

Salmon S E, Hamburger A W, Soehlen B, Durie B G M, Alberts D S & Moon T E. Quantitation of differential sensitivity of human-tumor stem cells to anticancer drugs. *N. Engl. J. Med.* 298:1321-7, 1978.  
[Sect. Hematol. Oncol., Dept. Internal Med., and Cancer Ctr., Univ. Arizona, Coll. Med., Tucson, AZ]

A new *in vitro* soft agar culture system developed in our laboratory was applied to testing clonogenic tumor cells ('tumor stem cells') from patient biopsies against anticancer drugs. Unique patterns of sensitivity and resistance were documented, and good correlations were observed between *in vitro* results and clinical treatment outcome, raising the possibility of predictive cancer chemotherapy. [The *SCI*® indicates that this paper has been cited in over 465 publications since 1978.]

Sydney E. Salmon  
Arizona Cancer Center  
University of Arizona College of Medicine  
Tucson, AZ 85724

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"As an investigator interested in cancer chemotherapy, I was perplexed by the lack of predictivity of clinical response in patients with tumors of the same histopathology and stage. I suspected that intrinsic differences in drug sensitivity might be responsible for this phenomenon. I had pursued this problem unsuccessfully during the early 1970s, in part because of difficulties in cultivating human tumors *in vitro*. The first big break came when Anne Hamburger, fresh from completing a post-doctoral fellowship at the Albert Einstein College of Medicine, applied for a position, in large part because her physician-husband had been assigned to duty at a local air base. Our central focus was to develop a clonogenic assay capable of supporting human tumor growth. This approach had been used for quantitating bacterial growth and antibiotic sensitivity. It had also been successfully applied to studying growth and sensitivity of transplantable murine tumors by W.R. Bruce, Makio Ogawa, and their colleagues at the Ontario Cancer Institute. Anne tackled the tumor cultivation problem vigorously. In little more than a year, we had devised an *in vitro* soft agar culture system capable of supporting clonal growth of a variety of hu-

man tumors while suppressing normal cell proliferation.<sup>1</sup>

"The next step was to standardize techniques for studying cytotoxic drugs. An important early decision was to use *in vitro* drug concentrations achievable in the patient's plasma. My coauthors and I mounted a multidisciplinary effort involving cell biology, pharmacology, medical oncology, and biometry. Although our 1978 clinical report in the *New England Journal of Medicine* involved only a limited number of patients, and some of the correlations were retrospective, the results indicated the potential feasibility of applying this approach to aiding in the development of new anticancer drugs and potential individual cancer chemotherapy. We cautioned that a number of methodological problems would need to be solved before our approach could be fully tested, but concluded that the results showed sufficient promise to warrant larger-scale testing.

"The reason that our paper has been so extensively cited is that it represents the first clearly positive approach to predictive cancer chemotherapy. Since the appearance of our paper, the Arizona Cancer Center has hosted four International Tumor Cloning conferences. The monograph published from our 1984 conference<sup>2</sup> provides a current review of this topic.

"Many investigators now use human tumor cloning assays. Such assay systems still need further improvement as not all tumor specimens give rise to adequate colony growth *in vitro*. Correlative clinical trials from various centers have been reported and were recently reviewed,<sup>3</sup> including one large prospective trial.<sup>4</sup> Overall, *in vitro* drug sensitivity to single agents has predicted clinical response with about 60 to 70 percent accuracy, and *in vitro* resistance has predicted treatment failure with over 90 percent accuracy. Prospective randomized trials are currently under way to determine whether assay-selected treatment has any advantage over empirically selected treatment for specific tumor types. Additionally, the National Cancer Institute now employs this assay system regularly in its program to discover new anticancer drugs.<sup>5</sup> Insufficient time has elapsed to assess the long-term impact of our approach to anticancer drug testing on either patient survival or new drug development."

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