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Human Effects of TCDD Exposure

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The Vietnam situation and the exposure of servicemen to the herbicide Agent Orange presented the Veterans Administration with a series of problems and questions that the agency had not encountered before. Since about 1978, the VA has undertaken a variety of programs prompted by the Vietnam conflict and herbicide exposure. Beyond the VA's programs, a number of related efforts are going on in the world about which one will want to know. Most of them have not been completed. We shall review them very briefly, but first there are certain differences among these various studies of which one must be cognizant.

In the first place, it is literally impossible to determine quantitatively the extent of herbicide-related exposure in any human study that is being conducted at present. It sometimes is possible to divide a population into groups with a high likelihood exposure, a low likelihood, and occasionally into even slightly finer divisions, but these divisions are not truly quantitative. The VA, therefore, is conducting a number of studies to determine the effects of the military experience in Vietnam partly on the assumption that military experience in Vietnam entailed exposure to Agent Orange which contained on the average about 2 parts per million of TCDD.

Other studies being undertaken, particularly by the Centers for Disease Control, will attempt to determine exposure to Agent Orange in the field. We do not know whether it is possible to do that, but it will be attempted in most of the studies that deal with the Vietnam experience. One must distinguish clearly between any attempt to study the effects of exposure to Agent Orange, and therefore TCDD, and an investigation to evaluate the effects of the military experience as a whole. In fact, it is possible to define only one population where we are certain of exposure to Agent Orange. That population is the Ranch Hand group being studied by the Air Force.

When we want to examine the results of exposure to TCDD apart from the other ingredients in Agent Orange, we have to go to industrial situations where TCDD has been generated in an industrial process

and is delivered, if not in pure form, at least in a fairly high concentration to that population. The VA has no such population available to it, but they are present around the world.

The Congress at the present time is considering compensation of veterans for certain conditions. I shall not discuss questions of compensation that are the responsibility of an entirely different subdivision of the VA. When such legislation is being considered, however, we are expected to advise Congress on what compensation should be established on "presumptive bases" without definite knowledge that exposure occurred or that any particular defect is due to exposure to Agent Orange.

For a scientist, this is an unsatisfactory situation. We have tried to convince Congress and others that it is important to come to some medical and scientific consensus as to whether exposure results in a particular effect before Congress considers compensation for it. As I am sure you know, there is no clear-cut way to arrive at a medical consensus even though a number of techniques have been tried. Basically, they all require that sufficient numbers of statistically significant and relevant data are available, that these data and the methods of obtaining them withstand peer review, and finally, that the results are duplicated. We do not want universal agreement. We are seeking only a consensus in the medical and scientific community that these effects can be attributed to TCDD, or to Agent Orange, in our instance.

The veterans themselves have reported a wide variety of effects. Many have recounted symptoms that occurred in Vietnam and, therefore, were presumably acute. In general, the acute effects they report, as well as the acute effects from other toxic agents, are more or less generalized: malaise, headache, nausea, sometimes diarrhea, or respiratory responses if it is an inhaled toxin. All of these have been reported by veterans. It is impossible for us to verify them now since they occurred more than 10 years ago. Some veterans complain of neurological problems. Some suggest that they have had liver problems as well.

Other reported reactions have not been discussed in this conference, but ought to be mentioned, namely, the reproductive effects. Some veterans have complained of sterility and impotence as well as miscarriages, abortions and birth defects, some of which occurred to their wives shortly after their husbands came back from Vietnam; they might be considered acute effects. More commonly, however, the veterans complain of chronic effects that have persisted from the time they left Vietnam. These also have varied. Leading the list a few months ago were probably birth defects and miscarriages. The complaints are less frequent now, in part because of some research results that are being reported.

The possibility of the development of cancers, including soft tissue sarcomas, is very much on the minds of the veterans. Many are afraid

that their lives are going to be shortened, that they will have a shorter life expectancy than they would otherwise.

There have been complaints and still are complaints of chloracne, a skin eruption, none of which has been verified as being present at the time of examination. Some veterans complain of porphyria cutanea tarda, either at present or during the time since they left Vietnam. Some have complained simply that they have dioxin in their tissues and it presents a threat to their future health. It has been said by some people, including at least one from St. Louis, that this constitutes a time bomb, that if they ever lose weight the dioxin will be released in the body and intoxicate them.

We are dealing here with questions of toxicity which have not been common in the past. Veterans are complaining of delayed toxic effects, where the individual has had no symptomatology, nothing wrong, for 10, 15 or even 20 years after exposure and then suddenly develops difficulties.

Interest in the delayed effects centers primarily on birth defects and cancer. A number of studies completed and underway at present are attempting to define any possible risk of birth defects or reproductive failures. Four studies have been completed, including one reported this year in Australia and one conducted in Arkansas for the EPA. One was done in Arkansas by EPA. The Australian study is a Vietnam experience study of veterans. They did not evaluate the exposure to Agent Orange or to TCDD. A New Zealand applicator study, a the National Institute of Occupational Safety and Health study in New York and the Arkansas study all deal with exposure to herbicides, primarily 2,4,5-T, which probably contains TCDD. All of the completed studies found no increased risk of reproductive failure.

Prior to the completion of those studies, two others were initiated. One is being conducted by the Centers for Disease Control (CDC) with support from the VA and the Department of Defense. It is expected to be completed next year. The other is the Air Force's Ranch Hand study which will also be reported early in the coming year. The latter is looking for reproductive effects in their population of Ranch Handers who are known to have been exposed to Agent Orange. The CDC study is a Vietnam experience study but an attempt will be made to determine exposure to Agent Orange and, therefore, to TCDD.

One of the major problems is that of soft tissue sarcomas. Every study that has been done on herbicides and soft tissue sarcomas and every study that is in progress is open to question on epidemiological grounds. None is methodologically clean and I know of no way to make them so. We are going to be faced with the results in a number of studies, all of which leave questions unanswered.

A group of Swedish studies began in 1978 with the chance observation that soft tissue sarcomas were occurring among forestry workers who

were exposed to herbicides. These studies deal with herbicides as do the others in New Zealand and Finland.

Some American industrial studies are a separate group. They have been mentioned already and I shall not review them in great detail. A total of seven cases of soft tissue sarcomas was reported among chemical workers in the United States. This caused great concern but reexamination of the cases has shown that only two workers had soft-tissue sarcomas and also had documented exposure to TCDD.

I can give what was reported to be the anticipated number of soft tissue sarcomas among the exposed population. I must qualify this in that the exact count of the exposed population has not been reported and so the number of expected cases is tentative. It is estimated that only 0.07 cases of sarcoma would have been anticipated and two were found. One can juggle numbers, and this is done very often, but I never have treated seven-hundredths of a case of any disease. I either had one case or I did not. The evidence is a little stronger if you have two cases, but clinicians know that two cases of a rare disease can appear within a short time even in the same location.

So it is unclear what those industrial studies mean, although they do tend to lend support to the Swedish studies that claim an association of the sarcomas with herbicide use. There is certainly no consensus now on the relationship of exposure to herbicides or TCDD and the appearance of soft-tissue sarcomas. Some other studies have been reported in industrial settings apart from those in the U.S. They have not indicated any relationship between the two experiences.

One study that has been completed in Midland, Michigan. There was an increased incidence of soft tissue sarcomas among women in that community, but the men showed no increase. The rate among women was less than the rate among women in other Michigan counties where there was no industrial plant. Midland is the home of two chemical companies, both of which made herbicides. No employment history of either the patients or their spouses and no geographic location within the city could be correlated with the sarcoma cases. So what it means is an open question.

Other studies include a New York State study that has been completed. Like the National Cancer Institute studies, it is concerned with exposure to herbicides rather than to pure chemicals.

The VA is undertaking a study which has also been mentioned already. The Armed Forces Institute of Pathology has the largest collection of soft tissue sarcomas in this country and probably in the world. All of the tumors will be reexamined and diagnosed by the same team, including Dr. F.M. Enzinger, generally considered the world's best qualified pathologist to characterize these sarcomas. The research will be a case/control study and is expected to be completed in 1985.

The National Institute of Occupational Safety and Health has created a registry of industrial workers exposed to TCDD and will use it for a case/control study. A similar but international registry is being compiled at present, and it also will be examined for possible causal factors of soft tissue sarcomas.

The CDC study that is concerned with the effects of exposure to Agent Orange in Vietnam will include an evaluation of the effects of the Vietnam experience. It incorporates as well a study of the soft tissue sarcomas in the civilian population, which now includes Vietnam veterans.

In addition to soft tissue sarcomas, several other forms of cancer have been reported to be associated with herbicides or TCDD. The studies, in general, have shown very disparate malignancies with no increased prevalence of malignancies as a whole in the various exposed populations. Many studies will extend into the future as the population is followed. Individuals exposed in Vietnam and during the Vietnam era are now 10 to 15 years past their exposure and are entering the period when we would expect most of the solid malignancies to appear if they were due to exposure at that time.

Mortality studies are being conducted around this country and the world to determine whether exposure to herbicides or TCDD shortens life. A number of them have been completed. They have found no increased death rate. There was likewise no increased mortality among Ranch Handers as a group. As is usually true in studies of industrial and military groups, the mortality rates were below those anticipated because of the so-called "well worker effect." This is particularly pronounced in the military studies where, at one point at least, each individual has had a careful health evaluation and has been given medical care throughout the military career.

There is no evidence of an increased mortality rate among veterans or among industrial workers exposed to TCDD. A major New York State mortality study is soon to be reported and a larger VA mortality study is underway. There are already reports of mortality rates among industrially exposed groups in England and Europe as well as the United States. The workers have been followed for two decades or longer in some studies without more deaths than expected. Also in the aggregate, they have not died from any single characteristic cause.

As you can see, research up to the present has not established definitely that phenoxy herbicides or TCDD cause any prolonged or delayed toxic effects when exposure has been relatively slight. The search for such effects has continued, however, and the answers to our questions may emerge more clearly as the work continues.

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