B.

PORTIONS OF DR. JOSEPH K. PRINCE'S CHAPTER ON "IMMUNOTOXICOLOGY & CHEMICAL CARCINOGENESIS" FROM THE BOOK ENVIRONMENTAL TOXICOLOGY.

THIS CHAPTER ESTABLISHES THE RELATIONSHIP BETWEEN A BREAKDOWN OF THE BODY'S IMMUNE SYSTEMS AND VARIOUS DISEASES, ESPECIALLY SOFT TISSUE CANCERS.

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• To whom correspondence should be directed.

28 November 1983; revised 17 January 1984

Dr Lemchis

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6 January 1984

Health Effects of Dioxin

The evidence of deleterious health consequences from the environmental use of substances containing 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has appeared in a multitude of studies. Philip H. Abelson's editorial (*1*) on the dioxin issue is based on a number of misleading inaccuracies about this evidence.

First, the results of the accident at Seveso, Italy, are not limited to mild cases of chloracne, despite Abelson's statement that "No significant change was observed in the incidence of spontaneous abortions, congenital malformations, or postnatal development." The Seveso data (*2*) show a sharp increase in spontaneous abortions during the first trimester of 1977, followed by a slow decrease to 1976 levels and significant increases in risk of malformations. For example, there was a 100 percent increase in the rate of spina bifida, a 71 percent increase in the rate of neural tube defects, an elevenfold increase in hypospadias, and a 110 percent increase in polydactyly. A number of these malformations are frequently observed in animals exposed to TCDD. The Seveso data are still being analyzed for postnatal effects.

Second, the National Institute of Occupational Safety and Health (*3*) and recently the Environmental Protection Agency (*4*) followed workers exposed to TCDD in industrial accidents and found, in sharp disagreement with scientists who analyzed that data for industry, a multiple increase in soft tissue carcinomas and lymphomas.

Third, the question is not whether TCDD has to be ingested before it is toxic (obviously it has to make effective contact) but whether there is an effect from the presence of elevated environmental levels of TCDD, especially as a result of herbicide spraying (*5*). There is ample evidence that the latter is the case. Multiple studies by Swedish investigators, notably, Axelson and Sundell (*6*) and Hardell and Erikson and their colleagues (*7*) show an increase in soft tissue carcinomas in railway and forestry workers exposed to environmental TCDD. Observations from Vietnam (*8*) have reaffirmed increased liver cancer among populations exposed to Agent Orange during the Vietnam War (*8*). Spontaneous abortions, stillbirths, and malformations are still reported in these areas (*9*).

Fourth, it is misleading to stress the great variability of the median lethal dose (LD_{50}) when commenting on the value of animal experiments. It would be more accurate to point to the uniformly low effective doses for producing carcinogenic and teratogenic effects (*10*).

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Pro and con evidence and differing points of view on questions concerning the toxicity of dioxin are cited in a large number of articles and books. Three publications that contain a total of hundreds of references are

1) *Further Review of the Safety for Use in the U.K. of the Herbicide 2,4,5-T* from the Advisory Committee on Pesticides, London, December 1980;

2) *Agent Orange Dioxin—The Health Effects of "Agent Orange" and Polychlorinated Dioxin Contaminants*, a technical report prepared by the Council on Scientific Affairs of the Advisory Panel on Toxic Substances of the American Medical Association, Chicago, Illinois, October 1981; and

3) *Human and Environmental Risks of Chlorinated Dioxins and Related Compounds*, edited by Richard E. Tucker, Alvin L. Young, and Allan P. Gray (Plenum Press, New York, 1983).

As Sterling points out, a number of investigators have taken the position that TCDD has been a causative agent of soft tissue sarcomas. However, to other experts, the evidence is not compelling.

The Agent Orange report includes the following statement (p. 28): "While 2,4,5,-T and 2,4-D pesticides (phenoxy herbicides in Agent Orange) have been used in agriculture, forest management, and residential landscaping for over 30 years, there is still no conclusive evidence that they and/or TCDD (a contaminant of Agent Orange) are mutagenic, carcinogenic, or teratogenic in man, nor that they have caused reproductive difficulties in the human."

—PHILIP H. ABELSON

26 January 1984

Monsanto

GR
TJL
FRJ
Dioxin

Monsanto Company
1101 17th Street, N.W.
Washington, D C 20036
Phone. (202) 452-8880

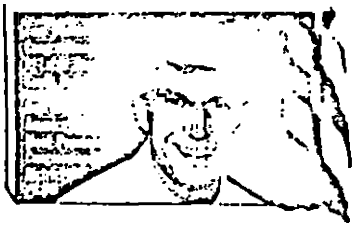
6/2/83

To: Jim Wilson
GSWG

John,

Enclosed is info from Daschle's office re Dow/Dioxin press release

Tom



NEWS/INFORMATION

FROM SOUTH DAKOTA CONGRESSMAN TOM DASCHLE

803 South M
Aberdeen, S.D. 57
605-225-8

818 Sixth St
Rapid City, S.D. 57
605-348-7

800 South
Sioux Falls, S.D. 57
605-334-9

439 Cannon Build
Washington, D.C. 20
1-800-424-9
or 202-225-2

DOW AND DIOXIN: A STUDY
Statement by Congressman Daschle
June 2, 1983

Paul Oreffice, president of Dow Chemical, recently told a national televisio audience: "There is absolutely no evidence of dioxin doing any damage to humans except for something called chloracne."

The study I am releasing, a study of which Dow was clearly aware, indicates Mr. Oreffice has either deliberately misled the public or is totally ignorant of studies possessed by his company.

This study, conducted by Dr. Milford Ward of the Department of Immunology, Royal Hallanshire Hospital, Sheffield, England, documents a long-term immune syste breakdown in humans exposed to dioxin some ten years prior to their examination. The study corroborates several similar studies on animals and humans.

Only yesterday, Dow invited journalists from across the country to its Midland, Michigan, headquarters to hear about new studies and receive the company approved line on the safety of dioxin. It is my understanding that these journali were told that Dow plans to spend more than $3 million to study dioxin damage in the Midland area.

I cannot help but wonder whether Dow told them of this study by Dr. Ward, or if Dow explained the damage this study does to the company's repeated claims about dioxin.

It is not surprising Dow has maintained silence about this study despite its obvious significance to the Agent Orange issue. Nor is it surprising the author of this study has described it as "confidential," and "never published in the scientific press."

These things have happened, and they are but the tip of the iceberg of efforts to suppress the facts and mislead the public about dioxin.

Yet just this tip of the iceberg, in the form of Dr. Ward's study, casts the gravest doubt on the claims of Dow and the United States government concerning Agent Orange and its deadly contaminant, dioxin.

...more...

Accompanying Congressman Daschle in today's News Conference is Dr. Joseph K. Prince a respected immunotoxicologist who is a Research Associate with the University of Illinois Medical Center and a Toxicologist with the Environmental Protection Agency in Chicago (Region V).

Confirmation of long-term immune system collapse as a result of dioxin exposu would revolutionize our thinking about this entire issue. It would explain the wide-ranging maladies reported for years by veterans exposed to Agent Orange. It would open Dow and the government to both military and civilian claims for legal and legislative remedy on a potentially massive scale.

And the Ward study raises a host of important questions for follow-up -- questions like:

- Why was the study kept confidential, thus preventing independent evaluation by the scientific community?
- What is the health status of the exposed victims today?
- Were follow-up studies made?
- If they were not, why not?
- If they were, what did they show and why have they remained secret?
- And finally, does Dow have further studies relating to dioxin which it is withholding?

And there are questions for the Environmental Protection Agency and other government agencies as well:

- How did E.P.A. obtain this study and why has so little been said about
- Was the Ward study shown to the Veterans Administration, to the Departm of Defense, or to others concerned with the Agent Orange matter?
- If not, why not?
- And if the V.A. was shown the study, why haven't tests for immune syste breakdown been included in the free health exams given thousands of Vietnam ve
- Similarly, why hasn't the V.A. awarded a single research proposal to study the effect of dioxin on the immune system?
- Leaving the Agent Orange matter entirely aside, was proper account of t Ward findings taken in considering civilian use of dioxin contaminated defolia use which continues to this day?

These are but a few of the questions raised by Dr. Ward's study. That these questions remain unanswered fully 20 years after the spraying of Agent Orange in Vie and five years after the Ward study was completed stands as an indictment of all involved in this matter.

I release this study, and continue my investigation into other materials which may have been suppressed, in the hope Congress and our government will at long last take the actions required to compensate those affected by dioxin and protect those as yet unaffected. It is surely the very least we can do.

A.

A-1 LETTER FROM DR. A. MILFORD WARD

THIS LETTER CONFIRMS THAT HIS STUDY -- "WRITTEN FOR AN INDUSTRIAL COMPANY" -- WAS CONFIDENTIAL AND NEVER PUBLISHED IN THE SCIENTIFIC PRESS.

CH 357
Tel: Sheffield (0742) 76484
Ext. 2837
Telex. 54348 Ulshef. G.

Director: Dr. A. Milford Ward

Supraregional Protein Reference U
Department of Immunology,
Royal Hallamshire Hospital,
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AMW/JA

6 April 1983

[redacted]

Dear [redacted]

Thank you for your letter of the 28th March regarding my paper on "Investigation of the Immune capability of Workers previously exposed to 2, 3, 7, 8 TCDD".

I would be most interested to know how this paper came into your possessi It was written for an industrial company in 1978 and was never published i the scientific press. As such it was a confidential document and was not written in a format for wider distribution.

Whilst this work was done some years ago, my interest in the subject is st current and I would be interested to hear your comments and experience.

May I also ask your interest or involvement in the problem area. I note reference to Agent Orange in your letter head and I can only assume that it is in this connection that your interest lies.

With best regards

Yours sincerely

A MILFORD WARD

A-2 PORTION OF TRANSCRIPT FROM E.P.A. CANCELLATION HEARINGS ON 2,4,5-T AND SILVEX (NOV. 14, 1980).

THIS TRANSCRIPT CONFIRMS THAT DR. WARD'S STUDY WAS DONE FOR DOW.

---

to push it any higher than that.

Q So, you really don't know at what stage in the chemical process the explosion occurred in the Coalite incident, do you?

A Perhaps I could put it differently. What I don't know is that Derbyshire and Amsterdam had the same amounts of TCDD formed; of course, I don't, I agree.

MR. BOZOR: I think we can take a break right now.

JUDGE FINCH: Let's come back at five minutes of 4:00.

(Whereupon, a short recess was taken.)

JUDGE FINCH: Back on the record.

MR. BOZOR: I'd like to hand you a cross-examination exhibit. This document is entitled "Investigation of the Immune Capability of Workers Previously Exposed to 2,3,7,8-Tetrachlorodibenzo-para-dioxin, TCDD, by Dr. A. Milford Ward.

This document says Strictly Confidential, but that is not Dow's stamp of confidentiality, it is not claimed by Dow to be confidential, and all the names of the patients involved have been blotted out.

JUDGE FINCH: Let's mark this 1480.

(Whereupon, the document was marked Cross-Examination Exhibit No. 1480 for identification.)

BY MR. BOZOR:

Q Are you at all familiar with this study?

A Yes, I am.

Q Are you free to -- well, let's turn to the first page.

A The fact that I've gotten to do, in effect, or have this work done again, doesn't in any way inhibit me from speaking about it, no.

Q Now, on the first page, there is an indication that the immune capability of three groups of adult males was examined, is that correct?

A Yes.

Q And one group was exposed to toxic levels of TCDD more than ten years previously, showing clinical evidence of toxicity in the form of chloracne?

A That's Group C.

Q That's Group C, and I might say that this Group C was not inked in by EPA. We received the document from Dow in this manner.

Do you agree that that is Group C, from your knowledge?

A Yes, that's Group C, and the others are Group B -- number 2 is Group B and 3 is Group A.

Q And Group B is the group exposed to TCDD, but not showing evidence of dermatological toxicity?

A That meant no chloracne. It meant that they were round about the place and could conceivably have come in contact with TCDD or not, nobody knew; they were an intermediate group.

Q And the third group, Group A, were the unexposed controls?

A That's right, who were apparently said to be certain not to have come into contact with it.

Q Now, the only numbering on this page is the number in the right-hand corner of these pages, and I think it's page 040708 that I would like to draw your attention to.

A I've got that. There's a lot of underlining on that page.

Q Again, we received the document in this form, from Dow. Now, the second paragraph states that "Test Group C shows a significant increase in the proportion of cases with reduced levels of Immunoglobin D and Immunoglobin M, and this group shows an increased proportion of cases with depressed PHA reactivity".

Now, this suggests that there was some immunosuppression of the group that was exposed to TCDD and exhibited chloracne, doesn't it?

A-5 IMMUNE STUDY BY DR. A. MILFORD WARD

THIS STUDY REVEALS THE PRESENCE OF LONG-TERM IMMUNE BREAKDOWNS IN ADULT MALES EXPOSED TO DIOXIN.

DO NOT CIRCULATE ©

Strictly Confidential

INVESTIGATION OF THE IMMUNE CAPABILITY OF WORKERS PREVIOUSLY EXPOSED TO 2,3,7,8, TETRACHLORODIBENZO - para - DIOXIN (TCDD).

Dr.A.MILFORD WARD
SUPRAREGIONAL SPECIFIC PROTEIN REFERENCE UNIT and DEPARTMENT of IMMUNOLOGY,
HALLAMSHIRE HOSPITAL, SHEFFIELD. UK.

[redacted] to TCDD was initiated as a result of the reported incidence of secondary immune defects in the Seveso population and in view of the available experimental evidence.

Studies in experimental animals, both rodent and primate have shown that thymic atrophy and lymphopenia are consistent and sensitive indicators of TCDD exposure or toxicity (Vos 1978). Preliminary studies in man have, however, failed to document a similar abnormality. The studies conducted on children exposed at Seveso (Fara 1977) have shown no difference in serum immunoglobulins, complement, or lymphocyte function between exposed and nonexposed control children.

The present study sets out to examine the in vitro immune capability of three groups of adult males

i) exposed to toxic levels of TCDD more than 10 years previously and showing clinical evidence of toxicity in the form of chloracne (Group C)

ii) exposed to TCDD but not showing evidence of dermatological toxicity. (Group B)

iii) unexposed controls. (Group A)

RESULTS

Strictly Confidential

Immunoglobulins.

IgG: There was no significant difference between the three groups or between the test groups and the laboratory reference range after due age correctio

IgA: There was no significant difference between the three groups or between the test groupd and the laboratory reference range after due age correctio 5% of the population are deficient in serum IgA and this proportion was reflected in each of the test groups.

IgM: There was no significant difference between test groups A and B and the laboratory reference range. Test group C showed a normal median value for IgM and an observed range which was indistinguishable from the other groups but there was a significant ($p<0.05$) increase in the proportion of cases which gave IgM values below the 5th centile for the laboratory reference range.

IgD: The distribution of this immunoglobulin in the normal population is trimodal with 10% having undetectable serum levels.
There was no significant difference in this subset of the population for the three test groups. 23.6% of Group B and 21% of Group C had values of IgD below the 5th centile. This represented a significant difference from the laboratory reference population ($p<0.005$) but there was no significant difference between test groups B and C.

IgE: 10% of the normal population have very high serum levels of IgE and these represent the pool of atopic individuals. There was no significant difference between the three groups and between the test groups and the laboratory reference range both with respect to median values and to the proportion of atopic individuals.

Table 1

Immunoglobulins

		n	median	observed range	No(%) below 5th centile of reference range.	
IgG	A	31	10.0	6.5 - 14.0	0 (-)	
g/l	B	56	9.7	6.5 - 15.8	0 (-)	
	C	38	10.2	5.6 - 13.1	1 (2.6)	N.S.
IgA	A	31	1.9	0.6 - 4.8	1 (3.2)	
g/l	B	56	2.0	0.4 - 4.1	1 (1.8)	
	C	38	1.5	0.4 - 4.8	1 (2.6)	N.S.
IgM	A	31	0.8	0.4 - 1.4	0 (-)	
g/l	B	56	0.8	0.2 - 2.4	2 (3.6)	
	C	38	0.7	0.2 - 1.4	7 (18.4)	p<0.05

Table I (Cont)

		n*	Median*	observed range*	No(%)below 5th centile*	No(%) not detected
IgD	A	28	21.5	8.5 - 85	1 (3.2)	3 (9.7)
IU/ml	B	52	16.0	1.0 - 88	13 (23.6)	4 (7.2
	C	34	13.0	2.0 - 121	8 (21.0)	4 (10.5)
					p<0.005	N.S

					No(%)below the 10th centile of reference range.	No(%)above 90th centile of reference range.
IgE	A	31	40	<5 - 980	4 (12.9)	3 (9.7)
IU/ml	B	56	44	<5 - >1000	6 (10.9)	8 (14.3)
	C	38	37	<5 - >1000	3 (7.9)	2 (5.3)
					N.S.	N.S.

* Cases in which serum IgD not detected are excluded.

Lymphocytes, lymphocyte subpopulations and mitogen transformati

There was no significant difference between the three groups or between the test groups and the laboratory reference range for total lymphocyte count, T-cells, or B-cells.
There was, however, an increased proportion of cases in test group C ($p<0.10$) in whom the lymphocyte transformation in response to phytohaemagglutin was reduced.

Table 11

Lymphocytes and in vitro mitogen transformation

		n	10th centile	median	90th centile	
Total Lymphocytes	A	29	1.6	2.3	4.3	
x 10^9/l	B	56	1.6	2.2	3.6	
	C	38	1.6	2.5	4.0	N.S
T - cells	A	29	1.0	1.3	2.7	
x 10^9/l	B	56	0.7	1.4	2.1	
	C	30	1.0	1.5	2.5	N.S
B - cells	A	29	0.2	0.4	0.9	
x 10^9/l	B	56	0.2	0.3	0.6	
	C	38	0.2	0.4	0.9	N.S
PHA transformation depressed	A	2/29	6.6%			
	B	2/56	3.5%			
	C	5/38	13.0%			p<0.1(

A-11

CONCLUSIONS

Test group A is indistinguishable from the normal population with respect to serum immunoglobulins IgG, IgA, IgM, IgD and IgE, and with respect to peripheral blood lymphocytes and their mitogen transformation.

Test group C shows a significant increase in the proportion of cases with reduced levels of IgD and IgM. This group shows an increased proportion of cases with depressed PHA reactivity.

Test group B falls intermediate between groups A and C with increased proportion of cases with IgD levels only, IgM levels and PHA reactivity being normal.

IgM is the antibody class associated with the initiation of the immune response and with immune response to viral and particulate antigen. IgD is thought to be associated with the transfer of immune capability from the T-cell to the B-cell and with short term immunological memory.

These results would seem to suggest that Test group C is relatively deficient in primary immune capability and in T-cell - B cell co-operation. The reduced PHA transformation response in this group is likely to be the result of viral induced T-cell depression as a secondary feature of the reduced humoral immune capability rather than a primary T-cell defect.
This would further suggest that toxic exposure to TCDD induces a lasting effect on B-cell memory and immune capability, the intermediate position of test group B being consistent with previous exposure to TCDD but at nontoxic levels.

Comparison of this data with the published literature on TCDD exposure in man is difficult in that comparative data has not yet been published. The studies by Vos et alia are confined to experimental animals whilst the studies on the Seveso incident reported by Fara are confined to children without exploration of the T cell - B cell co-operation axis and the possible envolvement of the cytotrophic antibody, IgD.

Superficially this data would seem to conflict with the findings from Seveso, but this may simply be on the method of approach to the problem. The possibility that this apparent difference is more fundamental and associated with degree of exposure in an adult rather than paediatric population must also be considered.

The concept that TCDD exposure can induce a lasting effect on B cell memory and immune capability could be tested by examination of the work attendance records of subjects of this study. Whilst there may be no overt increase in major infective illnesses amongst Group C, it would be interesting to know whether the individuals relatively deficient in IgM and IgD or showing altered lymphocyte subpopulation demonstrated an increased frequency of minor inflammatory disorders.

The exposed and contaminated groups are small, and the significance these findings would be improved if these groups could be increased. It would be an advantage to study further cases referrible to these two groups if they could be obtained, even if it means drawing them from an alternative Industrial Service.

Failing this it would be interesting to study workers exposed to or contaminated by chemicals related to TCDD, particularly if that contamination was associated with the development of chloracne as a toxic manifestation.

B-1

ENVIRONMENTAL TOXICOLOGY

Principles and Policies

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Chapter 5

IMMUNOTOXICOLOGY AND CHEMICAL CARCINOGENESIS

JOSEPH K. PRINCE

ABSTRACT

The influence of environmental chemicals on mammalian systems has been given much attention over the last several years. Bioassays of a chronic duration as well as short-term genetic assays have been developed with an eye toward the early recognition of the occurrence of a lesion in some target organ. Physiological and biochemical changes are targeted for analysis and surveillance in an effort to develop a screen that will signal the possibility of the occurrence of chronic disease.

Although the liver and kidney have been most intensively investigated, other systems have been used in this effort to establish an early warning system. The majority of the studies carried out have not taken into account the possibility that the immune system may be the ideal vehicle for such bioassays. For whatever reasons, investigators have underestimated the importance of the immune system as

* The author wishes to acknowledge helpful comments and suggestions contributed [illegible] by Dr. M. M. [illegible], M.D., Ph.D., Division of Clinical Immunology, and John [illegible], Ph.D., [illegible] Toxicology and Pharmacokinetics, of the University of [illegible] Hospital and Medical School Staff.

The author also wishes to acknowledge the very helpful clerical [illegible] provided by Mrs. [illegible] who [illegible] the typing and editing of the manuscript.

[illegible]

related to disease states. This author feels that a nucleus of information has been developed by immunological investigators to indicate that the immune system organs and tissue (thymus, spleen, bone marrow, lymphocytes, monocytes) may provide a fertile soil for such investigations that attempt to provide early detection of capacity for chronic disease by environmental chemicals.

Immune deficiency or modulation of the immune response has been known for many years. Irradiation, malnutrition, thymectomy and certain anticancer drugs currently in use are proven to cause a change in the immune system. Although the immune system is complex and not completely understood, sufficient information is available to indicate that various elements in the immune system appear quite sensitive to chemicals.

It is well established that active cells are the most sensitive to chemicals. A good deal of information has been developed on the use of anticancer agents and their capability to induce secondary and tertiary cancers in patients undergoing anticancer treatment. Some of the changes associated with such treatment at the cellular level are also seen *in vivo* and *in vitro* and of course raises the question of whether this activity can be at work during exposure to environmental chemicals? This author feels that there are some relationships that make the next decade in immunotoxicological research possibly the most exciting and potentially the most important.

Introduction

During the last five years, many of us have heard the statement that "a large number of cancers may have their etiology in the environment." This statement helped to propel an already energetic national desire to seek cancer causes and cures. Although there are many different opinions as to the actual numbers of cancer cases contributed by the various environmental factors, it has been generally agreed upon, among biomedically oriented research scientists, that environmental carcinogenesis is a real entity.[1] In an effort to seek a cure or to begin a prevention pro-

gram, the environmental chemicals that present a carcinogeni[c] risk to humans, are an ideal target for investigation.[4]

In order to establish some measure of risk, predictive toxicolog[y] has had to use the various available tools: epidemiology, statisti[cal] extrapolations of pharmacological dose response studies, the mu[l]tiple specie end target organ bioassays, microbial,[5] biochemic[al] studies, and chemical structure relationships.[6,7] These tools, us[ed] cautiously, have served us very well. However, the fact that huma[n] data is lacking in a majority of the cases has been a source [of] consternation.

Recent developments in the area of immunology have provide[d] a nucleus of data and of concepts that may help resolve some [of] these problems associated with extrapolations to humans. Althoug[h] immune mechanisms and the system has not been defined abso[]lutely, research data has been developed that shows that immun[e] system cells (small lymphocytes, T and B cells, macrophages) an[d] products such as lymphokines play a very important role in th[e] body's immune reaction to possible pathology from microbia[l] infection, graft rejection, and tumour production.

The fact that these cells are readily accessible and are huma[n] tissue present in extensive amounts in peripheral blood and ha[ve] potential for rapid proliferation makes them an ideal vehicle fo[r] the study of potential toxicity.

Immune Cell Analyses

One area that has not been well investigated but deserves attentio[n] is the human immune system. Vos[8] as well as Silkworth an[d] Loose,[9] have found evidence that supports the concept that env[i]ronmental chemicals can produce modifications in the activities [of] the immune system cells. Antibody mediated resistance, cell medi[]ated resistance, as well as increased levels of mortality due [to] lowered resistance to bacterial infections have been reported i[n] their reviews.

Immune Deficiency and Malignancy

One of the most significant advances in cancer information is the finding that immunodeficient states are associated with an increased incidence of malignancy. Kersey[6] has shown that patients who have naturally occurring states of immunodeficiency such as Wiskott-Aldrich disease, Ataxia telangiectasia, or agammaglobulinemia have an unusually high incidence of malignant disease.

Numerous experimental bioassays are cited in his review, showing that immune suppression facilitates transplants of malignant cells, increases a normally low incidence of viral or chemically induced cancers and accelerates growth of metastases.

Immunosuppressive therapy has been used for some twenty odd years and has had a significant impact in producing secondary and tertiary cancers in patients who were under such treatment. Penn[6] has been maintaining a tumour registry of patients who were on immunosuppressive therapy and classified them into five groups with the following results.

Patients with Transplanted Cancers

Sixty-one patients who had received organ transplants from donors who were neoplastic or within several months subsequent to donation developed evidence of malignancy showed that twenty-one patients or 34 percent had evidence of transmitted cancers. Cessation of immunosuppressive therapy and removal of the graft resulted in the complete disappearance of the disseminated neoplasms.

Transplant Patients with De-novo Malignancies

In a long-term follow up of the University of Colorado series of renal homografts, 32 of 564 patients developed cancer, an incidence of 5.7 percent. The Denver Transplant Tumor Registry data on 401 *de novo* cancers that have occurred in 378 patients who have received kidneys. The average age of the patients were thirty nine years old (range eight to seventy years) and the neoplasms occurred from one month to one hundred fifty four months (1–154) after the transplant (average 32 months). After the transplants, the following immunosuppressive procedures were used: Prednisone, Azathioprine, anti-lymphocyte globulin (ALG), Actinomycin, cyclophosphamide. Radiation, splenectomy, thymectomy and thoracic duct fistula procedures were also in use. In conjunction with ALG treatment, 6-mercaptopurine, methotrexate, and azaserine were also used.

The patients receiving irradiation, splenectomy, thymectomy or thoracic duct drainage treatment accounted for 217 *de novo* cancers, while the patients on pharmacologic therapy accounted for the remaining 164 cancers. The development of malignancy could not be related to the use of any one agent, but appeared to be an effect of the general immunosuppression. A significant finding was that the incidence rate of solid lymphomas among the organ transplant patients was disproportionally higher than the general population. One variety, Reticulum Cell Sarcoma, was calculated to be 350 times more common. The lymphoma patients were slightly younger than the other cancer patients (36.5 versus 40 years old), and the tumours appeared earlier than the other cancer patients (twenty-three versus thirty-five months). The solid lymphomas occurred in ninety-five patients with the following breakdown:

Reticulum cell sarcomas	
(One patient also had a Kaposi's sarcoma.)	
Kaposi's sarcoma	
Lymphoma	
(Including 1 plasma cell lymphoma).	
Lymphosarcoma	
Lymphoreticular malignancy	
Hodgkins Disease	
Histiocytic Reticulosis (?)	

Non Transplant Patients Treated with Immunosuppressives (Antiinflammatory therapy)

Data has been collected that indicates that of seventy patients who have been under antiinflammatory therapy, seventy-two cancers developed during treatment with various agents.

Disease	*No. Cases*	*Therapy*	*No. Cases*	*Cancer Type*	*No. Cases*
Psoriasis	24	Methotrexate	21	Lymphoma	1
		Aminopterin	3	Leukemia	1
		Other	8	Skin	5
				Misc.	16
Renal Disease	13	Azathioprine	7	Skin	5
		Cyclophosphamide	7	Lymphoma	2
		Other	10	Misc.	6
Rheumatoid Arthritis	10	Cyclophosphamide	8	Lymphoma	5
		Other	8	Leukemia	3
				Lymphoma	2
				Misc.	4
Systemic Lupus Erythematosus	7	Cyclophosphamide	3	Kaposi's Sarcoma	1
		Azathioprine	6		
		Other	6		
Other Inflamatory Diseases	16	Agents Used (as above, alone or as combined)	31	Cancers (Lymphomas, Leukemias, Hodgkins, and cancer of skin, bladder, colon, bronchus.)	16

Neoplastic Diseased Patients Without Transplants

In non-transplant patients with neoplasms receiving immunosuppressive cancer therapy, Penn[6] and Kersey[6] showed that second and even third tumours have arisen during treatment with chemotherapeutics. Of 165 patients with tumours treated with either Melphalan, cyclophosphamide, busulfan, 6-mercaptopurine,

chlormaphazine, chlorambucil, thiotepa, methotrexate, and prednisone, alone or in combination, [illegible] new malignancies developed. Various leukemias accounted for eighty-two of the new malignancies, thirty-five lymphomas, twenty bladder carcinomas, ten cases of cancer of the cervix, and one Hodgkins disease occurred. The remainder of the cases were sarcoma and miscellaneous forms of malignancy and totalled fifty-five.

Acute leukemia occurred in thirty-nine cases where the patient originally had multiple myeloma. Twenty-seven solid lymphomas developed in cases where the patient's original neoplasm was chronic granulocytic leukemia. These unusual occurrences would tend to dispel any ideas that these cancers were transition forms of the existing malignancy. Thus, one can cautiously extrapolate from data and identify a significant association between the development of malignancy of lymphoid elements and the use of chemicals that have the capability of suppressing elements in the immune/host defense system. (Chlormaphazine is the one agent capable of directly causing cancer in man since it metabolizes to betanaphthylamine. It has caused bladder cancer in aniline workers.)

Leukemias and Chemical Immune Modulation

Of the four major types of cytological leukemia, myeloid and lymphatic constitute the greatest percentage. Myeloid cases peak out at about [illegible] percent of all leukemias at age thirty to forty, then declines thereafter. The lymphatic type has the highest prevalence in children peaking at about 50 percent and then declines till age thirty to forty. It then rises to [illegible] percent peak between age eighty to ninety. On the way up to its peak, the lymphatic type passes myeloid type leukemia at about seventy years of age.[6]

An epidemiological study of solvent exposure and leukemia conducted among rubber workers by McMichael et al.[6] indicated that an association between leukemia and jobs that involved no solvents existed. Prior to this time, Kessler and Clifendell[6] as well as Vigliani and Saita[6] had prepared papers indicating they thought that the current evidence supported benzene, phenylbutazone, and chloramphenicol as being leukemogens, however they had found little epidemiological evidence to support it

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posture. McMichael et al.[48] had analyzed some 6600 co-workers (male rubber workers) who were working during the years 1964 to 1972, but had an employment duration of twenty-five years. They were followed for nine years with a 1 percent loss. Matched controls were also analyzed, with standard mortality ratios and proportional mortality ratios calculated. Of the various relationships that were analyzed, the association of death from lymphatic leukemia with a history of having worked in solvent exposure environment stood out. It is of interest that the lymphatic leukemia stands out as associated with solvent exposure jobs. This leukemia tends to be the myeloblastic or the stem cell type. McMichael had indicated that the leukemogenic effects may have been the result of concomitant exposure to other solvents that were used in the rubber industry.

However, Infante et al.[50] studied a population of workers who were occupationally exposed to only benzene during 1940 to 1949 and who were followed until 1975. Comparisons with two control groups show a significant excess of observed leukemia (p less than 0.002). A five fold excess risk of all leukemias and a ten fold excess risk of death from myeloid and monocytic leukemias combined were demonstrated in the comparison between populations. The environments of these workers were analyzed, and records have shown that the benzene levels were generally lower than the recommended limits at the time they were measured.

The observations are in agreement with Vigliani and Saita,[49] whereby a specific type of leukemia is associated with the exposure to benzene. The myelogenous or monocytic leukemia has been shown to correlate very well with the exposure and confirms the suspicion that benzene is a powerful bone marrow poison.[51] Goldstein[51] has written an excellent review of the toxic hemopoeitic effects of benzene exposure. These effects, although somewhat complicated by concomitant exposure in some cases, are fairly well demonstrated.

The mechanism by which this toxicity occurs is not known; however, the alteration of *stem cell* function is apparent.[51,52,53] Occupationally exposed persons as well as laboratory animal studies have shown chromosomal abnormalities, and correlates well with the known clinical picture of benzene toxicity.[54,55,56] Goldstein

has reported that in mice chronically exposed to 300 ppm of benzene, leukopenia, due primarily to lymphocytopenia, was clearl[y] demonstrated. These manifestations of pancytopenia may repre[-]sent a destruction of the stem cells, failure of the cells to mature or prevention of differentiation at some critical stage. Other agent[s] known to produce pancytopenia act in this fashion through mod[-]ification of nuclear material. They include ionizing radiatio[n], chloromycetin, vinblastine, mitomycin, puromycin, colchicine an[d] cytochalasin B. Many of these latter compounds have been used i[n] clinical treatment of malignancy.

Forni et al.[12] carried out cytogenic studies and have confirme[d] chromosomal aberrations occurring in peripheral blood lympho[-]cytes, due to benzene exposure.

If one examines the ontogeny of lymphocytes, it is readil[y] apparent that bone marrow stem cells develop into two differen[t] lines of cells. The one line produces hemopoietic precursors, an[d] the second line produces the lymphoid cells. Logically, interfer[-]ence at the stem cell level is bound to affect both the bloo[d] elements as well as the immune system elements. Laborator[y] investigations have observed pancytopenias such as monocytic and myelogenous leukemias due to benzene exposure also show stem cells that have produced abnormal mature erythrocytes, whic[h] further supports stem cell nuclear function interference.

Wolman[54] has indicated that ample evidence is present to show that chromosomal aberrations can be induced through exposure to benzene. Gaps and junction breaks have been observed i[n] cultured human cells (leukocytes and HeLa cells) at 1.1 or 2.2 × 10⁻ M. benzene. Higher doses caused inhibited DNA synthesis. Periph[-]eral lymphocytes stimulated by phytohemagglutinin (PHA) expose[d] to benzene for seventy-two hours revealed both numerical an[d] structural alterations. Aneuploidy and chromosome breakage occurred seven and eight times more frequently in treated cells.

Immunochemicals and Cancer

Advances in pharmacological therapy has produced problem[s] as well as remissions in the treatment of disease states. Patient[s] who have been treated with antihypertensive, antiarrythmic agent[s] as well as antitubercular or anticonvulsive agents have shown to be

susceptible to a syndrome related to the immune disease called systemic lupus erythematosus (SLE).[57,58,59] In SLE, the patient develops antibodies stimulated by the patient's own cellular material, especially the nuclear elements. It affects various tissues, and has a fatal form. One of the major findings in diagnosis has been the presence of an LE cell (polymorphonuclear leukocyte—PMN) that contains phagocytized nuclear material. This cell is formed as a consequence of reaction between an antibody present that can bind cellular nucleoproteins. Presumably the mechanism involves the lymphocytic nuclei that reacts with the antibody. Lymphocytes become saturated on their active sites, and PMN cells come to engulf the swollen lymphocytes. Digesting away (phagocytosis) the remainder of the lymphocyte, the PMN packages the nucleoprotein material as a residual body called LE. Although this disease is usually virally induced, therapeutic agents such as diphenylhydantoin, isoniazid, hydralazine, and procainamide have induced the syndrome that generally disappears upon withdrawal of the drug. These mechanisms that induce the SLE syndrome are not yet well understood; however, chemical influence on the immune system has produced antibodies that include anti-DNA, antinucleoprotein, antihistones, antinucleolar RNA, and antibodies to fibrous or particulate nucleoproteins. The importance of these data reflect that exogenous chemicals, which modify or influence biological systems, have unusual effects that are not always readily apparent. How this important defense mechanism has been modulated by interplay with chemicals is unknown, but any real capacity to effect nuclear material creates greater possibilities of biological dysfunction.

Zarrabi et al.[57] studied four groups of humans under treatment for some two and one-half years, with chlorpromazine and various other antipsychotic drugs. The main observation was the prevalence of immunologic and thromboplastic coagulative disorders. In patients on long term chlorpromazine, the authors found that patients had increased levels of serum IgM, 405 ± 55 (in chlorpromazine treated patients), whereas controls had 157 ± 21, and normal is considered to range from 60 to 250; patients who were given combined therapy, chlorpromazine plus another drug, for the same length of time showed levels of serum IgM at 263 ± 75. Other

antipsychotics used were thioridizine, trifluoperazine, thiothixe[ne], perphenazine, haloperidol, lithium, and amitryptaline. This gro[up] alone did not provide any significant differences when compa[ri]sons were made between the groups studied. Also noted was [an] increase in length of partial thromboplastin time. In both instance[s] significant correlation between increased levels of IgM in seru[m] along with thromboplastin time were noted in relation to dose a[nd] duration of therapy. Both groups had a positive antinuclear an[ti]body test (61%), both had nucleoprotein antibodies (58%), a[nd] both groups had antibodies to native DNA (30%).

It is interesting to note the authors' conclusion, "the IgM was t[he] coagulation inhibitor," and was identified through immune neutr[al]ization and immunoglobulin isolation techniques. A product of t[he] immunological analyses was the finding that the percentage of lymphocytes were below normal in thirteen out of forty-one patien[ts] treated with Chlorpromazine and twenty out of forty-two patien[ts] under single or combined treatment developed splenomegaly.

Recently, Doctor I. Fidler[58] at the Detrich Maryland Canc[er] Research Center, working with macrophages from mouse per[i]toneum, found that for some odd reason the macrophages bega[n] losing their tumoricidal activity during *in vitro* studies. Ordinar[i]ly, such macrophages in the peritoneum are not cytotoxic to tumor cells *in vitro*, however, a lymphokine released by an activate[d] lymphocyte, referred to as macrophage activating factor (MAF) has the ability to stimulate the macrophage to become tumoricidal. Such peritoneal exudate macrophages (PEM) can also be stimu[-]lated to become cytotoxic by bacterial products (lipopolysacchar[-]ide — LPS), endotoxins, pyran copolymers, double stranded RNA or during chronic infection with obligate bacteria. The *in vitro* studies were stopped and, in certain cases, the procedure modifie[d] because the PEMs were found to have lost the cytotoxic capability. A careful examination of the occurrence of lost activity seemed to correlate with a minor change in the drinking water used for the mouse colonies.

Water fed to the mice had a chlorine level of about twelve to sixteen parts per million (ppm). This high level is necessary to reduce the rate of early death syndrome in the colonies due to *Pseudomonas* infection since the mice had been lethally irradiated

Due to an unusually high incidence of such early death syndromes, the chlorine level was raised to 25 to 30 ppm, and the experimental studies were carried on as usual.

At the start of the experiment and just before treatment, the mean number of PEMs per mouse was $21 \pm 4 \times 10^6$. One week later the level of PEMs in the mice receiving hyperchlorinated water had decreased to $13 \pm 2 \times 10^6$ per mouse. Controls were yielding $25 \pm 3 \times 10^6$ per mouse. On consecutive weeks, PEM yield increased from the control mice, but mice on hyperchlorinated water had reduced PEMs or remained lower than controls. Mice that were receiving tap water yielded macrophages that when stimulated were tumoricidal *in vitro* to B16 melanoma cells or to UV 112 fibrosarcoma when activated by Concanavalin A-MAF, as measured by release of radioactivity.

The mice drinking hyperchlorinated water exhibited lowered levels of cytotoxic ability for the first two weeks, and, by the end of the third week of treatment, the cells, although stimulated by Con A-MAF, were not tumoricidal.

These studies show that hyperchlorinated water produces profound alterations in the numbers and tumoricidal capacity of PEMs. Lower levels (10-15 ppm) may also exert such influence although over a longer period of time.

Supporting these effects was a report by Fuller that showed that patients on long-term hemodialysis developed acute hemolytic anemia when treated with water that, although filtered by reverse osmosis, has 2 to 4 ppm chlorine. Chlorine compounds brought about a denaturation of the hemoglobin by direct oxidation and also by inhibition of the direct oxidative pathway (Hexose monophosphate shunt) of red blood cells (RBCs). The damage to RBCs was found to be cumulative over several periods of dialysis.

Although the mechanism for this depression of macrophage tumoricidal activity is unknown, Fuller suggests several possibilities. The vacuoles of the macrophage system are probably involved in the cytotoxic mechanism. This has been shown by Hibbs and Weinberg[36] whereby inhibition of the lysosomal enzymes of the macrophages occurs by addition of trypan blue, and stabilization of the lysosomal membranes occurs with the addition of hydrocortisone, and the cytotoxic activity is suppressed.

Macrophages that have been activated by lymphokines have enhanced bactericidal activity, and metabolically are shown to have a four to eight times increase in the uptake of glucose and its oxidation as compared to controls. Since the chlorine (compounds) inhibits the HMPS pathway[37] that is the major path for glucose oxidation in the RBC's, there is a possibility that chlorine and/or its compounds may sufficiently inhibit glucose oxidation to the point whereby macrophages that have reduced tumoricidal capacity will allow aberrant cells to continue growing and relocalizing.[38] Concurrently, indirect pathology also occurs.[39] Chlorine levels affect erythrocytes' glucose metabolism, and large amounts of hemoglobin degradation products and/or large numbers of damaged RBCs can suppress macrophage tumoricidal activity.

Regardless of the mechanism by which the chlorinated water or chlorine compounds may exert their influence, the important fact remains that macrophage activity is compromised. Since it carries a major role in host defense against neoplastic disease, the possibility exists that a host who is exposed to such compounds may in fact become immunocompromised. Silica, carrageenan, and trypan blue are substances that also have the ability to suppress macrophages in lab studies have been reported to decrease host resistance against transplantable tumours.

Dandliker et al.[40] recently reported their studies of the effects of pesticides on the immune response. Hamsters (LHC, LAK) five to eight weeks old and weighing about 100 grams were given a dose of pesticide equal to one-half the LD^{50} dissolved in 1 ml of corn oil. Aroclor 1260, Dinoseb, Parathion, pentachloronitrobenzene, piperonyl butoxide, mixed pyrethrins, and resmethrin were administered intragastrically. The animals were examined for an end point of "redness and swelling" (inflammatory response) and change in temperature of the foot pads, as well as histological exam, after an antigenic challenge. Serum antibody titer, binding affinity, and heterogeneity were determined by fluorescent polarization measurements.

The animals were first given an injection of fluorescein-labeled ovalbumin, allowed only water *ad lib* for twenty-four hours, and then given a bolus of food with the pesticide by intragastric feeding tube twenty-four hours after the immunization. The most

striking feature reported by the authors after immunanalysis indicated marked humoral and cellular immunosuppression to single doses of Dinoseb and Parathion, and a marked stimulation of the cellular response by resmethrin. The other pesticides showed little or no effect under these conditions.

In another study[41] using the pesticides Ametryne, Carbaryl, Chlordimeform, DDT, Malathion, Mirex, and parathion, a single dose of pesticide was given orally at the LD^{50} or the 0.1 LD^{50} five days before, two days *before*, or two days *after* immunization with sheep erythrocytes. Assays were then conducted using antibody plaque forming cells four days later. (Plaque forming cells—antibody producing cells that can form a hemolytic plaque in the presence of complement and erythrocytes.) All animals receiving the higher dose exhibited significant depressions in splenic plaque forming cell numbers. Low dose animals receiving the dose for either eight or twenty-eight days prior to immunization exhibited no significant reduction in the antibody plaque forming cell numbers. The author indicates that a lack of information prevents a conclusion as to the efficacy of these compounds on modulating the immune system. Since the methodology only uses one test for the erythrocyte receptor, little can be concluded. This is why multiple parameter assays are necessary.

Faith and Luster[42] have performed extensive investigations on the pre- and postnatal effects of Tetrachlorodibenzodioxin (TCDD) on the immune system and have found that TCDD appears a relatively excellent immunosuppressive in the Fischer/Wistar rat strains. The Fischer strain is reported to be less of a responder than its Fischer/Wistar cousin. However, dosing of nursing females has shown that the TCDD has the capability of causing immunosuppression in littermates. The effects have lasted as long as 270 days, from three doses to the mother at days zero, seven, and fourteen, applied at five micrograms per kilogram (ug/kg) body weight. At days eighteen and thirty-five, both female and male littermates showed depressed body weight as well as depressed thymic weights. These depressed values were evident at day 125 postdosing. The weight of the spleens were also found to be affected.

Effects of TCDD exposure on the homing patterns of lymphocytes were also studied in these same rat strains. Splenic cells taken from

the TCDD exposed rats were injected into nonexposed rats, and the thymus was found to significantly increase the uptake of such cells. Thymic cells taken from nonexposed rats were injected into TCDD exposed rats, and it was found that there was decreased homing ability to the thymus. The authors proposed that a change in cellular metabolism occurred altering the cell membrane, so that insertion of the TCDD into the membrane caused surface alterations, and this change in the cell modified its normal homing patterns. Various investigators have shown such alterations in immune function due to TCDD exposure.[43,44,45]

Thigpen[46] has shown that subclinical doses of TCDD had the ability to affect host response, when subsequent exposure to *Salmonella* infection resulted in reduced time to mortality. Thus far, exposure to TCDD has been shown to cause an increase in the susceptibility to bacterial infections (suppression of immune response) as well as suppression of mitogen responsiveness, suppression of the skin graft rejection, and depression of the delayed hypersensitivity response. (Suppression of the T-cell dependent immune functions appears to occur as an isolated response.)

Summary

The influence of environmental chemicals upon the public health is of considerable importance. Determining how such chemicals may cause adverse effects upon humans is a continuing problem that perplexes all phases of scientific inquiry. Genetic chronic toxicity and dose responses are derived from animal bioassays and microbial DNA studies for human use, and constitute a major source of controversy among predictive toxicologists.

A major step forward in resolving such problems could be attained with the use of human lymphoid cells, which are readily available from the peripheral circulating blood. The lymphoid cells of the immune system are an integral part of the defense mechanism known as immune surveillance and are very important in the recognition and removal of aberrant or malignant cells. It is this relationship that may be disturbed by environmental chemicals and allows carcinogenesis to proceed in susceptible individuals.

The use of immunosuppressive therapy has shown there is an increased frequency of various types of malignant disease associated with continued use of such agents. Secondary as well as tertiary cancers have been produced by therapeutic suppression of the immune system. Concurrently, investigators have also shown that occurrence of malignant disease is also found in individuals with genetic immunodeficiencies at a higher frequency than in immune normal hosts. So it has become apparent that malignant response in a given host may in fact be very seriously dependent upon an immune system that has been somehow compromised.

In vitro and rare studies using pesticides, metallo-organics and various pharmacological agents, have shown that certain activities of lymphoid cells are modulated by the presence of many of these compounds.

Lymphocytes have been either suppressed or stimulated, and either condition may be affecting immune response. The blood monocytes, which play a vital role in the B-cell/T-cell interactions, are shown to be very severely disturbed by excessive amounts of chlorine or hemoglobin degradation products. So, direct or indirect effects can modulate the immune response, showing the sensitivity of the lymphoid population to environmental influence. The cells themselves may become defective through direct action, or the tissue in which they mature and differentiate may be modified, producing an impotent cell.

The cell may be altered at the surface, within the cytoplasm where antigenic determinants are synthesized, or within the nuclear protein and/or chromosomal levels. Thus there exists a cell for all seasons: morphologists, biochemists, immunologists, pure chemists, pure biologists, all will find an abundance of suitable material to investigate. The most rewarding portion of our work may well be that we will be closer to effective extrapolation for human exposure.

Conclusion

The mechanisms whereby chemicals influence the immunological surveillance system are not understood. In fact, there are many who have asked questions that may dull the excitement over the immunosurveillance theory. However, they have not been sufficiently substantiated. What has been elucidated in this presentation is that we cannot deny the influences external chemicals have on the cells and products of tissue from the lymphoid-immune system. The role of chemically induced malignancy in the immune suppressed patients receiving therapy or the excess occurrences of malignant disease in immunodeficient individuals is significant and cannot be ignored. The complexity of the immune system, details of mechanisms, in fact, whether cells or products may be influencing this system is in most cases not known. However, it can be stated that many of the substances mentioned here today

are in the environment and they do have immunomodulating effects. How does this role of immunomodulation affect interpretation of previous studies that discerned that a mouse, rat, guinea pig, or some other lab animal has or has not responded with malignancy to a carcinogenic chemical? Have these modulating effects been taken into account in concluding that some chemical is or is not a carcinogen? Clearly such questions can establish a compromised position when making conclusions as to whether any chemical should be allowed in the human environment. Mice, rats, hamsters, and guinea pigs have variable systems. Has the chemical tested caused a depression of the system that allowed some virus to induce a cancer? Or has the animal perhaps a depressed immune system, due to repression of genetic expression due to inbreeding that now allows a neoplastic response to occur?

Immunotoxicology is the new kid on the block and is able to ask some very difficult questions. Questions for which we have not all the answers.

In the area of predictive toxicology, however, I would suggest the following. Because immunotoxicology may bring about an additional dimension in extrapolation, I would suggest that future studies be directed toward examining these immune system elements and how they respond to mutagenic or carcinogenic agents. Not only in the lab animal species, but by using the peripheral blood elements from humans. Establishing a tissue culture procedure with human lymphocytes and/or macrophages, even though *in vitro*, would allow function and surface identification studies as well as biochemical investigations to precede and perhaps promote greater confidence when possibly identifying toxic responses to humans. Other human cells have been cultured, such as fibroblasts and the HeLa cells, surely the same could be done for the immune system cells. It would go far in impacting the program of public health for which we are all responsible.

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C. BACKGROUND INFORMATION

THE ATTACHED REPRINTS FROM PERIODICALS AND THE CONGRESSIONAL RECORD ARE INTENDED TO PROVIDE BACKGROUND INFORMATION REGARDING AGENT ORANGE, DIOXIN, DOW, AND RELATED TOPICS.

THE LAST PAGE IN THIS GROUP IS A COPY OF THE AGENT ORANGE BILL INTRODUCED BY CONGRESSMAN DASCHLE (H.R. 1961), AND HIS REMARKS AT THE TIME OF INTRODUCTION.

WASHINGTON, TUESDAY, APRIL 19, 1983

Congressional Record

DOW CHEMICAL CO., AND DIOXIN

HON. THOMAS A. DASCHLE

OF SOUTH DAKOTA

IN THE HOUSE OF REPRESENTATIVES

Tuesday, April 19, 1983

● Mr. DASCHLE. Mr. Speaker, in today's New York Times, April 19, 1983, a front page article appeared revealing what many of us have been saying for some time; that the Dow Chemical Co. was aware of the health hazards and toxicity of dioxin, the contaminant found in agent orange and other herbicides, before extensive use of agent orange and these other herbicides occurred both in Southeast Asia and in the United States. Dow of course, made no effort to notify the USDA, DOD, or any other major governmental purchaser of dioxin contaminated herbicides of their concerns.

Dow's track record on dioxin has been far from exemplary and the information revealed in the Times article today further damages the claims of Dow, the Veterans' Administration and others that dioxin is relatively safe and that veterans in Vietnam are unlikely to be suffering unusual health effects as a result of their exposure to dioxin contaminated chemicals. I submit this article for the RECORD and hope that all Members and staff will take the time to read it.

The article follows:

[From the New York Times, Apr. 19, 1983]

1965 MEMOS SHOW DOW'S ANXIETY ON DIOXIN

(By David Burnham)

WASHINGTON, April 18—Almost 20 years ago, scientists from four rival chemical companies attended a closed meeting at the Dow Chemical Company's headquarters. The subject was the health hazards of dioxon, a toxic contaminant found in a widely used herbicide that the companies manufactured.

Shortly after the meeting in Midland, Mich., on March 24, 1965, one of those attending wrote in a memorandum that Dow did not want its findings about dioxin made public because the situation might "explode" and generate a new wave of government regulation for the chemical industry. Another scientist noted that Dow officials had disclosed at the meeting a study which showed that dioxin caused "severe" liver damage in rabbits.

Dioxin, which has also been linked to birth defects and skin disorders in laboratory animals, is believed to be the deadliest chemical made by man, but its effects on humans have been difficult to prove conclusively. Since the Midland session, various studies have yielded conflicting evidence on whether dioxin increases the risk of cancer in humans.

Although it has been known for many years that Dow held the 1965 meeting with its competitors, excerpts from corporate memorandums about the session are only now beginning to emerge as a result of a lawsuit filed in 1979 against Dow and several other chemical companies. The memorandums raise the possibility that Dow scientists have been saying one thing in private about dioxin while the company's management has said something else in public.

"There is absolutely no evidence of dioxin doing any damage to humans except for something called chloracne," Paul F. Oreffice, the president of Dow, said last month on NBC's "Today" show. "It's a rash." Dow has performed medical tests on individuals suffering from chloracne for "over 20 years," he added, "and there is no evidence of any damage other than this rash which went away soon after."

Dow's critics challenge the accuracy of Mr. Oreffice's flat assertion that there is no evidence that dioxin causes human damage other than chloracne and also charge that Dow has failed to publish all the information it has collected in its own dioxin research. Furthermore, they say, Dow has systematically resisted Federal and state efforts to learn about and regulate dioxin.

According to a pretrial motion filed by Yannacone & Associates, the legal organization created to represent the Vietnam veterans in the Agent Orange case, the 1965 meeting on dioxin was attended by eight of Dow's senior scientists and six officials of Hooker Chemical; the Diamond Alkali Company, which later became part of Diamond Shamrock, and the Hercules Powder Company. A representative of the Monsanto Chemical Company was invited but did not attend.

Donald R. Frayer, a spokesman for Dow confirmed in an interview April 5 that the giant chemical company had called the

(Over)

meeting to discuss the health hazards of dioxin. "We feel the meeting was pretty darn straightforward and proper," he said. "I think on the balance that the record shows we discovered a problem, sought out our competitors and tried to give them information and a means to control the problem."

INVITATION TO MEETING

The pretrial motion filed by Yannacone & Associates quoted a number of documents. V. K. Rowe, then director of Dow's Biochemical Research Laboratory, said in his invitation to the meeting that Dow had been researching "toxicological problems caused by the presence of certain highly toxic impurities in certain samples" of the herbicide 2,4,5-T and wished to share its findings. The Dow laboratory was and is recognized as one of the world's finest privately owned toxicology labs.

Two days after the meeting, C. L. Dunn, a chemist who was manager for regulatory affairs for Hercules, summarized in writing what he had been told.

"Dow says that their examination of their own and competitors' 2,4,5-T products contain what they call 'surprisingly high' amounts of the toxic impurities," he wrote.

"In addition to the skin effect," he wrote, describing the results of tests on rabbits, "liver damage is severe, and a no-effect level based on liver response has not yet been established. Even vigorous washing of the skin 15 minutes after application will not prevent damage and may possibly enhance the absorption of the material. There is some evidence it is systemic."

FEAR ON SITUATION

Dr. John Frawley, the chief toxicologist for Hercules, who had also attended the March meeting, got a follow-up telephone call four months later from Earl Farnum, a Dow executive. Dr. Frawley immediately wrote a confidential memorandum to the file.

Mr. Farnum, he wrote, said he was calling on behalf of a Dow vice president, Donald Baldwin, and "stated that Dow was extremely frightened that this situation might explode."

"They are aware that their competitors are marketing 2,4,5-T which contains 'alarming amounts' of acnegen," Dr. Frawley continued, referring to dioxin, "and if the Government learns about this the whole industry will suffer. They are particularly fearful of a Congressional investigation and excessive restrictive legislation on the manufacture of pesticides which might result."

A second memorandum written by Dr. Frawley, and quoted in part by lawyers for the veterans, said he had just received new information about health effects of dioxin from Monsanto, which did not sent a representative to the meeting. "From the data provided, a sample which contained 5 parts per million would be acutely toxic," he wrote. "Whether this refers to death or liver damage is not clear."

Daniel Bishop, a Monsanto spokesma said in an interview that his compa "didn't do any testing, period, not then a not now." He said that a fair reading of I Frawley's full statement would make it cle that he had not received the toxicity infc mation from Monsanto, but was not able identify the information's source becau the material in the Agent Orange case h been sealed by the judge. The documen were sealed at the chemical companies' r quest.

GROUP OF 75 COMPOUNDS

Dioxin is the name given to any of family of 75 compounds, called dibenz para-dioxins, composed of benzene mo cules and oxygen atoms. The compounds a an unwanted byproduct of several chemic processes, including the manufacture 2,4,5-T under certain circumstances; 2,4,5- is one of the two major components Agent Orange.

Proving the specific effects of toxic chem cals on humans is extremely difficul human experiments are generally prohibi ed by medical ethics. Animal tests, whic are universally accepted by scientists as pro viding essential guidance on appropriate ex posure levels for humans, are not a perfec guide because various species react differ ently.

In laboratory rats, concentrations as sma as five parts per 1,000 million have cause statistically significant increases of cance in rats.

Two studies, conducted on a group of for estry workers in northern Sweden and on group of agriculture workers in souther Sweden, point to a possible association be tween exposure to herbicides contaminate with dioxin and an increased risk of soft tissue cancers. Other studies, however, in cluding one in New Zealand, show no highe risk of cancers for a group of farmers, for esters and fisherman exposed to dioxin tha in men in other occupations.

WARNING ON DIOXIN STUDIES

Dr. Samuel S. Epstein, a physician who i professor of occupational and environmen tal medicine at the University of Illinoi Medical Center in Chicago, cites the Swed ish studies and other research on such ques tions as reproductive abnormalities to chal lenge the statement of Dow's president tha there is no evidence that dioxin causes an more damage than a skin rash. "For Mr Oreffice to make that statement is absurd," he said in a recent interview.

On March 23, Dr. Perry J. Gehrig, Dow's vice president for agricultural research an development and director of health and en vironmental science, cautioned the Hous Subcommittee on Natural Resources, Agri culture Research and Environment again "overinterpreting" the Swedish studies. Th reports, he argued, "are too incomplete both individually and in aggregate, to cur rently formulate a clear picture of the possi ble associations between TCDD and soft tissue sarcomas." TCDD is a form of dioxin

More

In 1982, Dow scientists published a report of a company survey on the occurrence of spontaneous abortions, stillbirths, infant deaths and several categories of birth defects among the wives of Dow workers who had been directly exposed to dioxin. The study concluded there were few differences in the number and kind of birth abnormalities found in these women compared with the wives of Dow workers not exposed to dioxin, and the report has been used frequently to support the theory that dioxin is not as dangerous as generally believed.

But Dr. Marvin S. Legator, professor and director of environmental toxicology at the University of Texas in Galveston, questions the study.

"Initially," Dr. Legator went on, "Dow planned on comparing the birth defects among the wives of Dow dioxin workers with two controls. First, a group of wives of Dow workers in Midland who had not been directly exposed to dioxin, and second, some wives of workmen who lived outside the Midland area. This second control group was important because the Midland area is quite polluted and the general population has a relatively high level of congenital abnormalities. But when they published the study the second control group was not included."

A "SAMPLING PROBLEM"

Mr. Frayer, the Dow spokesman, said the second group had been deleted because of "sampling problems."

"The women could not be compared with those in the first two groups, and they were questioned in a different way," Mr. Frayer said.

Information compiled by Dr. Alvin Young, an expert at the Veterans Administration, indicates that from 1961 to 69 American companies made a total of 154.5 million pounds of 2,4,5-T.

Of that total, 44 million pounds were applied to the jungles of Vietnam, 23.4 million pounds were exported to other countries and 78.1 million pounds were used domestically. The balance, 10 million pounds, was destroyed by the Government after it was decided to halt the Vietnam defoliation program.

Dr. Young estimates that 1,700 pounds of dioxin a year were produced in the United States from the mid-1950's to about 1975, when steps were taken to limit it through changing the manufacturing process.

There is broad agreement that a substantial portion of dioxin-contaminated wastes are buried in thousands of dumps around the country. The Environmental Protection Agency recently said there were 12,000 of these dumps. Other experts have estimated the number may be closer to 50,000.

SUITS AGAINST COMPANIES

Billions of dollars are at stake in the answer to the question of what the chemical companies knew and when they knew it. In addition to the tens of thousands of veterans who have sued the chemical companies because of their exposure to Agent Orange in Vietnam, thousands of other Americans living near toxic dumps, such as the one in the Love Canal area of Niagara Falls, N.Y., are seeking damages on the grounds that dioxin and chemical poisons left there have shortened their lives and caused cancer, birth defects and genetic damage.

In January 1979, a group of veterans brought a Federal suit in New York, charging that the dioxin contained in the 2,4,5-T sprayed in Vietnam was a cause of cancer and other diseases among their members and had resulted in genetic damage and the birth of severely deformed children.

Victor John Yannacone, Jr., a principal organizer of the association of lawyers handling the class-action suit, said in a recent interview that the group now represents 20,000 Vietnam veterans, widows and children of veterans who are seeking damages against the chemical companies that provided the Government with Agent Orange.

The suit against Dow and the other major manufacturers of 2,4,5-T is scheduled to go to trial in the Uniondale, L.I., court of Federal District Judge George C. Pratt Jr. in June.

In an annual report filed with the Securities and Exchange Commission in Washington called a 10-K, Dow said it was one of all chemical companies who were defendants in the suit. "Dow believes it has not been scientifically demonstrated that the injuries claimed by the plaintiffs were caused or could have been caused by exposure to Agent Orange," the report said.

The Dow report also noted that the chemical company was opposing a move by the Environmental Protection Agency initiated during the Carter Administration that would totally ban the use of 2,4,5-T in the United States. The herbicide therefore is still being used on rice fields, on range land and in industrial areas such as refineries, to control weeds.

The company's repeated public statements about the comparative safety of dioxin, including testimony to Congressional committees, press releases and scientific papers, have been accompanied by efforts on its part, particularly in the Reagan Administration, to block the Government from collecting information about the contaminant.

Evidence of the repeated contacts between Dow and E.P.A. officials in Washington, not of the subject of the meetings, is contained in the calendars and travel records of these officials that have been obtained by the House subcommittees investigating the agency.

(Over

Dow releasing toxic substances: EPA

New studies by the Environmental Protection Agency (EPA) show that the Dow Chemical Co. is releasing dioxin and at least 40 other toxic substances into waters downstream from its Midland, Mich., plant site, agency officials have reported.

Catfish placed in cages in the Tittabawassee River just downstream from the Dow plant for four weeks were found to have become contaminated with concentrations of the most potent form of dioxin of 110 parts per trillion.

That level is nearly 14 times the concentration found in fish tested in a similar manner just upstream from the Dow plant, indicating that site as the likely source of the contaminant.

The downstream concentrations are more than twice as high as the 50 parts per trillion level labeled by the Food and Drug Administration (FDA) as the "level of concern" for human consumption.

Officials pointed out, however, that comparisons may be inappropriate, since the EPA tested dioxin levels in the whole fish, while the FDA standard refers only to edible portions, which may not be comparable.

Regional EPA officials in Chicago long had charged that the Dow plant was a significant source of toxic contamination in downstream waters, including the Tittabawassee and Saginaw Rivers and Saginaw Bay — where catfish and carp are harvested commercially.

Earlier evidence had been ambiguous, however, and was disputed by Dow. EPA officials said. The new study "confirms for us the problem is there," said EPA Regional Administrator Valdus Adamkus. "Now we've got very good and clear evidence that dioxin and other toxicants are being released from the plant. The levels are of concern to us. It has to be controlled."

Dow officials said the new studies were not consistent with previous data, some of which had been provided by Dow, and that contamination levels were small.

The newly reported study also found traces of more than 40 toxic compounds in water samples taken downriver from the Dow plant, including methylene chloride, chloroform, various pesticides, PCBs, and herbicides such as Silvex. The dioxin found was in the form of 2,3,7,8-T, or TCDD, considered by many experts to be the most potent toxic chemical known.

The levels detected were extremely small — 50 parts per quadrillion of TCDD in water downstream from the plant — but the EPA analysis extrapolated from its findings the estimate that some 35 pounds of toxic chemicals were released from the Dow plant every day. The plant discharges more than 61 million gallons of waste water daily.

The water level study was conducted in 1981, Adamkus said, but results were delayed so long because of the difficulty of analyzing such small concentrations.

An earlier report by the EPA regional office led to the forced resignation of Acting EPA Administrator John W. Hernandez last month. Adamkus, in congressional hearings, had said that Hernandez had ordered the altering of the earlier report to eliminate conclusions that Dow was the source of contaminants in the downstream rivers.

AMERICAN MEDICAL ASSOCIATIC NEWS
April 15, 1983

LINKS TO GOVERNMENT

Anne McGill Burford, for example, made at least two trips to Midland, Mich., in her 22 months as the head of the Environmental Protection Agency. Rita M. Lavelle, the former head of the Government program to clean up toxic waste dumps, met at least 14 times with Dow officials in the 11 months she held office.

Mrs. Burford, Miss Lavelle and 11 other political appointees recently resigned or were dismissed amid Congressional inquiries on allegations that the agency's toxic waste program had been mishandled.

(Continued from previous page)

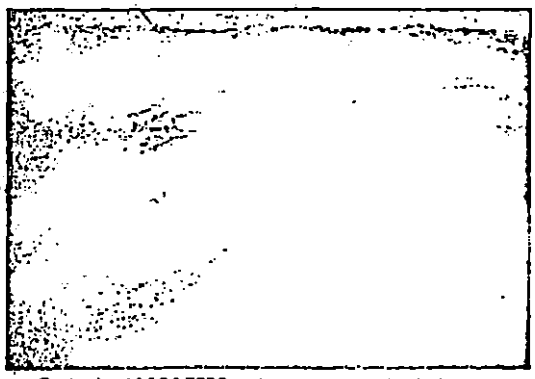
According to the public testimony of some officials of the agency, Dow used its connections with the top echelon of the agency's Washington officials to get its way on several important matters relating to the regulation of dioxin.

Three weeks ago, for example, agency officials in Chicago told the Investigations Subcommittee of the House Committee on Energy and Commerce that their superiors in Washington ordered them to change an important report on dioxin to comply with the wishes of Dow.

The key deletion from the report was the following central conclusion about Dow's Midland plant: "Dow's discharge represented the major source, if not the only source, of TCDD contamination found in the Tittabawasse and Saginaw Rivers and Saginaw Bay in Michigan." ●

Agent Orange finally gets its day in court

When the first phase of the long-awaited Agent Orange trial begins in U.S. Federal District Court (Uniondale, N.Y.) next month, it will focus on the "government contractor" defense. Chemical makers who supplied the Dept. of Defense with Agent Orange and other herbicides that contain 2,4,5-Tricholorophenoxyacetic acid (2,4,5-T) will argue that at the start of the Vietnam war, data concerning the potential human health effects of 2,3,7,8-tetrachloridibenzo-p-dioxin (2,3,7,8-TCDD), a contaminant of 2,4,5-T commonly known as dioxin, were equally accessible to both government and industry. And they will argue that what data existed were scanty at best.



Contaminant 2,3,7,8-TCDD, or dioxin, was sprayed in the Vietnam war.

But a closer look at some trial documents—sealed in the courtroom but publicly available elsewhere—indicates that a great deal more was known about potential health troubles associated with dioxin than most companies have allowed. In fact, data were emerging in Germany as far back as the late 1950s that suggested that dioxin was a potentially hazardous substance.

Outbreak. The early warnings about dioxin came from Karl Schulz, a young German physician who, in 1955, was treating a Boehringer Ingelheim factory worker for chloracne. The worker, says Schulz, told of similar cases among other 2,4,5-T workers in Boehringer's Hamburg plant. Boehringer stopped producing 2,4,5-T and asked Schulz, then a member of Hamburg University's dermatological program, and Josef Kimmig, the program's director, to help seek the cause of the outbreak.

By 1957, the collaborative effort was bringing results. Schulz's research identified dioxin as a by-product in the production of both 2,4,5-T and its precursor, trichlorophenol (TCP). Skin tests on his own body and on animals indicated a direct link between dioxin and chloracne. Monitoring of employees who had contracted chloracne showed a possible link between dioxin and liver disease.

At the same time George Sorge, a Boehringer chemist, was seeking ways to cut dioxin levels in finished products. "He believed that temperature was the key to dioxin control," Schulz says. Sorge subsequently developed a low-temperature TCP production process whose end-product showed negative results in Schulz's animal tests.

Liver damage. Schulz's findings were published in four German medical publications in 1957. They became widely available in the U.S. when one of the Schulz articles appeared in the Dec. 10, 1958 issue of *Chemical Abstracts*. The article clearly points to the presence of liver damage found in several Boehringer workers.

The chemical makers want to prove that the government knew of Schulz's work. About a year ago, two Dow lawyers met with Schulz and asked him whether he had been contacted by Air Force personnel or by Friedrich W. Hoffman, who in 1959 was chief of the research branch of the U.S. Army Chemical Warfare Laboratories and was charged with scouting Europe for potential chemical warfare agents. Schulz says he told them that he "had never been contacted by either Hoffman or anyone from the Air Force." But Dow asserts that a report by Hoffman noting Schulz's article was circulated widely throughout the military.

Dow Chemical apparently was conducting its own research in the 1950s. It had asked Joseph V. Klauder, a Philadelphia dermatologist, to conduct a series of human experiments to gauge the potential health effects of herbicides based on 2,4,5-trichlorophenol. Klauder, according to publicly available documents, noted that some of the materials he was working with were "highly allergenic." The documents are specific about some substances. For example, an internal Dow report on Klauder's findings indicates that a herbicidal composition containing 55% Silvex (2,4,5-TP) proposed for "control of aquatic weeds" is irritating only in concentrations exceeding 5%.

Warnings. It is not known whether Klauder, who died in 1962, carried out any experiments using 2,4,5-T. But Boehringer clearly did. In 1956 the company wrote to all manufacturers of TCP and 2,4,5-T worldwide, warning them of problems inherent in 2,4,5-T production and apprising them of its safer production process. While confirming the letter's existence, Boehringer declined to release a copy to *Chemical Week*.

Insight into its contents can be gleaned from "Early Dow History of the Chloracne Problem—Birchem's [Dow's Biochemical Research Laboratory's] Contribution," an internal report prepared by Dow just 13 days before its controversial Mar. 24, 1965 meeting with representatives of other TCP manufacturers, including Hercules, Diamond Alkali (now Diamond Shamrock) and Hooker Chemical (now Occidental).

> A lot more was known about dioxin's health hazards than many companies would admit

The report says that the Boehringer letter, which it dates to 1957, contained the "results of research on chloracne," including a description of "danger points" in the production process. The report states that Boehringer called for a process temperature limit of 160° C to "avoid producing the acne agent" in TCP and 2,4,5-T. The Dow document is annexed as an exhibit to the records of the 1979 Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) hearings to cancel the registrations of 2,4,5-T and of Silvex. Both materials contain dioxin.

Slow to move. The Biochem report notes a 1955 letter from Boehringer to the Swiss firm Givaudan, in which Boehringer sought safety information. Givaudan referred the letter to Dow, which, according to the document, sent its own letter to Boehringer describing "hazards and precautions for safe handling of 2,4,5-trichlorophenol."

Despite its interest in the Boehringer technology, Dow did not license it immediately. In early 1964, the company switched to a production technique that required plant process temperatures of 215° C. Measured in December 1964, TCP waste streams contained dioxin levels ranging from 6,000-10,000 parts per million, according to material introduced by Dow during its recent motion for summary judgment. The Biochem report indicates that it was, indeed, the high process temperature that generated the high dioxin levels, and led to a major outbreak of chloracne at Dow. Although Dow told the Michigan Dept. of Public Health about that problem, it did not mention it to the Dept. of Defense until 1967. Dow has contended in court that "knowledge of the precise occupational hazard" that occurred in 1964 is "irrelevant" to the government contractor defense because it "promptly remedied" the problem.

Neither the dioxin levels in finished product during this period, nor the amount of Dow's output that went into domestic or military use is known. But an Air Force sampling of Agent Orange's predecessor, Agent Purple, which was used between 1962 and 1965, showed dioxin levels as high as 45 ppm. Both Dow and Monsanto supplied 2,4,5-T to the military during this time. Citing the pending litigation, Monsanto has reserved comment.

Dow's rights. In March 1965—the same month as its meeting with other TCP makers—Dow purchased licensing rights to Boehringer's low-temperature TCP manufacturing process. From then on, Dow contends, its 2,4,5-T never contained more than 1 ppm of dioxin. The company has recently stated that 2,4,5-T containing 1 ppm or less presents no human health hazards.

Still, Dow seeks to prove that government officials were alerted to potential problems with dioxin well before 1964. In pre-trial documents, Dow notes a 1962 article in the Journal of Investigative Dermatology that purported 2,3,7,8-TCDD as a potent acnegen. The article was based on research into the physiology of acne, conducted at the University of Chicago Medical Center and commissioned by the Army.

Helen Krizer, a university chemist who worked on the project, recalls getting the idea to use TCDD as a standard to measure the strengths of other suspected acnegens from Schulz's article in *Chemical Abstracts*. Krizer cannot recall whether she mentioned Schulz's work in her own annual reports to the Army prior to 1962. But she does say that "it's possible." □

Dioxin Puts Dow on the Spot

Memos of 1965 meeting hint at company's fears

On a chilly morning in March 1965, a highly unusual gathering took place at Dow Chemical Co.'s headquarters in Midland, Mich. Without any corporate fanfare, Dow scientists met with colleagues from three rival firms, Hooker Chemical, Diamond Alkali and Hercules Powder. On the agenda that day was a discussion of the effects on human health of a family of chemicals known as dioxin. The chemicals, including Agent Orange, later used by the U.S. to defoliate the jungles of Viet Nam, are an unwanted byproduct in the making of herbicides. At the time, most chemists were only vaguely aware of dioxin, or its problems. But Dow had just experienced an outbreak of dioxin poisoning among workers in Midland. It wanted to sound a private alert to prevent similar incidents at other chemical plants, including those of its competitors.

Sitting along the Tittabawassee River, Dow's sprawling installation in Midland, Mich.

Ghosts from what seemed like a corporate gesture of good will to competitors.

Last week this seemingly generous gesture of good will came back to haunt Dow. According to a report in the New York *Times*, memorandums from participants in that almost forgotten session indicate that Dow's objective may not have been corporate benevolence. Rather, the documents show, the meeting appears to have been part of an effort to keep discoveries about dioxin's perils from exploding into a public scandal, which could have brought a new outcry for governmental regulation of the chemical industry. Wrote a participant from Hercules Powder: "They [Dow] are particularly fearful of a congressional investigation and excessive restrictive legislation on the manufacture of pesticides."

The documents were unearthed during the preliminary legal maneuvering in a class-action lawsuit that has been brought on behalf of 20,000 Viet Nam veterans, their widows and children against Dow and other producers of Agent Orange. Scheduled for trial on Long Island next month before U.S. District Court Judge George C. Pratt, the suit charges that the dioxin contained in Agent Orange caused cancer and other ailments among the soldiers and genetic defects in their children. Dow has resolutely denied the charges. In a television interview, Dow President Paul F. Oreffice said, "There is absolutely no evidence of dioxin doing any damage to humans, except something called chloracne. It's a rash."

Many scientists do not take the chemical so lightly. They say that even concentrations as low as 5 parts per trillion can cause birth defects, cancer and other serious illness in laboratory animals. Last week the Centers for Disease Control in Atlanta reported that 112 of 130 residents tested in Imperial, Mo., near dioxin-contaminated Times Beach, showed abnormalities in blood, liver or kidney functions. Says Dr. Irving Selikoff, director of the environmental-science lab at Mount Sinai Medical Center in Manhattan: "No question about it, dioxin is harmful to humans. It is man-made. As a result, the human body doesn't know how to break it down. We store it in our bodies and accumulate it."

In 1964, after 64 workers at its Midland plant developed chloracne following exposure to dioxin, Dow began a full-scale investigation of its effects. When dioxin was administered to rabbits, their livers were severely damaged. As one participant in the 1965 meeting later wrote, the Dow scientists reported that "even vigorous washing of the [rabbit's] skin 15 minutes after application [of dioxin] will not prevent damage and may possibly enhance the absorption of the material."

Now, 18 years after the private parley of scientists, the Midland area is still wrestling with dioxin. It continues to show up in tainted water from Dow's Midland plant, has been found in fish in ten Michigan rivers and is the source of considerable anxiety among local residents. Says Diane Herbert, a young mother of two children: "Almost everyone seems to have thyroid problems, and there are a lot of skin tumors and allergies in pets." To assess those fears, Michigan's state health department is seeking state or federal money for a major study of dioxin's effects on residents.

Whatever the private concerns of the Dow scientists at the 1965 meeting, they did not lead to public action. As a company spokesman said last week, "We found we had a problem. We corrected it. We reported it to the appropriate authorities. We called in our competitors, urged them to adopt our practice. This was really an attempt by industry to police itself." The Viet Nam veterans' lawyer, Victor Yannacone, has a harsher view. He calls the backstage parleying nothing less than "a conspiracy of silence." ■

TIME MAGAZINE
May 2, 1983

Congressional Record

NEW DISCLOSURES REGARDING AGENT ORANGE

HON. THOMAS A. DASCHLE
OF SOUTH DAKOTA
IN THE HOUSE OF REPRESENTATIVES

Tuesday, May 24, 1983

● Mr. DASCHLE. Mr. Speaker, a recent news story in the Robinson, Ill., Daily News, present striking evidence of the link between the dioxin in agent orange, to which many servicemen were exposed in Vietnam, and the illness that many of those servicemen have suffered.

I commend the writer, Tony Gordon, for his extensive research, and I recommend his article to my colleagues for their underatanding of this significant issue:

[From the Robinson (Ill.) Daily News, May 5, 1983]

APOCALYPSE LATER? "ORANGE-HOT" CONTROVERSY

(By Tony Gordon)

A medical specialist in Chicago has diagnosed a number of physical ailments in West York resident Sammy Davis and another Vietnam veteran as being related to the defoliant Agent Orange.

The diagnosis is believed to be the first time a physician has drawn a connection between illness and the exposure of U.S. servicemen in Vietnam to the dangers of dioxin, an ingredient of Agent Orange.

Davis, who was awarded the Medal of Honor for service in Vietnam, was one of the first three Vietnam veterans to be examined for possible dioxin-related illnesses by Dr. Bertram Carnow, president and senior scientist for Carnow, Conibear and Associates, Ltd.

Carnow is the director of occupational and environmental medicine at the University of Illinois School of Public Health, an attending physician at three Chicago hospitals and the author of more than 50 articles and publications on the effects of the environment on human health.

An advisor to the three veterans, Irv Wells, is chairman of the Vietnam Veterans Confederation of Milwaukee and a licensed surgical physician's assistant. He arranged to have the three men see Carnow for an examination.

"We wanted to have our guys examined by the finest expert in the country and a review of the research on dioxin led us to Dr. Carnow. He's pure physician, a non-political animal, and was willing to look for the reason these men are sick," Wells said.

Carnow performed a 12-hour series of tests and physical examination on the three veterans in March. Carnow's findings are markedly different from information the men received following examinations by Veterans Administration doctors.

The results of Carnow's independent tests show Davis and fellow veteran John Gromowski of Milwaukee suffer from abnormalities in their blood and vascular system, liver disorders, nervous system effects and severe depression.

None of these maladies were diagnosed through tests the men had in the VA's Agent Orange screening program. Davis was told by VA doctors he needed surgery on nerves in his wrist and should undergo psychological counseling. Gromowski, who has suffered from seizures since 1972, said VA doctors were unable to identify their cause.

The third veteran in the group, Medal of Honor recipient John Baca of Springfield, Mo., will require further examination before a diagnosis can be made, Wells said.

Both Davis and Gromowski went through the VA's Agent Orange screening at the VA Hospital at Wood, Wisc., a Milwaukee suburb. At the conclusion of tests there, they were sent letters signed by Dr. Michael O. O'Grady, the staff environmental physician, that said the results of their initial tests were "satisfactory."

The Daily News attempted to contact O'Grady on Wednesday, but was told he could not speak to the press and was referred to public relations spokesman Y. C. Parish. A woman in Parish's office said he would not return to work until Monday.

It is the present policy of the Veterans Administration to deny any disability claims based on dioxin's effects. The VA provides free physical examinations to vets who feel they may have suffered adverse health effects from exposure to Agent Orange.

The VA said Wednesday 260,000 Vietnam vets have gone to VA hospitals complaining of illnesses they thought could be related to Agent Orange in the last year and 9.46% of them were ill enough to be hospitalized, none for any illness the VA says is caused by Agent Orange.

Vern Rogers, a spokesman for the VA Office of Public and Consumer Affairs in Chicago, last week said the agency is "providing medical screening for any veterans who think they may have a problem and we are doing so without any medical proof in the entire world that a link between Agent Orange and medical problems exists. There is no piece of paper by any doctor anywhere that says anything at all is caused by Agent Orange.

Results from Carnow's testing and examinations may provide that piece of paper.

Although Carnow said "I have no intention of becoming involved in the politics of this issue," he said his diagnosis of Davis "is a matter of interpretation of studies of people who have the same things."

"It comes down to a question of whether you believe something that looks like a duck, walks like a duck and talks like a duck is a duck. There may be other animals with feathers that spend time in the water, but a duck is one specific animal and people should be able to determine that from investigation," Carnow said in assessing the link between dioxin and the health of the two veterans.

In an interview restricted to the results of the Davis examination and general information about his procedures, Carnow told the Daily News "Mr. Davis displays the same symptoms traditionally found in people who have been exposed to dioxin, and there is absolutely nothing else in his background to suggest any other exposure to dioxin than the Agent Orange in Vietnam."

According to both the doctor and patient, Carnow's examination of Davis detected the following:

—High cholesterol, high triglycerides and a large concentration of fatty cells in his blood, a condition normally found in people much older than Davis. These factors, Carnow said, pose "a very high risk of heart disease."

—A lowered level of liver functions and a white blood cell count pattern that is similar to one in a person whose immune system is depressed.

—Normal kidney functions, but an increase in uric acid level that could lead to kidney damage and bouts with gout or gouty arthritis. Davis has had attacks of gout since 1969, one year after he returned from his Vietnam service.

—A variety of nervous system dysfunctions. The medis nerve in his right hand is inflamed and interferes with sensory conduction, a condition often associated with a degenerative process. He also suffers from petty mall seizures, which make him nauseous, dizzy and blur his vision.

—Abnormalities in his reproductive system which, although it is still possible for him to father children, produce sperm forms that are not normal in their ability to impregnate or are mutated.

—An organically-based severe depression pointing to an imbalance of nourishment in some of the cells in his brain. Davis said Carnow told him he has not suffered brain damage, but some of the cells are damaged to the point where they are unable to absorb oxygen.

—His body also has difficulty in the process of energy production and transfer, which brings on occurrences of extreme weakness. Davis said the tests indicated the body produces an enzyme to fight the dioxin contamination which swells the nucleus of cells and retards the flow of energy through his body.

Gromowski said Carnow told him a likely cause of his seizures is damage to his brain caused by malformed cells. His liver and central nervous system are damaged, there is a blockage in his lungs and abnormalities in his blood.

"Dr. Carnow told me the diseases I have are all a result of exposure to the dioxin in Agent Orange," Gromowski said.

The diagnosis of Gromowski may be especially significant because while Davis was assigned to a combat unit in areas of Vietnam sprayed with Agent Orange, Gromowski was not. He was stationed as a cook in Da Nang base camp for six months and was never sent into a sprayed area.

"The diagnosis of John puts us in the position to rethink the incidents of exposure to included areas of South Vietnam previously unsuspected of posing a threat," Wells said.

Carnow said his testing on the three veterans involved "a study of the patient's history, a complete physical exam and laboratory tests to measure the functions of various organ systems: the liver, central and peripheral nervous systems, cardiovascular and reproductive systems. We also do a series of blood tests to determine blood counts in the liver and kidneys."

He said his firm employs "the state of the art in clinical medicine," but he has no equipment or procedures not available to the VA.

"The Veterans Administration has the capability to do anything we can, but not having the results of Mr. Davis' tests there, I don't know what type of examination they conduct. The VA has a two-volume book on the research into dioxin, they know what is being done. They have the toxologists, biostatisticians and laboratory physicians capable of doing these same tests. It becomes a question of whether or not they agree with me," Carnow said.

One group of people believed to have agreed with Carnow and his tests for adverse health effects caused by dioxin exposure are the 12 members of a Madison County jury who in August began granting judgments of between $1 million and $1.3 million to each of 47 railroad workers involved in an exposure related suit.

The workers charged in the suit they had suffered central nervous system damage and cancers because the Norfolk and Western Railway had failed to protect them when they were involved in a dioxin clean up operation after a rail accident in 1979.

Carnow testified on behalf of the workers and described the medical problems he has detected in them through his tests. After 10 days of his testimony the jury decided the workers had been affected and began making the financial awards.

In his interview with the Daily News, Carnow said he was [illegible] any other doctors of negligence even though the results of his tests on Davis and Gromowski show different results than the VA tests.

"I do not think anyone is faking the tests, but they may not be doing all of them and may not be viewing the results the same way. We have only examined three people and when and if we do 30 or more, we will

Congressional Record

● Mr. DASCHLE. Mr. Speaker, Mr. PANETTA as vice chairman of the Vietnam veterans in Congress, and myself as chairman, are introducing legislation that will to an extent provide financial relief for a limited group of Vietnam veterans suffering from the effects of toxic chemical exposure from their service in Vietnam; 111 of my colleagues from both sides of the aisle have joined with me in this effort.

I believe this legislation is even more compelling after the administration's decision to compensate the residents of Times Beach, Mo. Though the extent of Federal Government culpability at Times Beach is still somewhat unclear, the decision to purchase the property in the community implies an acknowledgment that dioxin, the same contaminant in the herbicide agent orange, is dangerous enough to pay for the evacuation of an entire community of 2,500 people. If this Government is willing to accept this responsibility for Times Beach, it has even more of a responsibility to provide compensatory relief to individuals it was directly responsible for exposing to the very same chemical in Vietnam.

My colleagues may be interested to learn that dioxin levels at Times Beach, averaging 100 parts per billion, are approximately 20 times less than the mean level of dioxin in agent orange, 2 parts per million. Dioxin levels in agent purple averaged 32 parts per million and in agents green and pink they averaged 65 parts per million. Herbicides pink, purple, and green used primarily before 1965, thus had dioxin levels hundreds of times higher than levels discovered at Times Beach and thousands of times above the EPA danger level of 1 part per billion for domestic use of herbicides containing the contaminant.

We thus believe it especially appropriate to introduce legislation which would compensate certain Vietnam veterans for illnesses and disabilities which may be related to their service in Vietnam. Current law allows for the establishment of presumptions, and the payment of compensation, when there is doubt as to whether a specific illness originated during a veteran's service or not. This legislation would establish three new presumptions for compensation purposes in section 312 of title 38, United States Code. The new presumptions are for soft tissue sarcomas, a liver condition known as porphyria cutanea tarda, and a skin affliction called chloracne. Scientific studies presently show a strong correlation between these illnesses and dioxin exposure. There would be no presumptive period applicable to these illnesses, but in recognition of the largest and probably most costly epidemiological study ever undertaken, there is a sunset provision which would terminate benefits within 1 year of the first report from the Centers for Disease Control epidemiology study unless the results of the study indicate that there continues to be a significant correlation between service in Vietnam and certain health effects. Since the CDC study is expected to have initial findings by 1987, the sunset provision would likely become effective sometime in 1988.

A few hundred veterans suffering from soft tissue cancers and porphyria cutanea tarda will benefit from this legislation as would some 2,500 veterans with chloracne or chloracneform lesions should Veterans' Administration extrapolations of current chloracne cases prove accurate. This legislation is expected to cost only $3 to $4 million a year. The following chart provided by the Veterans' Administration lists the number of agent orange related compensation claims filed with the agency as well as a breakdown of

AGENT ORANGE CLAIMS

	Number	Percent
A. Total number of claims	16,564	100.0
Claims with diagnosis confirmed	8,851	49.?
Claims with diagnosis not confirmed	4,2??	25.4
Claims with no disability alleged	3,???	2?.?
B. Claims with diagnosis confirmed	8,851	100.0
Allowed for causes other than agent orange	[1]1,275	15.4
Denied	[2]7,576	84.6

[1] Approximately 95 percent of 1,207 of the total 1,275 claims allowed [illegible] service connected [illegible] ... [illegible]

[2] [illegible] ... following categories:

Skin conditions (rashes, [illegible], [illegible] and [illegible])	4,232
Nervousness, headaches, and fatigue ([illegible])	2,032
[illegible]	951
[illegible] conditions	776
[illegible] ([illegible], [illegible], [illegible], [illegible] etc.)	501
[illegible] (alleged)	333
[illegible]	454
Lung [illegible]	270
[illegible] and [illegible]	231
[illegible]	146

As my colleagues can see, veterans have filed claims for a number of adverse health effects from agent orange exposure. Virtually all of these conditions have been described in scientific literature on phenoxy herbicides and dioxins. For reference purposes, I would refer my colleagues to chapter 5 of the Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins, ordered by Congress in Public Law 96-151, and completed in September 1981. An updated review should be available in several months. This document, as well as a bibliography with over 1,110 references on the subject is available from the Government Printing Office. Certainly, there is no shortage of information on this subject. Despite the large number of adverse effects noticed in exposed populations to dioxin, I felt that at this time the legislation should be limited to those illnesses which are most indisputable.

The efforts of the Army Agent Orange Task Force will also enable us to verify in most cases whether or not a veteran was actually exposed to herbicides. The task force, which has been busy identifying cohort groups of veterans who were exposed, not exposed, as well as those who did not serve in Vietnam for the two Centers for Disease Control epidemiology studies on the Vietnam experience and effects of agent orange exposure, is a most capable and credible source to conduct this research and is completely willing to assist the Congress and Veterans' Administration with this particular effort.

Mr. Speaker, the alleged scientific uncertainty surrounding all the definitive effects of agent orange exposure in my opinion will continue to be expressed for some time. After all, if we have been unable to find conclusive evidence after publication of over 1,100 studies and reports on the chemical spanning decades of work, what can we expect those studies now underway to add to the current knowledge that has not already been revealed. I personally believe that decisions can and must be made on the evidence which is already available and there is sufficient evidence to do so. The social policy implications of agent orange poisoning have been ignored too long. Regardless of whether agent orange can be definitely linked to an illness or is merely correlative, there are over 16,500 Vietnam veterans with severe illnesses they believe are caused by their exposure to agent orange. To hold their fate in the balance while Congress, the VA, and the scientific community deliberate the conclusiveness of the science is a mockery of their service to this Nation and to their suffering. The legislation I am now introducing is a tightly crafted bill which [illegible] diseases to compensatory relief currently not available. If compensation can be provided to residents of Times Beach, and I think it should, it definitely should be provided certain Vietnam veterans as well. Following is the text of the legislation:

H.R. 1961

A bill to amend title 38, United States Code, to provide a presumption of service connection for the occurrence of certain diseases related to exposure to herbicides or other environmental hazards or conditions in veterans who served in Southeast Asia during the Vietnam era

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Vietnam Veterans Agent Orange Relief Act".

SEC. 2. The Congress finds that—

(1) certain adverse health effects occurring among persons who served in the *Armed Forces in Southeast Asia during the* Vietnam era, and certain birth defects occurring among the children of such persons, may be the result of the exposure of such persons *during such service to phenoxy herbicides* (including the herbicide known as Agent Orange) and the class of chemicals known as the dioxins produced during the manufacture of such herbicides or to other factors involved in such service including exposure to other herbicides, chemicals, medications, or environmental hazards or conditions; and

(2) a comprehensive review and scientific analysis of the literature covering studies relating to whether there may be long-term adverse health effects in humans from exposure to any of the class of chemicals known as the dioxins produced during the manufacture of the various phenoxy herbicides (including the herbicide known as Agent Orange), as required by section 307(a)(1)(B) of Public Law 96-151, has been completed and submitted to the Veterans' Administration.

SEC. 3. Section 312 of title 38, United States Code, is amended by adding at the end the following new subsection:

"(c)(1) For the purposes of section 310 of this title and subject to the provisions of section 313 of this title, in the case of a veteran who served in Southeast Asia during the Vietnam era and who after such service suffers from a disease described in paragraph (2)(A) of this subsection, such disease shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of evidence of such disease during the period of service.

"(2)(A) The diseases referred to in paragraph (1) of this subsection are the following:

"(i) Soft-tissue sarcomas.

"(ii) Prophyria cutanea tarda.

"(iii) Acute and residual chloracne and chloracneform lesions.

"(iv) A disease listed in a regulation prescribed by the Administrator under subparagraph (B) of this paragraph.

"(B) The Administrator may determine, and prescribe by regulation, diseases (in addition to those listed in subparagraph (A) of this paragraph) that medical research has shown may be due to exposure to herbicides, chemicals, medications, or environmental hazards or conditions. The Administrator shall include in such regulations, a specification of the standards used by the Administrator in making such determination.

"(3) Paragraph (1) of this subsection shall terminate on the first day of the first month beginning after the end of the one-year period beginning on the date the Administrator submits to the appropriate Committees of Congress the first report required by section 307(a)(2) of the Veterans Health Programs Extension and Improvement Act of 1979 (Public Law 96-151; 93 Stat. 1095).".●

MARCH 8, 1983

Dioxin Made Human Wreckage Of Tough Trackmen: Carnow

Medical Tribune Report

FROM THE RECKONING of St. Joseph's Hospital's Dr. Gedney, a team of Missouri doctors spent a total of about 40 hours examining the Times Beach test population of 120. Dr. Carnow said each of the 47 railroad trackmen spent a total of 16 or 18 hours seeing his team of 12 specialists. The group were examined starting 10 months after the accident, and reexamined at intervals until last November.

"The stuff, which included phenol and orthochlorphenol, affected every major organ system and numerous enzyme systems," according to this specialist. His colleague in these studies was his associate, Dr. Shirley A. Conibear.

"Many of the workers had diabetes. Four had Peyronie's disease. A number had complete urinary obstruction. Five, or about 10 percent, developed skin cancer. One had a 1,400 triglyceride. Eighteen had abnormally low testosterone, usually with a marked decrease in libido. In many, peripheral neuropathy, a numbness and tingling, became deeply painful at night, causing insomnia. There were changes in muscle metabolism, an ATPase and CPK abnormality.

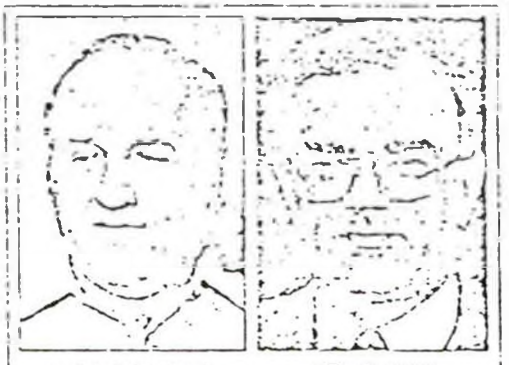
"Another major problem was a complex of extensive neurobehavioral abnormalities, often characterized by a severe depression. It was nonpsychogenic and in some cases amounted to what the Russians call a neurovegetative state. There were severe personality disorders, marked by a tendency to fly off the handle."

In 30 of the 47 men, almost two years after the dioxin spill, University of Illinois immunotoxicologist Joseph Prince, Ph.D., found impairment in neutrophil and lymphocyte function when compared with that in age-matched normals. The prime movers of host resistance to tumor had full dysfunction of the enemy.

"I saw some chemiluminescence studies he did with neutrophils," commented St. Louis U.'s Dr. Slavin. But did he incubate lymphocytes with mitogens?"

Yes, Dr. Prince averred, he did — with phytohemagglutinin, pokeweed mitogen and concanavalin-A. Moreover, he found the generation of superoxide radicals was affected. He said the changes indicate a change in bone marrow at the stem cell level. He speculates that with the lymphoproliferative ability of the body impaired, the freshly transformed neoplastic cells may no longer be swept away in time.

Dr. Carnow added that in animals, the dioxin is a cocarcinogen beyond belief. For example, 3-methylcholanthrene on its own is known to stimulate production of aryldeoxyhydroxylase and thereby, tumor growth. But when dioxin is added, the carcinogenic process is enhanced thousands of times.



DR. PRINCE DR. SLAVIN

Such inferential risks aside, to fully assess the individual risks in the Times Beach population, professional interviewers last January reached 800 or 900 residents with questionnaires eliciting data on lifestyle and possible exposure of all types from all different sources. From the answers, investigators drew the test group of 120.

A leading environmental specialist, the Palo Alto (Calif.) Medical Clinic's Dr. David Ehrlich, made this plea: "We very much need CDC's expertise here, to do the longitudinal epidemiologic follow-up that is needed, and with its experience following populations that are dispersing themselves around the nation, produce a study that everybody can live with. We should put our trust in CDC to do this."

Dying from dioxin: a horse on an Imperial, Mo. farm. Dioxin levels in nearby soil were 32,000 ppb, a statewide high.

Reactions to dioxin called complex, subtle

By Jon Van

THE ENVIRONMENTAL Protection Agency has agreed to buy the town of Times Beach, Mo., because it has been contaminated by accidentally hazardous doses of dioxin, and scores of other sites around the nation—many of them in Missouri, Illinois and Michigan—have also been exposed to the controversial chemical.

But in the continuing debate over the degree of danger that dioxin poses to humans, there now be added a new study by an Illinois researcher showing that exposure to very small amounts of dioxin can reduce a person's ability to ward off disease.

The study, conducted by Joseph Prince, an immunologist at the University of Illinois, illustrates how subtly dioxin can affect the human body and may represent an "early warning system" for long-term effects caused by the toxic chemical.

"I've never seen anything this toxic," he said.

PRINCE'S STUDY, one of the few dealing with dioxin exposure in humans, focused on workers exposed to dioxin after an accidental chemical spill in Newark, N.J., three years ago. The men were exposed to small amounts of dioxin for periods ranging from a few days to up to 12 weeks.

Prince found abnormalities in the white blood cell activity of two-thirds of the men. Among them was a reduction in the normal function of neutrophils, "Pac man"-type cells that scurry about the body "eating" bacteria and foreign debris.

Also found was a decrease in the number of eosinophils, cells that play a role in controlling allergic reactions, and a reduction in the concentration of oxygen-carrying hemoglobin in the red blood cells.

Although widely recognized as a toxin, the exact extent of danger posed by dioxin in the environment is a matter of controversy among scientists.

THE WHITE blood cells Prince studied normally will destroy cancerous cells that regularly occur in the human body as well as bacteria and other foreign materials. If the cells fail to recognize and destroy malignant cells, a person's risk of developing cancer will increase.

Changes in normal function of blood cells may also indicate basic changes in the bone marrow where blood cells are manufactured, Prince said. Such changes could mean a greater risk of developing leukemia, a cancer of the blood.

The changes Prince found in Illinois workmen are consistent with studies done in mice, he said. In mice exposed to large amounts of dioxin, the natural immune system shuts down. When mice are exposed to tiny amounts of the poison, their white blood cell production actually is stimulated, but function of those cells is altered.

"THE IMMUNE system is a delicately balanced regulatory operation," Prince said. "When you get too many of one kind of cell and not enough of another, it completely upsets the normal response. A compromised immune system is incapable of fighting off challenges in a normal fashion.

"This is a very subtle and complex reaction."

Prince said his study results are consistent with those done in Sweden where men working in a forest sprayed with a herbicide containing dioxin experienced lymphomas, tumors of soft tissue, at a rate six times greater than normal.

Richard Wilson, chairman of the physics department at Harvard University who has studied dioxin and has written a number of books estimating levels of dangers associated with toxins, said the studies done in humans, including the Swedish study cited by Prince, have failed to establish that chronic exposure to small amounts of dioxin causes cancer.

"SOME STUDIES suggest chronic toxicity is carcinogenic [cancer-causing] and others suggest it is anti-carcinogenic," Wilson said. "Studies have shown it can produce cancer in rats at high doses and because both defend at high doses. It is nasty at high doses, but so are lots of things."

Wilson said that use of Agent Orange in Vietnam by U.S. military forces to clear vegetation was done without normal safeguards for human exposure and with contaminant levels of dioxin that were significantly higher than those yet reported in the United States.

"Even under those battlefield conditions, we haven't seen conclusive evidence of effects from chronic exposure," he said, indicating that the dangers may be small.

A study of 10,000 Vietnamese families reported last week challenges that view. That study, undertaken by the Vietnam government, concluded that women whose husbands fought in the South during the war are significantly more likely to have miscarriages, stillbirths and children with birth defects than women whose husbands may have been exposed to Agent Orange in the South.

PRINCE SAID the Vietnam findings are "consistent with the animal data I would expect." The chemical has capabilities of interfering with all kinds of normal activities."

Another University of Illinois toxicologist, John Beberka, has studied the effects of a dioxin-contaminated herbicide sprayed accidentally on several Wisconsin farmland more than a decade ago.

A classic symptom associated with dioxin exposure is a skin rash called chloracne, but Beberka said even that obvious symptom isn't seen consistently.

"Fewer than 50 percent of a population exposed to dioxin will show a rash, at least very soon," Beberka said. "It's not a skin cancer in the sense that it may take years after exposure before it appears."