Uranium Mining and Cigarette Smoking Effects on Man

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A substantial excess of lung cancer, reduced pulmonary function and emphysema among uranium miners has been reported.[1-5] The excess has been attributed primarily to irradiation of the tracheobronchial epithelium by alpha particles emitted during the radioactive decay of radon and its daughter products.[1-3] These radioactive elements collect in the air and on the dust in mine atmospheres and are inhaled by miners. Control of this hazard has been largely by ventilation.

Since cigarette smoking was common among miners studied, it was necessary to consider this habit as a complicating variable to adequately study pulmonary function and lung cancer.[1-3] Cigaret smoking and irradiation were found to be associated with pulmonary function, emphysema, incidence of lung cancer, induction-latent period for lung cancer, and histologic types of cancer. These items are reviewed here.

The latent period of laboratory induced tumors is the elapsed time between application of the carcinogen and subsequent appearance of the tumor. Since inhalation of radon daughters by uranium miners occurs over a prolonged and variable time period, no single point may be considered as the time of tumor induction. Consequently, for uranium miners who develop lung cancer, there is an induction and a latent period which cannot be separated, so the time from start of uranium mining to tumor diagnosis is referred to as the "induction-latent period."

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Materials and Methods

Periodic medical surveys of uranium miners were conducted from 1950 through 1960. Before 1954, both miners and mill workers were examined but no attempt was made to examine all workers. From 1954 through 1960, an attempt was made to examine as many uranium miners as possible. In 1957 and 1960, approximately 90% of miners in the areas visited were examined.[5] All examined miners were included in a single Study Group.[1-3] Medical, occupational, social, and tobacco use histories were obtained. Physical examination, chest radiograms, expiratory pulmonary function tests, and other laboratory procedures were done. Examined men composed a Study Group which has been followed to date by an annual census of uranium miners, periodic questionnaires and death certificate searches.[1-3]

Radiation exposure was calculated for individual men by correlating radon daughter measurements made in mines with occupational histories.[3] Cumulative exposure was calculated as Working Level Months (WLM), a unit which reflects intensity and duration of exposure.[1-3] Vital capacity and one-second Forced Expiratory Volumes (FEV_1) were obtained by using six-liter water displacement spirometers.[4,5] Emphysema was determined by the clinical impression of the examining physician, who used such criteria as increased anterior-posterior diameter of chest, distant heart sounds, and use of accessory muscles in breathing.

Lung cancer deaths among uranium miners were ascertained from death certificate data for mortality analysis relating to Study Group members. For analysis of histologic type and induction-latent period, lung cancers among uranium miners were determined from clinical, biopsy, and autopsy data on cases both in and out of the Study Group.

Mortality analysis was done by a modified life table technique.[1-3] Analyses of FEV_1, emphysema, cell type and induction-latent period were based on frequency distributions for several variables, including radiation exposure, age and cigarette consumption,[4,5,6] and by appropriate statistical tests.

Results

During the four year observation period (1964-67) 39 of the Study Group of uranium miners died of lung cancer; two had never smoked cigarettes regularly; one of the two smoked cigars. By adjusting for age and residence in the mountain states in data on white males over a similar four year time span (1960-63) from a comparable study of nonminers,[7] we calculated that 0.3 cases of lung cancer would be expected among nonsmoking miners, and 3.9 cases among smoking miners. These numbers converted to incidence, are shown in Fig 1. Further comparison between uranium miners who had a high radiation exposure and nonminers who smoked two packs or more of cigarettes per day[7] is given in Fig 1. Respiratory cancer rates among smoking and nonsmoking uranium miners are six to nine times greater than among nonminers with

similar smoking habits; the highest lung cancer rates among uranium miners are about ten times greater than the highest rates among very heavy smokers who are city dwellers.

Comparative evaluation of data must be made with reservations because of differences in populations, unstable numbers for nonsmokers, and possibly inadequate adjustments for age and residence. However, they do serve to indicate the approximate current relationship between smoking and radiation exposure in the incidence of lung cancer among uranium miners.

Among a less well defined group of uranium miners (men outside as well as in the Study Group), we learned of 207 lung cancers, all but three of whom were cigarette-smoking males.[8] Since only 71% of uranium miners smoked cigarettes,[3] smokers are over-represented among those with lung cancer (98.6%). Of the three men with lung cancer who did not use cigarettes, one never smoked anything, one smoked cigars regularly, and one smoked a pipe regularly. In addition, the 207 cancer cases contain men who stopped cigarette smoking: 17 men 8 or more years before developing lung cancer, 16 between 4 and 7.9 years before developing lung cancer, and 19 who used less than 15 cigarettes per day (light smokers).

One hypothesis regarding the role of cigarette smoking in lung cancers among uranium miners is that it acts as a promoting agent in the development of cancer induced by other agents. The most important effect of a promoting agent is reduction in length of the latent period. Although we cannot look at latent period itself in uranium miners, we can look at induction-latent period and age at which cancer develops. To test the hypothesis that cigarette smoke is acting as a promoting agent, controls were selected for the above groups of non-cigarette users, former users, and light smokers. These controls were selected from among 152 other known lung cancer cases among uranium miners. The controls were matched as closely as possible on the basis of age at start of uranium mining, cumulative radon daughter exposure, and years of other hard rock mining. These items were used for matching because they are thought to exert some influence on age at cancer development and induction-latent period. In addition, none of the

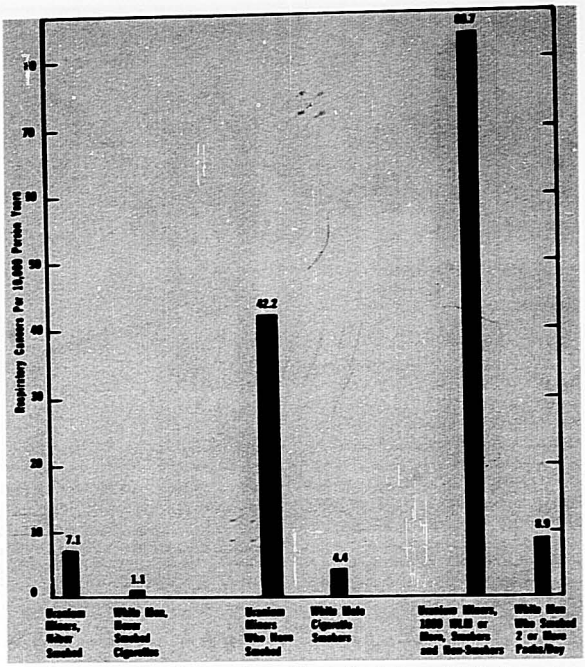

Fig 1. — Respiratory Cancer Rates among Uranium Miners by Cigarette Usage and Radiation Exposure Compared with Rates among Non-miners.

men selected as controls were known to have stopped smoking for more than one year before diagnosis of their cancer and all smoked 20 or more cigarettes per day.

Data on the four groups and their matching controls are given in the Table, with differences in age at diagnosis of lung cancer and induction-latent period illustrated in Figs 2 and 3. Significant shortening of the induction-latent period is shown to be associated with continued smoking of one pack or more of cigarettes per day. This shortened induction-latent period is associated with reduced age at diagnosis clearly evident among men who had stopped smoking for eight or more years. It is present, but less clear among non-cigarette users because of the small number involved and because of their advanced age at start of uranium mining. No differences in age at cancer diagnosis or in induction-latent period were observed between controls and light smokers or men who had stopped smoking for less than eight years.

Uranium miners are exposed to four influences which potentially reduce their pulmonary function: silica dust, radiation, aging, and cigarette smoke. Although no quantitative measurements of silica dust were available, its levels, in general, may be assumed to parallel those of radiation exposure as both are correlated with duration of mining and mine ventilation. Analysis was done on the three quantitated factors in relation to vital capacity, FEV_1, emphysema, and symptoms of chest disease.[4] No definite association between cigarette smoking and vital capacity was elicited, but a definite association was evident between prevalence of low FEV_1 and cumulative amount of cigarettes smoked as well as cumulative radiation exposure and age (Fig 4). There was also a definite association between prevalence of "Impression of emphysema" and cumulative amount of cigarettes smoked as well as

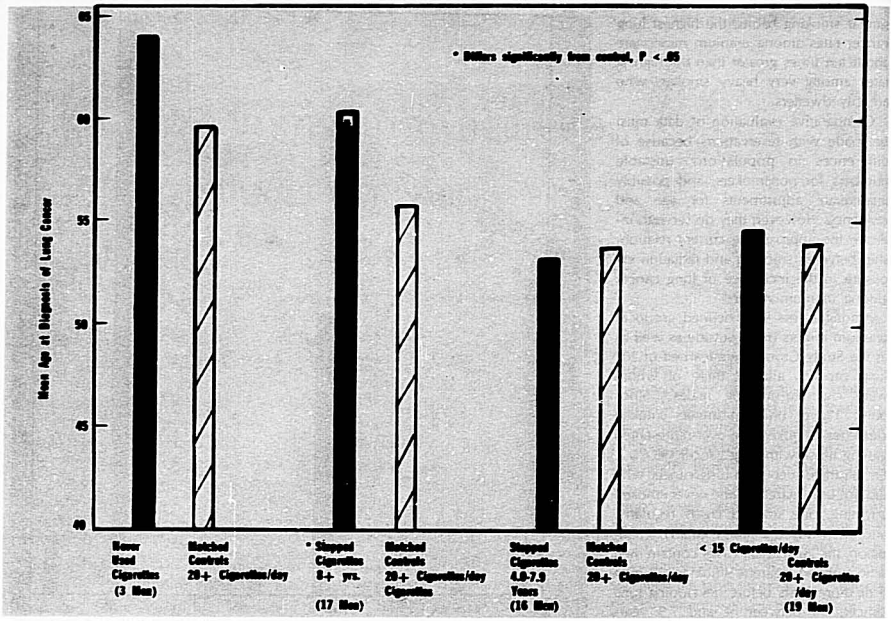

Fig 2. — Association of Cigarette Smoking with Age at Diagnosis of Lung Cancer among Uranium Miners.

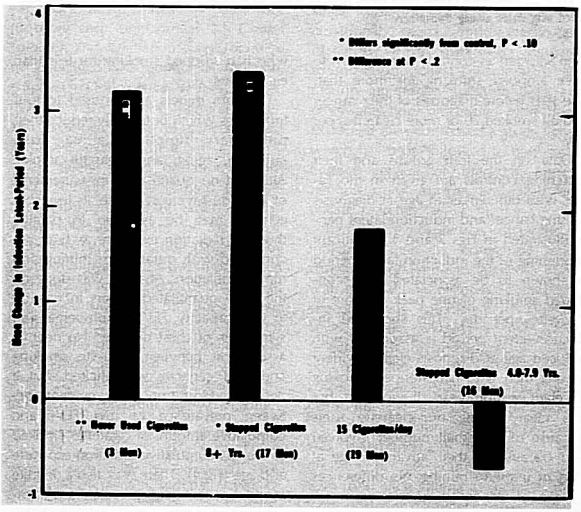

Fig 3. — Association of Cigarette Smoking with Decreased Induction-Latent Period for Lung Cancer among Uranium Miners.

with cumulative radiation exposure and age (Fig 5). In Figs 4 and 5 "low radiation exposure" includes men who have received less than 240 Working Level Months (approximately 480 rads) to their tracheobronchial epithelium. "High radiation exposure" includes men who received more than 240 Working Level Months.

The histologic cell type of the cancers developed by uranium miners was studied in relation to cigarette smoking, radiation exposure, and age.[6] Fig 6 illustrates the very strong relationship found between cumulative radiation exposure and histologic type. Fig 7 illustrates an attempt to find an association between histologic type and age or cigarette usage. The various WLM groups were distributed fairly evenly between the four groups shown in Fig 7. There appeared to be an increase of small cell undifferentiated (2A and 2B) tumors among heavy smokers under age 54 at diagnosis of cancer, but the validity of the association with cigarettes is doubtful because a similar association was not present among older miners.

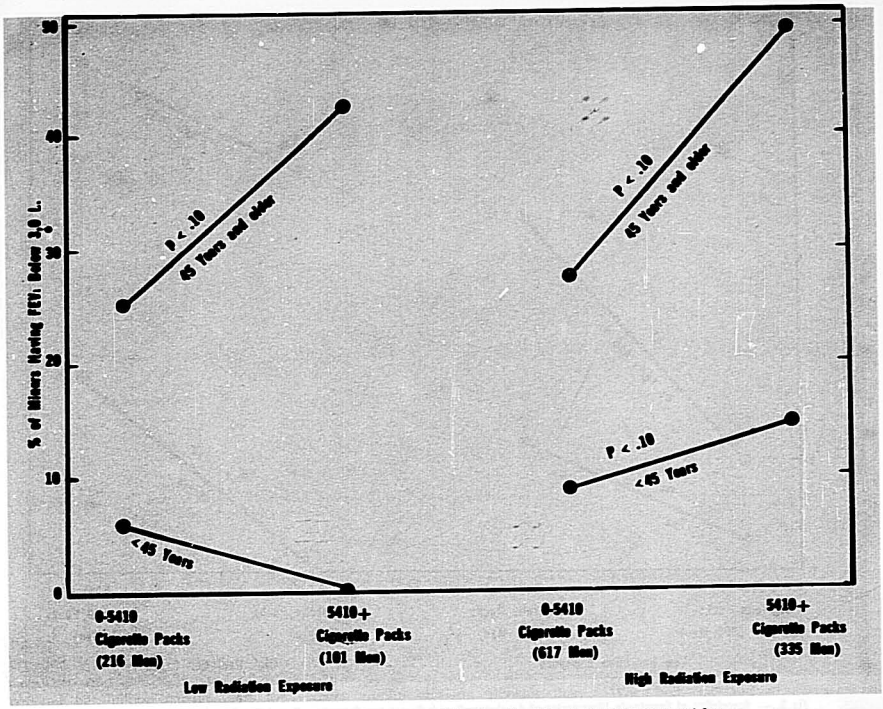

Fig 4. — Association of Low FEV1 with Cumulative Cigarettes, Cumulative Radiation Exposure, and Age.

Older miners who smoked heavily, in contrast, had a larger proportion of epidermoid types of tumors (1A, 1B, and 1C).

Discussion

It is apparent from Figs 3 and 4 that cigarette smoking contributes substantially to loss in ventilatory function in uranium miners. It is difficult to determine whether the cigarette smoking effect is simply additive to pulmonary function loss from silica dust, radiation, and aging, or causes an enhancement of injury from other agents. At any rate, the combination of agents leads to a substantial incidence of pulmonary disability among uranium miners.[8]

There is a definite association of small cell undifferentiated lung cancers with radiation exposure. This relationship appears to be enhanced among young miners by cigarette smoking, but not among older miners who have more epidermoid type tumors than their younger colleagues. The predominant histologic type of lung cancer among Erz Mountain miners (who were exposed to radon daughters in Joachimsthal and Schneeburg mines, but did not smoke during the 19th and early 20th century) was the small cell undifferentiated type[9]—the same as found among U.S. uranium miners (71% cigarette smokers). This observation plus data in Figs 6 and 7 indicate that radiation exposure and age are the two principal determinants of cell type among uranium miners, and that cigarette smoking, if it plays any role in histologic type, merely enhances differences resulting from age and radiation exposure. This is in marked contrast to the important role of cigarette smoking in determining the distribution of histologic types of lung cancer among the general population.[10 11 12]

Detailed analyses have shown that cigarette smoking by itself could account for only a small proportion of the excess lung cancer observed among United States uranium miners.[2 3] The verity of this conclusion is supported by the observation that miners with minimal radiation exposure (less than 120 WLM), did not have a significantly elevated lung cancer rate even though the cigarette consumption pattern within this category was similar to patterns in higher exposure categories which had markedly elevated lung cancer rates. This led to the conclusion that the principal agent in the lung cancer of uranium miners is radiation.[3 13]

Another observation which seems to minimize the role of cigarettes in lung cancer of uranium miners is the similarity of lung cancer risk among the Erz Mountain miners (who did not smoke cigarettes), and United States uranium miners (71% of whom smoked

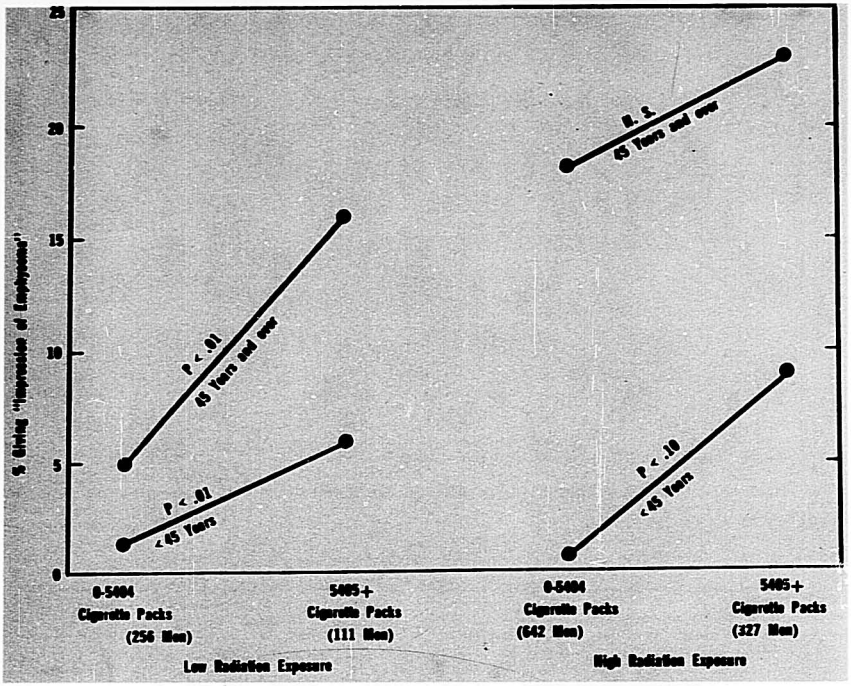

Fig 5. — Association of Examiner's "Impression of Emphysema" with Cumulative Cigarettes, Cumulative Radiation Exposure, and Age.

Data on Selected Groups of Uranium Miners with Lung Cancers and on Matched Controls

Group	No.	Mean Age at start of Uranium Mining	Mean Radon Daughter Exposure in WLM	Mean Years of Other Hard Rock Mining	Age at Cancer Diagnosis, Years			Induction-Latent Period, Years	
					Range	Median	Mean	Range	Mean
No Cigarette Smoking	3	52.0	1142.3	17.3	56-71	65	64.0	8-15	12.0
Matched Controls	6	50.5	757.5	19.8	50-65	62	59.5	6-14	8.8
Stopped Cigarettes 8 or more years	17	40.7	2621.2	5.9	47-74	62	60.3	10-43	19.6
Matched Controls	17	39.5	2532.2	5.0	31-71	56	55.7	6-31	16.2
Stopped Cigarettes 4.0 7.9 years	16	36.4	1748.9	5.2	38-67	53	53.1	7-34	16.9
Matched Controls	16	35.8	1707.6	7.9	36-66	54.5	53.6	4-28	17.6
Light Cigarette Smokers	19	36.0	1367.8	4.2	35-75	55	54.6	11-33	18.7
Matched Controls	19	36.8	1313.6	7.0	43-72	55	53.9	6-41	16.9
Unmatched Controls	94	35.4	1666.7	5.9	31-75	53	52.9	2-54	17.1

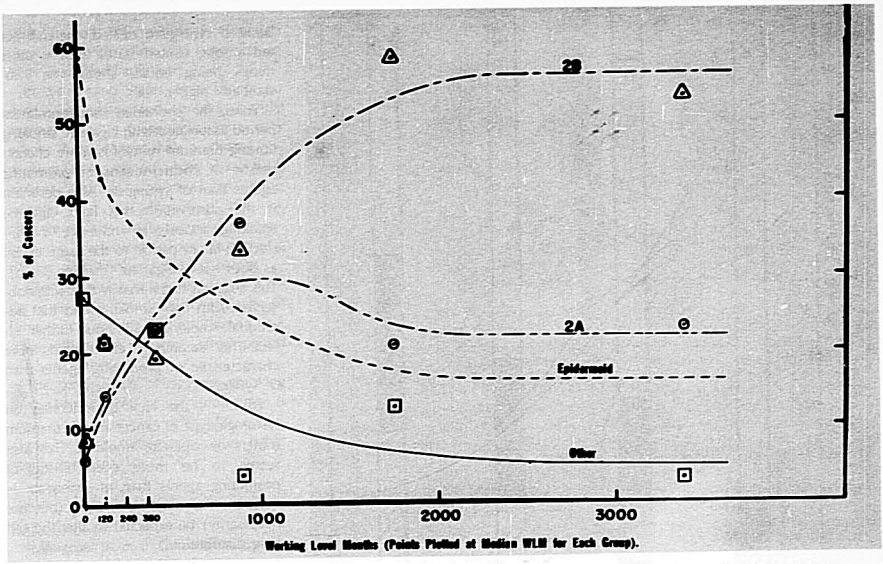

Fig 6. — Distribution of Histologic Types of Lung Cancer among Uranium Miners by Cumulative Radiation Exposure.

cigarettes) when expressed as cancers per unit of radiation. This value was calculated as 0.9 and 1.3 excess cancers per rad per million person years for United States and for Erz Mountain miners respectively.[14]

In sharp contrast to the above data which seem to minimize the role of cigarette smoking in the lung cancer of uranium miners are data in Fig 1 and the observation that, of 207 lung cancers among uranium miners, only 3 (1.4%) were among men who did not use cigarettes, while 29% of uranium miners are known to be non-users of cigarettes.[3] A cigarette influence on the induction-latent period is indicated in the Table and Fig 3. This observation is strengthened by the observation that the Erz Mountain miners (nonsmokers) had an average induction-latent period of 20 to 21 years[15] compared to an average of 17 years among United States uranium miners (Table). The value of 17 years, however, may become longer as United States miners are followed longer. Erz Mountain miners used fires for heat cracking of rock, but miners were not allowed in mines while fires were burning,[16] so it is unlikely that this smoke would be equivalent to cigarette smoking. The mean age at diagnosis of lung cancer among uranium miners was lower among cigarette smokers than among nonsmokers (Table and Fig 2). This was demonstrated only by matching the men on age at start of uranium mining, as the age at start of uranium mining appears to be nearly as important in determining age at diagnosis as is the induction-latent period.

There are thus two sets of data bearing on the influence of cigarette smoking in uranium miner lung cancer. One set indicates that it is of small importance, the other that it is of major importance. How can these two sets of data be reconciled?

Interaction between radiation and chemical agents in tumor production has been noted frequently in animal experiments.[3] Tobacco smoke condensate ("tar") is a mixture of compounds, some of which act as weak tumor initiators, and some as strong tumor promoters[17-21] or cocarcinogens.[19] Tumor initiation represents a permanent change whereas tumor promotion has only a temporary effect.[22] An important effect of promoting agents is to shorten the latent period.[23] This effect was a striking feature of an experiment which employed both beta radiation and cigarette "tar" to produce carcinomas in the skin of mice. When both "tar" and radiation were administered, cancers appeared six to seven months earlier than when radiation was administered alone. This shortened latent period gave an illusion of synergism, which was reported in a preliminary analysis based on tumor yield at 18 months[24] whereas, at the conclusion of the experiment, there was actually nothing more than an additive effect of cigarette "tar" and beta radiation.[25]

Epidemiological data on human lung cancer seem to be consistent with the dual role of cigarette tar seen in experimental carcinogenesis. The younger a person starts a continuing smoking habit, the greater is his risk of lung cancer at age 50 to 70.[7] This cumulative effect is similar to that for tumor initiators. However, if the same person were to stop smoking at age 40, his bronchial epithelium and lung cancer risk would both approach normal by age 50.[7 26 27] This temporary effect may be interpreted as supporting the concept that cigarette smoking seems to act more as a tumor

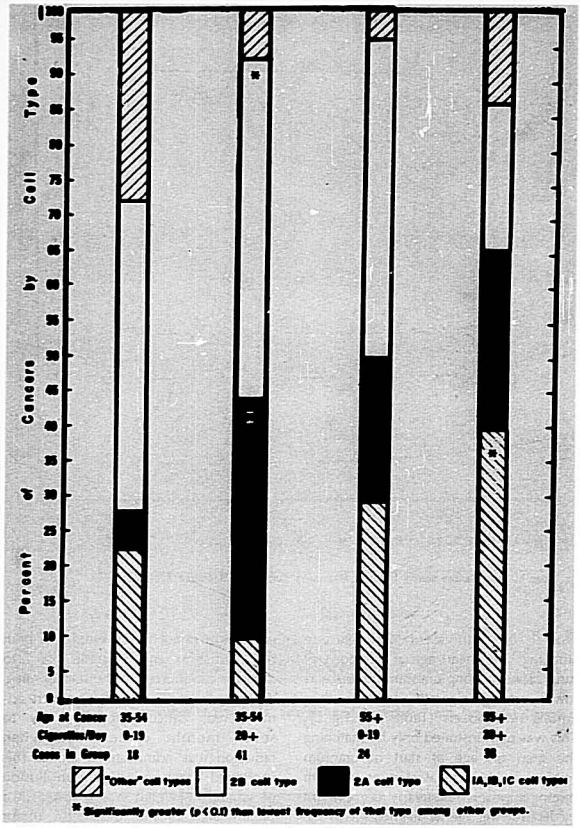

Fig 7. — Distribution of Histologic Types of Lung Cancer among Uranium Miners by Cigarette Smoking and Age.

promoter than as an initiator, even though it has some initiating activity.[27]

The role of cigarette smoking in the lung cancer of uranium miners must, therefore, be one of synergism, cocarcinogenesis, or promotion. Which is most consistent with the observations? There are four features of uranium miner lung cancer which argue against synergism as the relationship between radon daughter exposure and cigarette smoking.

First is the lack of specificity. A marked cigarette smoking effect has been noted among three different groups exposed to occupational pulmonary carcinogens: chromates,[28 29] asbestos,[30] and uranium miners.[2] In all three groups, smokers are overrepresented among lung cancer cases. The similarity of response to cigarette smoking among the three groups is characteristic of the nonspecific response to promoting agents. A summation of effects is the usual result when two carcinogens are administered together,[31] synergism being an unusual interaction that occurs between specific agents.

Second is the similarity of the lung cancer risk among Erz Mountain (nonsmokers) and United States uranium miners when compared on a per rad basis. If synergism existed, the risk per rad among United States miners, other things being equal, should be substantially higher.

Third, the shortened induction-latent period associated with cigarette smoking among uranium miners is more characteristic of cocarcinogens or promoting agents than of synergists. Also pertinent is the observation that light cigarette smoking appears to influence the induction-latent period to the same extent as does heavy cigarette smoking (Fig 3). This suggests that a maximal effect is observed with light smoking and that additional smoking is without further effect. This "saturation" effect seems more characteristic of promoting agents than of synergists.

Fourth is the lack of influence on histologic type of cancer among uranium miners by cigarette smoking. This also seems to be more characteristic of promoting agents than of synergists as the action of synergists might (but not necessarily) be expected to alter the cell type distribution.

In the Study Group of uranium miners up to 1967, 79.2% of the person years contributed by non-cigarette users were from men under age 50, whereas only 75% of cigarette users were under 50, suggesting that noncigarette users are younger than cigarette users and that proportionately fewer of them have reached ages at which increased lung cancer risk would be manifest. Since the induction-latent period for radiogenic lung cancer is longer in non-cigarette users than in cigarette smokers ($p < .10$), then it might be too early to expect many lung cancers among non-cigarette using uranium miners even though their lung cancer risk may eventually approach that of cigarette smokers with comparable exposures.

Although the above considerations cannot rule out synergism as the role of cigarette smoke in uranium miner lung cancers, it appears that promotion or cocarcinogenesis is the more probable role. Since many promoting agents act as cocarcinogens, and vice versa,[20] the two are probably indistinguishable in human epidemiological studies.

Summary and Conclusions

As reflected by FEV_1 measurements and "impression of emphysema", cigarette smoking by uranium miners

adds to loss of pulmonary function associated with aging and exposures to mine dust and radiation.

In the United States, lung cancer, to date, has appeared predominantly among cigarette using uranium miners whose lung cancer has a shorter induction-latent period than does lung cancer among non-cigarette using miners ($p < .10$). However, the incidence of lung cancer increases with increasing radiation exposure among groups with similar smoking habits.

Cigarette smoking appears to have little or no influence on histologic type of lung cancer among uranium miners, but does reduce the induction-latent period of those cancers.

The precise role of cigarette smoking in the lung cancers of uranium miners is not clear, but is probably cocarcinogenesis or tumor promotion rather than synergism.

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