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Discussion

Dr. M. Judah Folkman: During the development of the embryo hundreds of growth factors and inhibitors are switched on for brief periods of time, after which they fall silent, and remained unexpressed throughout adult life.

Dr. Donahoe and her associates have isolated and purified one of these inhibitory factors, the one that is secreted by the embryonic testis for the single purpose of preventing the development of any female genital tract tissue in the male. This is the müllerian inhibiting substance.

What Dr. Donahoe has reported to us this morning is an even more important and novel step, that is, the demonstration that this substance can inhibit the growth of human ovarian tumor cells *in vitro*. Why is this so important?

The answer is that, aside from its immediate potential practical value as a new approach for ovarian cancer, especially ascites, it also suggests to us that theoretically a whole new field of chemotherapy alongside conventional chemotherapy may be possible in the future for other tumors—a field of agents, highly specific, yet not immunologic, in which each antitumor agent is derived from some as yet undiscovered embryonic inhibitor.

This is, of course, high speculation, but any scientific achievement always starts that way. This speculation in particular is based on the experience that once you find one compound as a natural product, as Dr. Donahoe has, it is rarely the only one in existence, because nature usually makes many more like it, a whole class of such compounds, like the antibiotics.

Dr. E. Thomas Boles, Jr. (Columbus, Ohio): Most of our knowledge in the past of steroid biochemistry has been directed toward intersex disorders rather than on neoplasms. It is interesting, however, that a particularly interesting form of intersex, the male pseudohermaphroditic state, and particularly those that are lumped under the term androgen resistant disorders, both the complete and incomplete forms, do have an increased incidence of gonadal tumors. These, of course, are patients who are genetically, and from the standpoint of their gonads, males, but have a distinct tendency, usually in puberty, toward gonadal tumors.

We know that in such patients, probably because of the negative feedback mechanism involving the pituitary and the hypothalamus, and the effect of LH on the testis, there is an increased level of testosterone in the serum of these patients. I would like to ask Dr. Donahoe if she has any knowledge concerning MRF or the müllerian inhibiting substance, as she calls it, under such circumstances.

Dr. Patricia K. Donahoe (Closing discussion): Gonadal tumors occur in patients with dysgenetic gonads. Thyroid tumors occur as a result of high TSH levels. High gonadotropin levels caused by poor negative feedbacks from dysgenetic gonads may be tumorogenic in patients with dysgenetic gonads, although there is no direct experimental evidence to substantiate this hypothesis.

(slide) Future directions for müllerian inhibiting substance research include 1) purification; 2) development of a monoclonal antibody to müllerian inhibiting substance; 3) development of a radioimmunoassay for müllerian inhibiting substance; 4) application of recombinant DNA techniques to study the müllerian inhibiting substance mRNA and DNA; 5) study of the matrix biochemistry of the müllerian duct; 6) study of the interaction of the müllerian inhibiting substance glycoprotein with steroid hormones, and 7) study of müllerian inhibiting substance as a chemotherapeutic agent.