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DISCUSSION OF PART II: CHEMICAL CARCINOGENESIS (I)

Leonard Chiazze, *Moderator*

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DR. RODOLFO SARACCI (*Italian National Research Council, University of Pisa, Pisa, Italy*): I want to underline some general features of this session's papers, three of which stand out. First, chlorinated organic compounds have been known for a long time, as have their pharmacological and toxicological properties and effects. Classical compounds that one can mention are chloroform and carbon tetrachloride. However, members of this broad family of compounds recently have been shown to have a series of disturbing properties, among which are oncogenic, teratogenic, and embryogenic characteristics and action on genetic material, all of which were discussed in this session.

Second, studies like those presented this morning on humans are not only useful for identifying and quantitating risk loads but also in elucidating the actual paths of correlation among the different properties, such as oncogenesis, teratogenesis, mutagenesis, and embryogenesis. This same ensemble of properties is something that was underlined yesterday as being characteristics for short-term predictive tests. Today's epidemiological studies have beautifully shown the correlation between animal bioassay and human epidemiological findings.

Third, a rather broad spectrum of methodological approaches has been shown, ranging from animal studies to clinical case reports, formal epidemiological studies, evaluation of screening programs, and to evaluation of dose-response curves, both in animals and in humans.

The first paper, by Mr. Waxweiler and his colleagues, extended what can already be considered classic results, of cancer in workers exposed to vinyl chloride. It went further in classically documenting for the first time the parallel between the multiple-site oncogenicity found in animals and that found in humans exposed to vinyl chloride.

It was mentioned that in the factories studied, there was, of course, a mixture of compounds. In particular, vinylidene chloride was mentioned. Do the investigators have some information on other chemicals used, and were these compounds taken into account in the analyses or are investigations planned on these aspects?

I noticed that there was a deficit in cirrhosis of the liver. In view of the fact that the liver is the first target organ for vinyl chloride, could the deficit of liver cirrhosis be a function of the expectation being spuriously high because of the use of general population vital statistics?

Finally, I think that the way the data were presented doesn't tell the entire story. The data are presented in a cumulative form. That is, analyses of workers who had 10 or more years since onset of exposure and then of workers with 15 or more years since first vinyl chloride exposure really is analysis of a subgroup of the first group.

I especially enjoyed the paper by Dr. Infante, because he has moved success-

fully ahead in the same direction as we are moving with a similar study in the Tuscany region in Italy. I have, therefore, a few questions to ask him. Were environmental measurements done, and if they were measured, what pollutant mixtures were present? Also, I find the part related to congenital malformation more well founded than the part related to tumors. The part related to tumors is essentially based on current rates without taking migration into account. Because the study communities are small communities, migration may be important.

Dr. Corbett first reviewed the epidemiological studies of mutagenic, teratogenic, and oncogenic effects associated with anesthetic gases and then presented a new animal inhalation study of cancer following isoflurane administration. I would like to ask Dr. Corbett—why was this particular kind of experimental design used with administration of the anesthetic both antenatally and postnatally?

Next, Dr. Sakabe presented some interesting results; however, he unfortunately attached to them some p value that I didn't expect to appear. I think that the distinction between epidemiologic and clinical studies is, in a sense, just a matter of convenience. In another sense, it may be very misleading. I think that there are good studies and less good studies which stand on solid or less solid foundations. I would have preferred not having any statistics on that group of cases; rather, I would have preferred to have firm diagnoses. Of four cancer cases, there are two cases in which there are no histological findings. While I recognize the value of small studies, such as the original case reports of angiosarcoma among workers exposed to vinyl chloride and leukemia and past benzene exposure, I don't think one should prematurely force statistical interpretation to case reports.

The next paper, by Mr. Lemen and his colleagues, demonstrated a variety of statistical methods, from the case control study of sputum to the retrospective cohort study of cancer incidence. My only question is—do they plan to do a follow-up of the workers in order to see the effect of the sputum screening program?

In Dr. Nelson's presentation, I most appreciated the study of dose-response effects in humans. However, as he talked about speculative exposure and exposure score, I was hoping that he would expand a bit more on those points, because they are critical inputs to his study.

Finally, I entirely agree with what Dr. Lloyd said about the character of the data he presented so well, although he was called in at the very last minute to do so. I would emphasize the point he made about averages, that is, the need for more data related to the exposed population, not only to the cases. I would go a bit further than that. I'm always in a very difficult position when I have to evaluate what average age of the event means. It can come out in such a different combination of ways if one takes the pain of going back to the data. I frankly would prefer to have the distributions and then work out the proper statistics myself.

DR. HENRY FALK (*Center for Disease Control, Atlanta, Ga.*): Mr. Waxweiler began the morning session by presenting the results of a NIOSH mortality study at four vinyl chloride plants. As part of that study, in addition to the statistical data and death certificate information, we at NIOSH-CDC have been collecting medical record information and pathology specimens where indicated.

The finding of a statistically significant increased risk of lung cancer in the

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cohort was presented, but I think it is important to discuss this information more fully, to place it in the appropriate context.

The cohort study involved four plants. In three of them, only vinyl chloride (VC) workers were studied, although included in this group are polymerization workers and workers whose jobs would have brought them into the polymerization area on a regular basis; in one plant, compounding workers were also included. In the fourth plant, because of the high incidence of angiosarcoma previously seen, everybody, including nonvinyl chloride workers, such as those in synthetic rubber production, was assessed for input into the pathology study.

The total number of lung cancer cases observed was 47. Of these cases, 12 met the criteria of the cohort study, which were 5 years of exposure in a VC work area and 10 years of latency. Of the remaining 35 cases, 20 were VC workers with duration of employment or latency insufficient to meet the cohort study criteria, and 15 cases were among workers who had no direct VC exposure.

Pathology specimens have been obtained and reviewed at this point on 22 of the 47 cases. These 22 cases include eight of 12 in the VC cohort discussed by Mr. Waxweiler, seven of 15 nondirect VC workers, and seven of 20 VC workers not eligible for the cohort.

The 22 specimens were reviewed by Dr. Louis Thomas and Dr. Tad Powell of the National Cancer Institute, by Dr. Laslo Mock of Louisville, and by Dr. Marvin Kuschner of the State University of New York by use of the World Health Organization classification system of Kreyberg.

Of these 22, two were considered to be epidermoid carcinoma of the lung, three were small-cell anaplastic, six were adenocarcinoma, and 10 were large-cell undifferentiated, with one not classified. This distribution is virtually the reverse of that which was expected. Generally, epidermoids would be the most common, and large-cell undifferentiated cancers would generally be about 10% of the total in most series.

All 10 VC workers with more than one year of exposure had either adeno- or large-cell undifferentiated carcinoma. Most of the epidermoid and small-cell carcinomas were in workers with less than one year of VC exposure at the plants. Interestingly, five of the seven workers who had no direct VC exposure also had adeno- and large-cell undifferentiated carcinomas.

Next, consideration of the total time worked at the plant, regardless of exposure, shows very strikingly that all of the epidermoid and small-cell carcinomas were seen in short-term workers, whereas all 13 workers with more than one year at the plants had large-cell or adenocarcinoma.

The pathology to date suggests a strikingly unusual distribution of the histologic types. However, there still are several questions about these data. First, we obviously must complete the sample to eliminate the possibility of bias. We are currently putting together a control group of matched lung cancers in the four areas.

Next, although large-cell undifferentiated types do not correlate with smoking history, I think we obviously need more epidemiologic information on these cases, including exposure at plants other than the VC plants for people who left and worked elsewhere.

This is a very different distribution in terms of work exposure than we have seen in the angiosarcoma cases. In the angiosarcoma, all cases worked in polymerization areas at these plants. We've seen here, in these adenocarcinomas and large-cell carcinomas, a mixture of work exposure at the plants. We have

cases who have worked in the polymerization area. We also have cases who have worked in milling and packing areas, where VC exposure would be much lower. We have a few cases who worked in synthetic rubber production at these plants, where their exposure might be to other chemicals, such as vinyl cyanide. We also have a few individuals who worked at different parts of the plant, such as an electrician, a pipefitter, a guard, and a mechanic. I therefore think the specific relationship of these excessive cases of undifferentiated and adenocarcinomas of the lung is not yet really clear in terms of etiologic factors.

Having raised the question of complex chemical exposures, I would also like to stress that very little is known of the possibility that other vinyl compounds, for example, vinyl cyanide, vinylidene chloride, and vinyl alcohol, may enhance or accelerate the carcinogenic risks of VC. Virtually all of the American polymerization plants with cases of hepatic angiosarcoma have used other vinyl compounds. Detailed exposure data will have to be kept for all cases to document and study these interactions. I think that this point applies equally well to chloroprene. In preliminary discussions at that plant when this question first arose, it was learned that vinyl cyanide, vinyl fluoride, and other fluorinated hydrocarbons have been in use, and this says nothing of the possibility that trace amounts of VC might be released during production and polymerization of chlorobutadiene.

MR. R. J. WAXWEILER: Let me first answer the question raised as to whether vinylidene chloride was accounted for. It was not accounted for, insofar as we couldn't identify those who had been exposed to vinylidene chloride and those who had not been exposed to it. Some of the products that are made at some of these plants under study are vinylidene chloride, vinyl acetate, dibetal maliate, hydrogen betalmalate, methyl acrylates, styrene, acrylonitrile, and isoprene. At one point, Dr. Falk brought up the point that a lot of these chemicals haven't been tested for carcinogenicity. While this statement is true, it is difficult to evoke any etiology other than vinyl chloride for this excess of multisite oncogenesis, in light of the close similarity between the NIOSH epidemiologic observation and the findings previously demonstrated in animals by Dr. Maltoni. In answer to the second question, about cirrhosis, we often find deficits of cirrhosis of the liver during our occupational health studies. These cases can be directly related to alcoholism programs or screening physicals given by management prior to hiring.

In answer to the last question, latency was presented as it was because beyond 20 years of latency, the person-years were too small in the categories to permit any sound judgment.

DR. C. MALTONI: I was very interested to hear Mr. Waxweiler and Dr. Falk state that the feature of pulmonary tumor in the VC workers is quite peculiar, at least its distribution. I think that when 10 of 20 lung cancers are large-cell carcinomas, this figure is quite an abnormal distribution as compared with what one usually sees in pathologic laboratories. I would like to ask these two colleagues if they would provide some further detail. Are the tumors squamous-type large cell or are they of the large-cell adenocarcinoma type? When, in 1969, we looked at the sputum of people exposed to VC, we were quite impressed by the fact that, microscopically, we found cells of this aplastic type, which we had never seen with such a high frequency in any other group, never in heavy smokers or in the general population. I therefore think that this finding is quite interesting, because it matched very well with the different distribution of tumors shown by NIOSH-CDC. I would also add that little is known about

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DR. P. F. INFAN toring of environme small amount of prel

vinyl acetate. In 1970 we started an experiment on animals exposed to 10,000 ppm of vinyl acetate. At that dose, all hamsters died in a few weeks. The compound was quite toxic. Subsequently, we lowered our dose to 2500 ppm, and we succeeded in getting a few animals to survive for 20 months. In this group of 96 rats, although very few were alive after 600 days, we did not observe any tumors. However, since their survival rate was so poor, we are now repeating this experiment at a 100 ppm level.

DR. E. P. RADFORD: In the studies done by Monson *et al.* of VC workers in Louisville, I am told that the mortality statistics, based on mortality rates rather than on proportional mortality, are remarkably similar to those reported by NIOSH. The fact that there is such close agreement is, of course, not too surprising, because the Louisville plant was included in the NIOSH study. One discrepancy between the two studies is the fact that digestive cancers were found in excess by Monson *et al.* but not by NIOSH. Mr. Waxweiler, would you comment on this point?

MR. WAXWEILER: The study by Monson *et al.* included everyone in the Louisville plant, with no breakdown as to whether they were rubber workers or VC workers, and that plant does have a large rubber facility. Now, if one looks at the study by McMichael *et al.* of rubber workers, one finds an excess of digestive system tumors. The excess of digestive tract cancers in the Monson *et al.* study, therefore, would appear to be related to exposure of the rubber workers and not to VC exposure.

DR. A. ENGLUND (*The Swedish Confederation of Trade Unions, Stockholm, Sweden*): It might be of interest for you to know that we are also following a cohort of VC polymerization workers at one company in Sweden; this study started just after World War II. Approximately 800 persons have been employed at the firm since the study was initiated. However, only a few of them began to work there more than 20 years ago. Slightly more than 50 people have so far died in the cohort. We have not completed the study yet, but there are a few important experiences worth describing.

First, it has been very difficult to assign people to different exposure levels, because the workers move around quite a lot, and the exposure level changes a great deal all the time. In addition, no nice exposure levels exist for a dose-response study.

Second, with regard to effect, although there have been many pancreatic cancers in the group, liver tumors have been surprisingly infrequent. We feel that it is rather difficult to know exactly what is a liver tumor and what is a pancreatic tumor when talking in terms of this kind of statistics. Also, we are using for our analyses the National Bureau of Statistics death certificate diagnosis. We have, however, separately, quite separately, matched our findings against the cancer register, which covers the whole country since 1958.

Obviously, there are difficulties in diagnoses. For example, one of the pancreatic cancers has now been classified as angiosarcoma of the liver, as shown by the cancer registry records.

We have not, as far as I know, seen any excess in cerebral tumors, which has been mentioned by NIOSH. On the other hand, we are a bit curious about circulatory diseases because of reports that show VC to be associated with cardiac arrhythmias.

DR. P. F. INFANTE: Dr. Saracci asked whether there has been any monitoring of environmental pollution in those areas. To my knowledge, only a small amount of preliminary monitoring was done for VC in Painesville. As I

understand it, this monitoring was done well over a year ago, and monitoring techniques have been modified since that time. Perhaps they may want to monitor again, if we feel that the birth defects may possibly be related to VC. But, again, this was a population study, and I have made these observations, although we don't yet know what aspect of environmental exposure these birth defects are related to. I think that there are two factors to consider. One factor is out-plant VC pollution associated with these observations. If this factor has an effect, you certainly wouldn't expect it to have shown up in the experience in North Ridgeville, because that community is about eight or 10 miles from the Avon Lake VC facility, so the findings would have to be related to worker experience. However, in Painesville, there is a greater possibility that this factor is important, because this town has two VC plants. The community also had a significantly greater number of central nervous system anomalies in live and stillborn infants; central nervous system (CNS) cancers in adults were also much greater than expected. The second factor, with regard to migration, is that there were no CNS cancers in Avon Lake, where the population has increased 30% in the last 10 years, so there was quite an in-migration. And I think it would probably take a while for anything to show up environmentally. In Painesville, however, the population has been stable over the past 10–20 years, the period during which the brain cancers were observed.

DR. MURIEL L. NEWHOUSE (*London School of Hygiene and Tropical Medicine, London, England*): Dr. Infante, do you have any information on neural defects in earlier years and by geographic area, because these defects do have a very odd geographic distribution, which is not always easily explained?

DR. INFANTE: At the present time, I have just looked at the last four years in those specific areas and have just completed these analyses in the last week, but I am planning to go back to 1957. I have data available but haven't looked at them yet.

DR. T. CORBETT: I'd like to respond to the question raised by Dr. Saracci. He asked why we used the transplacental route for exposures in our study. We did this for two reasons. First, the fetus is usually considered to be more sensitive than the adult toward the action of a carcinogen. Second, it is a faster determination. Usually, you will see a spectrum of tumors earlier by this route than if you had gassed adult animals. We felt a sense of urgency in testing this particular drug, because it is undergoing human clinical trials at present and is being considered by the Federal Drug Administration for use in the general population. If it is carcinogenic, we wanted to find out prior to its release.

MR. R. A. LEMEN: One point that might further complement the studies presented this morning relates to some work recently completed by Dr. Frost and his colleagues at Johns Hopkins University. These investigators undertook a cytology program among three groups: utility, asbestos, and chemical workers. The latter group was identified as being possibly exposed to bis(chloromethyl)ether. The first screening identified a very definite dose-response effect for cytologic findings. Four weeks later, they did a repeat cytologic examination for all individuals who had nonnegative cytology on the first screening, and the results were 13% nonnegative cytologic findings in utility workers, 30% in asbestos workers, and 58% in the bis(chloromethyl)ether (BCME) workers, of which three frank malignancies were detected by the program. These cytologic findings certainly complement those presented this morning by NIOSH.

DR. WILLIAM WEISS (*Hahnemann Medical College, Philadelphia, Pa.*): Mr. Lemen referred to a study in Philadelphia on workers exposed to chloro-

methyl methylether. Our report in 1973 was rather skimpy. We have more details now, and I would like to mention two additional observations. At the end of 1962, we began a prospective study of 125 chemical workers, of whom 88 were exposed in some degree to chloromethyl methylether. Of the 88 workers, 49 had moderate to heavy exposure. During the first 5 years, we did periodic screening with x rays and symptom questionnaires. The questionnaires show, like some of the animal work reported by the New York University group, that there is a dose-response relationship for chronic bronchitis symptoms, chronic cough, and expectoration. In addition, we looked at smoking histories. Of the workers, 49 were exposed either moderately or heavily to chloromethyl methylether. Thirteen of these men were either nonsmokers or noncigarette smokers when we began this prospective study in December 1962. The remaining 36 were current smokers; most of them were light smokers, less than one pack per day. During the next 10 years, 11 lung cancers, all oat cell carcinomas, occurred among the total group of 88 workers.

First, the lung cancers all occurred among the moderately and heavily exposed workers. Second, six of them occurred in the 13 nonsmokers and noncigarette smokers. A more detailed breakdown shows three of eight nonsmokers, one of two pure cigar and pipe smokers, and two of three ex-cigarette smokers. We thus are comparing a 10-year lung cancer incidence of 46% among nonsmokers and noncigarette smokers against a 14% incidence among cigarette smokers who were current smokers when the observations began. These observations do not look anything like those seen among asbestos or uranium workers.

DR. V. K. ROWE (*Dow Chemical Co., Midland, Mich.*): It might be of interest to extend the information that Dr. Nelson gave on bis(chloromethyl)-ether. We have just finished a study that extended the work done in his laboratory, and this information was reported 2 weeks ago at the Society of Toxicology. In this study, we found that practically 100% of our rats exposed to 100 parts/10^9, the same concentration that Dr. Nelson's group used, had nasal cancers that invaded mostly into the cranium. We were very surprised to find that there were no tumors of this nature or others beyond the background when ~~10~~ animals were exposed for 6 months and then kept for their lifetime. These results (at 10 parts/10^9 or 1 part/10^9) indicate a very distinct dose-response relationship that seems to fit the experience even in people.

DR. E. FARBER: Dr. Nelson, it's always comforting if the experimental data fit more or less the human experience. I think this is true certainly in terms of the tumor patterns. One outstanding exception this morning is BCME, which seems to give a very striking incidence of bronchogenic carcinoma, and yet, as far as I know, this incidence has not been observed in rats. Is it true that one never sees oat cell carcinoma in a rat, only squamous or mixed? This point is not trivial because, as I'm sure you're well aware, there is a very urgent need for an animal model. Of course, one possibility is that the cell of origin in the human probably is not the epithelial lining cell but some special cell, perhaps a sclera cell. We don't know whether that cell exists in the rat, which may be the reason for the discrepancy. Do you have any comments on this point?

DR. N. NELSON: As a nonpathologist, I have a simple-minded approach to this point, which I guess comes down to the following. If the tumor is bronchogenic in origin, it's helpful to have that information. To expect direct mimicking of the precise pathogenesis is asking too much. I felt that the warning from the mouse adenoma was significant—not as significant as a bronchogenic cancer,

not nearly as significant, but still significant. If it had been oat cell in origin, it would have been even more significant, but I think we're quibbling over straws.

With respect to Dr. Rowe's statement, I would be very cautious in assuming that this dose-response result obtained by Dr. Leong reveals a very sharp decrease in incidence rates with the dropping from 100 to 1 ppm. These compounds are direct-acting carcinogenic agents. I am sure that you will see at least trace contamination with DNA. Therefore, to be practical, we should be very concerned about not assuming that this represents a sharp threshold.

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