Experimental approaches to endometrial and ovarian cancer

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THE most well-known types of hormone-dependent tumours are those of breast, endometrium and prostate, but several other types probably exist (Crowley, 1969; Crowley & Duwe, 1969). Because of their special nature they are open to endocrine manipulation in ways not possible in other tumours. Tumours of the ovary are not easily characterized in this respect as there are so many types and several are apparently quite insensitive to hormone therapy.

There have been very many studies on the effects of endocrine surgery and therapy in carcinoma of the breast (e.g. Forrest & Kunkler, 1968), but on the whole little real success has been shown. One factor in this lack of success is the great differences in the characteristics of the various cell types in breast tissue. In contrast, endometrium, though not of one pure cell type, is much less complex and valuable results can be obtained with endocrine therapy.

It has been clearly established that oestrogen has a growth-promoting effect on endometrial carcinoma (Gusberg, 1967, 1973) and that high doses of suitable progestagens have an inhibitory effect on tumour growth in many cases (Kelley & Baker, 1961; Varga & Henriksen, 1961; Kennedy, 1963). These effects are more marked in well-differentiated adenocarcinoma and are of little importance in undifferentiated tumours (Kennedy, 1963; Liggins, 1964; Varga & Henriksen, 1965).

Although it has long been thought that oestrogen may act as a carcinogen in the endometrium in certain circumstances, the balance of opinion now supports the view that natural oestrogens are not carcinogenic. The position of synthetic oestrogens such as stilboestrol is at present somewhat equivocal. Certain aspects of this problem are reviewed by Brush (1973).

Some ovarian tumours produce quite large amounts of hormones, some secrete only traces and others are quite inactive. The variations in morphology and behaviour are very great. Certain types are benign, but malignant tumours with a very poor prognosis are common. Ovarian carcinoma is normally treated by the conventional approaches of

surgery, radiotherapy and chemotherapy. In view of the poor results obtained it might be useful to explore the possibility of using endocrine therapy, in conjunction with the conventional treatments.

Endocrine therapy of endometrial carcinoma

High dose progestagen therapy in endometrial carcinoma was pioneered by workers in the U.S.A. and has been used in a rather limited way for some time. Some of these studies are discussed by Kennedy (1968) and Crowley & Duwe (1969). However, many gynaecologists, especially in the U.K., tended to think of this therapy as a last resort in metastatic or other inoperable cases (Phillips, 1966; Hudson & Stansfield, 1967). In September 1971 a symposium on Endometrial Carcinoma was held at St Thomas's Hospital, London in which various surgical, radiotherapeutic and endocrine approaches were discussed (Brush, Taylor & Williams, 1973). Recent developments in endocrine therapy were of particular interest and it became clear that although high-dose progestagen therapy was most unlikely to displace surgery it offered valuable advantages in pre-operative and postoperative treatment as well as in metastatic carcinoma. Intra-uterine progestagen therapy as a possible pre-operative treatment, especially when radiotherapy is not available, was also discussed and some striking results were described.

For details of dose schedules reference should be made to individual papers in Brush, Taylor & Williams (1973), but it should be emphasized that very high doses are required (e.g. 400-1000 mg/week depending on the progestagen involved).

Although progestagen therapy shows much promise, it is clear that there is still much to learn. Fortunately the synthetic progestagens used in endometrial carcinoma therapy (e.g. Provera, Primolut, Depostat) are almost completely without side-effects. It therefore seems completely ethical and reasonable to explore dose schedules, route and vehicle of administration very carefully, as it is almost certain that optimal conditions have not yet been arrived at.

Endocrine therapy in ovarian carcinoma

High-dose progestagen therapy has not yet been shown to produce significant objective remission in ovarian carcinoma. However, it does give considerable subjective relief through better control of fluid balance and pain. The diuretic effects of the progestagens are better than those obtained with conventional diuretics in this situation. In about 50% of cases, pain-relief is seen as measured by voluntary reduction in pain-killing drugs but the mechanisms involved are uncertain at present. These effects were first noted by Varga & Henriksen (1964) and are discussed by Dr H Marcus and Dr White in this symposium (Marcus, 1973; White, 1973).

It is still possible that progestagen or other hormone therapy might produce objective improvement in some types of ovarian carcinoma particularly if applied in conjunction with conventional therapy. The lack of adverse side-effects in progestagen therapy may encourage the exploration of these possibilities.

Endocrine profiles

Despite the interest in endocrine therapy of endocrine-sensitive tumours there is still very inadequate information on the endogenous hormone background of these patients. It will probably be necessary to build up a broad picture of the endocrine status of a number of patients before any firm conclusions can be drawn. The main approaches are via urinary and blood hormone levels and studies on steroid-tissue interactions. Ideally all these techniques should be used on each patient studied.

(i) Endometrial carcinoma

Despite the extensive indirect studies on the endocrine sensitivity of this tumour, there is very inadequate knowledge of hormone levels in blood and urine. The few studies that have been reported are discussed by Brush (1973). It was concluded that no marked abnormalities have so far been substantiated and in particular oestrogen excretion appears to be unchanged when measured by reliable methods (Charles *et al.*, 1965; Procopé, 1970). There is an urgent need for studies on serum FSH levels as urinary FSH excretion, though probably not abnormal, has been inadequately studied. There may be a tendency for some adrenocortical steroid metabolites (i.e. androsterone and aetiocholanolone) to be reduced in relation to oestrogen levels (De Waard *et al.*, 1968).

It is believed that about 10% of endometrial cystic hyperplasia patients may progress to endometrial carcinoma if not suitably treated (Gusberg & Kaplan, 1963; Ober, 1973). The endocrine background to this condition is almost completely obscure and any information would be valuable. It is hoped that a

project recently started by this Department in collaboration with the Imperial Cancer Research Fund will establish preliminary endocrine profiles on a number of endometrial carcinoma and cystic hyperplasia patients.

(ii) Ovarian carcinoma

Apart from the work reported by Dr Bulbrook here (1973), virtually no information is available on the urinary hormone excretion patterns in this condition and no blood hormone studies are available. However, some ovarian tumours, usually thought to be inactive in the production of steroids, can be shown to have some activity when carefully examined by suitable methods, e.g. *in vitro* techniques. This needs further exploration with respect to possible therapeutic exploitation.

(iii) Tissue studies

This approach is now yielding an increasing amount of useful information. Initially the uptake and intracellular distribution of oestradiol and other hormones by tissues was studied, but recently cytoplasmic and nuclear binding sites for oestradiol have been determined.

In this laboratory it was shown that endometrial carcinoma can take up oestrogen selectively and showed certain other biochemical similarities to normal endometrium (Brush *et al.*, 1967, 1968; Taylor *et al.*, 1971; Taylor, 1973). Later studies using oestrogen-binding-site methods confirmed the earlier findings by a very different approach (King, Brush & Taylor, 1972). The long-term aim is to find differences in endocrine behaviour which can be exploited therapeutically.

Tissue studies are discussed by Mr Taylor in this symposium with particular reference to ovarian tumours of unknown origin. (Taylor *et al.*, 1973).

Some unsolved basic problems

The mechanisms by which synthetic progestagens produce their subjective effects and pain relief are not well understood. It would be valuable to know more about the mode of action of progesterone and progestagens in producing their diuretic effects especially in metastatic cancer cases.

It is well established that progesterone in sufficient concentration has a direct effect on endometrial carcinoma tissue (e.g. Nordqvist, 1970), but insufficient is known about the mechanisms involved. A better understanding of these might help improve endocrine therapy in other situations.

Astedt, Svanberg & Nilsson (1971) demonstrated immunochemically the presence of fibrin degradation products in the serum of the majority of ovarian cancer patients studied, and the results seemed

promising enough to merit following up as a possible aid to diagnosis.

Knowledge of the mode of action of the more promising chemotherapeutic agents, e.g. L-phenylalanine mustard (L-PAM) and alkylating agents in general is at present rather empirical. A better understanding of the biochemistry and cell biology involved in their action could be very valuable.

Little is known of environmental factors that might be involved in this field, but it is worth remembering that some cancer authorities believe that up to 70–80% of some types of cancer may be due to environmental carcinogens. Griffiths (1973) discussed some interesting studies in this field at this symposium. Certain other environmental aspects are briefly discussed by Brush (1973), but in view of the small amount of evidence at present available it would be valuable if all leads were carefully reviewed. Much valuable work on the epidemiology of other types of cancer has been produced by people who were not primarily cancer specialists and perhaps this may encourage further observations.

Conclusions

Despite the gloom which besets ovarian cancer studies and the very cautious optimism in endometrial cancer work there are valuable new approaches to consider in the latter field and some possibilities in the former.

It is clear that applied studies on the use of progestagens need not be unduly expensive and are virtually free of toxicity risks and ethical objections. Thus, much valuable information may be obtained while benefiting patients subjectively and sometimes objectively.

Collaborative laboratory studies by a number of different approaches are clearly urgently needed. This will need the active collaboration of clinician and research worker.

In the view of many the field of human cancer needs constant and urgent exploration by all means available rather than the passive awaiting of a cure derived solely from basic research.

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