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INFLUENCE OF SYNTHETIC OESTROGENS UPON ADVANCED MALIGNANT DISEASE

BY

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In an investigation of the mechanism of action of tumour-producing compounds it was found that many carcinogenic hydrocarbons possess the property of retarding the growth of tissues, both normal and malignant (Haddow, 1935; for later references see Badger, Elson, Haddow, Hewett, and Robinson, 1942). In these compounds the correlation between carcinogenicity and growth-inhibitory activity assumes considerable statistical significance, and it was further suggested that it is of aetiological importance as well, tumour production by these substances being envisaged as a cellular adaptation to a protracted period of growth repression. In subsequent work to elucidate the molecular conditions determining inhibitory action, attention was paid to the synthetic oestrogens. It may be recalled that a few of the carcinogenic hydrocarbons themselves possess slight oestrogenic activity, while in certain cases these two classes show interesting relationships on chemical grounds. Thus the results obtained in animal experiments with a number of derivatives of the oestrogen triphenylethylene (which may be likened, for instance, to a 9-phenylphenanthrene with one ring disrupted) indicated that growth-inhibitory activity may still be shown by compounds which depart from the polycyclic structure and possess only a resemblance in their carbon skeleton.

These findings may possibly be correlated with the fact that, contrariwise, certain of the oestrogens exert carcinogenic action in animals, although in a somewhat restricted sense and in experimental circumstances (of dosage, strain susceptibility, etc.) which are unlikely to be duplicated under the conditions of medication in the human subject. The reviews of Gardner (1939) and Allen (1942) cite numerous instances of tumours occurring in experimental animals after long-continued treatment with oestrogens, examples being carcinoma of the cervix uteri in mice, uterine fibromyomas in guinea-pigs, mammary cancer, interstitial-cell tumours of the testis in mice, pituitary adenomatosis in mice and rats, tumours of the suprarenal cortex in mice, osteogenic transformations in mice, and various lymphoid and connective-tissue tumours, including sarcoma. The induction of animal tumours by oestrogens is most readily elicited, although by no means exclusively, in those tissues which are highly responsive to the physiological action of such compounds, and the greatest number of reports deal with the production of mammary cancer in mice—e.g., by the synthetic oestrogens stilboestrol (Lacassagne, 1938; Shimkin and Grady, 1940) and triphenylethylene (Robson and Bonser, 1938). Since the testis is markedly sensitive to oestrogen action, which results in varying degrees of atrophy, the production of hypertrophy and tumours of the interstitial cells in the testes of mice receiving oestrogens is of especial significance (e.g., Gardner, 1937; Hooker, Gardner, and Pfeiffer, 1940; Bonser and Robson, 1940). There is, in short, a group of growth-inhibitory substances which are clearly associated with the production of individual classes of tumour in laboratory animals under specially defined experimental conditions. The oestrogens thus provide a further example of the relation (only apparently paradoxical) that compounds possessing growth-retarding properties in certain circumstances may also have either with the physiological stimulation of growth or with the induction of tumours.

The growth-retarding property of polycyclic aromatic compounds, although under some experimental conditions more marked than that shown by the oestrogens, remains a subject for persistent investigation rather than clinical application. However, it was judged reasonable to undertake the clinical trial of synthetic oestrogens in advanced human cancer which was beyond treatment by either surgery or radiation, with particular reference to tumours arising from such normal tissues as are most reactive to the physiological stimulus of these compounds—e.g., tumours of the breast or of the testis. Such an investigation is facilitated by the ready availability and low toxicity of the synthetic oestrogens.

The present paper reports the findings in 40 cases of carcinoma of the breast and in 33 cases of malignant disease in other organs, the majority of which were treated with triphenylchlorethylene, and the first of which (carcinoma of the bladder—see below) began treatment on Feb. 18, 1941. Triphenylchlorethylene is of interest in two respects: first, because of its comparatively prolonged action (cf. Robson, Schönberg, and Fahim, 1938), which seems to be related to its insolubility in body fluids; and, secondly, since Emmens (1941) showed it to be a true oestrogen—that is, one acting directly, or after chemical changes which can be effected locally, in contrast with the pro-oestrogens (including the parent hydrocarbon triphenylethylene), which require to pass into the general circulation before exhibiting oestrogenic properties. Apart from those cases treated with triphenylchlorethylene, 7 were treated with the compound in which the chlorine atom is replaced by a methyl group (triphenylmethylethylene), and 14 with stilboestrol.

A. Triphenylchlorethylene

1. Late Malignant Disease of the Breast

Table I summarizes the data obtained in 22 cases. The drug was administered by mouth in all save Nos. 21 and 22, which received it by the intramuscular injection of an aqueous dispersion.

It is clear that a proportion of cases showed a significant —although temporary—retardation of the growth of the tumour. Indeed, an initial regression of the lesions occurred in 10 of the 22 cases (Nos. 1, 2, 4, 6, 7, 12, 17, 18, 20, 21, Table I). In Case 1 a skin nodule remained stationary for a period of three months, during which the primary tumour was regressing. Again, secondary deposits in the lung developed in Case 18 during treatment, although the lesion in the breast showed all of whom are now dead or have steadily advancing lesions. It may be noted that the degree of retardation obtained was probably much less than could be expected from local palliative *x*-irradiation.

In responsive cases the sequence of changes has been characteristic, consisting of a purplish discoloration of lesions previously red, a flattening followed by disappearance of small skin nodules, and the ulceration and disappearance of larger

TABLE I.—*22 Cases of Late Malignant Disease of the Breast treated with Triphenylchlorethylene*

Case	Age (yrs.)	Previous History	Condition at Beginning of Treatment (No biopsy or section unless stated)	Treatment (Amounts in Grammes refer to Triphenylchlorethylene)	Result of Treatment (b.t. = Beginning of treatment)
1	71	Lump breast for 1 yr., ulcerated	Ulcer 12 × 9 cm. replacing breast. Nodule over sternum. Enlarged lymph nodes both axillae	10 g. per week initial. 252 g. in 3 m. Interval of 2 m.; then 336 g. in 8 m.	Almost complete regression of tumour within 3 m., then steady growth. No regression of nodule or of axillary nodes. Died of lesion and metastases 16 m. after b.t.
2	33	Lump under arm 18 m. *X*-ray therapy. Recurrence 1 yr. later	Pregnant. Tumour lt. breast. Skin nodules; nodes involved	21 g. per week for 2 m. Interval of 2 m. while patient confined; then 525 g. in 6½ m.	Entire diseased breast sloughed off 4 m. after b.t. Fresh nodules in opp. breast. Death 10 m. after b.t.
3	71	Retraction and ulc. lt. nipple for 5 yrs.	Lt. nipple destroyed by ulc. Small tumour beneath nipple. Fixed supraclav. and axillary nodes	21 g. per week for 9 m. Total 756 g.	Stationary over 13 m. Death (cardiac condition) 13 m. after b.t.
4	40	Radical amp. lt. breast 2 yrs. ago, then *x*-ray therapy. *X*-ray therapy for recurrent nodule 8 m. ago	Extensive lesions thorax both sides. Nodes rt. axilla and rt. side neck	21 g. per week for 8 m. Total, 672 g.	Slight diminution in lesions. Treatment stopped; nausea and vertigo
5	53	Lump rt. breast 4 yrs. Local mastectomy and post.-op. *x*-ray therapy	Menopausal. Recurrence mastectomy area, 11 × 16 cm. Rt. supraclavicular nodes. Metas. rt. lung	21 g. per wk. for 3 m. Total, 252 g.	No alteration in recurrence. Growth of lung metastases. Died 14 m. after b.t.
6	48	Radical amp. 9 yrs. ago. Nodules in scar 1 yr. ago	Skin recurrence 13 cm. diam. Hard supraclavicular node. Spheroidal-cell carc.	21 g. per week for 18 m.	Within 5 m. ulc. nodules epithelized. Fresh nodules peripherally. Metas. in vertebrae and regional nodes during treatment
7	63	Lump rt. breast; *x*-ray therapy, then radical amp.	Multiple nodules chest wall; hard supraclavicular nodes. Spheroidal-cell carc.	14–21 g. per week for 15 m. Total, 980 g.	After 10 days regression marked. In 3 m. all lesions disappeared. In further 3 m. recurrence, although treatment maintained. Metas. locally and in lungs. Death 17 m. after b.t.
8	55	Lump rt. breast 1931, tr. radium 1932; recurrence 1942	Recurrence over sternum 5 cm. diam. Lt. supraclav. node	31·5 g. weekly. Total 756 g. in 6 m.	Extension of disease. Died 11 m. after b.t.
9	48	Amp. r. breast Jan., 1941; *x*-ray therapy Oct., 1941, to skin nodules. Disease advancing	Intradermal carc. chest wall. Nodes axillae and supraclavicular regions. Scirrhous carc.	21 g. per week. Total, 279 g. in 2 m.	Died, local extension and metas., 5 m. after b.t.
10	63	Lump rt. breast, ulc., 1939. *X*-ray therapy palliative, poor response	Ulc. tumour breast, fixed axillary nodes. Spheroidal-cell carc.	21 g. per week. Total, 588 g. in 7 m.	No change during treatment
11	60	Lump lt. breast, uncertain duration. Ulc. 1941	Ulc. tumour. Hard supraclav. and axillary nodes. Spheroidal-cell carc.	21 g. per week. Total, 420 g. in 5 m.	No regression. Died 6 m. after b.t.
12	52	Lump rt. breast and both axillae. *X*-ray therapy, incomplete resolution, July, 1941	Post-menopausal. Large mass rt. breast and axillae. Extensive skin involvement	21 g. per week. Total, 420 g. in 5 m.	Possibly slight local improvement. Lung metas. developed. Died 8 m. after b.t.
13	53	Recurrent nodules after radical amp. lt. breast	Nodules lt. chest wall, axilla, and supraclav. region. Scirrhous carc.	18 g. per week. Total, 429 g. in 6 m.	No regression. Not followed after 6 m.
14	65	Radical mastectomy, then *x*-ray therapy, 1941	Recurrence in scar; deposits lt. axilla and both supraclav. regions	21 g. per week. Total, 336 g. in 5 m.	No regression. Alive, but lesions advancing
15	49	Radical mastectomy, 1936. *X*-ray therapy to recurrence. Temp. improvement	Recurrent carc. lt. supraclav. and axillary nodes. ? Metas. dorsal vertebrae. Scirrhous carc.	21 g. per week for 3 m. Total uncertain	No regression. Alive but deteriorating
16	39	Recurrent carc. lt. breast. Radium and *x*-ray therapy	Large mass lt. breast and rt. axilla. Scirrhous carc.	21 g. per week. Total, 630 g. in 7 m.	After stopping treatment, severe menorrhagia. Lesions stationary; total observation 18 m.
17	54 (male)	Radical amp. lt. breast, 1939. *X*-ray palliative therapy local recurrence	Two nodules in op. scar lt. chest. ? Metas. lt. femur and ischium	21 g. per week. Total, 228 g. in 3 m.	Disappearance of nodules after b.t.; recurrence in next 6 m. Metas. in sacrum. Died 11 m. after b.t.
18	65	Lump rt. breast 2 yrs. Ulc. 1 yr.	Ulc. mass 11 × 13 cm. Nodes supraclav. region and both axillae. Spheroidal-cell carc.	21 g. per week. Total, 189 g. in 9 weeks	Mass reduced to 9 × 10 cm. Lung metas. developed during treatment
19	52	Lump lt. breast	Mass filling whole lt. breast. Large ulc. area; nodules lt. chest wall; nodes axilla and supraclav. region. Scirrhous carc.	21 g. per week. Total, 250 g. in 4 m.	Lesion advanced during treatment
20	56	Ulc. lump rt. breast; recurrence after *x*-ray therapy	Tumour 10 × 9 cm. whole rt. breast; ulcerated. Nodes rt. pectoral region	21 g. per week. Total, 1,000 g. in 9 m.	Tumour shrank to 6 × 5 cm. Ulcer smaller but not healed. 7 m. after b.t. ulcer enlarging, and 11 m. after, tumour enlarging, then slow advance. Slight vaginal bleeding and nausea
21	63	Radical amp. for carc. lt. breast, 1932. Recurrence over sternum	Ulc. mass 7 × 4 cm., 4–5 cm. deep. Spheroidal-cell carc.	15 c.cm. dispersion of triphenylchlorethylene by injection in 5 m.	Lesion much flattened, area unaltered. Fresh cervical metas. 4 m. after b.t., then palliative *x*-ray therapy. Nausea during treatment
22	63	Lt. breast "shrinking" for 2 yrs.	Whole lt. breast involved. Nodes lt. supraclavicular area. Lung metas.	9 c.cm. dispersion of triphenylchlorethylene by injection in 3 m.	Lesions progressed. Died 6 m. after treatment stopped

regression. No evidence was obtained to suggest that the drug will prevent the development of metastases. On the contrary, the impression was gained that the malignant cells become in time progressively more resistant to the inhibitory effects produced by the drug at an earlier stage. Thus only one of the cases has shown prolonged arrest, and the ultimate course of the disease has been in no way altered in the remaining patients, nodules and masses, followed by epithelization of the area. In exceptional cases the degree of response was considerable. One of these (Case 1) is illustrated in Fig. 1.

Biopsy material was examined in 4 of the cases showing regression of the primary tumour. All were highly cellular types, as were also 2 of the 3 cases which maintained a stationary condition, the remaining case being of scirrhous type.

Hence there would seem to be a greater sensitivity to the action of the oestrogen in highly cellular than in scirrhous carcinomata. In one case (No. 18, spheroidal-cell carcinoma) serial biopsy during treatment revealed the disappearance of mitoses, and a diminution in the staining affinities of the cells: the appearances did not resemble those seen after *x*-irradiation. The some degree of regression. Relief of pain seemed a real finding in 4 cases—Nos. 6, 10, 17, 21.

2. Miscellaneous Cases

This series consisted of 30 cases of advanced malignant disease other than carcinoma of the breast. They comprised

TABLE II.—*14 Cases treated with Stilboestrol*

Case	Age	Previous History	Condition at Beginning of Treatment	Date Treatment Started	Dosage of Stilboestrol	Result of Treatment
1	42	Rt. radical mastectomy, 1939. H.V. therapy to recurrence Dec., 1941–Sept., 1942. Further recurrence Dec., 1942	General condition good. Multiple skin nodules scar area. Chest clear	Dec. 2, 1942	276 mg. intramuscularly over 3½ months	Deposit in manubrium developed during treatment. Nodules became bluish, ulcerated, and later scabbed
2	68	Lump lt. breast noticed 1919. Ulcerated 1934. *X*-ray therapy to numerous areas rt. and lt. breasts, chest wall, and regional nodes Jan., 1939, to Aug., 1942. Recurrent skin nodules Dec., 1942. *No section*	Multiple nodules and induration scattered over rt. and lt. chest wall and sternum. *X*-ray chest—fluid at left base	Dec. 22, 1942	410 mg. intramuscularly over 3 months	Fresh nodules developed. Nodules became more raised and bright red. Uniform scabbing followed. *Biopsy:* Nodule showed highly cellular carcinoma of anaplastic type. Local area of necrosis present at centre of nodule. General condition deteriorated. Died 4 m. after onset of treatment
3	62	Lump in lt. breast noticed Oct., 1939. Treated H.V. therapy Oct., 1940. Diathermy excision residual growth April, 1941. H.V. therapy to recurrence Dec., 1941, and Oct., 1942. Further *x*-ray therapy Dec., 1942. *Section:* Undifferentiated columnar-cell carcinoma	Multiple nodules lt. chest wall. Underlying diffuse oedema from axilla across midline to rt. breast, which was widely infiltrated and fixed	Dec. 30, 1942	676 mg. intramuscularly over 6 months	In 1 month the rt. breast was softer; oedema of chest wall had diminished. Nodules were paler, softer, and smaller. This condition was maintained for 6 weeks, after which the local condition progressed. New crops of nodules developed
4	40	Lump in lt. breast noticed Mar., 1941. Treated *x*-ray therapy Mar., 1942. Recurrence Nov., 1942. *Biopsy:* Anaplastic carcinoma	Ulcer lt. breast 7·5 × 3·2 cm. Regional nodes not enlarged. *X*-ray chest—multiple secondary deposits	Dec. 22, 1942	199 mg. intramuscularly over 2 months	Ulcer increased in size throughout treatment
5	31	Complained of pain rt. hip Sept., 1942. *X*-ray pelvis—large secondary deposit pelvis	Lt. breast—mass 3 × 3 cm. firmly fixed to deep structures. Rt. axilla—2 firm nodes 1·5 cm. across. Pubis—localized tenderness	Jan. 23, 1943	262 mg. intramuscularly over over 7 wks., 252 mg. orally in 6 wks. H.V. therapy to pubis concurrently	Breast—slow increase in size of tumour with development of an adjacent skin nodule
6	49	Lump lt. breast noticed Sept., 1939. Treated H.V. therapy 1940. Recurrence Oct., 1942, treated H.V. therapy. Further recurrence Jan., 1943	Lt. breast—residual mass. Rt. breast—mass 12·5 cm. across. Skin adherent. Fixed deeply. Skin nodules over sternum	Feb. 10, 1943	450 mg. intramuscularly over 5 weeks	Tumour rt. breast progressed. Lt. breast — condition stationary. Secondary deposits in skull developed
7	47	Mass lt. breast noticed July, 1940. Hard nodes rt. axilla and rt. supraclavicular regions. Treated *x*-ray therapy July, 1941, and Oct., 1942. Recurrence Jan., 1943. *No section*	Rt. breast—skin diffusely infiltrated by growth. Rt. side neck—plaque of skin nodules 10 × 6 cm.	Feb. 15, 1943	433 mg. intramuscularly over 7 weeks	Slow progress of disease
8	50	Lump rt. breast noticed June, 1942. Treated *x*-ray therapy Oct., 1942. Recurrence Jan., 1943. *No section*	Rt. breast solid with growth but no deep fixation. Skin densely infiltrated. Reddened nodule 2 cm. across, above nipple. *X*-ray chest—many large secondary deposits lungs. Rt. axilla—hard fixed mass 5 cm. across	Mar. 23, 1943	660 mg. intramuscularly over 4 weeks	Mass rt. breast and rt. axilla increased in size. General condition deteriorated
9	61	Radical mastectomy 1935. Recurrence 1943. Treated *x*-ray therapy Oct., 1943. Recurrence Dec., 1943. *No section*	Nodules rt. chest wall	Dec., 1943	1 mg. daily 3 mths. orally	Many fresh skin nodules developed. Now in local hospital
10	57	Lump rt. breast noticed Aug., 1941. Treated *x*-ray therapy Aug., 1942. Radical amputation in 1942. Recurrence Sept., 1943. *Section:* Highly cellular intra-duct carcinoma	Nodules rt. chest wall, rt. axilla, and rt. supraclavicular fossa	Dec., 1943	1 mg. three times a day orally for 4 months. Still under treatment	After 2 months nodules flatter but size unaltered. In a further month nodules practically gone. After 4 months two fresh nodules developed
11	64	Lump lt. breast 1942. Untreated	Mass lt. breast 12 × 10 cm. with central ulceration. Mass lt. axilla 6·5 × 4·0 cm.	Feb., 1944	15 mg. weekly intramuscularly and 1 mg. daily orally. Still under treatment	In 2 weeks ulcer dry. In 12 weeks mass lt. breast 6 × 5·5 cm. Mass lt. axilla 3·5 × 3 cm. (Fig. 3.) *Biopsy:* Spheroidal-cell carcinoma
12	80	Lump lt. breast 1937. Grew steadily and ulcerated through skin. *X*-ray therapy 1938. Recurred 1939; treated by radium implantation. Recurred 1940	Ulcer 6 × 6 cm. fixed to muscle. *Section:* Cellular carcinoma of pavement-cell type	Sept., 1943	21 mg. weekly by mouth. Total of 315 mg. in 3½ months	By Dec. 24 ulcer reduced in size to 3 × 2 cm. By April 15 two tiny patches ulceration 2 × 1·3 cm. and 1·2 × 1 cm.
13	67	Lump lt. breast noticed Oct., 1943	Bright-red mass lt. breast 9 × 8 cm. fixed to skin and muscle. Large lt. axillary node. *Section:* Papillary adenocarcinoma (malignant intraductal pattern)	Feb., 1944	42 mg. weekly by mouth. Total of 348 mg. in 8 weeks	Breast mass 7 × 7·5 cm., flatter and purplish. Axillary node not changed in size. Slight nausea; gain of 4 lb. in weight
14	68	Radical mastectomy for carcinoma rt. breast 1936. In 1940 noticed lump lt. breast, and enlarged axillary and supraclavicular nodes. Palliative *x*-ray therapy 1940 and 1942. Extensive recurrence Oct., 1943	Massive involvement *en cuirasse* back and front of chest. *Section:* Adenocarcinoma invading subcutaneous tissue	Feb., 1944	42 mg. weekly by mouth. Total of 378 mg. in 9 weeks	Lesions progressed during treatment, and general condition deteriorated

cellular changes in this case are shown in Fig. 2. Case 17, in which a marked response was obtained, is of special interest as being the only male in the series.

The secondary signs of drug action included nausea, pigmentation of the mammary areola, uterine bleeding, improved appetite, and gain in weight. One or more of these changes occurred with special frequency in the group of cases showing carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis, with reticulo-endothelial growths, and one example each of chronic myeloid leukaemia and chronic lymphatic leukaemia. The period of treatment varied between 1 and 16 months. In nearly every case the drug seemed to have no effect on the course of the disease, although side-effects occurred in some. In other cases treatment was

terminated on account of the patient's being transferred to other hospitals, or referred for tumour excision or *x*-irradiation. Two cases which showed undoubted partial regression of the tumour merit special comment.

Case 1: Male aged 74; Carcinoma of Bladder.—The general condition was poor when treatment began. The patient complained of frequency of micturition, passage of blood in the urine, and shooting pains in the back and at the base of the spine. Cystoscopic appearances were typical of carcinoma of the bladder, and *x*-ray examination revealed a secondary deposit in D. 10. The bladder tumour was apparently slow in growth, since a second cystoscopy after 3 months showed little change. Treatment with triphenylchlorethylene was then begun, and was followed by a rapid improvement of the general condition. After 2 months a third cystoscopy showed marked amelioration of the local condition, with almost complete regression of the primary tumour. At this time tissue for diagnosis was taken through the suprapubic route, and doubtful areas in the bladder were fulgurated. An extract from the pathological report (by Dr. L. M. Hawksley) reads: "In the deeper part of the subepithelial connective tissue and in the fibromuscular tissue focal collections of squamous carcinoma cells, which are definitely identifiable as such, though of viable appearance in only one or two places, have undergone almost complete necrosis." The total dosage of triphenylchlorethylene administered was 760 g. over a period of 9 months. The patient died from circulatory failure 11 months after the beginning of treatment. Necropsy confirmed that viable tumour cells remained in the bladder wall after the disappearance of the primary tumour.

Case 2: Male aged 60; Carcinoma of Prostate.—In this case, admitted on account of frequency of micturition and later complaining of shortness of breath and fleeting chest pain, investigation with uroselectan revealed enlargement of the left kidney, with poor function, and a large filling defect in the bladder on the left side. *X*-ray examination suggested the presence of multiple secondary deposits in the bony pelvis, and in the following weeks similar deposits were recorded in the whole of the dorsal spine, in the ribs, femora, and humeri, and in the lungs. Cystoscopy showed enlargement of both lobes of the prostate, with a large papillomatous mass in the left wall of the bladder. Bladder capacity was much reduced (residual urine, 2 oz.). Biopsy at first gave no undoubted evidence of malignancy, but a second specimen (tissue from bladder removed through cystoscope 11 weeks after starting treatment with triphenylchlorethylene) was reported upon as follows by Dr. Hawksley: "Sections show intact and regular but thinned surface epithelium directly overlying a densely cellular mass of columnar-cell adenocarcinoma of prostatic type, in which well-formed gland lumina occur frequently in the solid cell masses. Although no signs of degenerative change are found, the tumour cells show an unusual absence of evidence of nuclear activity, no mitoses having been seen in the numerous sections examined, and the large, spherical nuclei showing a striking uniformity of size and structure."

Treatment with triphenylchlorethylene had been started on June 9, 1941, and soon produced side-effects (bilateral mastitis and oedema of the ankles) attributable to oestrogen action. Within 3 months the total dose administered exceeded 100 g., and the daily dose had reached 8 g. (maximum). The total dose after 6 months was 700 g., following which the daily dose was decreased (to 3 g.) on account of occasional nausea. During treatment there occurred a decrease in the frequency of micturition and some betterment of the general condition, which after 8 months was regarded as considerably improved. There was, however, no unequivocal radiographic evidence of change in the skeletal deposits, as judged by comparison, after repeated examination, of the various regions involved; but the prostate itself was described as "not obviously enlarged" after 13 months, when a total of 1,346 g. of triphenylchlorethylene had been administered. The plasma acid phosphatase values showed a distinct tendency to increase (from 17 units to 47 King-Armstrong units per 100 ml. over 15 months). The case was then transferred for treatment with stilboestrol in place of triphenylchlorethylene, and is included as Case 6 in a paper by Watkinson *et al.* (1944).

In this series of cases of malignant disease other than carcinoma of the breast, treated with triphenylchlorethylene, the number showing any degree of response was very small, and it may be noted that two of those chosen for comment represented types which might reasonably be expected to possess some special sensitivity to the action of oestrogens. Yet this is not invariably the case, and it is probable that a small proportion of tumours, not derived from tissues of any characteristic or obvious endocrine function or susceptibility, may give a similar response.

B. Triphenylmethylethylene

Four cases of carcinoma of the breast and 3 cases of Hodgkin's disease received treatment. The first group (all in advanced stages of breast cancer) were treated for two months or longer by intramuscular injection of the drug, and only one case (pathologically a spheroidal-cell carcinoma) showed any response. This took the form of flattening of the lesions and the development of a blue coloration of the nodules in the skin. In the four cases, total dosage of the drug varied from 1.4 to 3.8 g.

The main points arising during the treatment of the cases of Hodgkin's disease, in two of which biopsies and serial blood counts were taken, were as follows.

Case 1.—A woman aged 42 presented enlargement of the submaxillary, cervical, and inguinal lymph nodes and multiple opacities in both lungs. A biopsy specimen from a node was diagnosed as Hodgkin's disease. When treatment began the blood count was: red cells, 4,580,000 per c.mm.; white cells, 10,000 per c.mm.; total lymphocytes, 1,000 per c.mm. After one month (in which 12 g. of triphenylmethylethylene was given intramuscularly) the blood count had fallen to: red cells, 2,750,000 per c.mm.; white cells, 5,000 per c.mm.; total lymphocytes, 140 per c.mm. The tumours themselves showed no response.

Case 2.—A boy aged 15 showed enlargement of the liver to the level of the umbilicus, of the spleen to that of the anterior superior iliac spine, and involvement of the cervical and hilar nodes. His general condition was very poor. He lived for 2½ months, and during this time received 242 g. of the drug by mouth. After 1 month both liver and spleen were notably smaller, and remained so until accurate observation was no longer possible owing to the development of gross ascites. No diminution took place in the size of the cervical or mediastinal nodes. Conclusions based on the blood picture are not possible, since two transfusions of whole blood were given; but no remission occurred during the period of observation. Necropsy revealed destruction of the pancreatic parenchyma by sarcomatous tissue, in view of which it was thought necessary to designate the condition as malignant—viz., Hodgkin's sarcoma or polymorphic reticulum-cell sarcoma.

Case 3.—A male aged 20 presented enlargement of a single group of cervical lymph nodes. Neither the spleen nor the liver was palpably enlarged. Over a period of 1 month 28.9 g. of triphenylmethylethylene was administered by mouth and 8.6 g. by intramuscular injection. During this time the mass in the neck increased in size. The effects on the blood picture seen in Case 1 of this series were not reproduced, both the red cell and lymphocyte counts remaining stationary. The case was then referred for *x*-irradiation, when the lesions proved to be radiosensitive.

C. Stilboestrol

Table II summarizes the details relating to 14 cases of carcinoma of the breast treated with stilboestrol: the most favourable response is shown in Fig. 3 (Case 11). Whether or not by chance, this small series provided a slightly lower proportion of cases showing any marked effect in the shape of changes in the growth and behaviour of the tumour. Assuming such changes to be related wholly to the oestrogenic activity of a given compound, there is no reason to suppose that the repeated administration of stilboestrol, which affords the advantage of effective action in very low dosage, will be less effective in producing them than is continued treatment with triphenylchlorethylene, but rather the contrary. In a few of the present cases treated with triphenylchlorethylene or triphenylmethylethylene administered orally, Mr. F. L. Warren was able to recover from the faeces over 90% of the dose given in a measured period (usually 24 hours). This indicates that the drug absorption is relatively inefficient, and probably highly so when compared with stilboestrol. There remains the possibility that some advantage may accrue from the use of compounds of exceptionally long duration of action (as judged by the persistence of their oestrogenic effects): several such compounds are now available, and this suggestion is being explored.

It is clear that the cases now reported afford no contribution to effective therapy, but they are probably sufficient in number to set the subject, as it stands at present, in a fair light. The results, although illustrating well the special difficulties inherent in the problem, have considerable fundamental interest, and at least provide an incentive to further investigation.

Summary

73 cases of advanced cancer received treatment with the synthetic oestrogens triphenylchlorethylene, triphenylmethylethylene, or stilboestrol.

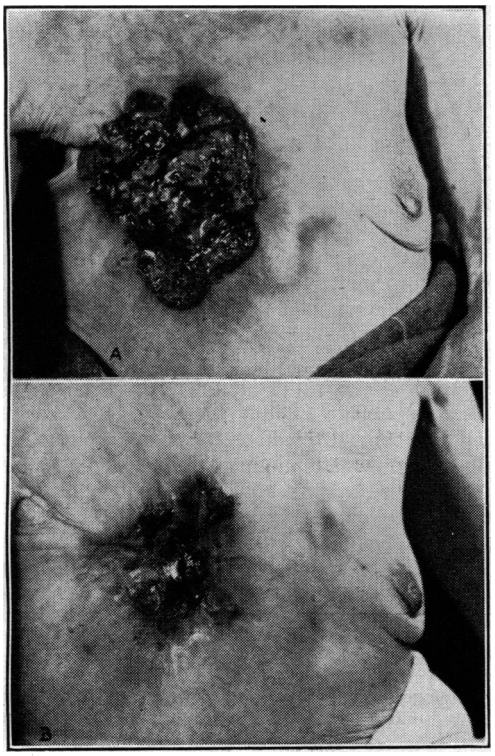

FIG. 1.—*Case 1 (Table I). Carcinoma of Breast.* The primary lesion (A) at May 20, 1941, and (B) at Oct. 29, 1941, after treatment with triphenylchlorethylene.

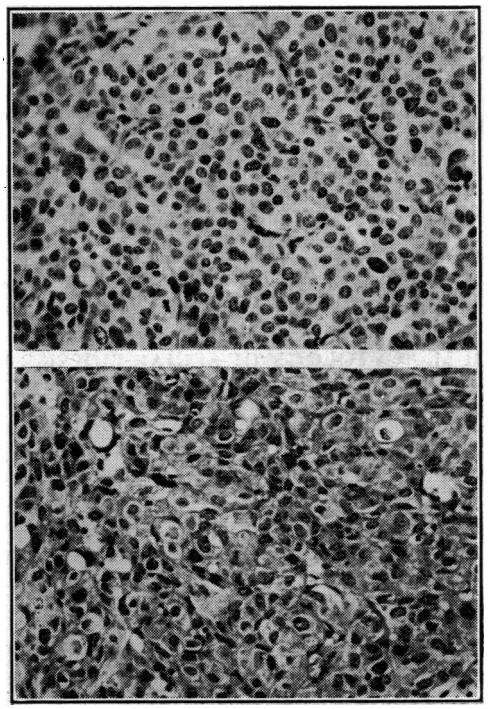

FIG. 2.—Histological section, Case 18 (Table I). Above:—Before treatment with triphenylchlorethylene. H. and E. ×300. Below:—After treatment for 1 month. Note irregularity in size, shape, and staining of nuclei. H. and E. ×300. Sections stained together.

Of 22 cases of late malignant disease of the breast treated with triphenylchlorethylene (usually in doses of 3 to 6 g. per day), 10 showed a significant although temporary retardation, or even partial regression, of the growth of the tumour. No evidence was obtained to suggest that the drug will prevent the development of metastases. The initial effect of treatment in these cases passed off comparatively rapidly, and only one has shown prolonged arrest, the ultimate course of the disease being in no way altered in the remainder. The degree of retardation was less than could be expected from local palliative *x*-irradiation.

Of 30 cases of advanced malignant disease other than cancer of the breast (including carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis, with reticulo-endothelial growths and leukaemia), and similarly treated with triphenylchlorethylene, only 2 (carcinoma of the bladder, carcinoma of the prostate) showed undoubted partial regression of the tumour.

Of 4 cases of mammary cancer and 3 cases of Hodgkin's disease treated with triphenylmethylethylene (usually by intramuscular injection) only one (spheroidal-cell carcinoma of the breast) showed even a temporarily favourable response.

Of 14 cases of carcinoma of the breast treated with stilboestrol (by intramuscular injection or by mouth over a period of several months), 5 showed alterations in the growth and behaviour of the tumour similar in nature to those produced by triphenylchlorethylene.

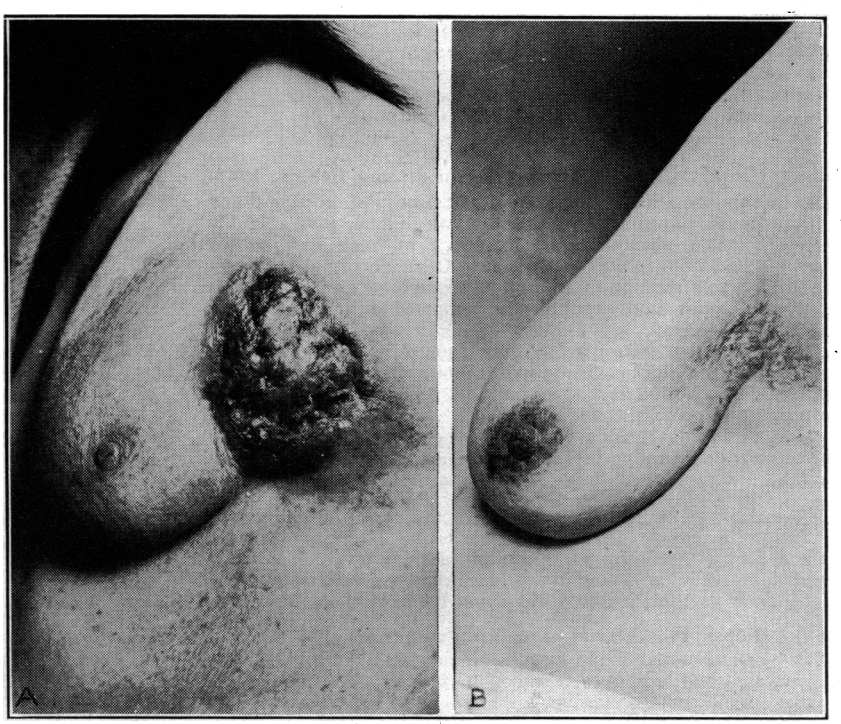

FIG. 3.—*Case 11 (Table II). Carcinoma of Breast.* The primary lesion (A) at Feb. 7, 1944, and (B) at May 22, 1944, after treatment with stilboestrol.

Serial biopsies in a few cases with a marked clinical response showed histological alterations (diminution of mitosis rate, variations of staining behaviour, and necrotic changes) of a type not resembling the changes following *x*-irradiation.

The secondary signs of drug action included nausea, pigmentation of the mammary areola, mastitis in the male, uterine bleeding, and oedema of the lower extremities. One or more of such changes occurred with special frequency in cases showing some degree of tumour regression. Several of these cases also manifested improved appetite, gain in weight, and diminution of pain.

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mittee of the Royal Cancer Hospital (Free) for permission to publish details of those cases under their charge, and to Imperial Chemical Industries Ltd. (Dyestuffs Division) for supplies of triphenylchlorethylene and triphenylmethylethylene.

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ADDENDUM.—CYTOLOGY OF SERIAL BIOPSIES FROM A CASE OF CARCINOMA OF THE BREAST TREATED WITH STILBOESTROL

BY

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The following is a summary of the cytology of serial biopsies from Case 11 (carcinoma of the breast, Table II, above) taken during a period of markedly favourable response (tumour regression) after treatment with stilboestrol.

Biopsy I. Before Treatment: Feb. 7, 1944

In respect of nuclear morphology two main cell types could be distinguished in the resting stage. One is characterized by a nucleus which contains several Feulgen-positive chromocentres (the potentially dividing cell). The other has a nucleus with one large or several small nucleoli (the differentiated cell). The proportion of potentially dividing cells in different regions of the biopsy material was found to vary between 12.5 and 27.3%. The division rate was determined in four cell populations (600 cells in each) taken from different regions of the specimen: in these the division rate was found to be 2.3, 5.2, 5.6, and 7.5%. Synchronous division of three or four tumour cells was frequently observed. Chromosome behaviour and spindle formation were normal. The highest incidence of degenerated cells was 2.5%.

Biopsy II. March 10, 1944 (Treatment started Feb. 9, 1944)

Nuclear and cytoplasmic changes were observed. Cells were found with one or more vacuoles in the nucleus, which latter gave a weakly positive Feulgen reaction. The frequency of such cells varied between 4 and 7.5% in different regions. Other abnormal cells were seen with deeply staining cytoplasm. The division rate was apparently lower in this biopsy specimen as compared with Biopsy I: the highest division rate found was 4.6%. In some dividing cells chromosomes were seen lying off the equatorial plate, and these were shorter and thicker than usual. While there appeared to be a decrease in division rate, a significant increase was observed in the proportion of degenerated cells. In one region it was found to be 12.5%. The morphology of the degenerating cells differs from that of cells degenerating as the result of *x*- or gamma-radiation.

Biopsy III. During Treatment: April 25, 1944

The number of cells showing nuclear and cytoplasmic alterations has further increased. Division rate was estimated to vary between 4.2 and 5.6%. Apart from chromosome lagging at anaphase in a few dividing cells, no other mitotic abnormalities were seen. The frequency of degenerating cells was about the same as in Biopsy II.

Biopsy IV. During Treatment: May 29, 1944

The biopsy material shows marked alterations. The division rate has increased and regions were encountered with 14.3% of cells in division. Synchronous division of several adjacent cells was very frequent. The chromosomes of cells in mitosis were thick and short, they failed to form an equatorial plate at metaphase, and were scattered in the cells. Cells with multipolar spindles were also encountered. The proportion of degenerating cells was found to vary between 7.3 and 16.3%. While the cellular abnormalities and the various stages of cell necrosis observed in the second and third biopsies indicated that cell degeneration is brought about by nuclear vacuolization, evidence was obtained from this fourth specimen that cell degeneration may also be due to a breakdown of the mitotic mechanism. The cytological evidence thus suggests that the primary effect of stilboestrol in this case may be localized to the nucleus of the tumour cell.

REACTIVE HYPERINSULINISM

CASE REPORT, WITH A DISCUSSION OF THE DIFFERENTIATION FROM ISLET TUMOUR

BY

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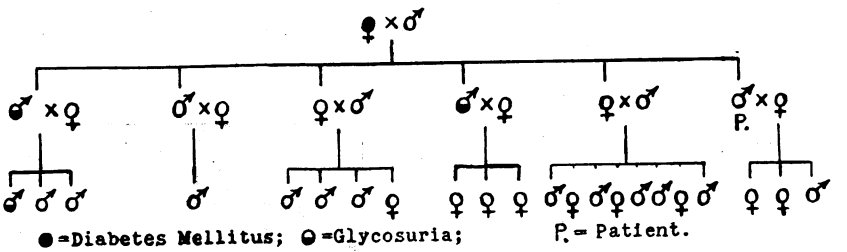
(From the Department of Pathology, St. Thomas's Hospital Medical School)

The condition known in this country as "hypoglycaemia" (Cambridge, 1924) is described under the term of "hyperinsulinism" or "dysinsulinism" in America, according to the manifestations encountered—dysinsulinism implying an erratic under- and over-secretion of insulin (Harris, 1934). According to this terminology, hyperinsulinism would not include hypoglycaemia due to hepatic damage. The conditions here to be discussed are those in which the pancreatic activity is mainly at fault, and therefore exclude those due to other glandular dyscrasias and hepatic disease. It is the object of this communication to draw attention to a condition which may be termed "reactive hyperinsulinism," as opposed to hyperinsulinism due to overactivity of the pancreas as a result of tumour of the islets, malignant or benign. The term "reactive hyperinsulinism" is to be preferred to that of "functional hyperinsulinism" of Conn (1940), since the word "functional" has other less well defined associations.

Case Report

A professional man aged 56 complained of attacks consisting of a sinking feeling during the preceding five years and of continual tiredness for four years. He had had three attacks of arthritis, mainly affecting the larger joints, in the course of ten years. The family history was noteworthy (see genealogical chart). The patient's mother had died of diabetes mellitus, but the father was a healthy man, and lived to the age of 84. The eldest brother had renal glycosuria, and his eldest son has been found to have glycosuria. A second brother has also had glycosuria for many years, recently having had an operation for cataract. There are also a healthy brother and two sisters.



The patient stated that for the last four years he had had a continual feeling of tiredness accompanied by considerable difficulty in concentrating. During this period his work had greatly increased and his hours had been long, with short intervals for meals. For five years he had had acute attacks consisting of a sinking feeling in the epigastrium and intense weakness, followed by a cold sweat. He was forced to sit down during the attacks, but never fainted. After the attack had passed off his appetite was ravenous. The attacks always occurred in the afternoon or early evening, about three hours after the last meal. It appeared that his wife had been in the habit of "fortifying" him daily with a large tea consisting mainly of carbohydrate, including a great amount of honey or jam. Furthermore, the greater the quantity of such food consumed the greater the severity of the subsequent attack. The attacks passed off spontaneously with rest for about ten minutes or on taking carbohydrate. Their frequency was variable, six weeks sometimes elapsing between them, at other times two occurring in a week. In general their frequency and severity had increased with the passage of time. Occasionally exercise—e.g., gardening—brought on an attack, but only at the time of day already mentioned. Usually he could take considerable exercise and little food without getting symptoms. He had had no polydipsia or polyuria and no headache. He had lost one stone in weight in three years.

On examination the patient was not obese. There were no physical signs and no evidence suggestive of glandular or hepatic disease. Circumstances did not permit of special investigations of liver function, but the blood-sugar curve does not conform to the type seen in hepatic disease. There was no glycosuria.