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Chapter 20

PANEL DISCUSSION - SECTION 4

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- GASIEWICZ: A very intriguing talk, Dr. Matsumura. But I have a couple of questions. First of all, do compounds other than TCDD, that decrease the concentration of EGF receptors, have the same type of toxicity as TCDD?
- MATSUMURA: They don't.
- GASIEWICZ: So a decrease in concentrations of EGF receptors clearly does not, by itself, explain the differences in toxicity. The second question is: Did you do pair-fed control animals in your studies?
- MATSUMURA: Yes, we did. There's no effect of pair-feeding. As to your comment, I hope I have made it very clear that we cannot say that the toxicity is directly related to EGF.
- GASIEWICZ: The third question is: At what doses did you get decreases in EGF receptor concentrations and how are these related to lethal concentrations?
- MATSUMURA: We have found the effect in the hamster at dose concentration ranges starting at 100 micrograms per kilogram, which is low compared to the lethal dose. However, toxic symptoms can certainly be observed; you can start seeing the changes in the liver and all that.
- CROSBY: I have a question for Dr. Suskind. I wonder if you could briefly outline the possible treatments available for chloracne, including skin grafting?
- SUSKIND: The treatment of chloracne, to begin with, has to be differentiated from the treatment of acne vulgaris. Most of the traditional medications and the modalities used for acne vulgaris are really contraindicated in chloracne except for the retinoic acid derivatives. This includes the kerolytic agents like salicylic acid, resorcin, and especially ultra violet light. The other modalities, which years ago we used in acne, were superficial radiation, that is, ionizing radiation (x-ray) and this also caused hyperpigmentation and didn't cause improvement of the chloracne. In the last ten years, however, the emergence of retinoic acid, and especially the cis-retinoic acid (Isotretinon) which is marketed as Accutane, has in some instances been very

beneficial. And it's interesting what effect retinoic acid has on the cell. It inhibits sebaceous gland function and keratinization. It affects the rapidity with which the squamous cell becomes keratinized. There have been, for example, outbreaks of chloracne from chlorinated azoxybenzene, and in these instances, topical retinoic acid has been very useful. I think that's all we really have to offer at the moment. I must say that in the group we recently examined, we were epidemiologists, not therapists, so we had no way to offer therapeutic modalities. But, I would think that if a good therapeutic study were done, it could be done on a population like this.

YOUNG: Dr. Suskind, in terms of the exposure time on the individuals that you reported, specifically on the 204 that did develop chloracne, am I to understand that once they developed it they were not continually exposed; or were they, in fact, in the plant where they continued to work for many years and where they could have continued to have a low level of exposure?

SUSKIND: The exposure period in the exposed group varied anywhere from one month or less to 15 years and more.

YOUNG: So when we say that the chloracne has persisted over 30 years, we've got to be careful to bring that in, then, is that right? I guess I'm concerned that some people have been saying, once you've had this acute exposure, you may show chloracne for 30 years, and I'm not sure that's what your data are telling us.

SUSKIND: What I'm saying is that in this group in which we have not been able to identify or quantitate actual levels of exposure, we do not know how much dioxin any one of these individuals was exposed to. We may know a little bit about duration of exposure, but even then the amount of dioxin to which a worker would have been exposed from 1949 to 1953 was very different than for the group which initially was exposed in 1960, because the hygienic conditions were very different. As a matter of fact, the building in which the accident occurred was ostensibly cleaned up, but acne was still occurring in new assignees who were getting into the building and working there. So they destroyed the building, and built new ones; first one to make trichlorophenol and another one to acidify it and make the 2,4,5-T, and finally they built a third building which incorporated both the synthesis of trichlorophenol and the synthesis of 2,4,5-T. The hygiene in that third building was superior to the initial one so that the degree of exposure was very different in different areas during that period from 1948 to 1969.

YOUNG: One last question. Recently the Mt. Sinai group, Dr. Singer specifically, published an article relating to part of the same population you studied, and discussed the issue of nerve conduction and potential damage from exposure. Would you care to comment on this?

SUSKIND: Well, my only comment is, that if you take seriously the expertise of those who know most about nerve conduction, nerve conduction velocity measurements have to be made under extremely controlled conditions. It's not a field measurement. It has to be done under controlled conditions of temperature, of humidity, and

the application of the electrode to the skin has to be uniform. The individual who does it has to be very expert at it and in the view of such experts as Schaumburg and Spencer, it does not provide a method to detect, for example, changes that you could not really detect by a good thorough neurological examination.

YOUNG:

Dr. Merlo, I noted that in Seveso there were reports of changes in nerve conductivity. Would you care to comment on that?

MERLO:

There were many doubts about the quality of those data. The International Scientific Advisory Committee (a group of scientists in charge of supervising and reviewing the Seveso research) was particularly critical about the control group the investigators chose. From these studies we cannot draw strong conclusions but also we can't reject a possible cause-effect relationship. Some subclinical effects (changes in nerve conduction) were detected more frequently among TCDD exposed people when compared with the control, thus, we can't keep our eyes closed.

SUSKIND:

We tried to get the best help that we could and we got the assistance of the NIOSH group that had probably the most up-to-date equipment and really the most experienced technical people, particularly Mr. Boyd. He was with us at the time and, from our results, we didn't find any differences, remembering that all of these have to be age-corrected. In addition, you have to eliminate your diabetics; you have to eliminate your alcoholics; and you have to eliminate all those in which neuropathy is possible. We did all of these things and we found no differences.

GILMAN:

Dr. Merlo, there's been a lot of confusion, I think, over the adverse pregnancy outcome issue from TCDD exposure. The situation in Seveso is a little cloudy. I'm wondering whether or not you can make any comments on more up-to-date findings. What about stillbirths, spontaneous abortions, congenital anomalies?

MERLO:

A Birth Defects Registry was set up in late 1978. Actually, final data are available and the statistical analysis has shown that hemangiomas are the only abnormalities that have reached statistical significance. About the occurrence of spontaneous abortion in this area, one can find information and evaluation in an Italian scientific journal (these data were never published in an international journal). A significant increase in abortion rate has been observed in 1977 in the A and B areas (the more contaminated by TCDD), and not in the less polluted zones (R and outer). Some people are actually working to investigate whether or not the observed increase in abortion rates may be related to psychological problems rather than to an embryotoxic effects. It is my opinion that the higher frequency of spontaneous abortion has been the consequence of a direct toxic effect of TCDD on the embryo.

BERNARD:

I think that dioxin provides the scientific community, and perhaps society as a whole, with really a unique opportunity to study some of the basic problems that exist in the relationship between science, congressional action, and regulatory action. I know that in my work I am faced many times with regulatory activity occurring based on a paucity of data. I think what we've heard

today is quite a bit of animal evidence as to what dioxin does, but I haven't heard, really anything that indicates that over the past 30 years a real problem exists with dioxin with regard to humans. We know 30 years ago we had chloracne problems. We have indications that on high acute exposures, we have liver problems. But after extensive expenditures and very careful studies we still have no evidence that a problem exists, much less are we able to quantify the risk that does exist; yet we are moving ahead. One estimate is that we are talking about spending up to five billion dollars to deal with a problem in Missouri. I think this is an extremely good example where regulatory activity and congressional activity have so leaped beyond any scientific basis that it behooves us to look at that very carefully. One question that I do have for the panel is: We obviously have a number of instances where humans have been acutely exposed to extremely high levels of dioxin, and yet we have no evidence that that has caused any long-term harm. How could one relate those acute high level exposures to possible chronic, very low-level exposures of living in a place such as Times Beach?

MATSUMURA:

Dr. Smuckler, would you like to answer that?

SMUCKLER:

You can't and the reason you can't is that there is a remarkable reserve on the part of the human body. You think how we, as a group, abuse ourselves, yet we respond and live 70 years without any problem; how we can be subject to mutilating surgical procedures and still survive. A single episode with the healing capacity of the human body provides us with evidence of that great reserve. Let me also second what you've said. We have had a number of examples in which the inability of our government as well as ourselves to handle hazardous problems leads me to some concern. In 1961 we attempted to have carbon tetrachloride removed from household fire extinguishers. There, we had plenty of human data. We didn't need rats to turn up their feet to heaven. We had humans that did it. The allied chemical industries were intransigent. They thought this was the most absurd thing they'd ever heard even though they admitted that it was a problem. Fortunately, we were able to remove the material. On the other hand, the evidence that Red Dye #2 had ever produced any disease in human beings is interesting. It was introduced into our own food chains shortly before World War I, and in the late '60s the average human being in the United States consumed 18 milligrams a day. Yet you don't find any red M&M's any more, do you? The problem is one that we've addressed here in part, and I think the difficulty is that our concept of injury is archaic, our understanding of injury is miniscule, and in large part, we have not expended the energy we should in attempting to understand interactions of chemicals with cells. We've done a better job with viruses and even there we don't know what's happening. We have no idea what the cell origin of a cancer is and need only ask: Is it monoclonal or polyclonal? - and you'll get into a family argument. We don't know what an acute effect is. As Dick Recknagle pointed out, until we can understand how a simple, symmetrical, saturated haloalkane like carbon tetrachloride can kill a liver cell, how can we expect something as complex as TCDD to become manifest?

McCONNELL:

I would like to respond to that and take a little bit different tack.

I would agree that it's hard to compare a Nitro, West Virginia, or an acute exposure in an animal to a Times Beach situation because the former are single exposures. I think people may or may not have been exposed in Times Beach, but if they were exposed, they were exposed chronically. Now, how do you compare that? We have shown in animals that chronic low-level exposures in several species of animals appear to be more potent than a single equivalent dose. In other words, it takes less of the TCDD, spread out over a period of time to produce a given effect than it does in a single exposure; just the opposite of what occurs with many, many chemicals. So, I am not sure that following the Nitro group in a negative sense will be able to predict anything in terms of a chronic exposure. If I did find something in a Nitro group, I certainly would look for it in the Times Beach people, but I might expect to find something different in the Times Beach exposed population.

McCloughlin

BERNARD:

I guess what I was saying is that all of the lectures presented today indicate that if there is a problem, it certainly is one we've had great difficulty identifying in humans. And if this is the case, how is the scientific community going to get across to the lay public, and perhaps more importantly to the regulatory agencies, that we are spending such vast sums of money on a problem which we are not sure really exists?

SUSKIND:

May I answer the comment made by the last speaker. I'm not altogether sure I heard him correctly, that you couldn't draw some conclusions about chronic exposure from a group of humans, many of whom were exposed for 15 to 20 years. These were not people who were exposed once. This was not an LD50 experiment. This was a regular plant operation in which people were exposed continuously for as long as 15 or 20 years or as short as a month or a week, and I think that you can learn a great deal from it.

BERNARD:

I think you can, too, but what I'm saying is: Those who were exposed for a week or a month, and there were significant numbers of those, were the people who were exposed to the highest levels. Correct?

SUSKIND:

I think that if they were exposed - let's say from 1965 to 1969 - their exposure levels were not nearly as high as those people who were exposed in 1948 and 1949, so that their dose levels were different.

BERNARD:

What I'm saying, though, is if you find something in that group, that certainly is something pertinent to look for in a group somewhere else. However, I would not be entirely surprised if I found something in another group that was chronically exposed that you did not observe.

SUSKIND:

Yes, but from the standpoint of biological information, you have a whole range of exposures in that relatively small population: 204. Incidentally, that represents about 60% of the estimated people who were exposed, not the whole population, and even that is a kind of a bias, epidemiologically, but that's the best we could do. I think that one does learn a great deal from this group, a small group with a wide range of exposure, which is even applicable to the Times Beach population in which the bioavailability of the

dioxin is very limited.

YOUNG: I'd like to ask just one very short question for Gene McConnell. In the literature, we see a reference to one particular animal study that came up with some soft tissue sarcomas. Would you care to comment on that particular study?

McCONNELL: The animal study that came up with the soft tissue sarcomas? I question that study as to whether those are real or not. However, I do feel that the liver tumors are real.

YOUNG: I'm referring to the work of Van Miller. That study is being cited a great deal to show that soft tissue sarcomas have occurred in an exposed animal population; therefore, one should expect to see them in exposed humans.

McCONNELL: No, I agree with you. There's a lot of other questionable literature. For example, I have referenced studies for many years that said that all that weight loss in dioxin-intoxicated animals is due to something other than not eating. I think it's now clear that a majority of the weight loss is due to not eating or not drinking. There are other examples of misleading literature, but this is not unique to this subject.

MATSUMURA: I hate to terminate such interesting discussions, but time is up, and I'd like to thank you all very much.

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