OESTROGENS IN THE TREATMENT OF CANCER

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The story of the isolation and characterization of the oestrogenic hormones begins in 1923, when Allen and Doisy first used the vaginal smear method to test the activity of substances isolated from the ovary. The smear is spread on a microscopic slide and stained with a suitable dye and the type of cells observed shows at which stage of the sexual cycle an animal is. At the 'resting' stage only epithelial debris and leucocytes are seen. As the reproductive period or oestrus approaches, the leucocytes disappear and the large epithelial cells increase in number. At the height of the reproductive period the nuclei or epithelial cells disappear and the smear shows keratinized plaques. In an ovariecotomized animal these changes do not take place and only the 'resting' stage is seen. However, if an active oestrogenic substance is injected into the ovariecotomized animal, the same characteristic changes can be reproduced as take place normally in the intact animal. Allen and Doisy found that by using a sufficient number of animals and graduating the dose, they could make this into a fairly accurate quantitative test.

The next step forward was the discovery by Aschheim and Zondek (1927) that large quantities of oestrogenic substance are excreted in the urine of pregnant animals. This is much easier material to deal with than the ovarian extracts and large quantities of purifiable material became available. By 1932 five oestrogenic compounds had been isolated in crystalline form. These are oestrone, oestriol, oestradiol, equilin and equilenine (Figs. 1 to 5).

Two very striking facts now became apparent. The first was that there should be no less than five distinct substances to be found in nature, all having oestrogenic activity in varying degrees. The second fact which came to light was that the proliferative changes occurring in the vagina in oestrus bear a certain resemblance to the proliferation caused by the application of carcinogenic hydrocarbons to the skin. It was obvious, therefore, that oestrogenic activity is not specific in the same way as other hormonal activities are specific and the possibility arose that it was not even confined to one chemical group of compounds. Two of the most potent carcinogenic hydrocarbons, namely, 1:2:5:6-dibenzanthracene and 1:2-benzpyrene (Figs. 6 and 7), were tested and they proved to be weakly but quite definitely oestrogenic. At the same time a series of compounds, containing the phenanthrene nucleus, but without the five-membered ring found in all the natural substances, were made. Of these the compound 1-keto-1:2:3:4-tetrahdrophenanthrene (Fig. 8) was found to be active, though still to a much lesser degree than the five naturally-occurring substances.

The work was continued, and it was found that the introduction of groups at the 9:10-position of 1:2:5:6-dibenzanthracene would convert this compound into a powerful carcinogen into a powerful oestrogen (Fig. 9). A long series of researches finally resulted in the synthesis of the three highly active oestrogens, stilboestrol, hexoestrol and dienoestrol (Figs. 10, 11 and 12). To these have now been added the bis-dehydro-doisynolonic acid of Miescher (1944) and the naphthalene carboxylic acid of Horeau and Jacques (1947) (Figs. 13 and 14).

No explanation has yet been found for the fact that these compounds, though bearing no very close chemical relationship one to the other, all share the property of oestrogenic activity. There is always the possibility that the active oestrogenic agent is some small chemical group belonging in common to all these active substances, but this is only a speculation.

Another curious fact that has emerged is that, just as certain carcinogenic substances possess oestrogenic activity, so oestrogens under certain circumstances have been shown to be carcinogenic. Lacassagne (1932, 1933, 1934, 1936) injected a mixture of oestrone, equiline and equilenine into castrated male mice and obtained mammary tumours in a few of them. In subsequent experiments he used two groups of mice, the first taken from a strain in which the females had a low incidence of mammary cancer, and the second from a strain in which the females had a high incidence of mammary cancer. In the first group injection of oestrogens produced mammary tumours in a relatively small proportion after a long period of time, whereas the animals of the second group all developed cancer within a short
Fig. 1: Oestrone

Fig. 2: Oestriol

Fig. 3: Oestradiol

Fig. 4: Equiline

Fig. 5: Equilenine

Fig. 6: 1:2:5:6-dibenzanthracene

Fig. 7: 1:2-benzpyrene

Fig. 8: 1-keto-1:2:3:4-tetrahydrophenanthrene
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Fig. 9

9:10-dihydroxy-9:10-dialkyl-2:5:6-dibenzanthracenes

Fig. 10

Stilboestrol

Fig. 11

Hexoestrol

Fig. 12

Dienoestrol

Fig. 13

bis-dehydro-doisynolic acid

Fig. 14

Naphthalene carboxylic acid

time. He also found that administration of oestrogens to mice would produce uterine tumours and lymphosarcomas as well as mammary tumours. The conclusion is that administration of oestrogens will produce tumours provided it goes on long enough and that the animals themselves have a spontaneous incidence of cancer. It is important to emphasize that, when tested by the standard method used by Kennaway and his colleagues, these compounds are not carcinogenic, since the painting of oestrone or stilboestrol on the skin will not produce an epithelioma.

Paradoxically the administration of oestrogens has been found to have beneficial effect in certain forms of cancer. The use of oestrogens in the treatment of carcinoma of the prostate gland is due to the work of Huggins. By experiments on dogs Huggins (1940) discovered that administration of androgens will stimulate the growth of the prostate and the secretion of prostatic fluid and that these effects can be reversed by the administration of oestrogens. He also found that prostatic tumours in dogs can be made to regress either by orchidectomy or by the administration of oestrogens.

Castration for prostatic tumours in man had been tried in the past from time to time, but results had been disappointing. Huggins (1945) attributes this to the fact that there was at that time no scientific basis for the selection of suitable cases for treatment. Much light was thrown on this problem by the work of Kutscher and Wolbergs (1935) and the Gutmans and their colleagues (1936, 1938) on the acid and alkaline phosphatases. The acid phosphatase is present in considerable quantities in the prostate gland of adult men but is found in only minute quantities before the onset of puberty. The Gutmans and their colleagues found that in carcinoma of the prostate gland the level of acid serum phosphatase becomes abnormally increased. The alkaline phosphatase of serum is increased in liver disease and in states of increased osteoblastic activity and is frequently increased in prostatic carcinoma with metastases. An estimation of these two enzymes, therefore, constitutes an im-
important diagnostic aid and enables the doctor to select suitable cases for treatment and to follow the progress of such cases.

Huggins (1941) began to treat 21 cases of advanced carcinoma of the prostate by castration or the administration of oestrogens. In 1946 he published a report of these 21 cases after five years. Out of the 21 cases, five were still alive, four with no signs of malignancy. The fifth had a slowly-growing tumour but was otherwise in good health. Only three out of the 21 received no benefit at all. The remaining 13 obtained some benefit lasting from 5 months to 44 years.

Many other workers both in America and in Great Britain have since confirmed Huggins’ findings. The experience of most workers has been the same as that of Huggins, namely, that all but a small percentage of cases show some response, but that a large number of cases which respond at first eventually escape from control. Huggins attributes this partly to the fact that an extra-gonadal source of androgens can be found in the adrenal cortex, and partly to the fact that some prostatic tumours are what he calls ‘androgen independent,’ that is, that the malignant cells are not such as depend on androgen stimulation for their growth, and therefore the inhibition of androgens has no effect.

In the cases which are found to benefit, the response to treatment is often very rapid and improvement, as shown by a decrease in acid and alkaline serum phosphatases and by improvement in appetite and general well-being, may take place in a few days. These effects are followed by an increase in weight and the disappearance of frequency due to obstruction of the urinary passages, and pain due to pressure on nerves is relieved. The degree of improvement naturally varies in different cases. In some the size of the tumour may not be decreased, in some others the primary tumour may regress while the secondaries go on growing. Very many patients who have been bedridden and acutely ill in great pain and discomfort have been enabled to get up and resume their normal activities. In any event, such a simple remedy as the administration of oestrogens by mouth would be more than justified by even a small improvement in such a disease.

This treatment has also been used empirically in the treatment of carcinoma of the breast. According to the statistics that have so far been collected, about 5 per cent. of these cases respond. Again the degree of response varies considerably; in some cases there is only slight relief of symptoms, whereas in a few very rare cases a complete disappearance of the tumour and secondaries has taken place.

Again, no explanation has been found for the beneficial action of stilboestrol and other oestrogens in these cases. The evidence at present points to the fact that they act mainly through the anterior lobe of the pituitary, seeing that the same result can be obtained by deep X-ray to the pituitary and also by castration. Immediately after the discovery of stilboestrol experiments were commenced at the Courtauld Institute to see whether it would have any effect on the incidence of 'take' of transplanted tumours and also upon the growth of tumours already successfully implanted. The experiments were entirely negative. Ludford and Dmochowski (1947) have reported extensive experiments on similar lines. They investigated the effect of stilboestrol on different types of transplatable mouse tumours and reported their results as follows:—‘On these tumours stilboestrol showed no specific inhibition of growth; such inhibition of growth as took place with relatively high dosages was the result of a non-specific toxic action. Neither in vivo nor in vitro did stilboestrol induce the same type of mitotic poisoning action as does colchicine.’

Until the mode of action of oestrogens in carcinoma of the prostate and carcinoma of the breast is explained, their use can only proceed by trial and error and it is impossible to lay down any hard and fast rules as to dosage and selection of cases. Until further facts come to light it is impossible to know beforehand whether a given case will respond or not, and there are bound to be disappointments. However, since the treatment is without danger, it is always worth trying.

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