dark total lunar eclipses with volcanic eruptions, although he referred only to the Krakatau eruption of 1883.
33. J. Pond, *Astronomical Observations Made at the Royal Observatory at Greenwich* (Royal Society, London, 1818), vol. 2; *ibid.*, vol. 3 (1820).
34. The connection between blurred telescopic star images and volcanic eruptions was first made after the Krakatau eruption of 1883, as demonstrated by E. D. Archibald in the Krakatoa Committee Report (*12*).
35. C. U. Hammer, H. B. Clausen, W. Dansgaard, *Nature (London)* **288**, 230 (1980); C. U. Hammer (personal communication). An annual background acidity of 1.2 ± 0.1 μeq was assumed by Hammer *et al.* for the Crête ice core. However, an assumed background of 0.9 ± 0.1 μeq yields annual and integrated acidity signals for the Tambora and Krakatau eruptions that are more consistent with the optical extinction data.
36. A. J. Dyer and B. B. Hicks, *Q. J. R. Meteorol. Soc.* **94**, 545 (1968); J. B. Pollack and O. B. Toon, *Geophys. Res. Lett.* **10** (No. 11) (1983), entire issue.
37. From ice acidity measurements, it is known that Krakatau's aerosol cloud began to fall out on Greenland in significant amounts well over a year after the 1883 eruption (*35*) (a delay indicated also by solar pyrheliometer measurements at Montpellier, France), even though parts of the cloud reached high northern latitudes within 3 months of the eruption (*12*). Therefore, most of the 1815 ice acidity peak may not be due to Tambora's eruption (perhaps it is due to the 1 February 1814 eruption of Mayon, Philippines). In that case, Tambora's integrated acidity signal should be reduced by 12 percent and the implied $(\Delta m)_0^D$ point for December 1815 in Fig. 3 should be eliminated; however, the three points for 1816, 1817, and 1818 would remain essentially unchanged under the new normalization.
38. S. C. Mossop, *Nature (London)* **203**, 824 (1964); D. J. Hofmann and J. M. Rosen, *J. Geophys. Res.* **82**, 1435 (1977); N. H. Farlow *et al.*, *Science* **211**, 832 (1981). The adopted value of r was based on in situ collections of stratospheric particles after modern volcanic eruptions. A value of $r \simeq 0.6$ μm, derived from the angular size of observed Bishop's rings (*21*), would have associated with it $Q \simeq 4$ [H. C. van de Hulst, *Light Scattering by Small Particles* (Wiley, New York, 1957), p. 151], so that the ratio r/Q, and hence τ_D, would not change. Numerically, $\tau_D = 6.5 \times 10^{-15} M_D$, if M_D is in grams.
39. D. Deirmendjian, *Adv. Geophys.* **16**, 267 (1973).
40. H. Wexler, *Bull. Am. Meteorol. Soc.* **32**, 10 (1951).
41. W. I. Milham, *Mon. Weather Rev.* **52**, 563 (1924); J. B. Hoyt, *Ann. Assoc. Am. Geogr.* **48**, 118 (1958); J. D. Post, *The Last Great Subsistence Crisis in the Western World* (Johns Hopkins Univ. Press, Baltimore, 1977); H. Stommel and E. Stommel, *Volcano Weather* (Seven Seas, Newport, R.I., 1983).
42. The modern study of a possible connection between volcanic eruptions and climate can be said to have begun with C. G. Abbot and F. E. Fowle [*Smithson. Misc. Collect.* **60** (No. 29) (1913)] and W. J. Humphreys [*Bull. Mt. Weather Obs.* **6**, 1 (1913)], the last of whom explicitly mentioned Tambora and the cold summer of 1816.
43. H. E. Landsberg and J. M. Albert, *Weatherwise* **27**, 63 (1974).
44. W. Köppen, *Z. Österreich. Gesell. Meteorol.* **8**, 241 and 257 (1873).
45. C. Mass and S. H. Schneider, *J. Atmos. Sci.* **34**, 1995 (1977); B. L. Taylor, T. Gal-Chen, S. H. Schneider, *Q. J. R. Meteorol. Soc.* **106**, 175 (1980); S. Self, M. R. Rampino, J. J. Barbera, *J. Volcanol. Geotherm. Res.* **11**, 41 (1981). In these papers, about 11 stations were used, whereas I adopted 50 [from Köppen (*44*)], for the period before 1820. More stations were used after 1820.
46. Daily temperatures in the tropics following the eruption are also informative; for example, Madras, India, experienced a remarkable cooling during the last week of April 1815; the morning temperature stood at 11°C on Monday and dropped to −3°C by Friday [*Asiatic Journal* **1**, 274 (1816)]. But the decline was not universal: for example, Canton, China, did not show a drop [*Asiatic Journal* **4**, 300 and 393 (1817)]. Yet it appears that other large volcanic eruptions have produced statistically significant local and hemispheric temperature drops within 1 to 2 months of the eruption dates [C. B. Sear and P. M. Kelly, *Clim. Monit.* **11**, 134 (1982)]. Evidently, the atmosphere responds very promptly to the massive injection of the primary ash and aerosols but more slowly to the buildup of the secondary aerosols.
47. S. Self and M. R. Rampino, *Nature (London)* **294**, 699 (1981); in preparation.
48. T. Simkin *et al.*, *Volcanoes of the World* (Hutchinson Ross, Stroudsburg, Pa., 1981).
49. The very small excess visual extinction in the Northern Hemisphere that was measured in 1963 and 1964 (*31*) suggests that Agung's acidity signal in Greenland ice would not be detectable. Mildly elevated acidities measured in 1963 and 1964 Crête ice layers (*35*) are probably due to far-north volcanic eruptions, such as that of Surtsey, Iceland.
50. Agung produced a peak visual extinction in the Southern Hemisphere of ~ 0.25 mag (*31, 39*). Antarctic ice core measurements [R. Delmas and C. Boutron, *J. Geophys. Res.* **85**, 5645 (1980); L. G. Thompson and E. Mosley-Thompson, *J. Volcanol. Geotherm. Res.* **11**, 11 (1981)] suggest that Southern Hemisphere aerosol accumulations from Agung, Krakatau, and Tambora were roughly in the ratio 1:2:6 (after removal of background), implying peak southern visual extinctions of ~ 0.25, ~ 0.50, and ~ 1.5 mag. These crude estimates suggest a relatively uniform global stratospheric aerosol loading for Krakatau and Tambora as opposed to Agung.
51. The resources of the Columbia University Libraries and New York Public Library were indispensable aids in this study. I thank J. E. Hansen for suggesting the study; C. U. Hammer for supplying details of his ice acidity records; M. R. Rampino, S. Self, and L. D. Travis for discussions and advice; and T. Simkin and T. M. L. Wigley for substantial improvements to the text.

T and Tn, General Carcinoma Autoantigens

Georg F. Springer

Carcinomas originate from internal and external body surfaces, including ducts and glandular structures. Hence, they arise in epithelial tissue, where rapid cell loss and regeneration are physiological and defects in cell proliferation, differentiation, and proper integration would seem to be more likely than in tissues with slow turnover. Epithelia constitute only a small fraction of total body weight, yet carcinomas comprise more than 70 percent of all clinically manifest cancers. In addition, in the United States the frequency of lung carcinomas is doubling every 15 years (*1*). In the past, carcinomas were generally considered autonomous structures that invaded surrounding tissues and spread the seeds of trouble randomly at distant parts of the afflicted patient. However, Paul Ehrlich observed in 1909: "Borrel stated some years ago that the understanding of natural immunity [of the patient] is altogether the key to the carcinoma problem. This is also my belief" (*2*). Bertrand recognized in 1910 that in experimental animals ". . . une inoculation cancéreuse suivie d'un résultat négatif confère . . . à l'animal une immunité durable . . . l'explication de cette immunité nous échappe encore" (*3*). Comprehension of the basis of this general immunity toward any foreign tissue had to await the recent advances in our understanding of histocompatibility and blood group antigens.

Current efforts to characterize cancer-associated antigens and to use them clinically are built upon early work on human "cancer lipids and globulins" (*4*), and on the demonstration in animals of tumor-associated antigens (*5*). That at least some human carcinomas possess characteristic structures capable of eliciting autoimmune responses was first shown about 25 years ago in this country and in England (*6*). This discovery prompted the probing of patient-tumor interactions. Such studies were limited in scope because the antigenic material from cancers permitted testing only in carcinoma patients. In the clinical setting today, however, antisera or monoclonal antibodies raised in animals against non-autoantigenic human carcinoma markers are used. Most prominent are the oncofetal carcinoembryonic antigen and α-fetoprotein. The xenoantibodies against these markers are useful in monitoring, and sometimes diagnosing, carcinoma (*7*). Yet, early carcinoma detection is a major goal, as the following data show.

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The overall actuarial fatality rate for operable pancreatic adenocarcinoma and for lung carcinoma is greater than 90 percent 5 years after surgery. For early lung carcinomas the mortality rate is 31 percent within 5 years of surgery; with the inclusion of data for the rapidly spreading, usually inoperable small-cell carcinoma, it is still about 50 percent (*8*). For all operable breast carcinomas, the fatality rate is greater than 70 percent at 20 years; however, for early breast carcinomas it was only 7 percent among 176 patients who had undergone surgery (*9*). These figures clearly show the need not only for detection of emerging clinical cancer "early" by today's standards, but the urgency for methods to discover and precisely locate carcinomas prior to this stage.

About a decade ago my co-workers and I found two novel carcinoma-associated antigens; they are the blood group precursor antigens T and Tn (*10*). We, as well as others, have shown them to be unmasked on the external surface membranes of most primary carcinomas and their metastases. T and Tn have so far not been detected on or in malignant mesenchymal and central nervous system tumors (except in malignant T-cell lymphomas and in thymomas), nor in benign tumors, nor in other diseased or healthy tissues (*10–18*). It is well established that T and Tn antigens, although present in most tissues, are occluded by covering structures and are inaccessible to the immune system. This was thought to be valid throughout life (*19, 20*). We have evidence, however, that T and Tn are stage-specific differentiation antigens expressed transiently on human fetuses (*21*), arising prior to tolerogenic development phases (*22*).

All humans have preexisting antibodies against T and Tn (*19, 20*). Boccardi *et al.* and we have demonstrated that these are elicited predominantly by the intestinal flora (*23, 24*). We have found that human antibody to T (anti-T), in the presence of complement, kills carcinoma cells in vitro (*7*). Obviously, however, anti-T does not kill carcinomas in vivo, at least not those that become clinically apparent. By far the most prevalent anti-T fraction is immunoglobulin M (IgM), which does not readily permeate blood vessels and has no access to extravascular structures. Zabel *et al.* (*25*) and we (*26*) have noted that anti-T and anti-Tn reagents, including monoclonal antibodies other than IgM, are able to locate tumors in mice. However, mice have little or no anti-T or anti-Tn; in contrast to the situation in man, injected anti-T and -Tn do not compete with the preexisting autologous antibodies to T and Tn (*23, 24, 27*).

In this article I take a step beyond the description of T and Tn as carcinoma-associated antigens and discuss some functional properties of human tumor antigens. T and Tn are not only general and specific carcinoma markers, but for some types of carcinoma they permit prediction of the tumor's likely clinical course. Both antigens may be involved in cancer invasion of healthy tissues.

Summary. Primary and metastatic carcinomas are epithelial in origin and comprise by far the largest group of malignant tumors in humans. In most of these tumors, T and Tn antigens, whose epitopes have been synthesized, are uncovered and immunoreactive. In all other tissues T and Tn antigens are masked and not accessible to the immune system; they are generally precursors in normal complex carbohydrate chains. Thus, carcinomas have antigens recognized as foreign by the patients' immune system. The expression of T and Tn antigens has pathogenic and clinical consequences, and the antigens themselves are powerful histological markers in carcinoma diagnosis and frequently in prognosis. Most patients distinguish their carcinoma from all other cells, as shown by strong autoimmune responses to T antigen. These responses are readily measured by assays, and they allow detection of carcinomas with greater sensitivity and specificity frequently earlier than previously possible. Moreover, the extent of T and Tn expression often correlates with carcinoma differentiation; on a molecular level, clustered T- and Tn-active structures on carcinoma cell surfaces may be involved in invasion.

Carcinoma-associated T antigen stimulates profound cellular and humoral immune responses in the patient early in the disease and throughout its course (*7, 10, 28–31*). These responses are readily measured with T antigen prepared from healthy red blood cell antigens by slight chemical degradation (*7, 18*). The presence of immunoreactive T and Tn antigens on the surface of about 90 percent of the most common human malignant tumors is likely to have considerable implications for an understanding of the pathogenic properties of carcinomas and for their management.

Nature of T and Tn Antigens

T antigen, the immediate precursor of the human blood group MN antigens (*32*) and a distant precursor in other complex carbohydrate chains (*33*), was discovered by Thomsen and Friedenreich about 50 years ago as a laboratory curiosity. Sialidase-producing microbes unmasked the cryptic T antigen on stored human red blood cells, and rendered them panagglutinable by complementary anti-T, which all humans possess (*19*). Tn antigen expression, in contrast, is caused by a somatic mutation in adulthood at the pluripotent stem-cell level (*34*). Tn antigen was discovered by Dausset *et al.* in a patient with hemolytic anemia and polyagglutinability due to anti-Tn (Tn syndrome) (*20*). Tn antigen on red blood cells is the result of a genetic block of a single biosynthetic step: the transfer of D-galactose (Gal) to *N*-acetyl-D-galactosamine (GalNAc) (*35, 36*). At the time of their discovery no association of T and Tn antigens with malignant tumors was suspected.

T and Tn antigenic specificities are determined by immunodominant carbohydrates. Their biosynthetic pathway has been established both by us and by French workers: (i) by stepwise degradation (*37*) and (ii) by biosynthesis (*35, 36*); the Tn immunodeterminant group is GalNAc linked α to the hydroxyl group of serine (Ser) or threonine (Thr) in the amino-terminal region of the active glycoprotein. Subsequent action of β-galactosyltransferase adds Gal from Gal-nucleotide, and this results in: Gal-β-1 → 3-GalNAc-α-*O*-Ser/Thr = T immunodeterminants. The T and Tn immunodeterminant structures have been synthesized chemically in Canada, Japan, Germany, and France (*38*). We have shown that high specific activity of these epitopes at least in vitro depends on their clustered occurrence in the amino-terminal region of erythrocyte-derived T antigen (*31, 39*). T and Tn also occur as carcinoma-associated immunogenic glycolipids (*40*); others have noted that they are probably β-linked to ceramide (*41*).

T and Tn Antigens Are Carcinoma-Associated

T and Tn are usually covered by covalently linked carbohydrates (*32, 33*), occasionally by tertiary structures (*42*), by high negative-charge density due to sialic acid (*43*), or are physically separated from the immune system (*44*). [We found traces of unmasked T in healthy persons'

nerve tissues (*7*).] In contrast, T and Tn antigens were recently shown to be abundantly expressed in immunoreactive form in about 90 percent of carcinoma tissues. American, French, and Danish authors found T antigen in all 45 colon and 25 of 26 breast carcinomas they examined (*11–13*). We found T antigen in 95 percent of 144 fresh surgical samples of all types of primary carcinomas from all major organs. Fewer specimens were tested for presence of Tn antigen, which occurred about as frequently as T. We also tested seven metastatic lesions from four patients up to 6½ years after removal of their T and Tn positive primary breast carcinomas; all metastases strongly expressed T and Tn (*10, 18, 27, 31*).

T and Tn antigens were detected by Anglin *et al.* (*12*), by Laurent *et al.* (*13*), and by us (*27*) in large quantity on the outer cell membranes of 25 of 26 human breast carcinoma–derived epithelial cell lines. The unmasked T- and Tn-specific epitopes are unique carcinoma markers. We found them, in addition, on the cell membranes of four lines of lung, pancreas, and colon carcinoma, in two human T-cell lymphoma lines, and in five rodent cancer cell lines (carcinomas and T lymphomas), but not in the single fibroblast and B lymphoid cell lines tested (*27*).

The authenticity of the T- and Tn-active structures was demonstrated (i) immunochemically, with specific haptens in antibody inhibition studies used by Kim and Uhlenbruck (*45*) and by us (*37, 46*), as well as by Bray *et al.* (*47*); (ii) by a solid-phase immunoassay developed in our laboratory (*48*); (iii) with glycosidases (*37*); and (iv) with glycosyltransferases by us and by Cartron *et al.* (*35, 36*).

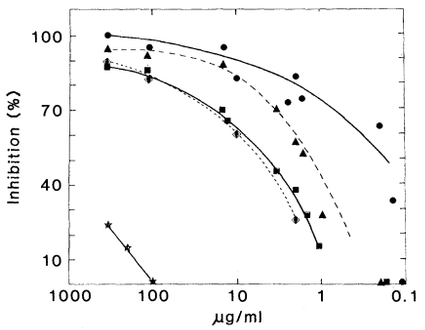

Fig. 1. Inhibition in vitro of murine Esb T lymphoma cell adhesion to syngeneic hepatocytes by T- and Tn-active asialoglycoproteins (AS-) and asialoglycopeptides (AS–LS–GP). Adhesion was measured by specific rosette formation of the invasive and metastatic ESb lymphoma cells with syngeneic hepatocytes. A suspension of 2×10^4 hepatocytes in 400 μl of supplemented Williams E medium was added to each well of multiwell tissue culture plates and incubated at 37°C in 5 percent CO_2 for 2 hours. Then the medium was exchanged and 2×10^6 tumor cells in 100 μl of medium were added. After reincubation for 1 hour and rewashing, rosette formation was counted microscopically. ESb cells did not adhere to nonepithelial syngeneic cells tested. In the inhibition assay, putative inhibitors were added to the preincubated hepatocytes and, after one additional hour, the tumor cells were added as in the adhesion test. There was no interaction between tumor cells and inhibitors. Percent inhibition is the ratio of rosette formation in the presence and absence of putative inhibitor in simultaneously incubated samples (*39*). T-specific substances were obtained by desialylation of isolated human erythrocyte blood group MM, MN, and NN glycoproteins, which do not inhibit adhesion. Where designated as "GP" the glycoproteins were cleaved by proteases and fractions were isolated. Ovine submaxillary mucin was the source of the Tn-specific macromolecule (*39*). Symbols: ●——●, AS–LS–α1 MM GP; ▲——▲, T antigen (MN blood group-derived); ■——■, AS–LS–αl NN GP; ◆----◆, AS-ovine submaxillary mucin; *, galactopyranosyl–β-1→3-*N*-acetyl-D-galactosamine.

T and Tn Expression and Carcinoma Aggressiveness

With Taylor and Howard [see (*27*)] we have recently shown that the relative proportions of T and Tn antigens on human carcinomas frequently correlate with the carcinoma's aggressiveness. In surgical specimens the expression of T and Tn could be studied in parallel. Of 15 well-differentiated breast carcinomas, 13 (87 percent) had more T than Tn, whereas only 2 of 25 (8 percent) highly invasive, anaplastic breast carcinomas had more T than Tn. T also was expressed to a lesser degree than Tn in the few poorly differentiated lung, pancreas, and stomach carcinomas we investigated. This finding is consistent with the precursor status of Tn vis-à-vis T. However, one anaplastic larynx carcinoma had more T than Tn, and some poorly differentiated carcinomas had neither T nor Tn; presumably these did not synthesize the precursor, Tn (*27*).

Coon *et al.* (*15*), on the basis of work by Limas and Lange (*14*), demonstrated the predictive value of the T antigen status for future invasiveness of grade I and II papillomatous transitional-cell urinary bladder carcinoma. Some of these papillomas are of highly malignant potential, while the majority take a rather benign course. Conventional histology does not separate these two categories. However, immunohistochemical detection of an abnormal T antigen status in these tumors heralded a subsequent deep muscle invasion in greater than 50 percent. A similar predictive value of T antigen expression and prostatic carcinoma invasiveness and metastasis has been recently reported by Japanese workers (*17*).

We have made likely, in an experimental system, a correlation between density of T and Tn receptors on tumor cell surfaces and tumor invasiveness. In two murine tumor lines—TA3 and Eb—live cells of a highly invasive, metastatic sub-

Table 1. Intradermal delayed-type hypersensitivity response to erythrocyte-derived T antigen (DTHR-T), at initial visit, of carcinoma patients and controls.

Category	DTHR-T⁺/total tested
Lung	
Carcinoma*	
Adeno	45/49
Bronchioloalveolar	5/6
Small-cell	15/17
Squamous-cell	12/14
Large-cell anaplastic	1/1
Other pleuropulmonary cancers†	1/5
Benign diseases‡	2/35
Pancreas	
Adenocarcinoma	23/26
Pancreatitis	0/13
Breast adenocarcinoma	
Ductal	
Stage I noninfiltrating	10/12
Stage I infiltrating	32/37
Stage II and III§	37/42
Stage IV	17/17
Total	96/108
Lobular	
Stage I noninfiltrating	7/10
Stages I infiltrating, II, and III	7/19
Total	14/29
Tubular¶	1/4
Benign breast disease**	11/144
Urinary bladder	
Transitional-cell carcinoma	19/23
Cancers originating elsewhere	
Adenocarcinoma††	11/11
Melanocarcinoma	3/5
Other cancers‡‡	5/24
Noncancer diseases not related to lung, pancreas, or breast	
Tumors	0/14
Other diseases	0/40
Healthy	0/85

*Two of four carcinoma tissues from negatively reacting patients had T antigen. †Positive: one patient with malignant T pseudolymphoma; his tumor tissue had T. Reactions were negative in one of one mesothelioma patients and three of three with carcinoid. ‡For the two positive patients, see text. Their DTHR-T turned negative within 1 year. §Cancer tissues of the five negatively reacting patients tested; two lacked T but had Tn. ¶Tubular breast carcinoma is rare and has the most favorable outlook among breast carcinomas (*54*). **All but one of the 11 patients with positive DTHR-T had severe hyperplastic disease; one subsequently developed histologic carcinoma. ††The four colon, two esophagus, one ovary, two stomach, and two salivary gland adenocarcinoma patients reacted positively. ‡‡Of four patients with head-neck squamous-cell carcinoma, two reacted positively; also positive were two of two patients with T lymphoma and one of one with germ-cell carcinoma. For those who had negative reactions, see (*56*). For staging of carcinomas, see text.

line were compared with those of the minimally invasive parent. Both sublines, TA3-Ha and ESb, had more Tn than T on their outer cell surfaces, and the parent lines, less of both antigens but more T than Tn (*27*). That Tn is an important antigen in carcinoma metastasis accords with our finding that of 11 monoclonal antibodies, prepared by others against, and specific for, human breast carcinoma metastases, three were strictly anti-Tn–specific; the extent of expression of carcinoma-associated T and Tn varied in time and space (*27*).

T and Tn in Cancer Cell Adhesion

Do density and mode of distribution of T and Tn antigens on the carcinoma cell surfaces bear on the cancer's invasiveness? In an initial analytical attempt at the molecular level we used an in vitro model, based on the work of Davey *et al.* (*49*) and Schirrmacher *et al.* (*50*): the specific adhesion between invasive, metastatic ESb T-lymphoma cells and syngeneic hepatocytes (*50*). The liver is one of the most frequent sites of metastasis; direct molecular binding is the principal event in adhesion, which is one of the primary steps of invasion. We found that the ESb cells strongly expressed T and Tn on their outer cell surfaces. Figure 1 shows that attachment of the ESb cells to hepatocytes was competitively inhibited by minute quantities of T antigen, and by asialo-ovine submaxillary mucin (*39*), which we had shown earlier to be highly Tn-active (*37*). Its carbohydrate moiety is almost exclusively composed of GalNAc-α-Ser/Thr clusters. The effect of the inhibitors was specific, their sialylated parent compounds and other structures with different asialo-heterosaccharides (not shown in Fig. 1) had little or no activity (*39*).

Products of T glycoprotein cleavage that possess T-active heterosaccharide clusters were most active in the adhesion inhibition assay, and the potency of inhibition increased with the extent of clustering per peptide chain; the free T hapten, Gal-β-1 → 3-GalNAc, had only trace activity. Asialoglycopeptide derived from blood group M was about ten times more active than the N-derived one (Fig. 1). We showed earlier that the former has a carbohydrate chain linked to the NH_2-terminal amino acid, which is absent in NH_2-derived glycopeptides (*39*).

The high, specific inhibitory activity of tumor cell adhesion to hepatocytes by T- and Tn-specific glycoconjugates suggests that they may be involved in specific cell-cell adhesions required for invasion and metastasis by cancer cells. I have already pointed to the possible role of T and Tn in adhesion during normal morphogenesis (*21*).

The structural preconditions for adhesion inhibition in this model resemble those for uptake from the circulation of damaged serum glycoproteins by Ashwell's asialoglycoprotein receptor (*39*). Adhesion of tumor cells to hepatocytes may therefore be viewed as the host's misdirected effort to eliminate his tumor by nonimmunologic means.

Table 2. Detection of the earliest clinical stages of lung carcinoma ($T_1N_0M_0$) and breast carcinoma (Tis = in situ) at the patient's initial visit. Staging is postsurgical resection-pathologic (for explanation of this term see text).

Method	Positive carcinoma reactions/number of carcinoma patients tested	
	Lung	Breast
Skin reaction, DTHR-T	17/18*	Ductal, 10/12 Lobular, 7/10
Anti-T, Q_M measurement	10/11†	6/7‡

*Positive: 11 of 11 patients with adenocarcinoma, 4 of 5 with bronchioloalveolar carcinoma, and 2 of 2 with squamous-cell carcinoma. †Positive: 6 of 7 patients with adenocarcinoma and 4 of 4 with squamous-cell carcinoma. ‡Positive: 3 of 3 patients with lobular carcinoma in situ with 3 of 4 with intraductal carcinoma. The negative reaction was given by a patient with an apocrine intraductal carcinoma who reacted positively in the DTHR-T.

Autoimmune Responses to T Antigen

As I have already noted, carcinomas comprise nearly three quarters of all clinically manifest cancers, and, with the exception of skin carcinoma, therapies other than early surgery are only rarely curative. By measuring patients' cellular and humoral immune responses to T antigen, we have detected a high proportion of early carcinomas, some of them earlier than standard biopsy and radiology could detect.

The T/anti-T system has exceptional features: We have measured for years, in vivo and in vitro, the patients' own immune responses to their carcinoma-associated T antigen (*10, 18, 51*). This contrasts with the studies of other tumor antigens which uniformly used xenogeneic antibodies in the clinical setting. T antigen is readily derived from healthy tissue. We and others obtain it by mild enzyme treatment (and subsequent boiling) of isolated blood group MN antigens prepared from healthy human erythrocytes obtained from outdated, banked blood (*51*). This material is free of pyrogens and HLA- and viral hepatitis B antigens; it may be safely used in vivo; in over 600 persons no untoward reaction has been observed.

Patients reported on (Tables 1 to 4) are those whose primary tumor had been verified and localized (usually after our testing), and who had never had any other known cancer. Because of the vital importance of early carcinoma detection, the earliest tumor stages detectable by histology (diagnosed after surgery) are listed separately (Table 2) in addition to their inclusion in the general tables. Only for breast carcinoma are all stages listed in the latter, because of the large number of patients tested. Stages represent the carcinomas' life history with regard to local growth of primary tumor (T), spread to local lymph nodes (N) and distant metastasis (M). There are two predominant forms of staging. One, referred to as clinical-diagnostic, depends on all information available prior to the first definitive treatment and before pathologic determination of the extent of disease by invasive techniques. The other, referred to as postsurgical resection-pathologic staging, depends on all clinical information plus that obtained on surgical exploration and examination of completely resected tissues. Postsurgical resection-pathologic staging depicts more accurately the period in the life of a cancer and is proportionally more valuable. Postsurgical resection-pathologic staging is used here. Stage I carcinomas ($T_1N_0M_0$) are of minimal size and have not spread. Stage I carcinoma may be subdivided into (i) the more favorable noninfiltrating (in situ) = noninvasive carcinoma and (ii) invasive carcinoma. Stage IV is most advanced with distant spread [for details, see (*52*)].

Where possible, both cellular and humoral immune responses were determined simultaneously. For each individual the result of the initial testing only is listed. Prior to the testing we fulfilled all institutional, U.S. National Cancer Institute, and U.S. federal regulations concerning informed consent and ethical standards.

Cellular immune response. The cellular immune response was measured intradermally on the upper outer arm with the delayed-type hypersensitivity reaction to T antigen (DTHR-T) and with controls, as described elsewhere (*18*). Readings were taken independently by three or four persons about 24 and 48 hours after injection. T and control antigen injections caused no demonstrable side effects in any person. Injection of a

standard test dose of T antigen into each of nine healthy volunteers revealed no sensitization 3 weeks later (*31*).

Table 1 summarizes all results after a single injection of T antigen. It shows that the DTHR-T reaction detected 112 of 124 patients with adenocarcinoma, squamous-cell carcinoma, or small-cell carcinoma in body cavities; 87 of these had primary lung carcinoma, of whom 78, that is, nearly 90 percent, reacted positively. The detection rate for all major types of lung carcinoma was similar. Table 2 shows that the DTHR-T test detected 17 of 18 patients with the earliest clinical stages of lung carcinoma ($T_1N_0M_0$), that is, it uncovered lung carcinomas $\leqq 3$ centimeters in diameter (T_1), with no lymph node involvement (N_0), and no metastasis (M_0) in 94 percent of the cases tested. The DTHR-T reaction has, therefore, high sensitivity (= true positive ratio) in the discovery of all major types and stages of lung carcinoma. Its specificity (= true negative ratio) is also remarkable. Table 1 shows that all 85 healthy persons (100 percent) and 33 of 35 (94 percent) patients with benign lung diseases [listed in (*53*)] reacted negatively. Two of 17 patients with chronic bacterial lung infection were positive. Lung tissue of one of these was available; it absorbed anti-T and had sialidase-producing β-hemolytic streptococci which apparently unmasked autochthonous T antigen (*31*).

With R. L. Goodale we found 23 of 26 patients (88 percent) with pancreatic adenocarcinoma, 2 operable, to be positive, whereas all 13 patients with pancreatitis reacted negatively (*31*).

More than 90 percent of breast carcinoma patients have the serious ductal form of the disease (*9, 54*). Of 108 ductal carcinoma patients tested, 96 (89 percent) were positive (Table 1). It is important that, of 12 patients with early, noninfiltrating ductal breast carcinoma, 10 reacted positively (Table 2). Lobular carcinoma is found in less than 10 percent of breast carcinoma patients and is rather benign in noninfiltrating Stage I (in situ), in which it may remain indefinitely (*54*); overall, the DTHR-T was less sensitive here (Tables 1 and 2).

Of 147 breast disease patients diagnosed histologically as benign, 14 had initially a "false" positive DTHR-T. The original slides from some of these patients were sent to P. P. Rosen (Memorial Sloan-Kettering Institute, New York). He diagnosed three as noninvasive carcinoma and they are listed as such in Tables 1 and 2. Of the remaining 11 false-positive patients (7.6 percent of 144 with benign breast disease, see Table 1), 10 had hyperplasia, in 7 cases premalignant (*55*). The premalignant tissues tested had T antigen and all except one had Tn antigen. In one instance the benign lesion turned into a histologic carcinoma in the ensuing $2\frac{1}{2}$ years (still listed under "Benign breast disease" in Table 1). The DTHR-T, therefore, has an overall specificity in excess of 90 percent among patients with benign breast disease.

A positive DTHR-T was also given by 19 of 23 (83 percent) patients with transitional-cell carcinoma of the urinary bladder (*31*).

We tested 15 patients with malignant nonepithelial tumors of the mesenchyme or of the central nervous system (*18, 31*). They are listed among "Other cancers" in Table 1. The reactions were negative except in two patients with T lymphoma; the cancer types of the negatively reacting patients are listed elsewhere [see (*56*)].

An additional 54 patients tested who had benign diseases not yet discussed are listed in Table 1. These 54 patients had neither lung nor breast disorders but either benign tumors or infectious, degenerative, or autoimmune diseases; none reacted positively.

The histology of skin biopsies of the DTHR-T positive tissues of all 11 breast and lung carcinoma patients studied was characteristic of a delayed reaction of the tuberculin type, but the peak of the T reaction was frequently earlier than that of a standard tuberculin test (*18, 31*).

Measurement of cellular immune responses in vitro oversimplifies conditions in vivo. Accordingly, we and others found responses to carcinoma-associated T antigen to be less sensitive and less specific than the DTHR-T (*18, 57*) and even insignificant by some assays (*58*). In vitro responses to T antigen's defined cleavage products, which carry hapten clusters on their peptide chains, were more sensitive than those toward the intact T antigen or the synthetic T-haptenic disaccharide (*31*).

All humans have anti-T (see above), but healthy persons do not have a positive DTHR-T. This situation is akin to that for the antibodies to blood groups A and B, which are stimulated the same way as described above for anti-T (*23, 24*). Everyone has the antibody not corresponding to his blood group, but no DTH to A and B substances. Two groups of investigators have shown, however, that DTH is readily induced by parenteral injection of A and B antigens (*59*). This dichotomous response of humoral versus cellular immunity is observed frequently, it can be induced experimentally, and progress in understanding its basis has been reported (*60*).

Humoral immune response. Anti-T agglutinin levels have been found by others to remain rather steady in a given healthy adult (*19, 23, 30*). We found that anti-T IgM constitutes 7 to 14 percent of total IgM. Its concentration was about 2.5 and about 5 times that of anti-T IgG and anti-T IgA, respectively (*48*).

We found that of 287 consecutive patients with breast carcinoma or carcinoma of the respiratory or gastrointestinal tracts, 105 (36.5 percent) had severely depressed anti-T scores at the initial visit. This contrasted with the depressed scores in 29 of 309 patients (9.5 percent) who had benign diseases of the organs from which the carcinomas originated, and with 17 of 200 healthy persons (8.5 percent) ($P < 0.001$ for carcinoma patients as opposed to other persons). In addition, not all "false positive" reactions in persons without histologic carcinoma turned out to be false (*31, 51*). We followed 19 patients with histologically benign breast disease and four healthy persons all with severely depressed anti-T, for 5 to 8 years; five of these developed histologically verified carcinoma 5 months to 5 years after the original nonmalignant diagnosis. The remaining cases have as yet shown no sign of transition to carcinoma. Table 3 shows the findings on those who developed carcinoma and is an argument for surveillance

Table 3. Severe anti-T agglutinin depression in persons

Patient No.	Date of biopsy or surgery and diagnosis	Date blood obtained and anti-T agglutinin score (normal range: 20 to 25)		
383	3 Sept. 1974 Breast, fibroadenoma	3 Sept. 1974 6	Sept. 1975 9	Dec. 1978 11
394	6 Sept. 1974 Breast, ductal-lobular hyperplasia	6 Sept. 1974 10	3 Jan. 1975 11	
1365	May 1977 Normal mammogram	8 Dec. 1975 21	9 Nov. 1978 14	3 Dec. 1980 12
3072	16 Sept. 1976 Breast, fibrocystic	16 Sept. 1976 11		
3403	15 Oct. 1975 Uterus, leiomyoma	15 Oct. 1975 10	April 1978 10	

without histologic carcinoma who subsequently developed histologically verified carcinoma.

Date blood obtained and anti-T agglutinin score (normal range: 20 to 25)		Date of biopsy or surgery and diagnosis	Date blood obtained and anti-T agglutinin score		
13 May 1979 8		15 May 1979 Breast, infiltrating ductal carcinoma, Stage III	21 May 1980 14		
6 Feb. 1975 10		6 Feb. 1975 Breast, intraductal carcinoma, Stage I	18 May 1979 17		
22 Jan. 1983 15	28 Dec. 1983 14	28 Dec. 1983 Breast, infiltrating ductal carcinoma, Stage I	5 March 1984 21		
12 Dec. 1979 10		2 Jan. 1980 Breast, noninfiltrating lobular carcinoma, Stage I			
20 Oct. 1980 9		22 Oct. 1980 Lung, adenocarcinoma, $T_1N_0M_0$, Stage I	1 June 1981 12	2 Oct. 1981 10	Nov. 1981 Brain metastases

of persons with depressed anti-T but no histologic carcinoma.

Twenty-seven of 38 breast carcinoma patients (71 percent), and all of three who received curative surgery for lung carcinoma, had a strong increase of anti-T score (> 25 percent) 1 to 5 months after surgery for the primary carcinoma (see, in addition, Table 3). Only 1 of 42 patients with biopsy and benign breast disease, and none of 22 who underwent major noncarcinoma–associated surgery responded similarly. That these differences are due to chance has a P value of < 0.001 (*51*). This rebound implicates carcinoma as the cause of depressed anti-T, rather than a genetic defect that would render the patient unable to produce anti-T.

Novel observations on anti-T in carcinoma patients have recently been made. Bray and her colleagues found cytotoxic anti-T in the sera of all healthy persons, and a specific, quantitative, inverse correlation between hemolytic anti-T and tumor burden in patients with gastrointestinal carcinoma (*30*). Thatcher *et al.* reported a direct relation between severely depressed anti-T, poor response to chemotherapy, and decreased survival in patients with melanocarcinoma (*28*). Vos *et al.* found that in a South African province where esophagus carcinoma is endemic in adults, anti-T was depressed in adults with this carcinoma, whereas it was strongly elevated in healthy children in the same area (*29*).

Serum titer scores for anti-T were acceptably specific for carcinoma, but the agglutinin titration assay's sensitivity was not. Hence, we developed a quantitative solid-phase immunofluorescence assay to measure anti-T immunoglobulins and total serum immunoglobulins (*48*). The assay showed that, in carcinoma patients, only anti-T IgM levels differed from those of other patients and healthy persons; total IgM was within the rather broad normal range in 95 percent of all groups of test subjects, however. The detection of carcinoma was most sensitive when a person's anti-T IgM was related to total serum IgM by establishing the value Q_M, calculated from the formula [(anti-T IgM)^2/total IgM] $\times$ 100 [for its derivation, see (*48*)].

As Table 4 indicates, Q_M levels between 100 and 360 are considered normal. This range was established on sera from healthy persons, generally corresponding in age and socioeconomic background to the patients (*48*). The studies are also being extended by others, including commercial institutions.

Table 4 lists all 187 carcinoma patients tested (7 of these are recorded in its first footnote, and are not included in the following calculations). All patients were tested preoperatively, and 164 of 183 patients had a Q_M outside the normal range, that is, the tests' sensitivity was 89.6 percent. In contrast, 8 of 70 patients (11 percent) with noncarcinoma diseases were outside normal range; 5 of these had clearly premalignant breast disease. Three of 62 healthy persons (5 percent) had an abnormal, depressed Q_M. The specificity of the assay is therefore on the order of 90 percent. Most other results in the body of Table 4 and in the footnotes are self-explanatory. Although 95.5 percent of all abnormal Q_M values in carcinoma patients were depressed, in seven patients with squamous-cell lung carcinoma, the abnormality was due to a highly elevated Q_M; these patients had advanced carcinoma and a negative DTHR-T but no demonstrable liver abnormality. The first footnote lists in addition two advanced adenocarcinoma patients who had a highly elevated Q_M. The 2 patients with abnormal Q_M (1 elevated, 1 depressed) among the 35 with benign lung disease both had chronic bacterial lung disease. The patient with elevated Q_M also had a positive DTHR-T; the likely reason for the false positive reactions is discussed under "Cellular immune response."

This solid-phase assay, which measures serum globulins, lends itself to automation and thus to screening. We detected early carcinoma with it, that is, in 10 of 11 patients, subsequently proved to have $T_1N_0M_0$ lung carcinoma, and in 6 of 7 patients with in situ breast carcinoma (Table 2).

Statistical analysis was done on all Q_M values listed in Table 4. The differences in Q_M between all carcinoma patients and all those with benign diseases and between carcinoma patients and healthy persons were highly significant. The overall probability that these differences were due to chance is < 0.00005. It is clear from the nonoverlapping of the confidence intervals that the population means were very different (*61*).

T and Tn Antigens in Carcinoma Pathogenesis

The basis for the unique presence of T- and Tn-immunoreactive structures in carcinomas is unknown. As already indicated, T and Tn may be stage-specific fetal differentiation antigens (*21*). They may be analogous to receptor molecules on murine embryonal carcinoma cells, which are thought to be encoded by the Qa/TL region of the major histocompatibility complex. Activation of this region has been postulated in murine embryogenesis as well as oncogenesis (*62*). T and Tn do present as immunoreactive immediate precursors of the fully differentiated products of the MN biosynthetic pathway (*35, 36*). Others (*7*) and we (*63*) have isolated T and Tn specific glycopeptides with authentic, *O*-glycosidically linked haptens from breast carcinoma cell cultures. T and Tn distributed three-dimensionally over the entire cell-surface glycoconjugate coat (*11–13, 15, 27, 39*) may be directly involved in the temporal processes of invasion and uncontrolled growth. Perhaps the carcinoma cell membrane has a causative role

in both and regulating it may control carcinoma. Carcinoma adhesion may initiate feedback to further proliferation and invasion.

Radiological and histological studies on human carcinomas, excepting those of the skin, indicate that a carcinoma detected clinically early, that is, 0.5 to 1 centimeter in diameter, has already passed about two-thirds of its life-span, unless it could grow to a size exceeding that of the patient. Studies, from early tar tumor work in mice to recent ones in man and in avian leukosis virus–induced tumors, support the single-cell origin of the majority of cancers (*64*). The average doubling time of breast and lung carcinomas is about 200 days, and they are 10 to 12 years old at minimal detectable size (*65*). Hence, today's standard diagnostic procedures detect rather old and not early carcinomas.

With a powerful immune arsenal at the patient's disposal, and the preexistence of humoral immunity, how can a carcinoma with T- and Tn-specific surface structures establish itself in an otherwise healthy individual? Besides the fact that most anti-T is IgM, whose size does not readily allow permeation of vessel walls, this seeming paradox may be partly explained by the current "sneaking through" hypothesis. Immunogenic early carcinoma is thought to be too small for detection by the immune system, and if it were detected and destroyed—a reasonable possibility—it would not become clinically apparent. Both sneaking through and cell surface antigen shedding, which neutralizes patient defenses, may apply to carcinoma-associated T and Tn antigens who have so far been a common denominator of primary lesion and metastases.

T and Tn antigens in carcinoma appear to be unmasked, normally penultimate carbohydrates (*32, 43*). Incipient carcinomas may have a gradual sialylation decrease, leading to local redistribution of negative charges, coupled with conformational changes at the outer cell membrane. This may be a key factor in allowing the carcinoma to attach itself to healthy cells via the uncovered T- and Tn-specific structures. These changes, however, may not satisfy the free energy requirements for interaction with cellular and humoral anti-T components of the immune system. It would be a narrow view to consider only one mechanism for survival and establishment of carcinoma cells. Nevertheless, "sneaking through" finds support in studies in vitro. During gradual desialylation of MN cell membrane glycoproteins, human anti-T begins to interact only at approximately 70 percent desialylation, while T receptors are uncovered at < 25 percent sialic acid removal (*43*).

T and anti-T promise to elucidate important aspects of carcinoma pathogenesis; also, they may permit truly early diagnosis. In this respect, analysis of the following immune responses is promising.

1) The nine patients among over 180 with a large carcinoma burden, who had a strongly increased Q_M ($\overline{X}$ 488.9), had normal total immunoglobulin levels and no demonstrable liver disorder. This reflects an active, specific, and extraordinary immune response that was confined to anti-T IgM.

2) It is difficult to explain, merely by tumor-antibody interaction and by immune complex formation with shed carcinoma antigens, the severe, persistent anti-T depression frequently observed with minimal carcinoma.

3) The long duration of severely depressed anti-T preceding histologic carcinoma detection in the patients listed in Table 3 is difficult to interpret as classical immune response.

4) The difference in T reactivity of 3 patients with malignant carcinoid (nega-

Table 4. Anti-T IgM and total IgM in carcinoma patients and controls, measured by quantitative, solid-phase immunofluorescence assay, expressed as the quotient Q_M = [(anti-T IgM)^2/total IgM] × 100 (at initial visit).

Category	Number of subjects tested*	Number with Q_M			Statistical comparison of Q_M's of carcinoma patients, of patients with benign diseases of the same organs, and of healthy persons (*51*)				
		Depressed (< 100)	Normal (100 to 360)	Elevated (> 360)	Mean	Standard deviation	95-percent confidence interval, and assertion of difference between benign and carcinoma		*P* value for malignant versus benign
Lung									
Carcinoma									
Adeno-	40	36	4	0	75.6	61.1	52,	122	0.0000
Small-cell	14	13	1	0	73.2	55.2	51,	118	0.0001
Squamous-cell									
(A) Depressed Q_M	9	9	0	0	69.6	30.2	63,	113	0.0000
(B) Elevated Q_M	7	0	0	7	486.0	122.0	215,	442	0.0000
Benign	27	1	25	1	162.9	75.8	437,	209	0.0000
Pancreas									
Adenocarcinoma	18	17	1	0	57.1	24.8	42,	134	0.0043
Pancreatitis	5	0	5	0	145.1	37.7	115,	19	
Breast									
Carcinoma (all types)									
Stage I, noninfiltrating	7	6	1	0	71.4	25.5	28,	79	0.0000
Stage I, infiltrating	40	30	10	0	83.8	67.5	17,	66	0.0014
Stages II and III	34	28	6	0	86.3	68.9	3,	63	0.0017
Stage IV	3	3	0	0	55.2	14.4	41,	98	0.0025
Benign	38	6	32	0	125.1	37.9	62,	32	<0.0015
Urinary bladder carcinoma									
Transitional-cell	11	9	2	0	81.9	22.7	57,	94†	0.0000†
Healthy	62	3	59	0	171.0	77.1	56,	115	0.0000‡

*Not listed are two colon carcinoma patients with severely depressed Q_M, three lung carcinoid patients with normal Q_M levels, and two patients with Stage III breast ductal adenocarcinoma who had highly elevated Q_M's. For details on abnormal Q_M's in patients with benign lung and breast diseases, see text. †Compared to all noncarcinoma disease. ‡Compared to all carcinoma.

tive) from that of 17 with small-cell lung carcinoma (15 positive) is striking (see Table 1). Both cancers have common ancestry, but the former is of comparatively low malignancy and the latter is extraordinarily malignant.

5) While patients with carcinoma generally showed cellular and humoral immune responses to carcinoma-associated T antigen, the humoral response was stimulated preferentially by tubular and early lobular breast carcinomas, which had T activity comparable to other carcinomas. Significantly, these carcinoma types have a favorable prognosis among breast carcinomas (*8, 54*).

The Tn/anti-Tn system may complement the T/anti-T system in elucidating aspects of the pathogenesis of carcinoma and in early diagnosis. While the link between Tn and carcinoma has been known for a decade (*10*), this system has not been studied in the present context. Research is complicated by the usually low concentration of anti-Tn. Tn's immunodominant structure, GalNAc-α, is also the dominant part of the blood group A and Forssman haptens, which may prevent some anti-Tn immune responses. Furthermore, Tn antigen is not readily obtainable from healthy tissues (*7*). There are, however, some highly instructive experiments by nature herself that show not only how unmasked Tn arises in hematopoietic stem cells, usually persisting indefinitely without malignant change, but that Tn, the epigenetic sequela of a rare, benign, somatic mutation, occasionally precedes and then accompanies leukemia, disappears upon chemotherapy-induced remission, and reappears in relapse (*66*).

Conclusion and Prospects

The studies described here have revealed, in a large number of carcinoma patients, a close link between malignant transformation and early, persistent changes in common carcinomas: unmasked precursor antigens T and Tn, that allow the patient's immune system to qualitatively differentiate carcinoma from noncarcinoma.

On rare occasions, demonstrable T and Tn antigens occur in premalignant lesions, which may either remain that way permanently or progress to frank malignancy. Some tissues with such changes are accessible to longitudinal study and thus aid in determining the decisive point of malignant transformation. This approach may be facilitated by manipulation of immune responses, as well as by locating incipient carcinomas with labeled mono- and polyclonal anti-T and anti-Tn reagents (*25, 26, 67*) [but see the introduction and (*27*)]. Our monoclonal antibodies to T and Tn were generated by desialylized human O erythrocytes. We obtained three relevant specificities: anti-T, anti-Tn, as well as a specificity directed toward a moiety shared by T and Tn haptens (*67*). The three types of antibodies reacted strongly and specifically with carcinomas in immunohistochemical analyses of surgical specimens but less well in antibody absorption studies (*27*).

Our recent observation (*68*) in carcinoma patients, but not healthy persons, of a significant increase in lymphoid cell cytolytic activity against target cells with surface-exposed T and Tn antigens supports T and Tn's importance in the malignant process—especially since there was often a concomitant decrease in natural killer cell activity. The findings discussed here, although they are in an emerging phase, indicate that uncovered T and Tn antigens endow the carcinoma cells with a multitude of novel functions. These functions may be fundamental to the multistep processes of invasion and spread of carcinoma, and clearly have a profound, measurable effect on the tumor bearer's immune system. T antigen is likely to be a powerful probe in early carcinoma detection.

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53. Lung disease patients with negative DTHR-T had: caseating granuloma (1), silicosis (3), tuberculosis with pleural effusion (1), intravascular angiogenic tumor (1), chronic bronchiectasis (5), chronic organizing interstitial pneumonitis (4), recurrent cyst (1), coccidioidomycosis (1), sarcoidosis (2), chronic obstructive pulmonary disease (8), chronic asthma emphysema, and pneumonitis (5), pneumonia (3).
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61. The two-sample comparisons of the statistical results on carcinoma patients with those on patients with benign disease of the same organ are in most instances extremely significant statistically, with *P*-values of the order of several one-thousands. This also applies to both categories of squamous-cell carcinoma. In the case of pooled pancreas and pancreas benign, P is 0.0043; there are only five benign pancreas patients. However, if all pancreas carcinoma is compared with all pooled noncarcinoma, P is 0.0000. The same pertains if breast carcinoma Stage I infiltrating is compared with all noncarcinoma, while for breast carcinoma Stages II and III P is 0.0001 when compared with all noncarcinoma. A two-sample Student test of the hypothesis that the combined carcinoma and the combined noncarcinoma populations are the same has a P of 0.0000 and yields the very large, extremely significant t-statistic of > 9.5. Additional statistical information will be furnished on request to the author, as will be the individual Q_M ranges.
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National R & D Policy: An Industrial Perspective

Roland W. Schmitt

Industrial policy has become one of the hot issues on our national agenda, with various advocates telling us how to beat the Japanese and solve the problems of unemployment, inflation, and industrial stagnation. The 1984 presidential candidates are picking up these ideas and testing them.

Industrial policy has many components—fiscal, monetary, and regulatory, for example. It touches on many areas, from international trade to retraining the work force. I can bring my expertise to only one corner of this many-sided subject: research and development policy. To me, industrial policy means what the government must do to shape our national industrial posture, and a clear understanding of what government should not do.

There has been no lack of proposals. Bills put before Congress in recent years have called for such changes as the establishment of a National Technology Foundation, or a Cabinet-level Department of Trade and Industry; the selection of a National Commission on Technological Innovation and Industrial Modernization to tell us "what the economic, educational, and industrial priorities of the United States ought to be"; a Presidential Program for the Advancement of Science and Technology; and a Commission on High Technology and Employment Potential. Another proposal would establish a government program to conduct research and development on improved manufacturing techniques; others would exempt joint research and development efforts from the antitrust laws.

All these proposals to aid U.S. R & D show a healthy and encouraging concern about the state of American industrial technology, but they may at the same time distract politicians and policy-makers from the most important need and the most important step that government can take to strengthen U.S. innovation. That task is to ensure and strengthen the health of our university system—in both the performance of basic research and the training of research manpower. The distraction is especially great if Washington pays too much attention to the growing number of calls for the government to take over the job of selecting and supporting R & D programs aimed at commercial results.

The Federal Role

In the commercial R & D area there are some things that government must and can do, and other things it cannot and should not do. Government has a crucial role to play in creating favorable conditions for commercial innovation, but not in actually producing those innovations. There are several reasons for this.

First, successful innovation requires a close and intimate coupling between the developers of a technology and the businesses that will bring products based on that technology to market and are themselves in touch with that market. This is essential in a diversified company, and even more essential in a complex and diversified economy. The R & D people must comprehend the strategies of the business as well as know what the market constraints are and what the competition is up to. The business people, in turn, must understand the capabilities and limitations of the technology. They must possess the technical strength to complete the development and believe strongly enough in the technology's potential to make the big investment needed to bring it to market.

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