Effects of Pesticides on the Immune System

CASE REPORT

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With pesticide use and exposure, and review of pesticides altering the immune system, this article shows data from four groups of patients at the Environmental Health Centre - Dallas, and two case reports are presented. These data not only revealed pesticides in most patient populations around the world, but also 81% out of 107 patients with initial exposure had depressed levels of T and B cells. There was a significantly greater frequency of several abnormal immune parameters in 40 proven chemically sensitive patients with more than two organochlorine pesticides than in 20 patients with less than two. Six patients showed improvement of various T- and B-cell parameters as pesticides cleared from the bodies.

Keywords: pesticide, immune system, immune parameter, chemical sensitivity, less polluted, environmental unit.

INTRODUCTION

Pesticides are toxic substances designed to kill insects. Other toxic substances which are designed to kill weeds, fungus, and act as fumigants are often included when discussing pesticides. These latter substances will be included only briefly in this discussion.

Pesticide Use and Exposure

The estimated total pesticide purchase by farmers in the USA increased from 184 million dollars in 1955 to 1 billion dollars in 1968 [1]. This increase in the sale of pesticides occurred in spite of the fact that harvested acres fell during this period from 335 million to 294 million acres. As the use of pesticides has increased over the succeeding years, the killing of insects has decreased by one half. Certainly these facts emphasize the failure of pesticides. In other fields, a search for new methods for solving a problem would be made. However, agriculture has been slow to do so. This was emphasized by the fact that the world market for herbicides, insecticides, and pesticides continued to grow, and these markets now have been estimated at 4688, 3190 and 1761 billion dollars, respectively, in 1989. Agriculture has applied 264 million pounds of pesticides in California in 1980 and 7.8 million pounds of these have been shown to be carcinogenic.

The long-term consequences of chronic pesticide exposure in the parts per billion and trillion are unknown. However, the massive increase of cancer in the farming areas in the USA suggests an adverse relationship [2]. The cancer rate in the nearly industry-free farming state of Iowa is about the same as the number one cancer-producing chemical dump state of New Jersey [3]. This is probably primarily due to the use of pesticide and herbicides in the growing of corn. In addition, the massive upsweep of chemical sensitivity has supported the fact that chronic pesticide exposure is harmful.

The following observations emphasize the fact that chronic exposure to pesticides is now a global problem. Often, spraying in one area results in not only local contamination but, depending on weather conditions and patterns, may result in contamination hundreds to thousands of miles away. For example, one study on the spraying for a grasshopper epidemic in Central Africa showed those particular pesticides to be in Key West, FL, five days later. These were then traced up the eastern coast of the USA following the Gulf Stream to Bermuda and then off toward the UK [4]. Another US Environmental Protection Agency study showed farmers spraying in Lubbock, TX, with a particular pesticide which ended up in Cincinnati, OH, roughly 1500 miles north east [5]. As a result of the widespread use of pesticides, they are now found in air, food and water. Virtually 100% of the US food supply contains pesticides and herbicides [6]. If one realizes that pesticides are in air, food and water, it logically follows that they should be in humans. This is indeed the case as evidenced by a series of chemically sensitive patients seen at our center.

Pesticides in Patient Populations

Studies performed at the Environmental Health Center (EHC)-Dallas have shown pesticides in most patient populations around the world. All individuals in the study groups from Australia, the UK, Saudi Arabia and the USA were chemically sensitive patients. Those from China were undetermined as to health status, but the South American Indians were virtually disease free. They were also pesticide free except for one individual. This group of individuals was protected by a thick jungle canopy, got their water from springs coming from the Andes and grew their own food. This set of environmental circumstances will probably not occur again on earth (Table 1).

Immune Effects

There are many substances in pesticides, mitocides, herbicides and fumigants that alter the immune system. These include organochlorine, organophosphate, carbamate, pyrethrin and arsenical pesticides as well as mitocides such as Milbex. Pesticides can stimulate, suppress or deregulate the immune system. Most can do all three, depending on the concentration and duration of the dose, the virulence of the pesticides, mitocides, herbicides and fumigants on the immune system, as well as the total body pollutant load and state of nutrition of the individual. The simplest change on can see in the immune system is proteins altering to become haptens. These alterations can be caused by many substances such as toluene diisocynate. However, a fumigant, formaldehyde, is known to trigger the IgE mechanism, resulting in hapten formation [7]. It is suspected by some that other pesticides may also alter proteins [8].

Direct cytotoxic effects may be seen on cells. Mercury-containing insecticides and fumigants may trigger this effect [9].

Immune complexes between IgG and complement are known to occur with toxic chemicals. Many of the organochlorine pesticides are known to dysregulate complement [10, 11].

Direct T-cell triggering is found with many organochlorine pesticides. Often they cause suppression of the suppressor T-cells [12]. Numerous substances, such as DDT [13-18], hexachlorobenzene [19-21], and penta chlorophenol, may alter the bacteriocidal, viricidal and phagocytic ability of the neutrophils [13, 22]. They may also decrease the responder plasma cells in the lymph nodes [23, 24]. Many pesticides, such as DDT, will deregulate the basophil, thus preventing histamine release and anaphylaxis; however, they also suppress skin whealing capacity for immediate antigen reactions [18, 25-28]. Ishikawa has shown a correlation of high levels of organochlorine and organophosphate pesticides with the change of Behç et's disease [2]. Other Behç et's pesticides may alter the antigen recognition sites on cells [8, 29], resulting in the spreading phenomenon seen in many chemically sensitive patients. Also, receptor sites for substances such as hormones may be altered, particularly by organochlorines [8, 29]. Transport enzymes may be altered, damaging the sodium pump [8, 29].

Organochlorine pesticides that are known to alter the immune system are DDT [23, 24], chlordane [23], aldrin [30], lindane [30, 31], hexachlorobenzene [19-21], mirex [32], and arochlor (a PCB) [23]. Organophosphates that cause changes in the immune system are anthio [33], malathion [31], leptochos [34], chlorophos [10, 24, 35-37], and parathion [17, 23, 38, 39]. Carbamates are known to cause immune changes [23], as well as arsenicals [401, and mitocides such as chlorobenzylate [41] and Milbex [41]. Other substances, such as herbicides, are known to cause immune dysfunction. Those are the phenoxy herbicide barban [41], TCD dioxin [42-46], nonum [41], TEC furan [47], nitrophenols, diquat and paraquat [41]. Fumigants such as chloroform, carbon tetrachloride, formaldehyde are known to be on the animal carcinogen list and we suspect them to be carcinogens in humans [48] (Table 2).

PREVALENCE STUDIES

Studies in chemically sensitive patients performed at EHC-Dallas have confirmed these reports. The distribution of pesticides in the blood of a group of 200 consecutive chemically sensitive patients is shown in Table 3. Fifty out of these 200 displayed symptoms triggered by pesticides on inhaled double-blind challenge. In 107 of them who reported initial pesticide exposure, 81% had depressed levels of both T- and B-cells. These individuals also frequently showed symptoms of depression, impaired memory, impaired concentration, lack of energy and general inability to function, and it was noted that as pesticide levels decreased, brain function improved.

Once these chemically sensitive individuals are withdrawn from pesticides in the air, food and water in the less polluted environmental unit and de-adapted for a minimum of four days, many responses to pollutant challenge can be seen. Individual inhaled challenge of ambient doses of orthochlorophenol and 2,4,DNP pesticides resulted in triggering of the immune system as well as other related parameters. The case histories below, and Figs. 1 and 2, show illustrative cases.

In another series of patients studied at the EHC-Dallas, 66 proven chemically sensitive patients (9 males and 57 females), who had either environmentally triggered (essential) hypertension [23], porphyria [11, vasculitis [33] or multiple sclerosis [20] were studied. Table 4 shows the frequency of individual pesticides in the blood of this group. There was a significantly greater frequency of several abnormal immune parameters in the group with more than two organochlorine pesticides than in those with less than two (Table 5).

If one compares the *means* of T- and B-lymphocytes in these same patients with the 60 patients of a normal control group measured at EHC-Dallas, one finds significant differences at the 0.1-0.001 level. The white blood count (WBC), though in the normal range for both groups, was significantly lower - 5520 versus 7560 - in the group with more than two pesticides present in their blood, with resulting significance to the 0.001 level. The means of the blood cell parameters showed significant differences at the 0.01-0.005 levels in the WBC, lymphocyte count. T11%, T4%, T4/T8 ratio and B-lymphocytes count.

Further study showed improvement of various T- and B-cell parameters as pesticides cleared from the patients (Table 6). Other studies at EHC-Dallas have also shown a negative correlation between the cell-mediated immunity by delayed skin hypersensitivity and the total number and mean of organochlorine pesticides seen in the blood.

CONCLUSIONS

It is quite clear from laboratory and clinical studies that pesticides of all categories may influence the immune system resulting in human dysfunction. Improvement in immune parameters also occurs when pesticides are removed from the body as seen in six patients in Table 6. Further studies are clearly required, but clinicians should already be mindful of these phenomena when evaluating and treating patients with disorders of the immune system.

CASE REPORTS

Evidence that pesticides effect the immune system is emphasized in two patients. The first was a 41-year-old white female nurse who developed spastic tetanic contraction of her peripheral muscles. In addition, she developed intractable spastic vascular phenomena of her coronary, femoral, popliteal and dorsalis pedis arteries with resultant symptoms. When she was placed in the Environmental Unit for total load reduction and de-adapted for a week, her spastic phenomena cleared and her T-lymphocytes increased. An inhaled challenge of a pesticide (2,4,DNP) at an ambient dose (<0.0034 ppm) reproduced all the vascular and tetany problems including angina and loss of peripheral pulse. In addition, T-lymphocytes decreased to 19%. It took four days with a pesticide-free diet, water and atmosphere to allow the T-cells to return to near normal (Fig. 1).

The second patient was a 69-year-old female who presented *in extremis*, malnourished at a weight of 70 lbs, with a diagnosis of amyotophic lateral sclerosis, with inability to swallow. She went into respiratory failure and had to be placed on a respirator for total ventilatory support. As one can see by Fig. 2, the patient, who had lived near a high intensity pesticide-spraying, chicken-raising operation, had high levels of organochlorine pesticides and depressed T-cells. As she improved with prolonged ventilation and nutritional support, her T-lymphocytes increased and her pesticide levels decreased.

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EDITORIAL COMMENT

The editors are well aware of the shortcomings of this paper, most notably the statistical inadequacies of the reported clinical findings. They consider, however, that it contains important information, particularly in the literature review and the case histories, which they hope will stimulate further research on a subject of potential importance to humanity in general.

The following list (courtesy of Dr John Howard) gives alternative names of common pesticides and related substances.

Chlorinated pesticides Uses Some other names including trade names

Aldrin I Aldrine, Compound 118, HHDN, Octalene,

Aldrec, Algran, Soildrin
Dieldrin I HEOD, Compound 497, Octalox, Panoram
Alpha-BHC IR
Beta-BHC IR Various mixed isomers. See Gamma-BHC
Delta-BHC IR
Gamma-BHC IR Lindane, Gammexane, Gammopaz, Gexane, Kwell,
Lindex, Lindust, Lintox
Alpha-chlordane I Chlordan, Octachlor, Octa-Klor, Chlorogran,
Gamma-chlordane I Chlor-Kil, Prentox, Penicklor, Corodane,
Heptochlor I Drinox, Hepatagran, Heptalube, (Chlordane),
Heptachlor epoxide from break down of Heptachlor
DDT I Dicophane, Chlorophenothane, Chlorophenotane,
Pentachlorin, Anofex, Dinocide, Genitox,
Gesarol, Gesapon, Gesarex, Neocid, Neocidol,
DDE I present in, and break down product of, DDT
DDD I
Dichlorobenzophenone DBP, a breakdown product of DDT
Endosulphan I (Mixed isomers 1 & 2); Chlorthepin, Cyclodan,
Endosulphan 11 I Malax, Thiodan, Thiofor, Thimul, NAI-4562
Trans-nonochlor I
HCB F HXB, Hexachlorobenzene, Anti-Carie
Kelthane M Dicofol, VW-293, DTMC, Keltane
Methoxychlor I DMDT, Dimethoxy-DT, Methoxy-DDT, Mariate,
Moxie, Dianisyltrichloroethane
Mirex I Dechlorane, GC-1283, $C_{10}CL_{12}$
Toxaphene IM (Mixture of champhene polychlorides of which
the two most powerful are 'Toxicants A & B),
Camphechlor, Alltox, Estonox, Chem-phene,
Geniphene, Gy-Phene, Phenacide, Phenatox,
Toxadust, Toxaspra
Pentachlorophenol IFHD PCP, Penta, Penchlorol, Dowicide, Santobrite,
Chlorphen, Santophen, Glazd penta
(Main uses are on timber and in packaging)
Tetrachlorophenols F (Often mixed with PCP [see above] in wood
treatment fungicides)
Trichlorophenols
2,4,6- BF Dowicide 2, Omal (mainly used to control
fungal slimes)
2,4,5- BF Collunsol
2,3,6-
2,3,5-
2,3,4-
3,4,5-
Dichlorophenols: total 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-dichlorophenols
Chlorinated pesticides Uses Some other names including trade names
o-Dichlorobenzene T DCB, ODB, Ortho dichlorobenzene
p-Dichlorobenzene T Di-chloricide, Paracide, Paradow, Paramoth
Trichlorobenzenes HI TCB, TCBA, Polystream, (1,3,5- and other
isomers with 1,2,3,4-tetrachlorobenxene)
2,4-D H 2,4-dichlorophenoxyacetic acid, Chloroxone,
Weedar, Weedone, Salvo, D-50, etc
2,4-D esters H Crotilin, Esteron, Weed-B-Gon, DMA-4, etc
2,4-DES (sodium) H Disul, Sesone, SES, Natrim, Crag Herbicide I
2,4-DP HG Dichloroprop, Cornox-RD, RD-406, Fernoxone
2,6-DBN H Dichlorbenil, Code 133, Casoron 133 & GSR
Disugran G Racuza, 60-CS-16
2,3,6-TBA H 2,3,6-Trichlorobenzoic acid-mixed isomers
with 2,3,4-, 2,3,5-, 2,4,5-, 2,4,6-, 3,4,5-
TCB, 2,3,6-TCB, Trysben, HC-1281
Polychlorinated biphenyls: very stable, toxic, compounds
PCB Aroclor 1016, 1221, 1232, 1242, 1248, 1254,
(industrial use, especially 1260, 5432, 5442, 5460 (The last two digits
heavy electrical equipment) are the approximate percentage of chlorine)
Phosphate esters and related pesticides
Azinphosmethyl IM Gusathion, Guthion, B-17147, Catnion methyl
Azinphosethyl IMO Gusathion A, Ethyl Gusathion, B-16259
Carbophenothion IM Acarithion, Garrathion, Trithion, R-1313
Chlorothion I Chlorthion, Clortione, B-22190
Dicapthon IK Dicapton, Isomeric Chlorthion, AC-4124

Ethion IM Nialate, NIA-1240
Malathion AMK Emmaton, Karbophos, Chemathion, Cythion,
Malaspray, Malathon
Parathion IM AAT, SNP, Alkron, Allerton, Etilon, Foldol,
Fosferno, Danthion, Niran, Parawet, Phoskil,
Nitrostigmine
Methyl parathion IM Parathion-methyl, dimethylparathion, DALF,
Metron, Metacide, Nitrox-80
Methyl trithion IM Methyl carbophenthion, Tri-Me, R-1492
Disulfoton IMN Di-Syston, Dithiosystox, Ekatine, Frumin,
Solvirex, B-19639
Disulfoton sulfone I Di-Syston Sulfone
Phorate I Thimet, Granutox (systemic)
Demeton-o IKM (Mixtures of -o and -s)
Demeton-s IKM Mercaptophos, Systox, B-8173,
Demeton-methyl IM (Mix of Demeton-o-methyl & Demeton-s-methyl)
Metasystox, B-21/116
Demeton-s-methyl IM Azotox, Demetox, DSM, Duratox, Metasystox 1,
Metasystox-55
Demeton-s-methyl-sulphone IM Metaisosystox-solfon, B-20315, M3/158
Dichlorvos IT DDVP, Dichlorovos, De Devap, Nogos, Nuvan,
Mafu, OKO, Nerkol, Vapon
Diazinon IMN Busudin, Diazitol, Nucidol, Sarolex,
Spectracide, Neocidol, G-24480
Dimethoate IMK Cygon, De-Fend, Ferkethion, Fostion MM,
Perfekthion, Rogor, Roxian, AC-12880
Menazon IM Siaphos, Sayphos, Saphicol, Saphizon, PP-175
Naled IM Bromex, Dibrom, RE-4355 (reducing agents
convert this pesticide to Dichlorvos [DDVP])
Mevinphos IM Phosdrin, OS-2046
Phosphamidon IM Dimecron, C-570
Shradan IM OMPA, Prestox 111, System
Chlorinated pesticides Uses Some other names including trade names
Sulfotepp IM Sulfatep, Sulphatepp, Bladafum, Bladafume,
Dithio, Dithiotepp, Lethalaire, Dithione
Tepp IMK Bladan, Nifos-T, Tetron, Vapotone
Tetrachlorvinphos I Gardona, Rabon, SD-8447
Thionazin IN Zinofos, Zinophos, Zenophos, Nemafos, Cynem
Other pesticides
Carbaryl I Sevin
Daminozide G ALAR, Aminozide, B-Nine, B-9, B-995, DMSA,
Kylar (NOW BANNED)
Derris I Rotenone (Plant source, but it is toxic to
humans-especially if it is inhaled)
DNOC IFGH Dinitrocresol, DNC, Elgetol, Sinox, Dinitrol,
Ditrosol
Tetradifon MO Chlorodifon, Tetradiphon, TCDS, Tedion V-18,
Tedion, Duphar, NIA-5488

Uses: A, Algaecide; B, Bacteriocide; D, Defoliant; F, Fungicide; G, Plant growth regulator; H, Herbicide; I, Insecticide; K, Aphicide; M, Miticide; N, Nematocide; 0, Ovicide; R, Rodenticide; T, Fumigants.

Names: The common names and some trade names are included. We apologise that trade marks have not been acknowledged.

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TABLE 1. Comparison of the frequencies (%) of chlorinated pesticides in six nationalities

	SA Indians (12)	USA (100)	Saudi Arabia (9)	UK (100)	China (20)	Australia (45)
Aldrin	—	—	0	1	5	0
Dieldrin	—	54	100	100	5	33.3
Alpha-BHC	—	1	11.1	8	95	0
Beta-BHC	—	68	89	100	100	31.1
Gamma-BHC	—	3	11.1	9	0	0
Delta-BHC	—	0	0	0	0	0
DDT	—	43	77.8	88	95	33.3
DDE	8.3	100	100	100	100	100
DDD	8.3	3	0	2	80	0
Alpha-chlordane	8.3	0	—	0	0	0
Gamma-chlordane	—	1	—	2	5	0
Heptachlor	—	0	—	0	0	0
Heptachlor epoxide	—	89	44.4	5	70	17.8
Trans-nonachlor	—	92	—	8	35	17.8
Endosulfan I	—	7	—	4	0	0
Endosulfan II	—	1	—	0	5	0
HCB	—	92	89	100	90	73.3
Endrin	—	1	—	4	50	0
Mirex	—	0	—	2	—	—
Oxychlordane	—	—	—	—	—	11.1
Mean	8.3	31	47	33	41	17.0

TABLE 2. Pesticides and Herbicides Known to Cause Immune Change

DDT	Perelygin *et al.* [13]; Latimer & Siegal [14]; Atabaev *et al.* [15]; Klotz *et al.* [16]; Wiltrout *et al.* [17]; Koller *et al.* [18]
Chlordane	Street [41]
Aldrin	Giurgea *et al.* [30]
Lindane	Giurgea *et al.* [30]; Desi & Farkas [31]
Hexachlorobenzene	Loose *et al.* [19, 20]; Silkworth & Loose [21]
Mirex	Glick [32]
Arochlor (a PCB)	Street & Sharma [23]; Loose *et al.* [19, 20]; Thomas & Hinsdill [49]
Antio	Aripdzhanov [33]
Malathion	Desi & Farkas [31]
Leptophos	Koller *et al.* [34]
Chlorophos	Friedman [24]; Olefir [10, 35, 36]; Shubik *et al.* [50]
Parathion	Street & Sharma [23, 38]; Wiltrout et al. [17]; Dandliker *et al.* [39]

Sevin — Friedman [24]; Perelygin *et al.* [13]; Dinoeva [51] Olefir [10]
Carbaryl — Street & Sharma [23, 38]; Wiltrout *et al.* [17]
Carbofurun — Street & Sharma [23, 38]
Dicresyl — Koller [52]
Pyrethroids — Dandliker *et al.* [39]
Arsenicals — Agranulocytosis — Hayes [53]
Mitocides — Chlorobenzilate — Street [41]
— Milbex — Street [41]
Phenoxy — Barban — Street [41]
— TCD dioxin — Moore *et al.* [42]; Thigpen *et al.* [43]; Allen & Van Miller [44]; Faith & Moore [45]; Thomas & Hindsill [46]
— Monum — Street [41]
— TEC furan — Luster *et al.* [47]
Nitrophenol — Agranulocytosis — von Oettingen [54]
— Cataracts — Spencer *et al.* [55]
Diquat and paraquat — Street [41]

TABLE 3. Distribution of chlorinated hydrocarbon pesticides in 200 environmentally sensitive patients (1986)

Pesticide	No. of patients	Distribution in 200 patients (%)
DDT and DDE	124	62.0
Hexachlorobenzene	115	57.5
Heptachlor expoxide	108	54.0
Beta-BHC	68	34.0
Endosulfan I	68	34.0
Dieldrin	48	24.0
Gamma-chlordane	40	20.0
Aldrin	13	6.5
Endrin	11	5.5
Delta-BHC	8	4.0
Alpha-BHC	7	3.5
Mirex	4	2.0
Endosulfan II	3	1.5

TABLE 4. Comparison of the frequency of chlorinated pesticides (CP) between CP <2 and CP>2 groups

	CP<2 group n=20		CP>2 group n=40	
Pesticides	No. of positive	%	No. of positive	%
Beta-BHC	4	8	27	67.5
DDT	2	10	9	22.5
DDE	13	65	40	100
Dieldrin	0	0	17	12.5
Endosulfan I	0	0	2	5
Heptachlor epoxide	3	15	34	85
Hexachlorobenzene	2	10	35	87.5
Gamma-chlordane	0	0	1	2.5
Trans-nonachlor	1	5	28	70

TABLE 5. Comparison of the frequency of abnormal immune parameters between CP<2 and CP>2 groups

	CP<2 group n=20		CP>2 group n=40		
Immune parameters	No. abnormal	%	No. abnormal	%	*p* value
WBC	1	0.0	14	35.0	<0.001
Lymphocytes (%)	0	10.0	8	20.0	<0.01
Lymphocyte count	2	10.0	15	37.5	<0.01
T11 cells (%)	2	10.0	12	30.0	<0.05
T11 cell count	2	5.0	21	52.5	<0.001
T4 cells (%)	1	5.0	13	32.5	<0.001
T4 cell count	1	5.0	14	35.0	<0.001
T8 cells (%)	1	0.0	8	20.0	<0.05
T8 cell count	0	5.0	2	5.0	<0.001
T4/T8 ratio	1	15.0	11	27.5	<0.01
B1y cells (%)	3	5.0	7	17.5	<0.05
B1y cell count	1	0.0	12	30.0	<0.01

TABLE 6. Improvement in the number of chlorinated pesticides and in the number of abnormal immune indices following treatment in the environmental unit

Before treatment		After Treatment	
No. of	No. of abnormal	No. of	No. of abnormal

Patient pesticides immune indices pesticides immune indices
1 6 7 2 0
2 4 4 1 0
3 5 4 1 0
4 5 1 1 0
5 5 1 1 0
6 5 7 1 0