

Also, in conditions 2 and 3, the left eye sees more of the floor than the right, and this might contribute to the evident potency of the left-eye treatment. Ocular dominance was measured in all of our subjects but the results of right- and left-eye dominant individuals were not notably different.

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5. The measured compensatory shift in judgment was found to increase for about the first 8 minutes and then level off. The 10-diopter group achieved only about half the magnitude of shift observed in the 20-diopter group. In both cases compensation was considerably less than complete. Similar effects for adaptation to tilting prisms have been reported by S. M. Ebenholtz [*J. Exp. Psychol.* 72, 629 (1966)].
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  10. Supported by National Research Council of Canada grant APA-1.
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## Carcinogenicity of Tobacco-Smoke Constituents

In their work on experimental carcinogenesis by constituents of tobacco smoke, Wynder and Hoffmann (1) have relied heavily on mouse skin assays for their conclusions concerning carcinogenicity. Although they point out that study of the respiratory epithelium may be preferable, they conclude that it is not suitable for routine studies, and they also conclude that "mouse epidermis adequately represents various epithelial surfaces susceptible to carcinogens on contact." Their work has dealt largely with assaying hydrocarbon fractions of tobacco smoke condensate, and they believe that polynuclear aromatic hydrocarbons are the main tumor initiators in the condensate.

The suitability of mouse skin for assaying carcinogenicity of tobacco smoke constituents on the bronchial epithelium can be questioned on several grounds. For example, the role of alpha-emitting radioisotopes such as polonium-210 (2) could not have been assessed by this technique, since the alpha particles have a limited range of 40 microns or less in tissue. Thus they would not be likely to penetrate to the deep dividing cell layer of skin, but they can penetrate the respiratory epithelium to the more superficial basal layer of stem cells.

In their review, Wynder and Hoffmann state that  $^{210}\text{Po}$  may be of importance as a carcinogen only in relatively high concentrations. The implication is that low tissue concentrations

that result from smoking are unimportant, and they cite calculations by Rajewsky and Stahlhofen (3) indicating that polonium from cigarette smoke on the surface layers of mucus results in low radiation doses to epithelium. Wynder and Hoffmann's discussion of this subject does not include mention of our measurements of actual polonium concentrations in bronchial tissues of 25 smokers (4). We have commented previously on Rajewsky and Stahlhofen's conclusions (5), and have shown that their techniques were not capable of detecting "hot spots" such as we have found at bronchial bifurcations. The other paper cited by Wynder and Hoffmann relative to this question—Casarett's brief review (6)—is chiefly concerned with other effects of radiation on pulmonary tissues, with only passing mention of the carcinogenic possibilities.

Wynder and Hoffmann also failed to mention an experimental study by Yuile and his co-workers (7), who showed that bronchial squamous cell carcinomas developed in rats 2 years or less after a single exposure to polonium aerosol, with cumulative lung doses from 70 to 540 rads. Exposure, in uranium mines, to alpha radiation from radon daughters is now generally accepted as an etiological factor in the genesis of bronchial cancer in miners. In these cases relatively low doses of radiation appear to be significant (8). These studies in miners, as well as the

experimental evidence, support the view that radiation exposure from polonium in cigarette smoke continues to warrant serious consideration as an important carcinogen.

The question at issue is how much any particular component of cigarette smoke can be implicated in the increased incidence of bronchogenic carcinoma in cigarette smokers. We believe that assigning the extent of causation to any particular agent will be difficult indeed. If cigarettes can be made which remove one or more of these suspected components from smoke, many years of very careful evaluation will be required to show whether such removal has had a significant effect on the incidence of bronchial cancer. Identification of the causative agent or agents in cigarette smoke is nevertheless of great importance, in view of the fact that the general public may be exposed to such agents from sources unrelated to cigarette smoking—for example, from general environmental contamination with radionuclides or aromatic hydrocarbons as air pollutants.

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The evidence that polonium-210 plays a role of any importance in tobacco carcinogenesis must still be considered inadequate. Little and Radford's finding (1) that a significantly

higher concentration of  $^{210}\text{Po}$  existed in the bronchial epithelium, and especially in the segmental bifurcations, was not confirmed either by Hill (2) or by Rajewsky and Stahlhofen (3).

In discussing the Little and Radford paper, Holtzman (4) states that the "discrepancies are still not fully resolved either in the light of existing data or regarding some theoretical considerations." Recent studies by Kelly and Homburger (5) have shown no increase in the tumorigenicity of tobacco "tar" on mouse skin, even when the "tar" was supplemented with 1000 times the amount of  $^{210}\text{Po}$  found in freshly prepared "tar." Alpha-emitting radioisotopes were found in both urine and feces, indicating that  $^{210}\text{Po}$  was absorbed, as one would have expected for this and other components of the applied condensate. Stahlhofen calculated that the radiation in "hot spots" reported by Little *et al.* (6) accounts for only 8 rem a year—about 40 to 50 times less than the lowest dose of  $^{210}\text{Po}$  used by Yuile *et al.* (7) to induce one

bronchial squamous carcinoma and three adenomas in 132 rats.

These data led to the conclusion that, at present, it appears unlikely that  $^{210}\text{Po}$ , in the amounts contained in cigarette smoke, plays a role in tobacco carcinogenesis.

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## Subclinical Malnutrition

In their article "Nutrition and learning" Eichenwald and Fry (1) state: "No methods exist to identify and quantitate the biochemical abnormalities of mild, moderate, and severe malnutrition." This statement overlooks recent surveys (2) in which circulating thiamine, biotin, riboflavin, pantothenate, nicotinate, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, folate, vitamin A,  $\beta$ -carotene, ascorbic acid, vitamin E, total cholesterol, and triglycerides were analyzed in 642 10- to 13-year-old New York City school children of Chinese, Puerto Rican, Negro, and Caucasian ancestry. Levels of thiamine, biotin, and ascorbate were markedly below the mean values for the total population in the cases where protein intake was inadequate. Circulating levels of these vitamins may be taken as a practical index of subclinical malnutrition. The results obtained with these methods are in excellent agreement with data derived from studies of clinical states involving vitamin imbalances (3).

Most methods used in these surveys are relatively new (4). They are practical for large-scale nutritional surveys for the detection of clinical as well as subclinical malnutrition. As has been

pointed out (2), evaluation of clinical nutrition without laboratory evidence is a poor indication of nutritional adequacy when overt signs of nutritional deficiencies are absent. "Subclinical malnutrition" poses problems of detection, but it certainly does exist (2, 3). Perhaps malnutrition resulting from multiple deficiencies is an everyday reality even in New York; while remaining clinically unapparent in some children, it may become manifest with age. Further studies are obviously needed.

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In their technical comment on our article, Baker, Frank, and Hutner apparently equate mild, moderate, and severe malnutrition with subclinical malnutrition. We do not agree with this idea; even though some cases of mild and even moderate malnutrition may be characterized as subclinical, severe malnutrition is manifested in overt clinical signs.

The primary emphasis in our article was on the relationships of protein and calorie deficiencies to learning and the biochemical processes of nervous tissue; little emphasis was placed on the relationship of vitamins, cholesterol, and triglycerides to these processes. The references cited by Baker, Frank, and Hutner are indeed valuable for their contribution toward the detection of below-average circulating levels of vitamins, cholesterol, and triglycerides in certain groups of children. These authors related the levels of these substances to either adequate or inadequate dietary protein intake. Our opinion remains that existing laboratory methods have not been sufficiently well established to permit one to distinguish clearly between individuals with mild, moderate, or severe malnutrition. Ratios of urea nitrogen to creatinine (1) and amino acid ratios in serum (2) may prove useful indices of protein intake, but more experience is needed to assess their validity. One of the more recent promising developments, which Baker *et al.* should examine, is the report from Ibadan (3) that changes in transferrin concentration were useful in distinguishing between cases of mild, moderate, and severe protein-calorie malnutrition.

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## Carcinogenicity of Tobacco-Smoke Constituents

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