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This Week's Citation Classic®

Rosen S W, Weintraub B D, Vaitukaitis J L, Sussman H H, Hershman J M & Muggia F M. Placental proteins and their subunits as tumor markers.
Ann. Intern. Med. 82:71-83, 1975. [Clinical Endocrinol. Branch, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases. Reproduction Res. Branch, Natl. Inst. Child Health and Human Devel., NIH, Bethesda, MD; Dept. Pathol., Stanford Univ. Sch. Med., CA; Dept. Med., Wadsworth VA Hosp., Los Angeles, CA; and Dept. Med., Albert Einstein Coll. Med., Bronx, NY]

This review discusses the use of placental proteins and their subunits as markers to help monitor the response of certain tumors to therapy. [The *SCI*® indicates that this paper has been cited in over 215 publications.]

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The work began in 1962 when Frank Fusco, then a resident at the Washington, DC, Veterans Administration Hospital (VAH) and now a pulmonologist in Vienna, Virginia, diagnosed lung carcinoma in a chronic smoker with gynecomastia and referred him to the Clinical Center for endocrine studies. During the following two years, Fusco referred three additional cases of lung carcinoma to us, and beginning with that first patient, we began gathering evidence that these carcinomas produced ectopic gonadotropin.[1]

Soon after, Bruce Weintraub came to my laboratory as a clinical associate; he is now a branch chief in the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases. Weintraub developed a sensitive assay for placental lactogen (PL) to determine whether ectopic PL was responsible for gynecomastia in the vast majority of lung cancer patients with no ectopic gonadotropin. Ectopic PL production was found in occasional cancers but was uncommon. Nevertheless, we were intrigued that PL could be a "marker" of neoplasm, since it was not detected in blood from men or nonpregnant women.

Many other workers helped us with pieces of the puzzle. The question of whether another placental protein, the placental isozyme of alkaline phosphatase (PAP), could also be a tumor marker was addressed in 1971 by Howard Sussman, then in the Clinical Center and now chief of the Division of Laboratory Medicine at Stanford University Medical School.[2] We also enlisted the collaboration of Franco Muggia and Heine Hansen, then at the Washington, DC, VAH and now, respectively, director of the Division of Oncology at New York University and chief of the Chemotherapy Service at the Finseniastitutet in Copenhagen, who furnished sera from their extensive lung-cancer population.

Meanwhile, back at the NIH, Judith Vaitukaitis, then in the National Institute of Child Health and Human Development (NICHHD) and now chief of endocrinology at Boston University, had developed a novel radioimmunoassay that discriminated between chorionic gonadotropin (CG) and luteinizing hormone and allowed the easy assay of multiple sera. She, Glenn Braunstein, and their colleagues in NICHHD assayed more than 1,000 cancer sera and found evidence in 12 percent for the ectopic production of CG. The subunit nature of CG was then being recognized, and Weintraub and I found cases of unbalanced and even isolated production of one or the other CG subunit. Moreover, Alan Rabson, then senior investigator at the NCI and now director of its Division of Cancer Biology, succeeded in establishing a cell line *in vitro* that mirrored the unbalanced ectopic production of CG and its subunits in the patient from which it was derived. (To commemorate this blessed event, Weintraub and I gave Rabson a poster showing the long-distance capture of a fly by a frog with an enormous tongue. The caption read: "When you're hot, you're hot!")

In California, Jerome Hirshman, then and now chief of endocrinology at the Wadsworth VAH, had been studying what appeared to be placental thyrotropins (but that we now realize were probably will-o'-the-wisps related to thyrotropic activity inherent in massive amounts of CG). The time seemed ripe for pulling together this disparate material, and the Combined Clinical Staff Conference of the NIH Clinical Center, an institution still going strong, seemed a nice locus.

I suspect the review has been highly cited because it summarizes in one place the work with a new group of proteins perceived as potentially useful tumor markers. CG is still widely used to monitor non-germ-cell testis cancers, and PAP is beginning to be used in testicular germ-cell cancers; the other placental proteins, however, have been disappointing as tumor markers. Nonetheless, the questions of why the placenta produces them and what is the mechanism of their biosynthesis and regulation are still much studied.[3]

1. **Fusco F D & Rosen S W.** Gonadotropin-producing anaplastic large-cell carcinomas of the lung. *N. Engl. J. Med.* 275:507-15, 1966. (Cited 160 times.)
2. **Sussman H H, Weintraub B D & Rosen S W.** Relationship of ectopic placental alkaline phosphatase to ectopic chorionic gonadotropin and placental lactogen: discordance of three "markers" for cancer. *Cancer* 33:820-3, 1974.
3. **Bischof P & Klopper A,** eds. *Proteins of the placenta: biochemistry, biology, and clinical application.* New York: Karger, 1985. 205 p.

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