complex. Farther to the south, rubidium-strontium whole-rock ages between $600 \pm 50 \times 10^6$ and $500 \pm 35 \times 10^6$ years have been reported (*27*) from the Pampean ranges of northwestern Argentina. They could also be related to the Late Precambrian orogeny, if we consider that the numerous Hercynian granitoid intrusions in this area have produced thermal effects that may have opened the rubidium-strontium system of the Late Precambrian rocks with quite high rubidium-strontium ratios (*28*).

3) The presence of the granulite-charnockite complex 2×10^9 years old along the Peru-Chile Trench must be taken into account in genetic models of Andean volcanism. James *et al.* (*29*) and Hamet *et al.* (*30*) have suggested crustal contamination as a possible explanation for the variation of $^{87}Sr/^{86}Sr$ isotope ratios (0.7055 to 0.7080) in recent calc-alkaline lavas (Arequipa and Barrosso units) erupted through the thick Peruvian continental crust; these data contrast with lower isotopic ratios (0.7030 to 0.7042) generally found in similar rocks associated with subduction zones, where the crust is intermediate or oceanic. New strontium isotopic measurements have been carried out on rocks of the same units (*31*). Evaluation in terms of "mixing models" (*31, 32*) of all these strontium data support the assumption that the observed high strontium isotopic ratios are due to a crustal contamination.

Note added in proof: While this report was in press, a paper by Cobbing *et al.* about similar Rb/Sr studies was published (*33*).

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Cancer Mortality in U.S. Counties with Petroleum Industries

Abstract. *A survey of cancer mortality from 1950 to 1969 was conducted in U.S. counties where the petroleum industry is most heavily concentrated. Male residents of these counties experienced significantly higher rates for cancers of the lung, the nasal cavity and sinuses, and the skin (including malignant melanoma) compared to male residents of counties with similar demographic characteristics. Further study is needed to determine whether these patterns result from exposure to chemical carcinogens, including polycyclic hydrocarbons, involved in the manufacturing of petroleum.*

Polycyclic aromatic hydrocarbons (PAH) are found in crude petroleum, in the high boiling residues of catalytically cracked oils, in other pyrolysis products, in soots, and in air surrounding refining operations (*1*). Although exposure to PAH in several occupational groups has induced cutaneous and pulmonary cancers in man (*1, 2*), there has been no clear indication that petroleum refinery workers are exposed to excess risk (*3*). However, indirect evidence of a hazard was suggested recently by a national survey of lung cancer mortality indicating that such mortality was higher among males in U.S. counties with petroleum manufacturing industries, and by a Los Angeles study correlating lung cancer rates in census tracts to airborne levels of PAH emitted, in part, from petroleum refineries (*4*). To evaluate this issue further, we compared the mortality rates from various cancers during 1950 to 1969 in U.S. counties involved in petroleum manufacture with the rates in a group of counties with similar demographic characteristics but no involvement in the industry.

A total of 604 U.S. counties had plants engaged in petroleum manufacture (standard industrial classification code 29) according to the 1963 *Census of Manufactures*, although there were less than 20 employees in over one-third of these counties (*5*). Selected for study were 39 petroleum-industry counties (PIC) where at least 100 persons were employed and where the estimated number of workers divided by the county population exceeded 0.01. The fraction employed reached 0.07 in one PIC but was usually under 0.02. It was 0.017 for the 39 PIC combined, involving about 50,000 petroleum workers. The number employed by sex was not available per county, but national statistics show a predominance of

Table 1. Demographic indices for the petroleum-industry counties (PIC) and control counties in 1960.

Indicator	PIC	Control counties
Percentage urban	74.2	71.1
Population density*	53.5	58.1
Median school years completed by adult population	10.6	10.7
Median family income	6083	5635
Percentage nonwhite	11.2	9.4
Percentage foreign parentage	10.5	11.1

*Population per square mile.

male workers over female (ratio 7:1). with 95 percent of all of the employed being white (*6*).

Nearly all the PIC were involved in petroleum refining, at least since 1940. Although located in 16 states, over one-half were concentrated in Texas, Louisiana, Arkansas, Oklahoma, and Kansas. The PIC ranged in population from about 5000 to 500,000 (median 37,000) as of 1960, the midyear of the study period, with a total of about 3 million.

For comparison, we selected 117 counties comparable by geographic region (same or neighboring state), population size, and various demographic indicators (Table 1). Nonpetroleum manufacturing industries were nearly equally apportioned between the PIC and control counties, except that chemical manufacturing plants tended to occur in the PIC. In 11 of the 39 PIC the chemical and petroleum work forces were about equal. Only 6 of the 117 control counties had similar involvement (a fraction employed of at least 0.01) in the chemical industry.

Age-adjusted mortality rates during 1950 to 1969, for 23 cancer sites, were calculated among white residents in the individual PIC and control counties (*7*), in all PIC combined and all control counties combined, and in groups of PIC and control counties stratified by urbanization category. Standard errors were computed (*8*) for comparisons (Student's *t*-test) of the differences in mortality rates between the PIC and control groups.

Ratios of the age-adjusted cancer mortality rates among white males in the PIC to the rates in control counties are shown in Table 2. Mortality in the PIC was significantly high for all cancers combined. The largest ratios were for cancer of the nasal cavity and sinuses and for lung cancer. In addition, mortality was significantly high for cancers of the skin (both malignant melanoma and nonmelanotic skin cancer), testis, stomach, and rectum. Low mortality was observed for brain cancer.

Table 3 lists the mortality ratios for these cancers among white males in three groups stratified by population. The rates for cancers of the nasal cavity, lung, and skin were high for all three groups, while the excesses for other cancers were limited to highly populated counties (*9*). Among white females in the PIC, the mortality rates were significantly high for lung cancer but not for cancers of the nasal cavity and skin nor for all cancers combined (*10*).

The cancer patterns in the PIC may be due partly to the concomitant presence of chemical industries, which have been previously correlated on a county level with various cancers, including cancers of the nasal cavity, lung, and skin (*11*). For the 11 PIC with heavy involvement in the chemical industry, the nasal cancer mortality rate was exceptionally high, while the rate for the remaining 28 PIC exceeded the control rates to a far lesser extent (*12*). For lung and skin cancers, rates were also highest in those PIC with chemical plants, but the relative excess associated with the presence of both industries was not as great as for nasal cancer (*13*). Bladder and liver cancers, prominently correlated with chemical industry counties (*11*), were not excessive in the PIC.

If, in fact, the higher cancer rates in the PIC resulted mainly from the small percentage of males employed in the industry being exposed to petrochemicals,

Table 2. Ratios of age-adjusted mortality rates, 1950 to 1969, among white males in petroleum industry counties to those in control counties by cancer site.

Cancer site	Ratio
Buccal cavity and pharynx	1.04
Esophagus	1.06
Stomach	1.09*
Colon	1.02
Rectum	1.07†
Liver	1.06
Pancreas	1.05
Nasal cavity and sinuses	1.48*
Larynx	1.09
Lung	1.15*
Prostate	0.98
Testis	1.10†
Kidney	1.05
Bladder	1.02
Melanoma and other skin	1.10†
Brain	0.94†
Thyroid and endocrine	1.04
Bone and connective tissue	0.98
Hodgkin's disease	0.96
Other lymphomas	1.01
Multiple myeloma	1.05
Leukemia	1.03
All sites combined	1.06*

*$P < .01$. †$.01 < P < .05$.

Table 3. Ratios of age-adjusted mortality rates from 1950 to 1969 among white males in petroleum industry counties to rates in control counties separated according to population size for selected cancer sites.

Cancer site	Population (1000's)		
	<25	25 to 99	100+
Stomach	0.99	1.02	1.15*
Rectum	0.85	1.01	1.13*
Nasal cavity and sinuses	1.29	1.78*	1.45*
Lung	1.10†	1.15*	1.17*
Testis	0.89	0.94	1.18†
Brain	1.01	0.98	0.93
Melanoma and other skin	1.21	1.03	1.12†
All cancers combined	1.03	1.05*	1.08*

*$P < .01$. †$.01 < P < .05$.

and if the remainder of the population were at normal risk, then the relative risk to workers would be substantial, particularly among subgroups exposed to hazardous processes. However, these correlations should be interpreted cautiously. Information was not available on the occupations or other exposures of county residents who died of cancer, or on their specific location or duration of residence within the county. Nonfatal cancers were not ascertained, and the information obtained from death certificates may not accurately reflect incidence. Although the PIC and control counties were generally comparable with respect to region, urbanization, and socioeconomic status, there may be differences in other variables that influence the results.

Nevertheless, the geographic patterns are in line with published observations on cancer in related occupational groups. Squamous skin cancers have been reported as a complication of exposure to PAH among wax pressmen, workers in the shale oil industry, and mule spinners and machinists exposed to cutting oils (*1*). A possible excess of melanoma was recently noted among workers who handled polychlorinated biphenyls in a northeastern petrochemical plant (*14*). Nasal cancers have not been related to petroleum exposures, except for tumors of the ethmoid sinus in a small group of workers manufacturing isopropyl alcohol (*15*). Potentially leukemogenic is exposure to benzene in the petroleum industry (*16*), but no significant excess of leukemia was found in the PIC. The correlations with lung cancer in the study are a cause for concern because lung cancer occurs excessively among other PAH-exposed groups, including roofers, coke-oven workers, and gas-generator employees (*1, 2*); and the

high rates of lung cancer among female residents in the PIC raise the possibility of a pollution hazard spreading beyond the workplace.

The findings of this survey suggest the need for industry-wide epidemiologic studies to clarify the risk of cancer among various groups of petroleum workers and to evaluate the possible effects of petrochemical emissions released into neighboring communities.

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10. The PIC/control counties mortality ratios for white females were (total and three urbanization categories of Table 3, respectively): lung cancer, 1.06, 1.21, 1.07, 1.05; nasal cancer, 0.77, 0.70, 0.58, 0.76; skin cancer, 1.01, 1.00, 1.05, 0.99; all cancers combined, 1.01, 0.98, 1.02, 1.02.
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12. The mortality rate for nasal cancer for the 11 PIC combined was 0.8 (about double the control and national rates) and exceeded 0.7 in eight of the 11 counties. The rate for the 28 PIC without heavy chemical industrial involvement was 0.5.
13. The mortality rates for each of nasal, lung, and skin cancers were reported to be higher by 10 percent in chemical-industry counties (*11*). The mortality rates for lung and skin cancers in the PIC where chemical industries were heavily concentrated were roughly 10 percent higher than in the PIC without a heavy concentration of chemical industries, which were in turn higher (12 percent for lung cancer and 7 percent for skin cancer) than the control rates. However, rates for nasal cancer in the PIC with chemical industries were over 50 percent higher than rates in the remaining PIC.
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Bifunctional Intercalators: Relationship of Antitumor Activity of Diacridines to the Cell Membrane

Abstract. *The in vivo antitumor effectiveness [as measured by the percentage increase in life-span (ILS%)] of 28 diacridine bis-intercalators of nucleic acids shows a highly significant correlation with their effect on phenomena associated with plasma membrane as well as a high degree of structural specificity. In contrast, the ILS% does not correlate with the uptake of these diacridines by cells, nor with the inhibition of RNA synthesis or of DNA synthesis or with the inhibition of growth of cells in culture. The possibility that the antitumor effectiveness of actinomycin D, another DNA intercalator, is associated with sites of action other than the hibition of RNA synthesis is discussed.*

In an attempt to develop new antitumor compounds, we have enhanced the well-known ability of the acridine ring to intercalate with DNA by synthesizing diacridines (*1–3*). These compounds consist of two acridine rings connected through their 9-amino position by hydrocarbon chains of various lengths. In addition, various substitutions have been made on the acridine rings; only symmetrical compounds have been synthesized, the two acridine rings of each diacridine are identical (see Table 1). It was anticipated that such compounds would intercalate more strongly with DNA. In order for the DNA to be free of the diacridine, both rings would have to deintercalate simultaneously; a delay of one ring would permit the other ring to reintercalate. Work done in our laboratory (*1, 2*), as well as in others, with a limited number of diacridines (*4*) has shown them to bind more strongly than monoacridines to DNA and RNA.

In the biological studies described below, the diacridines in which the connecting paraffinic chain has six or more methylene groups ($n \geq 6$ in Table 1) have proved more effective than when $n \leq 4$. This result seems to find an explanation both in model building (*1*) and in studies on PM 2 DNA with Wakelin *et al.* (*5*). These studies (*1, 5*) indicate that when $n \geq 6$ the diacrines can effectively act as bifunctional intercalators with PM 2 DNA while they act only as monofunctional intercalators when $n \leq 4$; when $n = 5$, intermediate results are obtained.

The diacridines are potent inhibitors of the growth of P-388, L-1210, and HeLa cells in culture (*6*). More detailed studies with these cells indicated that RNA synthesis was the primary site of action; DNA and protein synthesis were affected to a lesser extent (*6, 7*). Additional studies showed that the synthesis of 45*S* ribosomal RNA was specifically inhibited as well as the further processing of this RNA to 28*S* and 18*S* RNA (*8, 9*) and the methylation of transfer RNA (tRNA) (*9*). A study of the synthesis of well-defined messenger RNA's (mRNA) in vitro (T7 DNA-dependent RNA polymerase transcribing the late cistrons of T7 DNA in vitro) showed that the diacridines inhibited the initiation of RNA synthesis in contrast to actinomycin D, which inhibited elongation (*10*). In addition, we have found the diacridines to be extensively taken up by cells in culture (*8*) and by tumor cells in vivo (R.M.F., unpublished observations). The diacridines also have considerable in vivo antitumor effect when assayed in BDF/1 mice bearing P-388 leukemia tumors in ascites form (*1*).

It was therefore of interest to establish whether the in vivo antitumor effect of these diacridines, as measured by the percentage increase in life-span (ILS%), would correlate with the well-defined inhibition of RNA or of DNA synthesis or with their cellular uptake. Using all the diacridines for which we have in vivo antitumor data (ILS% values), we related the ILS% with the ability of the diacridines to inhibit RNA synthesis (Fig. 1a) and DNA synthesis (Fig. 1b), as well as their uptake by P-388 cells in culture (Fig. 1c). These results indicate that there is no significant correlation between any of these three parameters and the antitumor activity of the diacridines as represented by ILS%. A corresponding study relating ILS% to the inhibition of growth of P-388 cells in culture also showed no significant correlation (*3*).

However, we also evaluated the cell membrane as a possible site of action of