. This was followed on alternate days by 30 mg. until a maximum of 285 mg. had been given. If the white-cell count fell below 2,000/c.mm. or the platelets below 100,000/c.mm. the drug was stopped.
3. Full blood counts were carried out every second day.
4. Some cases had two courses of treatment.

Results

Pattern of Treatment Response (Table I)

A total of 46 patients were initially selected for treatment, and five of these died as a result of it. This mortality of 11% was comparable to what we have experienced with hypophysectomy. Of the 41 patients who survived treatment 17 had an objective remission as judged by the criteria already given. This was 37% of the total number of patients in the series and 41% of those who survived the treatment. The mean duration of the period of control was 7.5 months and the mean survival after the disease had become reactivated was 4.5 months. It was of interest that this latter figure was almost the same as the duration of survival in those who failed to show any response.

TABLE I.—Incidence and Duration of Remissions

Number of cases in series	..	..	..	46
Treatment deaths	..	..	..	5 (11%)
Objective remissions (overall)	..	..	..	17 (37%)
Mean survival after completion of treatment (months):				
Remissions:				
Period of response	..	..	..	7.5+
Total survival	..	..	..	12.0+
Failures:				
Total survival	..	..	..	4.0+

Factors Associated with a Good Clinical Response to Thiotepa

At present, treatment of metastatic breast cancer is frustrating from many points of view, not least of these being the usually unpredictable way patients respond to any given approach. A search was therefore made for any details in the history or in the previous behaviour of the tumour which might serve as a guide to the outcome of treatment. The positive findings are set out in Table II. From the Table it will be seen that the most important single factor determining response to treatment was the speed at which the tumour progressed. Those cases with a time-interval of more than one year between the first appearance of their primary tumour

TABLE II.—*Influence of Certain Factors on the Clinical Result of Treatment*

Factor Investigated	Alternatives	No. of Cases	Response	
			No.	Statistical Analysis
Pattern of tumour development	With distant metastases	25	13 (52%)	$\chi^2 = 2.8$
	Local extension only	16	4 (25%)	$P < 0.1$
Menstrual status	Pre-menopausal	8	5 (62%)	$\chi^2 = 1.6$
	Post-menopausal (natural and artificial)	32	12 (37%)	$P < 0.2$
Duration of disease from first symptom to recurrence	0-12 months	15	3 (20%)	$\chi^2 = 4.2$
	13 months +	22	12 (54%)	$P < 0.05$

and recurrence responded much more frequently than did those cases where the period was less than one year. The factor next in value was the site of disease, and it seemed that the variety of breast cancer which remained confined to the chest wall had a poorer chance of successful response than the type where metastases were present distantly. Patients who were still menstruating were more likely to benefit than those who were not, though statistically these latter results did not reach a significant level.

A number of other factors not shown in the Table were also investigated, but were found to bear no relation to the clinical response. These factors included age, results of previous endocrine therapy, delay between recurrence and starting of treatment, and the degree of marrow depression.

Side-effects of Treatment

No subjective symptoms due to thiotepa were complained of, but a number of women developed signs of intolerance to testosterone. These included nausea, abdominal discomfort, and oedema of the legs, but they usually abated when dosage of the latter drug was reduced by half.

In general, the quantity of thiotepa given depended on the rate of fall of the white-cell and platelet counts. This usually began about the end of the second week of treatment, which was stopped when the white cells fell to 2,000/c.mm. and the platelet count to 100,000/c.mm., as already described. This trend continued for ten to fourteen days after the drug was stopped, often reaching levels far below those generally considered compatible with immunity to infection and an intact capillary system. We were interested to see the infrequency of petechial haemorrhages and infection in patients with white-cell counts below 300/c.mm. and platelet counts of less than 30,000/c.mm.

In seven patients almost total ablation of the bone-marrow took place. Four of these had foetal liver transfusions with a successful outcome in one which

has already been reported (Bridges *et al.*, 1960). One had a possible response to this measure, and the other two died. The remaining three cases, to whom foetal liver was not given, all died.

Marrow Depression and Thiotepa Dosage

Marrow depression occurred in all cases. For practical purposes it was regarded as either "moderate" or "severe." Moderate was defined as a white-cell count not falling below 500/c.mm. or a platelet count not falling below 50,000/c.mm. Severe depression referred to any case with either count below these levels.

Table III shows the wide variation in marrow tolerance to the drug. The distribution of cases between moderate and severe depression, with or without fatal outcome, was almost the same in the group receiving

TABLE III.—*Marrow Depression Produced by Different Doses of Thiotepa*

Dose of Thiotepa (mg.)	No. of Cases Stopping at the Dosage	Marrow Depression Encountered	
		Moderate	Severe
105/165	3	2	1
166/225	23	10	13
226/285	20	9	11
Total	46	21	25

the smaller dose (166-225/mg.). It was also observed, but not shown in this Table, that no correlation existed between the degree of marrow depression and the clinical response to treatment.

Second Courses of Thiotepa

In a number of instances second courses of thiotepa were given, either because no response was obtained to the first course or because the response obtained had come to an end. Of the 13 cases given the second course, death occurred in 5, remission in 3, and failure in 5.

The mortality resulting from second courses of treatment was prohibitive and the remission rate poor. It

was perhaps significant that none of three cases which failed to respond to a first course of thiotepa responded to a second. On the other hand, among the five patients who responded to a first course further control resulted in three. These remissions, however, were disappointingly short, lasting only about three months.

The effect on the marrow of a second course of thiotepa is shown in the accompanying Chart. This result was obtained in a patient who made a good response to the first course of thiotepa but not the second. It illustrates the greater depression of the marrow produced by this second course in spite of a considerably reduced dosage.

Possible Role of Testosterone

It could be argued that testosterone, itself capable of producing remission, might have been the active therapeutic agent. This point can be adequately dealt with only by a random trial—one group receiving the therapy here described, the other testosterone alone though in similar dosage. Unfortunately such a trial has not been made, but the results obtained by the combined therapy have been correlated with those found in the same patients who had previous treatment with testosterone alone (Table IV).

TABLE IV.—*Previous Response to Testosterone and Result with Thiotepa*

	Response	Total	Response to Thiotepa
Testosterone not given			
Testosterone given	Yes	14	6 (43%)
	No	10	4 (40%)
		17	7 (41%)

The numbers were small, but there appeared to be little relation between any previous response to testosterone and that subsequently obtained by the method described.

Treatment of Marrow Depression

This will be discussed more fully in a subsequent publication. It was observed that, apart from the treatment fatalities noted, remarkable degrees of white-cell and platelet depression were compatible with subsequent spontaneous return of blood counts to normal.

Treatment, if indicated, consisted of: (1) Cessation of all injections. Testosterone (sublingual) was continued by the oral route and no further thiotepa was given. (2) A broad-spectrum antibiotic was used even when efficient barrier-nursing was practicable. (3) Prednisone 15–20 mg. daily. It was recognized that this treatment was empirical. (4) Foetal liver suspension as already mentioned.

Discussion

We have not been able to obtain the same satisfactory results in advanced breast cancer as those reported by Watson and Turner (1959) or by Cree (1960), but it is clear that useful control of the disease was possible in some patients (Table I). Taking the group as a whole, one patient in three had objective benefit for an average period of 7.5 months. It could be argued that this prolongation of life is apparent rather than real, being merely longer survival in a group of patients with a more slowly evolving type of disease. The only absolute answer to this would be a controlled clinical trial, which has not been done. It was noted, however, that the patients did not merely survive but showed evidence

of objective remission, as already defined, and it is hard to believe that such improvement would not be associated with a true increase in survival-time. Had we included as remissions periods of improvement lasting less than three months from the last injection our figures would have been better, but we felt that responses of such short duration could not justify the protracted and hazardous treatment.

The purely subjective improvement made by many patients who failed to benefit objectively was also of value, but might have been the result of the large amounts of testosterone used and could probably be obtained by this drug alone.

From these observations it can be concluded that the frequency and duration of objective remissions were disappointing in view of the original optimistic reports of Watson and Turner (1959). However, despite the high mortality from the drug (11%), an objective remission in one-third of patients whose only alternative treatment was major endocrine surgery was not entirely unsatisfactory. The treatment therefore has a part to play in the overall management of advanced breast cancer, and an attempt must be made to define just what this is.

Although the Joint Committee of the American Association (1961) found little difference between the results obtained by hypophysectomy and those by adrenalectomy, other workers have shown hypophysectomy to be the superior procedure (Atkins *et al.*, 1960; Ray and Pearson, 1960), and we feel that comparison with this latter operation is more relevant. As practised in Belfast, this combines surgical removal of the pituitary with intrasellar radiation, using yttrium 90 in wax (Edelstyn *et al.*, 1958) and has a mortality of 11% and an objective remission rate of 58% with a mean duration of 20 months. The comparable figures from thiotepa were 11%, 41%, and 7.5 months. In addition a number of patients are in their fourth, fifth, and sixth years of remission after hypophysectomy, while none of the thiotepa group has been controlled more than 15 months. In view of these results there is little doubt which method of treatment is the better.

It was hoped that the two remedies might have been effective in different groups of patients. Table II shows that a good response to thiotepa could be expected when the patient was pre-menopausal and had a slowly evolving disease process with distant metastases. Selection of cases for hypophysectomy may be based on similar criteria (MacAlister *et al.*, 1961). This unfortunately means that these two techniques must be regarded as alternatives rather than as complementary.

While hypophysectomy offers properly selected patients the better chance of palliation there are certain indications for thiotepa. It is useful for the patient who refuses to consider hypophysectomy or is unfit for it. It can be tried if there is no response to the operation or when a period of control so obtained terminates. Responses have been observed in one out of two cases who failed to respond to hypophysectomy and in three out of seven cases who had relapsed after an initial response.

It must be emphasized that the criteria for the selection of patients for any method of palliation are imprecise and can serve only as a guide. It is never possible to say that a patient will not respond; and, conversely, another patient will have all the factors likely to make for response and yet disappoint. It is therefore easy to

understand how a decision may be influenced by the patient's particular circumstances and personality.

It might be thought that the large quantity of testosterone given with the thiotepa played a part in producing the responses observed. The possibility cannot be excluded, and it is probable that this substance was partly responsible for the subjective benefit so often seen. If, however, testosterone was also responsible for the objective remissions produced, one would expect some relationship to exist between response to it at a previous stage and subsequent benefit from thiotepa (Table IV): this was not found. On the other hand, the fact that hypophysectomy and thiotepa were effective in similar types of disease suggested an endocrine basis for its action.

We have been unable to note any relationship between the clinical outcome of treatment and the dose of drug administered or the marrow depression produced. This may mean either that similar clinical results could be obtained by a reduced dosage, with possibly a smaller mortality, or that our data are inadequate because of the small number of patients. Improved results might be obtained by increasing the maximum dose (285 mg.) of thiotepa in patients who at that level of dosage did not show a serious depression of their blood counts. This would certainly increase the lethal effect of the drug, and in view of the alternative and, as it seems to us, superior methods of treatment, could not be justified.

Can the treatment be made safer? Table III shows that a rapid fall in the blood count to levels necessitating cessation of therapy did not give much information about the ultimate depth of marrow depression. Thus 13 (56%) out of 23 patients able to tolerate doses between 166 and 225 mg. showed eventual severe depression, while those given 226 to 285 mg. showed a similar result. It must be concluded that about half the cases treated will suffer a dangerous degree of marrow depression, and it is difficult either to prevent it or to predict when it will occur. The only way to make treatment safer would be to raise the white-cell and platelet levels at which treatment is stopped. It is likely that this would reduce the number of remissions.

We cannot recommend second courses of treatment. The mortality produced (5 deaths out of 13 cases) was high, though it must be admitted that these cases had very advanced disease and were in poor general condition.

Summary

The results of treatment with thiotepa and testosterone in 46 patients suffering from advanced breast cancer have been presented. The mortality rate was 11%, and an overall remission rate of 37%, lasting an average of 7.5 months, was obtained. It appeared that premenopausal women with a slowly evolving disease and metastases in bone were more likely to respond to this form of therapy. The hazards and protracted nature of treatment were comparable to those from hypophysectomy, but it was concluded that the results were inferior to those of the operation.

We wish to thank Dr. G. A. Lynch for his co-operation in producing the series; Dr. A. T. Barker, whose supervision of in-patients was invaluable; and Dr. G. F. Tinsdale and his staff, who performed many clinico-pathological studies, without which the investigation would have been impossible. We also thank the nursing staffs of the Northern Ireland Radiotherapy Centre and Ward 22 of the Royal Victoria Hospital, Belfast, for carrying out the large amount of work

the treatment placed on them. Our appreciation also goes to Mrs. Convey for secretarial help.

REFERENCES

- A.M.A. Joint Committee on Endocrine Ablative Procedures (1961). *J. Amer. med. Ass.*, **175**, 137.
 Atkins, H. J. B., Falconer, M. A., Hayward, J. L., MacClean, K. S., Schurr, P. H., and Armitage, P. (1960). *Lancet*, **1**, 1148.
 Bridges, J. B., Bridges, J. M., Edelstyn, G. J. A., Lyons, A. R., and Nelson, M. G. (1960). *Ibid.*, **1**, 629.
 Cree, I. C. (1960). *Brit. med. J.*, **2**, 1499.
 Edelstyn, G. A., Gleadhill, C. A., Lyons, A. R., Rodgers, H. W., Taylor, A. R., and Welbourn, R. B. (1958). *Lancet*, **1**, 462.
 McAlister, A., Welbourn, R. B., Edelstyn, G. J. A., Lyons, A. R., Taylor, A. R., Gleadhill, C. A., Gordon, D. S., and Cole, J. O. Y. (1961). *Brit. med. J.*, **1**, 613.
 Ray, B. S., and Pearson, O. H. (1960). In *Cancer*, vol. 6, *Hormone Therapy*, edited by R. W. Raven. Butterworth, London.
 Watson, G. W., and Turner, R. L. (1959). *Brit. med. J.*, **1**, 1315.

DIET, SERUM CHOLESTEROL, PROTEIN, BLOOD HAEMOGLOBIN, AND GLYCOSURIA IN A WEST INDIAN COMMUNITY (ST. KITTS, W.I.)

WITH OBSERVATIONS ON ISCHAEMIC HEART DISEASE

BY

KENNETH L. STUART, M.D., F.R.C.P.Ed.
M.R.C.P., D.T.M.&H.

Senior Lecturer in Medicine, University College of the West Indies, Jamaica

ROLAND E. SCHNECKLOTH, M.D.
Assistant Medical Director, American Heart Association

LENA A. LEWIS, Ph.D.
Member of Staff, Research Division, Cleveland Clinic Foundation

FELIX E. MOORE, B.A.
Professor of Biostatistics, School of Public Health, University of Michigan

AND

A. C. CORCORAN, M.D., C.M.
Head of Department of Clinical Investigation, St. Vincent Charity Hospital, Cleveland

During the spring of 1958 a representative sample of the rural population of St. Kitts, W.I., aged 20-49 years was studied with reference to cardiovascular disease, and with special reference to distribution of blood pressure, prevalence, and severity of hypertension. Findings in this negro group were that means of arterial pressure and prevalences of hypertension were greater than in white populations of like age; associated hypertensive disease was not regarded as severe. Supporting data, including detailed descriptions of the population sample, are published elsewhere (Schneckloth *et al.*, 1962). The present report describes aspects of this survey listed above.

Observations

Diet

Four families in each of three villages served and kept uneaten total single adult servings at each meal during two week-days and one Sunday. Accumulated samples were collected daily and constituents listed by the district public health nurse. Daily portions from each family were combined and homogenized with water in a Waring blender, the mixture was weighed, and an