

This Week's Citation Classic

Gold P & Freedman S O. Specific carcinoembryonic antigens of the human digestive system. *J. Exp. Med.* **122**:467-81, 1965.
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The finding of a human colon tumor-specific antigen led to a search for this material in other human tissues. This manuscript describes the presence of the same constituent in all entodermally-derived gastrointestinal cancers and in embryonic and fetal digestive tissues in the first two trimesters of gestation. The material is, therefore, designated carcinoembryonic antigen (CEA) of the human digestive system, and the genetic control of its expression is considered. [The *SC*[®] indicates that this paper has been cited over 655 times since 1965.]

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"My colleague, Samuel Freedman, and I were delighted and flattered to learn that the second paper in the series dealing with our discovery of the carcinoembryonic antigen (CEA) as a human tumor marker¹ had achieved the designation of a *Citation Classic*. It would be very satisfying, indeed, to state that we undertook this series of investigations with clear insight into the ultimate value of the data to be obtained and the potential experimental difficulties that might be encountered. However, it is perhaps more accurate to say that any success that we achieved in the antigenic analysis of human colon cancer tissue was due at least as much to good luck as good intention, and was performed with the somewhat naive hope that the burgeoning probes of immunologic technology would provide, at once, the specificity and sensitivity that had been lacking in the tools previously employed in human cancer research.

"By the early 1960s, studies of the rejection of well-defined transplantable tumors between highly inbred animals had

demonstrated the existence of tumor-specific transplantation antigens in such animal models²⁷ Lacking a syngenic human population, to say nothing of the moral and ethical prohibitions to human tumor transplantation, we employed the techniques of antiserum absorption and immunologic tolerance to compare colon cancer tissue with normal colonic mucosa taken from the same donors. This comparison had led to the demonstration of a tumor component in the cancer tissue which we were unable to demonstrate in the corresponding normal tissue.¹ In the manuscript under consideration, then, we had gone on to show that the same cancer antigen was also present in all entodermally-derived gastrointestinal tumors and in fetal digestive organs in the first two trimesters of gestation, but in no other human tissues examined.

"The question of whether or not CEA or CEA-like substances exist in even trace quantities in other cancerous, otherwise diseased or normal tissues, remains controversial and the structure and biologic function of CEA are under continuous and active investigation in numerous laboratories including our own. We believe, however, that the frequent citation of the paper in question is most likely due to the fact that the work resulted in the development of a radioimmunoassay for CEA that presently enjoys widespread use, internationally, as a tumor marker in the management of cancer patients, both preoperatively and post-operatively.

"It is perhaps an interesting aside that prior to submitting the initial manuscript of CEA to *The Journal of Experimental Medicine*, we had been warned by colleagues in the field that the late Peyton Rous, then on the editorial board of the journal, and presumably most involved in the evaluation of manuscripts related to cancer research in general, was not very favorably disposed toward the immunologic approach to cancer investigation. If this was, in fact, the case, we are very glad that Rous apparently relented."

1. **Gold P & Freedman S O.** Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J. Exp. Med.* **121**:439-62. 1965.
2. **Baldwin R W & Embleton M J.** Neoantigens on spontaneous and carcinogen-induced rat tumours defined by *in vitro* lymphocytotoxicity assays. *Int. J. Cancer* **13**:433-43. 1974.
3. **Baldwin R W, Embleton M J, Price M R & Robins A.** Immunity in the tumor-bearing host and its modification by serum factors. *Cancer* **34**:1452-60. 1974.
4. **Klein G.** Tumor antigens. *Annu. Rev. Microbiol.* **20**:223-52. 1966.
5. **Oettgen H F & Hellstrom K E.** Tumor immunology. (Holland J F & Frei E. eds.) *Cancer medicine* Philadelphia: Lea and Febiger. 1973. p. 951-90.
6. **Old L J & Boyse E. A.** Immunology of experimental tumors *Annu Rev. Med.* **15**:167-86, 1964.
7. **Smith R T.** Tumor-specific immune mechanisms. *N. Engl. J. Med.* **278**:1207-14; 1268-75; 1326-31. 1968.