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ENDOCRINOLOGICAL CANCER

OVARIAN FUNCTION AND DISEASE

Editors:
H. Adlercreutz, R.D. Bulbrook,
H.J. Vander Molen, A. Vermeulen
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Welcoming address

Rome welcomes you with the usual enthusiasm and thanks you for having accepted the invitation to attend the Ninth Symposium of the International Study Group for Steroid Hormones. This shows that our Group, since the first meeting in 1963, almost 17 years ago, is more alive and vital than ever.

The topics to be discussed over the next two days – Endocrinological Cancer, and Ovarian Function and Disease – were both chosen by the International Committee in December 1977, and have not lost their originality and importance even if recently there has been an increasing proliferation of Conferences and Congresses dealing with these topics.

The first of these which is of extreme interest is closely connected to our IV and VII Meetings which concerned 'Steroid protein interactions' and 'Steroid receptor proteins'. From this fascinating subject of molecular biology we hope to broaden our knowledge on the intimate mechanisms regulating cell growth and differentiation and to have ideas for further investigations, especially on the synthesis of compounds capable of modifying the hormone receptor action to dominate the development of hormone dependent neoplasms.

The second topic is equally interesting and concerns all that is new in ovarian physiopathology with special reference to disorders in the menstrual cycle, hyperprolactinaemia syndromes, hirsutism and modern techniques in the detection and treatment of ovarian disorders.

I am confident that the lectures presented and the general exchange of ideas will lead to a better understanding of many, as yet, unsolved problems in this intriguing field of research, and provide a basis for future study programmes.

Rome, December 1979

CARLO CONTI

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On behalf of the Executive Committee of the International Study Group for Steroid Hormones I express my gratitude to the Chairman, Professor H. Adlercreutz, and members of the Programme Committee, Drs. R.D. Bulbrook, M. Neves e Castro, H.J. van der Molen and A. Vermeulen, for their hard work in the organization of the meeting.

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I am taking this opportunity to thank the President of the National Research Council for the use of the Conference Hall.

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CARLO CONTI

BREAST CANCER

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Endocrine determinants of risk of breast cancer

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Classical studies of the epidemiology of breast cancer have identified several major determinants of risk, most of which are associated with reproductive function. For example, an early age at menarche, a late age at first child or nulliparity, and a late age at menopause are all related to increased risk, while early oophorectomy leads to a marked diminution in incidence (MacMahon et al., 1973). But these studies have not led to a clear understanding of the biological mechanisms involved. In the absence of a unifying hypothesis, refuge has been taken in statements such as 'endocrine features contribute to the aetiology' or 'hormones play an important part', which have very little real meaning.

It might have been expected that the introduction during the last 15 years of reliable analytical methods for the measurement of endocrine function, would have clarified the situation but this has not been the case. Until recently, results obtained from direct measurements of hormones in blood or urine have added further confusion.

In the last few years some interesting leads have appeared. Three endocrine abnormalities* have been tentatively identified which appear to be correlated with an enhanced risk of breast cancer and which fit in with classic aetiological features of the disease. The three determinants of risk involve the ovaries, the adrenal glands and the pituitary.

Ovarian function

Results from work with laboratory animals have shown beyond doubt that the oestrogenic hormones are of cardinal importance in the genesis and maintenance of mammary carcinomas (Noble, 1964). But the oestrogenic status of women with breast cancer is not at all clear. The number of contradictory reports leads to the conclusion that there are certainly no gross abnormalities and that what is being observed is merely a random fluctuation about a normal mean (Wang et al., 1972; Bulbrook et al., 1978).

The role of the second important ovarian hormone, progesterone, has

*The word 'abnormality' is not ideal: the term is used here to mean that significant differences between cases (or high-risk groups) and controls have been demonstrated although in almost all instances, the values lie within the normal range.

been much neglected until recently. Grattarola (1964) found that the majority of his patients with breast cancer had endometria which showed a lack of a progestational effect. This, and other evidence, led Sherman and Korenman (1974) to propose that corpus luteum inadequacy, in the face of normal oestrogenic stimulation, might explain the principal epidemiological features of breast cancer. Considerable experimental support for this hypothesis has come from the work of Mauvais-Jarvis et al. (1980) who have shown in a series of incisive investigations that patients with benign breast disease (and hence, at high risk) have subnormal levels of plasma progesterone in the luteal phase of the menstrual cycle. Furthermore, Bulbrook et al. (1978) found a correlation between the calculated risk of developing breast cancer (using the model of Farewell, 1977) and progesterone values: the greater the risk, the lower were the plasma progesterone levels.

Korenman (1980) now seems to have some doubts about the validity of the hypothesis. He cites the findings that young women with a strong family history of the disease have been shown to have normal luteal phase progesterone levels (Henderson et al., 1975) and that normal luteal phases were found in case-control studies (England et al., 1974; Skinner et al., 1975; Sherman, 1979). But the crucial point about such studies is the selection of patients. For example, it appears that none of the women in the England and Skinner studies had anovulatory cycles, which is extraordinary when one considers that the incidence of such cycles in a normal population may be as high as 15% (Doring, 1969). One group of workers studied only women with a normal LH peak (Strax, 1978). Thus, the literature is biased against women with abnormal or anovulatory cycles. A thorough re-investigation of progesteronal status, taking serial cases and random controls would not come amiss.

If it is true that an intermittent corpus luteum dysfunction is an important determinant of risk and that the dysfunction is not all-or-none but quantitative, then what may be required is measurement of oestradiol-progesterone ratios over considerable periods of a woman's reproductive years. In technical terms, such experiments would not be easy to carry out and this may explain why the easy option of studying only those women with 'normal' menstrual cycles has so often been taken.

The attraction of the corpus luteum dysfunction hypothesis is that it would leave the oestrogens as the prime carcinogens (or promoters), in accord with much laboratory evidence. Risk would then be determined by the intensity and duration of oestrogenic stimulation not modified by progesterone secretion. Cycles in adolescents and in women approaching the menopause are characterised by such an abnormality and it would be logical to expect an increased incidence of breast cancer in women with an early menarche or a late menopause. Oophorectomy would diminish both oestrogen and progesterone secretion. The differentiating effect of progesterone might explain the protection afforded by an early first child, given a prolonged exposure to high concentrations.

Adrenal function

The majority of case-control studies show that patients with breast cancer have sub-normal plasma levels of various androgens and also excrete amounts of urinary metabolites at the lower end of the normal range (Wang, 1979). Prospective studies of a large normal population have shown that these abnormalities in adrenal androgen synthesis may precede the clinical appearance of breast cancer by up to a decade (Bulbrook et al., 1971). Similar abnormalities have been found in women with benign breast disease (Wang et al., 1972; Brennan et al., 1973; Thomas et al., 1976), with myasthenia gravis (Papatestas et al., 1977), in kindred of patients with breast cancer (Wang et al., 1975) and in women with a high calculated risk of the disease (Wang et al., 1979).

There has never been a wholly satisfactory physiological explanation for these findings, nor for the curious correlation between androgenic status and response to endocrine ablation (Bulbrook, 1974). A new interpretation will be discussed subsequently.

Pituitary function

The results of most case-control studies have been equivocal. One reason for this is the tardy appreciation of the nycthemeral rhythm of prolactin in which the plasma hormone levels tend to peak at night. When blood samples are obtained in the early hours of the evening, then there is some evidence that higher levels are related to enhanced risk of breast cancer. Early morning samples do not show this relationship (Bulbrook and Wang, 1979).

Relation between endocrine abnormalities

It would be tempting to suggest that the abnormalities in ovarian, adrenal and pituitary function are related. If the primary lesion were an enhanced oestrogenic stimulation due to a defective production of progesterone, then an effect on adrenal androgen production might be expected, since it has been shown that steroidal contraceptives containing small amounts of progestagen, relative to the oestrogenic content, depress plasma dehydroepiandrosterone sulphate levels and that urinary androgen metabolites are sub-normal. These effects are not found when the contraceptives contain large amounts of progestagen (Bulbrook et al., 1973).

Early reports also indicate that women using steroidal contraceptives have increased plasma levels of prolactin, an effect ascribed to the oestrogenic component of the pill (Robyn et al., 1973). But formal evidence that the three endocrine abnormalities occur simultaneously in women with a high risk of breast cancer and are inter-linked is still lacking and new studies will be required to investigate this point.

If this proved to be the case, the next question would be whether administration of progesterone would correct the endocrine imbalance and lead to a diminution in the incidence of breast cancer, as suggested by Mauvais-Jarvis et al. (1980).

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Effect of diet on estrogen metabolism in women*

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A number of large epidemiological studies have demonstrated a strong association between the amount of fat and protein in the diet and breast carcinoma mortality (Lea, 1966; Drasar and Irving, 1973; Armstrong and Doll, 1975; Berg, 1975; Carroll, 1975; Miller et al., 1978). Vegetarians have a much lower incidence of breast cancer but the mechanism by which diet lowers the risk of breast cancer is still unknown. Most mammary carcinomas are estrogen dependent. Of all steroid hormones the estrogens have the most extensive enterohepatic metabolism because of the large proportion of estrogens which are excreted with the bile into the intestinal lumen (see review Adlercreutz and Martin, 1980). It is well known that intestinal bacterial enzymatic activity is changed by diet (Finegold et al., 1974; Goldin and Gorbach, 1976, 1977) and that altering the intestinal microflora, particularly by diminishing the number of anaerobic bacteria, e.g. by ampicillin, causes a great increase in the excretion of fecal estrogens (Martin et al., 1975; Adlercreutz et al., 1976). It was therefore decided to investigate whether diet has any influence on estrogen metabolism. The preliminary results obtained indicate that vegetarians excrete much more estrogen in the feces and that this may influence the plasma levels of estrone and estradiol.

Material and methods

Four female subject groups living in the Boston area (U.S.A.) are being investigated: young and old omnivores and young and old vegetarians. This allows a 2 x 2 factorial design of the study. Each group will come to consist of at least 10 subjects, each of whom is investigated 4 times at 4-month intervals. In the young subjects aged 20-30 yrs and with normal menstrual

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