LETTERS TO THE EDITOR

The Author’s Reply—Partial Explanation?

To the Editor—The letter of Jetha and Godolphin reports no correlation between histochemical and biochemical estrogen receptor data in 28 cases of breast cancer. Poor histochemical preparations probably have accounted for some of their difficulties. After examining several of their slides, I wrote to Dr. N. Jetha, Immunopathology Laboratory, Vancouver General Hospital the following.

On September 18, 1980: “I have looked at the four cases of breast cancer you sent to me on September 12, 1980. I found the fluorescent sections did not match those of the hematoxylin and eosin stain in size and shape for the same cases. Please cut serial sections from the same tissue block and pick up the sections with glass slides at a constant angle, say 90°, to the cutting knife. One must evaluate adjacent serial sections to be certain of the cells being viewed in the fluorescence microscope.

In addition to obtaining high-quality preparations, a pathologist experienced in interpreting frozen sections of breast cancer should be available as consultant when the sections are examined. Not only benign epithelial cells, but eosinophil leukocytes also have cytoplasmic estrogen receptors. They may masquerade as cancer cells to inexperienced eyes in the fluorescence microscope.

Similarly, dextran-coated charcoal (DCC) assays of estrogen receptor proteins must be performed with adequate quality control since sometimes there is hardly any correlation between values reported by different biochemical laboratories, even when common tissue samples are submitted for assays.

On February 26, 1981: “The slides on cases No. 18a, 18b, 19 and 20, which you sent to me on February 19, 1981 cannot be interpreted. The tissues seemed to have been poorly preserved prior to staining. The receptor-positive cancer cells show very weak fluorescence, and many connective tissue cells exhibit strong fluorescence.

Please look into the technical procedure, and see whether there has been any deviation in the last two months.”

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Cervical Condylomatous Atypia and its Relationship to Cervical Neoplasia

To the Editor—We compliment Ludwig, Lowell and Livolsi on their excellent paper entitled “Cervical condylomatous atypia and its relationship to cervical neoplasia.” Unfortunately, the literature now contains four different names for diffuse, non-papilliferous, papillomavirus—induced hyperplasia of metaplastic cervical epithelium.1,2 The lesion was designated “flat condyloma” by Meisels2 and “noncondylomatous cervical wart virus infection” by Laverty3 and Syrjanen4 misinterpreted this latter term, using “condylomatous” to describe the lesion in question and “noncondylomatous” to mean non-viral (instead of non-papilliferous) wart. Most practicing histologists recognize this entity, but still call it “koilocytic atypia.” However, the meaning of this term has been blurred by the use of “koilocytic atypia” to mean mild dysplasia of mature squamous epithelium. Koss5 originally used koilocytosis to describe the pathognomonic “hollow-cells” seen in this lesion, and the term would be best retained in this context. Condyloma derives from the Greek “kondylus, a knuckle” and years of clinical usage have established condyloma to mean a focal, raised lesion. Hence “flat condyloma is an inherent contradiction of terms which does not adequately contrast the subclinical nature of this diffuse, non-papilliferous lesion from the focal, verrucous appearance of an overt condyloma. However, “noncondylomatous” is cumbersome and ambiguous, and Laverty now prefers “subclinical papillomatoviral infection” (SPI) as a literally correct designation which accurately describes both the macroscopically invisible nature of the lesion and its histologic similarity to condylomatous epithelium.

We, at Sinai Hospital of Detroit, are

References
currently engaged in a comprehensive epidemiologic survey of the prevalence of SPI in a widely representative urban population. We agree with Ludwig and coworkers that 1-2% of all routine Pan-panicolau smears, and up to 10% of smears from an indigent clinic, will show definite cytologic evidence of wart virus infection. The prevalence of papillomavirus infection in the transformation zone had hitherto been seriously underestimated, because it was not previously appreciated that most cases are subclinical.2-4 This erroneous impression persisted because colposcopists and pathologists usually misinterpreted SPI as either a physiologic change or as cervical intraepithelial neoplasia (CIN).1,4

Masquerade aside, it is quite clear that SPI and CIN commonly coexist. Last year, Reid, Laverty, Coppleson and associates also suggested that this association may be causal and supported their contention with a similar discussion of the premalignant potential of the papillomavirus. To answer the question of whether SPI is a mimic or a precursor of CIN, Reid and associates2-4 have since completed a comparative survey of the prevalence of SPI in a representative sample of hysterectomy specimens for malignant and premalignant cervical lesions. Age, race and socio-economically matched controls were generated from patients who had hysterectomies for other genital cancers or for benign gynecologic disorders. Ninety one per cent of cases displayed SPI in the non-neoplastic epithelium at the disease margin, compared with 12.5% controls.5,6 The power of this association (a sevenfold increase in relative prevalence) and its internal consist-

tency (the same rate of SPI in malignant and benign halves of the survey) suggest that the relationship may be causal. Moreover, there is a broad fabric of supporting epidemiologic, virologic, and clinicopathologic evidence to support the biologic plausibility of this contention.8 It is a matter of common observation that a histologic spectrum exists from SPI-through mild moderate dysplasia-to unremarkable carcinoma. in situ (CIS). Substantial support for the premise of progression along this spectrum would derive from the demonstration that there is a significant increase in mean age at these different points along the continuum. Ludwig and colleagues1 table 4 does not answer this question because (1) statistical significance was not cited, (2) "CIN III plus CIS" is not at valid grouping, since CIN 3 is defined as either severe dysplasia or CIS, and (3) cases can only be meaningfully graded according to maximal cytogenetic atypia. Subdivision according to whether associated condyloma was seen in these isolated biopsy fragments may not have held if more material had been available from each case. We would like to know whether the mean or median age of patients with (1) SPI alone, (2) CIN 1–2 ± SPI, and (3) CIN 3 ± SPI are significantly different by Student's t-test or its nonparametric equivalent (e.g., Wilcoxon's rank tests). We would also like to see age-frequency distribution curves compared for these three diagnoses.

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The Author's Reply

To the Editor.—We thank Drs. Reid and Husain for their letter regarding our paper on condyloma virus infection and cervical neoplasia. Their criticism of the terminology in this field is appreciated and we await a consensus term acceptable to all (gynecologists, colposcopists and pathologists). If however, history serves as an example, we need only recall the years required for the acceptance of the CIN terminology; we may have a long wait!

Reid and Husain cite impressive data from their hysterectomy specimens of the subclinical prevalence of the condyloma virus infection; our studies which concentrated on detected lesions indicate a much lower incidence.

Addressing their specific comments regarding age incidences of pure condyloma, CIN 1–2 ± condyloma and CIN 3 ± condyloma, we have performed statistical analyses on the original data base, using the Student-Newman-Keuls procedure to determine differences be-