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Letter to the Editor

A Hypothesis on the Etiology of Malignant Melanoma: the Role of Chemicals Interfering with Melanin Synthesis

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MALIGNANT melanoma is one of the tumors whose incidence has increased most rapidly over recent decades.

The factors associated with this remarkable situation are largely unknown in spite of the efforts put into epidemiological research. A major causative role has been attributed to exposure to the sun and the relation between incidence of melanoma and latitude, ethnic group and modality of exposure has been widely analyzed. No conclusive results have been obtained: solar radiation surely contributes to the etiology of melanoma but now it has been assumed that other carcinogens or co-carcinogens might play some role in the etiology of the disease.

In this paper we want to suggest that increasing melanoma incidence and mortality are likely to be due to the interrelation of sun exposure with chemical pollution of the environment. Furthermore, on the basis of the available evidence, we have identified aromatic compounds interfering with melanocytic activity as being the most likely candidates.

Epidemiological evidence pointing to a possible role of chemicals in the specific induction of melanoma essentially stems from several investigations on mortality and cancer incidence among people working in chemical industries. Two were conducted in Du Pont, the third in the Lawrence Livermore National Laboratory (Alameda County, U.S.A.).

The first paper that we take into consideration [1] is a retrospective cohort study of mortality and cancer incidence among chemists of the Du Pont Company: 3686 white males and 75 white women who were employed between 1964 and 1977. The observed number of cancer cases diagnosed during that time is compared with the estimated expected number based on (a) the experience of non-chemists employed in the same industry as active salaried employees, i.e. 19,262 white males and 673 white women; (b) the Third National Cancer Survey (TNCS) rates.

The data pertaining to the present analysis are summarized in Table 1. From the data, it can be observed that (1) the total incidence of cancer of all sites is 54% of the reference population (TNCS) among chemists; (2) that the incidence of melanoma is 97% of that of "non-chemists" and 2.39 times that of the TNCS population; (3) an excess of melanoma cases (SIR = 223) is observed in the non-chemists themselves as compared with the TNCS population. The data of this research therefore indicate the presence of a factor among the workers of Du Pont, both chemists and non-chemists, and such a factor specifically increases the incidence of melanoma, without affecting the overall incidence of tumors.

The authors suggest that the observed excess risk of melanoma among Du Pont employees could be due to solar radiation. Actually 65% of the Du Pont salaried employees are located in the south-

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Table 1. Epidemiologic evidence on a possible role of chemicals in the etiology of melanoma

Reference	Pell *et al.* [2]	Hoar *et al.* [1]	Austin *et al.* [3]
Study area	U.S.A.	U.S.A.	Alameda and Contra Costa Counties (U.S.A.)
Period	1956–1974	1964–1977	1972–1977
Type of study	Cancer registry	Retrospective cohort	Retrospective cohort
Population	Du Pont Company employees	Du Pont Company male "chemists"	Lawrence Livermore National Laboratory Employees
Person-years			
Male	1,616,457	44,657	23,631
Female	269,497	747	4840
Reference group	Third National Cancer Survey	(2) Third National Cancer Survey (1) Du Pont male "non-chemists"	California Tumor Registry for Alameda and Contra Costa Counties
Melanoma SIR*			
Male	123	(1) 97 (2) 239 (2)§ 223	304
Female	124	†	250
All sites SIR*			
Male	79	(1) 71 (2) 54	
Female	111	†	

*SIR = Standardized incidence ratio = No. observed cases/No. expected cases ×100.
†Because of the small number of cases the authors do not present an analysis of the women's experience
§Non-chemist cohort compared with TNCS population.

eastern U.S.A. where melanoma incidence rates are higher.

Geographic differences in incidence, as reported by Cancer Registries [2], however, cannot completely explain the observed excess risk.

The average incidence rate in south-eastern U.S.A. has been estimated 15.6 per 100,000 for white males (being the incidence of Atlanta Register = 19.6 per 100,000 and that of New Orleans = 11.6) and the average incidence in the northern U.S.A. is equal to 10.8 per 100,000 (New York State = 11.2; Connecticut = 13.4; Detroit = 8.8; Iowa = 9.7).

Therefore only a 45% increase in incidence, at most, may be attributed to the southern localization of the plants while the observed SIR is equal to 2.39.

The data of this research are in agreement with those of a previous investigation also conducted on Du Pont workers [3], although the observed incidence of melanoma was somewhat lower (Table 1). It is worthy of notice that the population examined in this study is substantially different from the previous one, and the average time of employment in the Du Pont plants is surely much lower.

In the study conducted on the employees of Lawrence Livermore National Laboratory (LLNL) [4], a large increase in the cases of melanoma was also noted (Table 1). The reference population was that of the San Francisco Bay Area and was comparable as age, race, sex and geographic location. The LLNL is engaged in nuclear weapons research and development, energy research concerned with magnetic and laser fusion, geothermal energy, coal gasification and biomedical and environmental research. The excess of malignant melanoma seemed to occur only among laboratory employees and not among the surrounding community, which suggest that an occupational factor is responsible. A possible explanation could be a greater health care utilization by the LLNL personnel with respect to the surrounding community. The authors themselves, however, notice that "more access to medical care should not substantially affect the number of cases of any specific type of invasive malignancy in a population in which records are kept of nearly all cases of cancer, but it could result in cases tending to present early" [4].

The data also suggest that the risk of melanoma is not correlated with the monitored radiation exposure. Moreover, in the population of the laboratory no cases of acute lymphocytic or chronic myelocytic leukemia (the types of cancer most often associated with radiation exposure) were observed.

A possible explanation for the observed excess risk of melanoma among employees of the Du Pont Company and LLNL may be occupational exposure to some chemicals.

Unfortunately, experimental data cannot help much in determining the possible agents contribu-

ting to the etiology of melanoma. Chemicals are not routinely tested for melanoma induction, and the experimental animals (albino mouse and rats) generally used in most tests are not suitable for research on melanoma. In experiments conducted using Syrian Golden hamster, DMBA (7,12-dimethylbenzanthracene) has shown a certain specificity in the induction of melanoma [5].

On the other hand, the epidemiological research has thus far indicated only two chemicals as possible causative agents of melanoma: PCBs (polyclorinated biphenyls) [6] and L-dopa [7].

In the study of Bahn *et al.* three cases of melanoma were detected among 72 workers heavily exposed to PCBs and the increase seems highly statistically significant. A retrospective mortality study on individuals occupationally exposed to PCBs [8] failed to show any increase in mortality rate of melanoma. This study shows that at non-toxic concentrations PCBs do not affect significantly the incidence of melanoma. Doubts remain, however, that PCBs at high dose may have a role in the cause of melanoma.

Although it is doubtful, these drugs may be implicated in the increasing trend in the incidence of melanoma. At first glance, they may not seem to be correlated with each other; however, it may be noted that they share two common characteristics: (1) they are aromatic compounds and (2) they interfere with melanin synthesis.

It is well known that the intoxication by PCB produces a blue-gray color of the skin due to the production of abnormal melanins. L-Dopa is a natural substrate of tyrosinase (being the second step in the synthesis of melanin from tyrosine), the enzyme responsible for the synthesis of melanin in the melanocyte. Also DMBA, which is a well-known carcinogen after liver hydroxylation, is likely to be a substrate of tyrosinase. Therefore we want to suggest here that a possible cause of melanoma (possibly working in conjunction with sun exposure) may be the artificial stimulation of the melanocytes with unnatural substrates or with an excess of the natural one.

The selective inhibition of the melanogenesis could also lead to the same result.

The three compounds that we have indicated are surely not responsible for the continuous increase in the incidence of melanoma because they are not sufficiently widespread and their introduction into the environment was much too recent. These compounds may however indicate a class of drugs which may be involved in the process. All aromatic compounds with electron donor groups in the molecule act as substrates of tyrosinase and all aromatic compounds with powerful electron acceptor groups act as competitive inhibitors of the enzyme [9]. At present a great number of compounds which, as such or after the liver hydroxylation have the previously indicated requirements, are being produced by the chemical industries and used as pharmaceutical drugs, pesticides, as well as in cosmetics and industrial processes (*p*-hydroxyanisole, hydroquinone, phenol, paracetamol, gallates, 7-OH-chlorpromazine).

We therefore suggest that the possible role of these agents should be thoroughly investigated by simulating natural conditions (i.e. with an without exposure to the sun) on suitable experimental animals and, when possible, through epidemiological research.

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