BRITISH MEDICAL JOURNAL

LONDON

SATURDAY MAY 19 1945

SYNTHETIC OESTROGENS AND CANCER

Not long after it had been announced that stilboestrol had some effect on the course of prostatic cancer, practitioners, acting on the assumption that cancer is a unity, give stilboestrol in other types of the disease, notably of the breast. Following desultory correspondence in the columns of this *Journal* the treatment of mammary carcinoma with stilboestrol was discussed at the Royal Society of Medicine,[1] and a committee was formed, with Prof. E. C. Dodds as chairman and Dr. Alexander Haddow as vice-chairman, to investigate the subject further. Not long afterwards we published two papers by Dr. Haddow and his colleagues on synthetic oestrogens and malignant disease.[2] These workers pointed out that many carcinogenic hydrocarbons also had the property of retarding the growth of both normal and malignant tissues. A few of these hydrocarbons had in addition slight oestrogenic activity. This interesting story is rounded off by the observation that oestrogens, both natural and synthetic, in certain circumstances are carcinogenic and in other circumstances have growth-retarding properties. In their first paper Haddow and his colleagues gave an account of the treatment by synthetic oestrogens of 40 cases of carcinoma of the breast and 33 cases of cancer elsewhere. The first of their cases was treated in February, 1941. In 10 of the 22 cases of mammary carcinoma given triphenylchlorethylene there was an initial regression of the tumour, which was unfortunately not maintained. In the most dramatic of these cases there was almost complete regression within three months of taking triphenylchlorethylene by mouth, but this was followed by a regrowth of the tumour and final death from cancer. Similar results were experienced in the treatment of breast cancer with stilboestrol. This painstaking work makes it clear that these remedies do not provide a cure for cancer; but another fact is added to the mass that has accumulated round this subject—namely, that synthetic oestrogens do have some retarding effect upon the cancer cell.

In their 10 cases of prostatic cancer treated between 1941 and 1943 Haddow and his colleagues observed symptomatic and general improvement in all except one, improved appetite and gain in weight, regression of the primary tumour in 4 cases and of secondary deposits in lymph nodes in 3; but in other cases, in spite of general improvement, the number and size of secondary deposits in bone continued to grow. As the stilboestrol treatment of carcinoma of the prostate was first introduced in 1940, we are not yet in a position to assess the results in terms of "cure." The progress of 7 cases of proved adenocarcinoma of the prostate treated with stilboestrol or stilboestrol dipropionate since March, 1940, has been described by Kahle, Schenken, and Burns.[3] A detailed account[4 5] was given in 1942, and the present communication deals with the 5 of the original 7 patients who could be traced. One of the 5 died of urinary sepsis and heart failure. The findings are so important that the statements made by the authors are quoted: "In all 5 cases, including the fatal case, serial histologic examination showed definite regression in the carcinomatous tissues. There was a regression of metastatic osseous lesions, as demonstrated by serial roentgenologic examination, in the single case in which such lesions were present, and a regression of metastases to the lymph nodes in another instance." Massive doses of the drug produced no ill effect except in one instance of transient gynaecomastia. Another interesting point brought out is that in one case a recurrence of carcinoma occurred and the patient was equally responsive to a second course of treatment. The histological findings on sections taken at various periods throughout the treatment are also extremely interesting. The authors noted the following: "(1) In the untreated specimen the neoplastic cells present large vesicular nuclei, prominent nucleoli, and granular, reticular cytoplasm. (2) In the first stage of regression there is a decrease in the size of the nuclei associated with condensation of the nuclear chromatin. Nucleoli are no longer visible and mitoses are absent. Cytoplasmic vacuoles appear and are located predominantly at the bases of the cells. (3) In the second stage of regression the nuclei are pyknotic." These observations are highly important. The relief of symptoms—even though this may be only temporary—is an advance in therapeutics. The regression of the primary tumour is a very startling fact. But it is difficult yet to appreciate fully the significance of this work. If the effect of stilboestrol on prostatic adenocarcinoma cannot be repeated on adenocarcinomas in other parts of the body it is tempting to suggest that carcinoma of the prostate is different from other forms of malignant disease, which is tantamount to suggesting that cancer has more than one cause, just as an inflammatory reaction has more than one cause. Haddow and his colleagues did, however, observe an effect on carcinoma of the breast treated by stilboestrol and of the bladder treated by triphenylchlorethylene. We must emphasize that the benefit observed in these cases during treatment with synthetic oestrogens —and possibly, therefore, resulting from this treatment— was only transitory, and that the hopes raised in the sufferers and their relatives were finally dispelled by death. And although apparently dramatic results are obtained in the treatment of cancer of the prostate, the cautious reader will observe that bony metastases can grow and extend during a treatment which is associated with a regression of the primary tumour.

Kahle and his colleagues discourage speculation on the mode of action of stilboestrol. Theoretically the curative effect may result from action of the pituitary, or direct action on the cancer cells or on the testes and the cells producing the androgenic hormone. Another possibility is that

1 See *British Medical Journal*, 1944, **2**, 20.
2 Ibid., 1944, **2**, 394, 398, 492.
3 *J. Urol.*, 1943, **50**, 711.
4 Ibid., 1942, **48**, 83.
5 Ibid., 1942, **48**, 99.

the stilboestrol may upset the balance between androgens and oestrogens in the body and thus influence the growth of the new tissue. Others have suggested that the action may be due to some particular molecular configuration of the oestrogen. Dodds and his colleagues, responsible for the synthesis of the stilboestrol group of substances, have always pointed out that the structural resemblance of these substances to naturally occurring hormones is only superficial, and there would appear to be little advantage in speculating along these lines. Stilboestrol, hexoestrol, and dienoestrol are used in enormous quantities all over the world, mainly in the treatment of menopausal disturbances and the termination of lactation. The quite unforeseen use in the treatment of carcinoma of the prostate may prove to be the opening of a new and more hopeful chapter in the control of malignancy.

CHEMOTHERAPY OF TUBERCULOSIS

With the discovery first of arsphenamine, then of sulphonamides, and most recently of penicillin, effective drugs are now available for the cure of many of the infections of temperate climates. Others can be controlled by the prophylactic use of serum and vaccines. Among those conditions for which there is no effective cure are the common cold, influenza, and tuberculosis, and the last of these undoubtedly forms the biggest problem for chemotherapy. Numerous compounds have been tested for their action upon tubercle bacilli; most of the tests have been done *in vitro*, but some have been performed *in vivo*, mostly on guinea-pigs. Unfortunately the disease is so chronic, even in guinea-pigs, that a large number of animals are required over a long period to complete a single test; progress is accordingly slow. Among compounds which have been demonstrated during recent years to inhibit the growth of tubercle bacilli *in vitro* may be mentioned 2 : 4-dichlorobenzophenone[1] (active 1 : 100,000); sulphur compounds, especially mercaptobenzothiazole[2]; 3 : 5-diodo-2-hydroxylbenzoic acid[3] (active, 1 : 10,000); and 3 : 6-diamino-10-methylacridinium iodide[4] (active *in vitro* 1 : 250,000, but inactive *in vivo*). The compounds shown to be active *in vivo* have been mostly salts of heavy metals. Of these, gold compounds have received the most attention and are the best known. During the past twenty years preparations such as sanocrysin or solganal B have been used extensively in the treatment of human disease. Experts on tuberculosis are still far from unanimous about their value. Cadmium sulphate has been recommended as being as good as sanocrysin, while being cheaper and non-toxic.[5] In Germany a preparation of copper called "ebesal" was found to be useless for human pulmonary tuberculosis.[6] In a review in 1940 Findlay[7] concluded that none of the remedies up to that date had been shown to have a decisive influence on the course of the human infection.

In 1941 a more hopeful chapter was opened by the work of Hinshaw and Feldman[8] on sulphone derivatives. The earlier sulphonamide compounds had proved disappointing when applied to tuberculous infections, but these workers demonstrated that promin (sodium *p,p'*-diamino - diphenyl - sulphone - N,N' - didextrose sulphonate) arrests but does not completely suppress tuberculous infection in guinea-pigs. However, when promin (or promanide, as it is known in this country) was tested in human tuberculosis the results were disappointing. It caused toxic effects such as anaemia, cyanosis, agranulocytosis, gastrointestinal disturbances, and other symptoms, and its therapeutic action was not very pronounced.[9] It was clear that promin was not the long-awaited remedy, though perhaps it might point the way towards it. The most successful method of using promin was that reported in 1942 by Tytler and Lapp,[10] who applied it locally to tuberculous ulcerations; but this report does not seem to have been amplified or confirmed. Various improved forms of promin have been announced, the most hopeful being promizole (4'-2'-diamino-phenyl-5'-thiazole sulphone),[11] which is somewhat similar to sulphathiazole; but clinical reports are not yet available. The sulphone group of compounds is the most promising one discovered so far. A most interesting development, however, has recently been reported[12]—namely, the use of the antibiotic substance, streptomycin, against tuberculosis; this is described in more detail on another page. In guinea-pigs it is as effective as promin.

The latest example of bactericidal action against tubercle bacilli *in vitro* is reported by Faulkner,[13] who has shown that diethylstilboestrol (4 : 4'dihydroxy-α : β-diethyl stilbene) is active in this respect. In a previous paper she had demonstrated that stilboestrol is bactericidal *in vitro* for Gram-positive organisms such as staphylococci, haemolytic streptococci, and diphtheria bacilli. When incubated at 37° C. for 24 hours in an aqueous medium, tubercle bacilli are killed by stilboestrol at a concentration of 1 : 20,000. If the bacilli are suspended in a medium containing 25% of serum the activity of the compound is much reduced, and a concentration of 1 : 3,000 is needed. In the light of these results it is interesting to recall clinical experience on the association of tuberculosis and pregnancy. During pregnancy phthisical women may appear to improve in health, but in the puerperium the tuberculous disease usually advances more rapidly. Tuberculosis of the placenta is very rare, but it occurs occasionally in women with acute generalized tuberculosis or advanced chronic pulmonary tuberculosis. It is stated in Faulkner's paper that the antituberculous action of stilboestrol is being investigated *in vivo*, and the results will be awaited with interest. But in view of the low activity in the presence of serum, and the long history of previous disappointments in this field, it seems most probable that the search for an effective remedy for tuberculosis will still have to go on. The chemotherapy of tuberculosis should be investigated on a much greater scale than in the past, once the war is over.

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[5] Ray, K. S., *et al.*, *Indian med. Gaz.*, 1941, **76**, 204.
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[12] Feldman, W. H., and Hinshaw, H. C., Ibid., 1944, **19**, 593.
[13] Faulkner, G. H., *Amer. Rev. Tuberc.*, 1944, **50**, 167.