anamycin, an ansa macrolide closely related to maytansine (*19*) but lacking the carbinolamide functionality involved in -SH alkylation (and which does not show antileukemic activity), is 1000 times less effective in inhibition of sea urchin egg cleavage. However, at $5 \times 10^{-5} M$ geldanamycin affects the MA in a manner analogous to that of maytansine and the effect is reversible.

Why some tumors should be sensitive to maytansine in vivo when it is an antimitotic agent which can also inhibit normal cells is not clear. We know of no evidence that tubulin of tumor cells differs from that of normal cells. However, microtubules have been implicated in certain cell surface related processes in lymphocytes, polymorphonuclear leukocytes, and other cells (*20*); and, since tumor cell surfaces differ from those of normal cells (*21*), it is not unlikely that specificity resides in such cell surface properties.

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18. Maytanbutine 9-*n*-propyl thioether was obtained in 55 percent yield by treatment of maytanbutine in methylene chloride and trifluoroacetic acid with *n*-propyl thiol for 16 hours at room temperature. The physical constants for the thioether are: melting point (with decomposition) 202° to 204°C; specific rotation at 23°C for the sodium D line ($[\alpha]_D^{23}$) -97° (*c*, 0.0421, chloroform); ultraviolet absorption maximum (ethanol) (log ϵ), 233 (4.41), 245 (4.38), 255 (4.41), 281 (3.71), 289 (3.69) nm; infrared absorption maximum (chloroform), 2.92, 3.34, 3.37, 3.41, 5.74, 5.86, 6.03, 6.12 μm; mass spectrum *m/e* 777 (M^+); elemental analysis, found: C, 59.96 percent; H, 7.34 percent; N, 5.55 percent; calculated for $C_{39}H_{56}ClN_3O_9S$, C, 60.17 percent; H, 7.26 percent; N, 5.40 percent.
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Cancer by County: New Resource for Etiologic Clues

Abstract. *Mapping of U.S. cancer mortality by county has revealed patterns of etiologic significance. The patterns for bladder cancer in males point to industrial determinants: some are known (chemical manufacturing) but others (automobile and machinery manufacturing) represent new leads for epidemiologic study. By contrast, the geographic clusters of high rates of stomach cancer in both sexes are consistent with ethnic susceptibility.*

Geographic variation in cancer mortality in the United States has usually been evaluated on a state-by-state basis. The paucity of clues to cancer etiology arising from such surveys can be traced to the heterogeneity of statewide populations. Counties may provide a compromise, as units small enough to be homogeneous for demographic and environmental characteristics that might influence cancer risk, and yet large enough for stable estimates of site-specific cancer mortality. We have made some preliminary observations that illustrate the value of county mortality measurements in providing leads to the origins of cancers.

We obtained age-, race-, and sex-specific numbers of cancer deaths for the 3056 counties of the contiguous United States over a 20-year period, 1950–1969, from the National Center for Health Statistics, Rockville, Maryland. Corresponding county populations were provided by the 1950, 1960, and 1970 censuses (*1*), with intercensal estimates derived by linear interpolation. For 35 cancer sites, we calculated age-standardized mortality rates by race and sex in each county, the standard being the age distribution of the entire U.S. population in 1960. Ninety-five percent confidence intervals were computed using the standard error of the age-standardized rate as determined by the method of Chiang (*2*). Differences between the county and national rates were statistically significant when the 95 percent confidence intervals for these rates did not overlap. Tabulations of cancer mortality rates by county were recently compiled (*3*).

Table 1. Industrial categories in which the percentage of men employed in counties where the bladder cancer risk is high differed significantly ($P < .05$) from the percentage of men employed nationwide. See text for method of selecting high-risk counties. Abbreviations: Exp., expected; Obs., observed.

Industry	Percentage of employed men		
	In the U.S. (Exp.)	In high-risk counties (Obs.)	Obs./Exp.
Agriculture	15.8	4.2	0.3
Mining	2.2	0.3	0.1
Manufacturing	27.0	42.2	1.6
Furniture, lumber, wood	2.7	1.4	0.5
Nonelectrical machinery	2.8	6.3	2.3
Electrical machinery	1.3	2.8	2.2
Motor vehicles	1.9	4.8	2.5

Although population-based mortality data are a crude means of testing hypotheses concerning public health hazards, geographic correlations with environmental measurements can be done quickly and inexpensively, and may be a valuable first step in evaluating possible dangers. In this manner we have assessed cancer mortality patterns among people residing where drinking water is contaminated by asbestos (*4*), where homes are built on radioactive tailings from uranium mines (*5*), and where the chemical industry is highly concentrated (*6*).

The major contribution of the county resource, however, is in hypothesis formulation, namely the detection of geographic clustering that suggests etiologic clues, which can then be pursued by epidemiologic studies of an analytical type. Computer-generated maps were produced to visualize the spatial configuration of cancer mortality by county. We first plotted the distribution for bladder cancer, the tumor most strongly linked to occupational exposures (*7*). In white males there were clusters of elevated mortality in heavily industrialized areas (Fig. 1), a pattern that was not duplicated in females. The clusters in males suggest industrial hazards that should be evaluated.

To further characterize the possible hazards, we selected for correlation analysis a

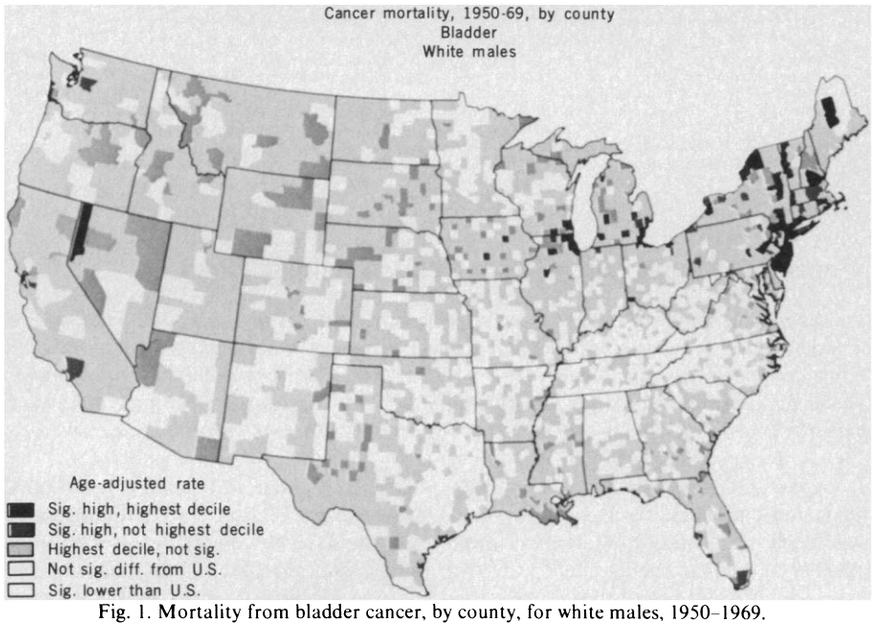

Fig. 1. Mortality from bladder cancer, by county, for white males, 1950–1969.

group of counties with the following criteria: a significantly high mortality from bladder cancer among males when compared with the national rate, a greater male-to-female ratio of bladder cancer than found nationally, and a lung cancer rate among males not significantly different from the national average. While this last stipulation eliminated counties with valuable information, it enabled us to assemble 64 areas where the bladder cancer risk is more likely related to industrial exposure than to cigarette smoking. We determined the industrial makeup of these counties from the 1950 census (*1*), and compared the percentages of workers in 41 separate industries with corresponding percentages for the entire country.

As shown in Table 1, the study counties had a significantly low percentage of workers in three industries, which were mainly concentrated in rural areas, where the risk of bladder cancer is known to be low (*7*). On the other hand, the study counties had a significantly high percentage of workers in three categories: nonelectrical machinery manufacturing, electrical machinery manufacturing, and motor vehicle manufacturing. The study counties are on the average more urban than the United States as a whole. However, overrepresentation of these three industries in the study counties is not simply secondary to an urbanization association. When the study counties were split into two equal groups based on the percentage of the population living in an urban area (percent urban), motor vehicle and nonelectrical machinery manufacturing were overrepresented in both the more rural and the more urban groups. In fact, the association with motor vehicle manufacturing was more impressive in the rural group. In this group (including counties ranging from 0 to 72.5 percent urban, weighted average = 55.5 percent), 7.7 percent of the men employed worked in the automobile industry. Suspicions regarding the automobile industry were deepened by recent results from the Third National Cancer Survey, 1969–1971 (*8*). Detroit had the highest bladder cancer incidence rate (but only the fifth highest lung cancer rate) among white men in the seven cities and two states participating in the survey. Wayne County (Detroit) was excluded from our correlation study on the basis of a significantly elevated lung cancer rate. However, its mortality rate for bladder cancer is significantly high among men but not among women.

Because of the many comparisons involved with data for 3056 counties over 20 years, it may be dangerous to single out a particular county or even a small group of counties for special attention. In certain situations, however, the unusual experience of a county warrants further investigation. For example, Salem County, New Jersey, leads the nation in bladder cancer mortality among white men. We attribute this excess risk to occupational exposures, since about 25 percent of the employed persons in this county work in the chemical industry (*1*), particularly the manufacturing of organic chemicals, which may cause bladder tumors. After the finding was communicated to New Jersey health officials, a company in the area reported that at least 330 workers in a single plant had developed bladder cancer during the last 50 years (*9*). It is urgent that surveys of cancer risk and programs in cancer control be initiated among workers and former workers in this area.

We then selected stomach cancer for mapping, since an earlier analysis failed to reveal the consistently elevated rates previously reported for lower social class communities (*10, 11*). The geographic distribution of stomach cancer mortality for white males is shown in Fig. 2; the pattern for females (not shown) is nearly identical. Elevated mortality is prominent in major cities and in areas characterized by low socioeconomic class (such as certain counties in Pennsylvania and Kentucky). Overshadowing these areas is a cluster of exces-

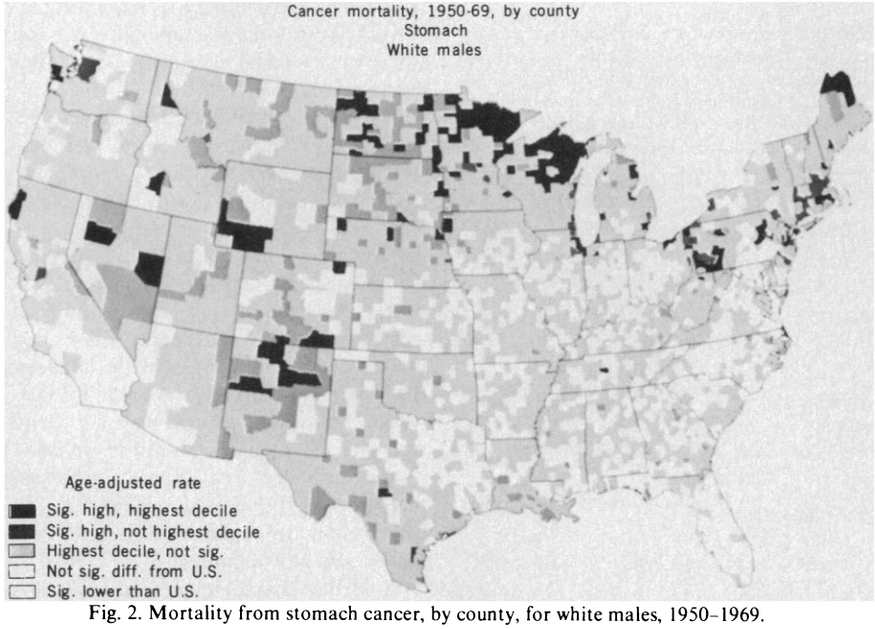

Fig. 2. Mortality from stomach cancer, by county, for white males, 1950–1969.

sive mortality in primarily rural counties in the North Central region (Minnesota, the Dakotas, Michigan, and Wisconsin). Concentrated in these areas are people of Russian, Austrian, Scandinavian, and German descent. In fact, the 306 counties with the highest rates (highest decile) have three times as many first and second generation Finns, Austrians, and Russians as expected, and 40 to 60 percent more Norwegians, Swedes, and Germans than expected on the basis of the national percentages for these ethnic groups (*12*). The possibility that these migrant groups are prone to stomach cancer is compatible with the high incidence of this tumor in their countries of origin (*13, 14*). The smaller cluster in New Mexico and Colorado seems consistent with reports of elevated stomach cancer rates among Spanish-Americans in this area (*15*). Thus, although urbanization and socioeconomic factors affect mortality from stomach cancer, ethnicity seems to be the major determinant of geographic variation within the United States.

A color atlas of U.S. cancer mortality by county for 35 cancer types has recently been published (*16*). For various cancers, the maps reveal a surprising number of clusters or "hot spots." In these areas, physicians, public health officials, county medical societies, occupational health groups, and others concerned with cancer may help to identify previously unrecognized causes of cancer and plan programs in cancer control.

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Somatostatin: Abundance of Immunoreactive Hormone in Rat Stomach and Pancreas

Abstract. *Growth hormone release–inhibiting hormone (somatostatin), a hypothalamic peptide that inhibits the release of growth hormone and also the secretion of insulin, glucagon, and gastrin, was found in the rat stomach and pancreas in a concentration similar to that in the hypothalamus, as measured by radioimmunoassay. Somatostatin was also found in the duodenum and jejunum, but in a smaller concentration. Gel filtration of the extracts of the pancreas and stomach on Sephadex G-25 yielded two immunoreactive peaks, one corresponding in each case to the somatostatin tetradecapeptide. The hormone was not detected in other viscera or the ovaries. The results imply that somatostatin may be synthesized in the pancreas and the stomach in addition to the brain, and may be involved in local regulatory mechanisms for pancreatic and gastric secretion as well as secretion of growth hormone.*

Growth hormone release–inhibiting hormone (somatostatin) was isolated from ovine hypothalamic tissue, and the structure was characterized as H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH (*1*) by Brazeau *et al.* (*2*). We found a similar peptide in porcine hypothalami (*3*). Both natural and synthetic somatostatin inhibit not only the release of growth hormone (GH) from the pituitary in vitro and in vivo, but also the release of thyrotropin and, in some cases, of prolactin (*4*). Furthermore, somatostatin suppresses the release of insulin, glucagon (*5*), and gastrin (*6*) by direct action on their respective secretory cells. However, whether the inhibitory effect of somatostatin on these nonpituitary cells is a true physiologic action or a reaction caused by pharmacologic doses of the tetradecapeptide remains obscure.

As judged from the extremely low level of other hypothalamic hormones, such as luteinizing hormone–releasing hormone, in the peripheral blood (*7*) and the requirement of a fairly large dose of somatostatin to suppress insulin, glucagon, and gastrin secretion (*5, 6*), it would be reasonable to assume that the hypothalamus is not the only source of somatostatin if this hormone is involved in the regulation of gastric and pancreatic secretion under physiologic conditions. Like substance P (a kinin-like undecapeptide), somatostatin may be present in gastrointestinal organs as well as in the brain, and it may play a physiologic role as both a hypophysiotrophic and gastrointestinal regulatory hormone. Accordingly, we have examined organs other than the brain for somatostatin content.

We have prepared an antiserum to synthetic somatostatin and developed a radioimmunoassay for the hormone (*8*). Since somatostatin lacks tyrosine and histidine, which can be iodinated, [Tyr^1]somatostatin was synthesized, labeled with ^{125}I, and used in the assay system. The binding of [^{125}I-Tyr^1]somatostatin with the antiserum was inhibited by the presence of unlabeled somatostatin in a dose-related manner in a range from 8 to 512 pg.

The radioimmunoassay system appeared to be specific, as judged by the failure of various hormones to inhibit binding of the tracer with the antiserum. The hormones tested included thyrotropin-releasing hormone (Abbott); luteinizing hormone–releasing hormone (Sankyo); melanophore-stimulating hormone release–inhibiting hormone (Pro-Leu-Gly-NH_2) (*9*); a decapeptide formerly proposed as a GH-releasing hormone (Val-His-Leu-Ser-Ala-Glu-Glu-Lys-Glu-Ala) (Merck) (*10*); adrenocorticotrophic hormone (Cortisyn, Organon); arginine vasopressin; oxytocin (Syntocinon, Sandoz); ovine luteinizing hormone (H. Papkoff); rat follicle-stimulating hormone [rat FSH-I-1, National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD)]; rat GH (rat GH-I-1, NIAMDD); human GH (HS 1216C); luteinizing hormone (LER 960); follicle-stimulating hormone (LER 1366); thyrotropin [National Institutes of Health (NIH)]; bovine thyrotropin (TSH-B5, NIH); pig glucagon (Lilly); insulin (Iletin, Lilly); human gastrin 1 (Imperial Chemical Industries); substance P (N. Yanaihara); and the COOH-terminal fragment of the β chain of insulin [H-Glu-Arg-Gly-