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Immune Studies in Dioxin-Exposed Missouri Residents: Quail Run

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2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic member of the halogenated hydrocarbon compounds in experimentally exposed animals (McConnell and McKinney 1978). Although the pathologic findings seen in TCDD exposure vary in type depending on the species and on the dose and duration of exposure, a consistent finding in all animal studies thus far has been thymic atrophy (McConnell and McKinney 1978; McConnell 1980; Vos et al. 1980). In other organs, such as spleen and lymph nodes, there is depletion of T-dependent areas. Subsequent investigations in animal models have defined a number of altered cell-mediated immune functions, including: depressed delayed-type hypersensitivity reactions, reduced ability to reject allografts, and an increased susceptibility to certain infectious agents (Vos and Moore 1974; Vos et al 1974). In vitro studies corroborated these observations, revealing depressed mitogen-stimulated lymphoproliferative responses (Vos et al. 1980; Vos and Moore 1974; Vos et al. 1974; Luster et al. 1980; Faith et al. 1978) and depressed generation of cytotoxic T lymphocyte (CTL) responses (Clark et al. 1981; Clark et al. 1984).

To date, there have been no reports of significant evidence of immune toxicity in humans due to acute or chronic TCDD exposure (Reggiani 1980; Knutsen 1984). However, in a pilot study of Missouri residents exposed to dioxin-contaminated soil, there was an increased prevalence of inverted T4/T8 ratios in dioxin-exposed persons (Knutsen 1984). Results of the present study were summarized earlier (Hoffman 1986); the present paper discusses the immune studies in more detail and hypothesizes potential pathophysiology.

MATERIALS AND METHODS.

Any individual who lived at the Quail Run Mobile Home Park for six or more months between April 1971 and May 1983 was eligible to participate in the study. The Quail Run Mobile Home Park was selected for study because TCDD had been measured at higher levels there (up to 2,200 ppb) than at any other residential site in Missouri. TCDD was detected along the entire length of the road, with levels ranging from 39 ppb to 1,100 ppb in composite samples. TCDD was measured at levels above 4 ppb along both road shoulders, in 4 of 8 yards tested, in dust samples collected from the interiors of

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21 of 31 trailers tested (the highest level being 11.5 ppb), in the wall insulation of one trailer, and in the furnace air filters of at least one trailer. The comparison group was formed from individuals who had lived for six months or longer in one of 3 mobile home parks in the St. Louis area. Five composite surface soil samples were collected from road shoulders in each park and tested by the U.S. Environmental Protection Agency; TCDD was not detected at levels > 9 ppb.

In vivo assessment of cellular immune function was determined by applying 7 recall antigens with a Multi-test CMI (Merieux Institute USA) device for delayed hypersensitivity skin tests, (Kniker et al. 1979; Corriel 1985). At 48 hours the number of positive skin tests ($\geq$ 2 mm induration and the sum of the diameters of induation (mean score) were recorded. Skin tests on 26 participants living outside the St. Louis area were read by a variety of public health personnel in the area where the participants lived. Because these outside readers were not trained, we excluded these readings. In addition, we found that the frequency of anergy in unexposed participants for two of the four regular readers was significantly higher than published norms and was significantly higher than for the other two readers. Furthermore, the DTH response measures in the other two readers were similar to those observed in published reports of clinically immunocompromised patients using the same skin testing device (Kniker et al. 1979; Corriel 1985). Since the high rates of anergy among unexposed participants examined by two of the readers could not be explained by other factors, we concluded that it was due to reader error and therefore excluded from further analysis of DTH skin test responses from all participants examined by these readers.

T lymphocyte subset analysis was performed with slight modification of the method described by Hoffman et al (1981). Monoclonal antibodies used were T3 (pan T cell), T4 (T helper/inducer), T8 (T suppressor/cytotoxic) and T11 (E-rosette marker), and the cells with positive fluorescence were analyzed in a Spectrum III flow cytometer.

In vitro lymphocyte proliferative responses to mitogens and tetanus toxoid were measured using methods previously reported (Schiff et al 1974). Mononuclear cells (MNC), isolated from heparinized venous blood by Ficoll-Hypaque density centrifugation, were cultured with optimal concentrations of the mitogens phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) and the antigen tetanus toxoid). One microCi per well of ^{3}H-thymidine, (6.7 Ci/mmole) was added for the last 6 hours of culture prior to harvesting the cells on glass filter paper, and the 3H-thymidine incorporated into DNA for each culture was measured in a liquid scintillation counter. The results were expressed as counts per minute of stimulated minus unstimulated cultures.

T cell cytotoxicity (CTL) was measured by lysis of an allogeneic target cell by purified T cells obtained from MNC which formed rosettes with AET-treated SRBC (Knutsen and O'Connor 1985), as previously described (Namiuchi et al. 1984). T cells ($5x10^{5}$) and autologous adherent cells ($5x10^{5}$) were first cultured with stimulating allogeneic mitomycin-C-treated MNC ($1x10^{5}$), and then on the seventh day of culture, the effector T cells were incubated with fresh ^{51}Cr-labelled allogeneic target cells ($1x10^{4}$) at effector:target ratios of 25:1, 12.5:1 and 6.25:1 for 6 hours. Maximum

and spontaneous ^{51}Cr release was obtained by culturing target cells in 1% Nonidet P-40 and medium, respectively. ^{51}Cr released into the supernatant was counted in a gamma counter and percent cytotoxicity was calculated as:

$$\% \text{ cytotoxicity} = \frac{\text{cpm (sample} - \text{spontaneous)}}{\text{cpm (maximum} - \text{spontaneous)}} \times 100$$

Because of the relatively small sample size, most of the statistical analyses were conducted on the total study population; however, we also performed analyses on certain subgroups: male and female adults (defined as $\geq$ 20 years) and children (defined as $<$ 20 years). We used analysis of covariance to evaluate for possible confounding associations with exposure status, using a priority reasoning on variables to be included in a given model. We also compared the proportions in the two groups with "abnormal" test results, using logistic regression, Chi square, or Fisher's exact test. ("Normal" was defined as within two standard deviations of the mean of the unexposed group for a particular test.) Anergy and hypoergy were defined as 0 and $\leq$ 1 positive DTH responses, respectively. The maximum responses of in vitro functional assays, lymphoproliferative responses to mitogens and tetanus toxoid, and T cell cytotoxicity were logarithmically converted to normalize the data before statistical analysis (Oppenheim and Schecter 1976).

RESULTS AND DISCUSSION

For the reasons stated in METHODS, only two of the readers were considered reliable, so statistical tests were performed only for their readings. In the individuals read by these readers, DTH were significantly depressed in TCDD-exposed subjects compared to the unexposed controls (Table 1). This group of dioxin-exposed subjects had fewer mean number of positive skin tests compared to controls ($P < 0.05$), decreased induration (P = N.S.) and increased percentage of individuals with anergy ($P < 0.05$). TCDD-exposed subjects also had increased percentage of individuals with hypoergy, defined as DTH response to 1 or 0 skin test antigens, in the total group ($P < 0.05$), in adults ($P < 0.05$) and in children ($P < 0.05$). Since the degree of skin reactivity is influenced by the subject's age and sex (Kniker et al. 1979; Corriel 1985), the exposure groups were further classified by age and sex. Again, all subgroups of dioxin-exposed subjects displayed less skin reactivity than their respective unexposed subjects. Evaluation of skin reactivity to individual antigens showed that exposed individuals had less induration to Streptococcus ($P < 0.02$) compared with unexposed individuals. Exposed individuals also tended to have less skin reactivity to tetanus, diphtheria, Candida and Proteus than unexposed individuals, though the average indurations were not statistically significant.

The results of T cell phenotypes showed statistically significant alterations of percentages, but not of absolute numbers of T cell subpopulations in TCDD-exposed subjects (Table 2). Dioxin-exposed subjects had slightly decreased percentages of T3 cells ($P < 0.05$), T4 cells ($P < 0.05$), and T11 cells ($P < 0.05$). Histograms of the percent T4 cells and T4/8 ratios suggested increased numbers of persons in the exposed group with decreased values even though the overall means were virtually the same for exposed and unexposed groups (data not shown).

Table 1. Delayed hypersenstivity skin test results in subjects potentially exposed to dioxin (TCDD)[1]

	Exposed	Unexposed	P
No. Positive Antigens[2]			
Total	2.3 ± 1.6 (51)[5]	3.1 ± 1.4 (93)	<0.05[8]
Adults[3]	2.5 ± 1.6 (35)	3.2 ± 1.4 (71)	NS
Children[3]	1.9 ± 1.7 (16)	2.9 ± 1.1 (22)	NS
Score, mm			
Total	10.1 ± 7.9	12.9 ± 6.4	NS
Adults	11.1 ± 7.9	13.3 ± 6.5	NS
Children	8.1 ± 7.9	11.4 ± 1.3	NS
% Anergic			
Total	11.8	1.1	<0.05[9]
Adults	11.4	1.4	<0.05
Children	12.5	0.0	NS
% Hypoergic[4]			
Total	35.6	11.8	<0.05[9]
Adults	28.6	11.3	<0.05
Children	50.6	13.7	<0.05
Tetanus,mm[6]	3.3 ± 2.6 (51)[5]	4.1 ± 2.3 (93)	NS[8]
%[7]	69.2	84.9	<0.05[10]
Diphtheria,mm	1.8 ± 2.3	2.4 ± 2.2	NS
%	42.3	61.3	<0.05
Streptoccus,mm	0.5 ± 1.4	1.2 ± 1.8	<0.02
%	11.5	33.3	<0.05
Tuberculin,mm	1.1 ± 2.4	1.2 ± 2.2	NS
%	21.1	26.9	NS
Candida,mm	1.8 ± 2.1	2.5 ± 2.1	NS
%	48.1	62.4	<0.05
Trichophyton,mm	0.9 ± 1.8	0.7 ± 1.7	NS
%	21.1	18.3	NS
Proteus,mm	0.4 ± 1.2	0.8 ± 1.5	NS
%	13.5	23.7	<0.05

1. Data presented as mean ± SD.
2. Induration > 2 mm at 48 hours is considered a positive reaction.
3. Adults are > 20 years-old and children < 20 years-old.
4. Hypoergy is defined as a positive reaction to one or none of the seven antigens.
5. Number of subjects in each group.
6. Induration expressed as mm.
7. Percentage of persons with a positive skin test.
8. P value comparing exposed group or subgroups by analysis of covariance.
9. P value comparing exposed group or subgroups by logistic regression.
10. P value by Chi-square analysis comparing exposed versus unexposed.

Table 2. T lymphocyte populations and lymphoproliferative responses in TCDD exposed versus unexposed individuals[1]

Number	Exposed 135	Unexposed 142	P[3]
T3 cells/mm³	1698±519 (2)[2]	1673±493 (2)	NS
%	72.2±7.5 (6)	74.2±7.4 (6)	<0.05
T4 cells/mm³	1021±353 (1)	1033±346 (0)	NS
%	43.5±8.8 (12)	45.9±7.6 (4)[4]	<0.05
T8 cells/mm³	592±223 (2)	578±198 (0)	NS
%	24.8±6.2 (5)	25.8±5.7 (1)	NS
T11 cells/mm³	1801±550 (2)	1796±493 (3)	NS
%	77.8±6.6 (8)	79.8±6.0 (7)	<0.05
T4/8 ratio	1.92±0.80 (11)	1.89±0.60 (9)	NS
PHA, cpm	43,954 (6)[2]	45,920 (5)	
log x ± SD	4.64±0.15	4.66±0.17	NS
Con A, cpm	41,495 (5)	40,551 (5)	
log x ± SD	4.61±0.17	4.60±0.17	NS
PWM, cpm	36,559 (0)	32,063 (7)	
log x ± SD	4.56±0.13	4.50±0.21	<0.05
Tetanus, cpm	17,258 (8)	18,707 (4)	
log x ± SD	4.23±0.47	4.27±0.37	NS

1. Data expressed as mean ± SD for T cells and as geometric mean and log ± SD for lymphoproliferative responses.
2. Values in parentheses are the number of individuals with an abnormal decreased value < 2 SD below normal unexposed controls.
3. P value determined by analysis of covariance adjusting for sex, age, socioeconomic status.
4. P value by Fischer's exact test.

Dioxin-exposed subjects' responses to stimulations by PHA, Con A, and tetanus toxoid were comparable to responses of the unexposed controls' lymphocytes, while the PWM response was slightly elevated in the exposed group ($P < 0.05$) (Table 2). Slightly more dioxin-exposed subjects were unresponsive to tetanus toxoid stimulation compared with unexposed subjects, 8 (5.2%) versus 4 (2.1%), but this was not statistically significant.

The percent of T cell cytolysis was slightly decreased at all three E:T ratios of 25:1, 12.5:1 and 6.25:1 in the dioxin-exposed subjects compared with normal controls ($P < 0.02$, < 0.03, < 0.03, respectively) (Figure 1). The subgroup of TCDD-exposed adults and the subgroup of adult females displayed less CTL reactivity than their control groups, 22.4 versus 26.3 ($P < 0.03$) and 21.9 versus 25.1 ($P < 0.06$), respectively. Histograms, particularly for the adult female subgroup, suggested two populations of CTL responses in the TCDD exposed group (data not shown).

When the anergic/hypoergic individuals' immune studies were analyzed, dioxin-exposed subjects appeared to have more abnormalities of other immune studies than unexposed subjects. Anergic/hypoergic TCDD exposed subjects were more likely to have at least one other disturbance of T cell phenotype and/or function compared with their unexposed subgroup, 5 subjects (26.3%) versus 1 subject (9.1%) (P = NS). Thus, in the TCDD-exposed group there tended to be clusters of abnormal immune responses; whereas, an abnormal immune response in the unexposed control population was frequently the result of an isolated abnormal laboratory study.

Both host and exposure factors influence the degree of immune suppression induced by TCDD. Clearly, there is a strain susceptibility to TCDD-induced immunosuppression that correlates well with TCDD induction of the aryl hydrocarbon hydrolase (AHH) system in animal models (Vecchi et al. 1983; Poland and Glover 1980). Recently, Nagayama et al (1985; 1985), using human cell lines, demonstrated that genetic susceptibility to TCDD among humans is similar to that reported for different mouse strains. Since AHH inducibility by TCDD appears to be associated with a cytosol receptor protein identified in the highest concentration in the thymus (Vecchi et al. 1983), we may hypothesize that an immature cellular immune system may be more sensitive to TCDD immunotoxocity than a mature one. Dosage and duration of TCDD exposure also influence the toxic effects of TCDD (McConnell 1980; Vos et al. 1980). In interpreting the results of the present study, genetic susceptibility to dioxin probably existed and that the amount of exposure to TCDD, as a function of duration and dosage, was probably quite heterogenous within our TCDD-exposed population. Thus, we might expect only a proportion of individuals living in the exposure area to be affected.

In the present study, the persons exposed to dioxin showed evidence of depressed cellular immunity consistent with that expected from animals studies. The dioxin-exposed population showed evidence for depressed DTH responses to recall antigens. The Multitest CMI was used in the present study as a way of assessing cellular immune function in vivo because it was reported to be standardized and reliable. It was our experience that the reading of the skin tests, which was critical to ensuring valid data, were subject to possible reader error. We excluded the DTH results for participants read by two of the four regular readers

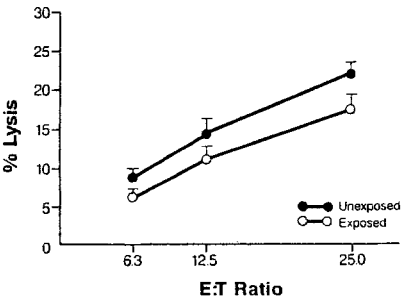

Figure 1. Results of CTL (geo mean + SE) showed that TCDD exposed persons had decreased lysis at E:T ratios of 25:1 ($P < 0.02$), 12.5:1 ($P < 0.03$), and 6.3:1 ($P < 0.03$) compared to controls.

because there was evidence that they were not measuring DTH responses properly. This might have introduced bias by selecting a nonrandom subsample of the study. However, the findings were essentially the same when all participants were included in the analysis, although not quite as strong. In the design and conduct of future field studies, careful attention should be given to ensure the quality of DTH skin test measurements.

We also observed alterations of T cell subpopulations with decreased percentages of T cells and T helper cells. Clark et al (1981) reported decreased T helper cells, though found increased T suppressor function in the pathogenesis of the diminished CTL activity in TCDD-exposed rats. Another finding was the increased number of dioxin-exposed anergic/hypoergic individuals with a decreased (T4 + T8)/T3 ratio, suggesting an increased calculated percentage of $T3^+T4^-T8^-$ cells. An increased percentage of this cell population has been reported previously in various T cell immune disorders (Semenzato et al 1983; Van DeGriend et al 1982). Van De Griend et al (1982) demonstrated that a pure population of $T3^+T4^-T8^-$ cells proliferate poorly to PHA and to alloantigens. Since TCDD is known to affect thymic epithelium in rodents, and since the T3 surface marker is acquired after T4 and T8 (Acuto et al. 1985), our findings, if the result of dioxin, then suggested that the thymic effect(s) of dioxin in humans might be highly selective on thymocytes at the T4 molecule. Bekesi et al (1978) observed an increase of lymphocytes that were SRBC-rosette negative (T cell) and $smIg^+$ negative (B cell) in Michigan residents exposed to PCB. In the present study, we also observed a nonstatistically significant calculated increase of a non-$T3^+$ lymphocyte population in the anergic/hypoergic dioxin-exposed subgroup. Since complete phenotypic analyses of lymphocyte subpopulations were not performed, we can only speculate whether this increased population consisted of thymocytes, natural killer cells and/or B cells; however to understand the pathogenesis of TCDD-immunotoxicity we need to determine the make-up of this population.

Though lymphoproliferative responses were normal in the dioxin-exposed group, T cell cytotoxicity was slightly decreased. This was most demonstrable in the total adult population and the subset of female adults. This observation of decreased CTL is consistent with studies in mice by Clark et al (1981; 1984). They observed diminished CTL responses due to TCDD exposure at doses that did not induce abnormal proliferative responses or lymphoid atrophy.

A possible confounding issue in this study was the probability of significantly increased psychological

stress in the TCDD-exposed population. Several studies have reported diminished mitogen stimulated lymphoproliferative responses and lymphocytes in psychologically stressed individuals (Stein et al. 1985; Schleifer et al. 1982; Dorian et al. 1982).

Future studies need to define a dioxin-exposed group by determining TCDD concentrations in fat tissue and determining individual susceptibility to TCDD induction of AHH. Even without this information, our results suggest disturbances of T cell population and function in a small percentage of dioxin exposed individuals.

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