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Benign Proliferative Lesions of the Breast; Workshop Report

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INTRODUCTION

THE WORKSHOP on benign proliferative lesions of the human mammary gland considered new information and sought ways for future work of clinical usefulness. Abstracts of the posters which were discussed in the workshop are included in the Abstract book of the conference.

For this purpose proliferative lesions are defined as those having the essential characteristic of epithelial growth by cell mitosis. This epithelial growth is usually organoid in character with stromal participation. The stromal participation is classically viewed as reactive or inductive in kind, and often includes the multiplication of fibroblasts, the deposition of collagen and the formation of new blood vessels, as well as greater or lesser infiltrations by chronic inflammatory cells. The crucial current and future problem for the human mammary biologist is to clearly define the differing biological potentials, natural histories and precancerous potentials of the variety of epithelial proliferations classically found in the mammary gland.

To these ends the information reported and discussed by the contributors and participants of our workshop was organized under three general headings: (1) morphology and histogenesis; (2) determination of risk factors; and (3) endocrinology.

All of the discussions were related to the central theme of benign proliferative lesions of the human mammary gland.

MORPHOLOGY AND HISTOGENESIS

In this section of our workshop five presentations stimulated vigorous discussion among the participants. There was general agreement with Dr. L.-J. van den Bogaert (Brussels) that progress is hampered by three problems: (1) incompleteness and lack of uniformity of taxonomy and microanatomy; (2) overdependence on rodent models with shaky homologies, analogies and extrapolations; and (3) confusing and conflicting classifications of hyperplastic (proliferative) and presumptively preneoplastic epithelial changes.

A consensus was reached by the participants on several, but not all, issues and questions, as follows.

The terms 'epitheliosis' and 'adenosis', carefully defined, are preferable to a variety of popular equivalents (Dr. J. F. Hampe, Amsterdam). Epitheliosis is the abnormal multiplication of epithelial cells within pre-existing glandular structures without formation of new glandular structures (such as ducts, lobules, acini and end buds). Adenosis is the appearance of more and/or larger lobules by growth or branching of the mammary tree, and its lobular and terminating acinar ramifications. Thus in adenosis there is generally an addition of new lobules or enlargement of pre-existing ones. It was pointed out that epitheliosis and adenosis may occur in relatively pure and separate forms, or they may coexist in the same lesion.

The group was comfortable with the concept of the terminal ductal lobular unit (TDLU) [1], which morphologically defines the basic functional, endocrinologically responsive and pathologically reactive glandular element of the mammary gland. The TDLU consists of the lobule and its entering terminal duct. The terminal duct (TD) has extralobular (ETD) and intralobular (ITD) portions. ITD is actually the axial space of the lobule. The blindly ending sacs of the lobule are synonymously named 'acini' or 'ductules'. The name ductule is easily confused with duct; therefore, acinus (pl. acini) is preferable.

The discussion turned to consideration of a centrally important question. Where in the mammary tree do the majority of carcinomas arise? Favorable reference was made to the pioneering work of Dr. Edith Dawson [2] of the University of Edinburgh. Dr. Dawson believed that the vast majority of carcinomas, including so-called ductal ones, arise at or near the junction of the extralobular and intralobular terminal ducts; in other words, at the location where the ETD enters the lobule.

This concept of TDLU was supported by a 3-dimensional study comparing solitary duct papillomas and multiple peripheral papillomas (Dr. R. Abe and associates, Japan). This view of histogenesis is now widely held. There was a general dislike for the term papillomatosis because of its multiple different usages. A radial scar (RS) is a group of ducts and TDLU arranged in radial fashion around a central fibroelastic core. The precancerous potential of RS was discussed with uncertainty, and the participants believed further work was needed.

The unresolved and seemingly timeless problem of the relationship of fibrocystic disease, and especially epitheliosis, to carcinoma came up for discussion on several occasions. At least two somewhat conflicting views were held.

One view, first expressed by Dr. J. G. Azzopardi (London) in plenary session, holds that epitheliosis and carcinoma *in situ* (CIS) arise quite independently of one another without linear histogenetic relationship. This idea hypothesizes a possible early branching histogenetic divergence and would exclude the various benign formations of epitheliosis from the histogenetic pathway leading to cancer.

The other view [1] hypothesizes that the lesions of epitheliosis are intermediate steps along a linear histogenetic pathway progressing from normal to CIS. Then atypical terminal ducts and lobules (ALA) would become the hypothetical precancerous lesions along the histogenetic pathway.

In spite of differing views over this point, there was uniform recognition that CIS is the highest grade of non-obligate preneoplastic hyperplasia and that epitheliosis is at least an indication of phenotypic instability.

In order to approach the sticky problem of histogenesis, answers to the following questions are needed: (1) Are there one or more than one kind of epithelial stem cell in the mammary gland? (2) What are the histogenetic pathways by which epitheliosis and carcinoma arise from these stem cells? (3) What are the relationships between these pathways? (4) What are the hormonal dependencies?

Several means were discussed for improving our knowledge of the biology of normal and abnormal histogenesis in the mammary gland of humans, as follows: (1) development of a single inclusive classification and nomenclature for normal and abnormal microanatomy of the mammary gland applicable to all species; (2) *in vitro* culturing and cloning of pure epithelial cell populations employing solid-phase collagen gel matrix cultures; (3) comparative studies of angiogenesis by various normal, presumed preneoplastic and neoplastic human mammary lesions; and (4) the further quest for useful 'marker' proteins using modern immunological and chemical methods.

Dislike for the term 'marker' was expressed but not accompanied by suggestions for substitutes.

DETERMINATION OF RISK FACTORS

In the plenary review session Dr. F. de Waard (Utrecht) pointed out that in the last several years there have been few new developments in epidemiological studies of breast cancers. In this portion of our workshop two hopeful and courageous papers were presented. One described a prospective study (Dr. W. Misdorp, Amsterdam) and the other a follow-up study (Dr. M. Roberts, Edinburgh). Both studies aimed at the estimation of risk of benign proliferative disease. Considerable discussion was generated and agreement was reached that the main purpose of risk studies is to define more clearly subgroups of women with different risks of developing breast cancer. Elaborate multivariate data analysis of numerous known and suspected risk variables is required in order to achieve this end.

With regard to our specific topic of benign proliferative lesions, no new light was shed on the relationship of epitheliosis to carcinoma. Opinions in the literature of the past 40 yr vary from 0 to 10 times increased risk. After discussion the group felt that a figure of 2–3-fold increase of risk was a reasonable guess for the present. It seems distressing that we still have no clear answer after so many years of struggle.

The radiographic risk factors of John Wolfe [3] were briefly mentioned as an important means of correlating tissue pathology with clinically established risk. The validity of Wolfe's risk factors was not questioned; however, a number of participants believed they were too high.

ENDOCRINOLOGY

The third and final portion of the workshop dealt with hormones, hormone receptors, binding proteins and 'marker' proteins of possible future usefulness in identifying patients at risk of developing benign proliferative mammary disease

and carcinoma, and for following progress of treatment. These agents of possible usefulness are found in serum or breast cyst fluids or breast tissue. Included are estrogen, progesterone, sex hormone binding globulin (SHBG), prolactin, adrenal steroids, DHEA, T3, T4, estrogen receptors, progesterone receptors and a new non-endocrine 'marker' protein, breast cyst fluid protein (BCFP). In the following paragraphs, salient points are mentioned.

Importance is attached (Dr. L. Berta and associates, Torino) to sex hormone binding globulin (SHBG), which controls the magnitude of the free estrogen and progesterone fractions, the only form active on target cells. There is a positive correlation between a decreased plasma SHBG and the presence of fibrocystic disease and carcinoma. SHBG may be a useful measure of risk and of treatment progress.

An interesting comparison of serum hormone profiles from age-matched 'normal' premenopausal women and women with benign proliferative breast disease was reported (Dr. P. F. Bruning and associates, Amsterdam). All women were in the luteal phase, and were followed by continuous sampling of blood at 20-min intervals for 8 hr, using a special technique. Noteworthy was the wide and rapid fluctuation in plasma levels of prolactin, estrogen, progesterone and adrenal corticoids. A most important finding was a significant increase in plasma concentration of prolactin and DHEA in women with histologically proven benign proliferative breast disease, suggesting a means of identifying patients at risk of developing breast cancer.

The relationship of thyroid hormone to breast disease has never been clear and, in this regard, it was reported (Dr. A. Angeli *et al.*, Torino) that T3 and T4 accumulate in breast cyst fluid in concentrations as high as ×10 the level in plasma. This accumulation occurs in about one-half of the cysts, and may represent active transport into the cysts or *de novo* synthesis by apocrine cells lining the cysts. It is apparently only the apocrine-lined cysts which accumulate T3. Since T3 probably modulates the activity of prolactin by increasing prolactin receptor activity, these findings suggest a relationship of T3 to the development of benign proliferative breast disease and possibly carcinoma.

Estrogen and progesterone receptors were dealt with by Dr. R. A. Hawkins and associates (Edinburgh). A positive correlation was shown between tissue cellularity and tissue concentration of both estrogen and progesterone receptors. This work begins to clarify heretofore poorly understood relationships between benign proliferative breast disease, hormone action and hormone receptors.

Finally, work was presented by Dr. P. F. Zangerle and associates (Liège) identifying a new 'marker' protein called breast cyst fluid protein (BCFP). Serum BCFP can be measured by immunochemical methods. Elevated serum BCFP is significantly associated with proliferative breast disease and with breast cancer. BCFP has the properties of a potentially useful indicator molecule of diagnostic, therapeutic and prognostic usefulness.

The discussion ended where it began, with a mention of several difficult diagnostic and therapeutic decisions of patient management. It was pointed out that individually optimized patient treatment is incompatible with controlled therapeutic trials, which are therefore of limited usefulness. The discussion ended on the hopeful note that the study of human breast tissue using the tools of modern biology has only just begun, and a brighter future for our patients lies ahead.

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