[redacted]. GARDNER, M.D.
[redacted]

CLINICAL PROFESSOR OF MEDICINE
HEMATOLOGY-ONCOLOGY

[redacted]

February 14, 2005

Linda Laurent, Esquire
Reich & Binstock
[redacted]

RE: Cause: C-4885-99F
Alicia Acevedo, et al. vs. Union Pacific Railroad Co.; In the 332nd Judicial District Court of Hildago County, Texas

Dear Ms. Laurent:

I am Clinical Professor of Medicine at the University of Texas Medical Branch in Galveston. I have practiced Hematology (blood and blood forming organs) and Oncology (cancer) as medical specialties since 1949. I have directed divisions of Hematology and Oncology at the Peter Bent Brigham Hospital, Harvard Medical School, Boston, Massachusetts; the Presbyterian University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and the University of Texas Medical Branch at Galveston. Throughout these past decades, I have had an active laboratory program related to studies of bone marrow function and platelet physiology funded primarily by the United States Public Health Service. These studies have been oriented to the preservation and clinical use of blood platelets. I have authored and co-authored more than 170 articles in national and international scientific journals. I served on the initial National Breast Cancer Task force during 1970-1974. Because of the local industries, I have had an interest in malignancies associated with the petrochemical plants. A current Curriculum Vitae with a complete list of appointments and publications, as well as more information concerning my qualifications, is attached (Appendix I).

From your office I have received a request to evaluate and confirm the diagnoses of plaintiffs' malignancies related to pesticide exposure, and, also to assess from their clinical histories and information, the evidence that they had exposure to pesticides that were the cause of the malignant changes. From your office I have received hospital and clinical records of the four plaintiffs; namely, Jose Maria Solis; Guadeloupe Garza; Noelia Morales; and Irma Gomez. I have also

received depositions of company workers, Cyril Weber and David Garza. From your office, I have received a list of references relating to non-Hodgkin's lymphoma and specific exposures, as well as copies of reports from defendants' reviewers, a Phase I & II survey of remedial investigation of the Hayes-Sammon facility, and a background study from the State Superfund.

To understand the evaluation of the plaintiffs, there is a need to briefly comment about the geographical location of their exposures. The plaintiffs lived in proximity to the Hayes-Sammon facility (HS) in Mission, Texas. The plant operated from 1950 to 1968 under the direction of the above company. They provided a variety of pesticides, predominately in powder form, to farmers and homeowners. From my understanding of the company workmen's deposition, the company received pesticides from a variety of chemical companies, and fabricated the great majority of the pesticides to powder (Appendix II). Thereafter, they were packaged in various sizes for distribution. Formulation of different pesticides were made for crop control, according to evaluation of the insect infestations, as well as farmers requests. Because of the formulation of the chemicals are in powder form for application, there was a perpetual dust problem in the facility, and this was spread in the neighborhood in part by fan exhausts from the workplace. Some pesticides were stored outside of the facility in bags and in some instances, as loose powder with protective covering from the weather; but, not necessarily restrained in a formal compartment from runoff after rain or dust control. A variety of chemicals were used and are noted in Table 1:

DDT*	Arsenicals	Chlordane*
Heptachlor	Dieldrin*	Aldrin
Toxaphene*	BHC*	Lindane
Phosdrin	2,4-D	2,4,5-T
Methyl parathion	Parathion	Ethyl parathion
Manlate	Paris Green	Malathion
Diazinon		

HS prepared some chemicals in powder form.

Table 1. List of chemicals processed by Hayes-Sammon.

Because of the onset of B-cell malignant lymphomas near HS, an effort has been made to evaluate soil samples for toxic levels of stable chemicals in the soil since the HS ceased production of powdered chemicals in 1968. The pesticides with asterisks listed above in Table 1 have been evaluated since they have stable degradation which will allow analyses in later decades after HS closure. Other pesticides would have had earlier decay and not be available for assessment at this

time, but it should be recognized that they may have contributed, in part, to exposure of the plaintiffs.

All of the four plaintiffs had malignant B-cell lymphomas, non-Hodgkins type (NHL) (Appendix III). For an understanding of their particular historical evolvement of their particular malignancies, I have listed a clinical summary in Appendix IV. A clinical chronology for each of the four plaintiffs is outlined in Appendix V.

Since World War II and the discovery of the value of the pesticide, DDT, there has been an expanding list of pesticides for widespread agricultural use.(1)(2)(3)(4)(5) For decades, wide distribution among farmers created human toxic complications, leading to the elimination of many pesticides from the agricultural industry. Numerous studies in the United States and abroad have noted the increased frequency of malignant B-cell lymphomas among agricultural workers exposed to pesticides such as those used by HS.(6)(7)(8)(9) It has been difficult to assess the specific chemical products because of the demand for mixtures of several pesticides to combat the different infestation from year to year with evolving pest infestations. The various combination formulations were especially needed in the Rio Grande Valley with the variety of crops.(9a) Efforts have been made in studies of farm groups to dissect specific usage and high risk of exposure to organic chloride pesticides, and five long-lasting organic chloride pesticides that have been found on the home sites and past air sampling of the four plaintiffs listed.(10) A strong relationship has been noted for organochlorines to be causative for NHL.

The literature has indicated the causative risk of NHL as related to the specific organochlorine pesticides noted in these plaintiffs (Appendix VI). Dr. R. Sawyer has evaluated each of the organochlorines related to the four plaintiffs and made calculations to indicate the increased risk associated with them. He has related the exposure to the E.P.A. acceptable risk (1.10^6). The marked increase in exposure listed indicate a high risk of mutagenesis for the plaintiffs living in proximity to the HS facility.(10) Data is not yet available on particle inhalation to add the pulmonary toxicity to the determined elevated risk.

All of the plaintiffs had onset of the lymphocyte B-cell malignancy (NHL) after closure of the HS plant in 1968. Molecular gene alterations to induce malignancy have a "multiple hit" damage with progressive gene changes. Hence, the initial response to the organochlorine toxicity may have limited altered genetic response. However, more exposure causes progressive changes. Such damage can then increase cellular mutations of the gene to an autonomous malignant function to induce an uncontrolled proliferation as noted in Appendix VII. The understanding is, at the present, that the early progenitor cells of lymphocytes have altered DNA in their gene pattern as they enter into the germinal center of lymph nodes for maturation and differentiation into specific lymphocytic function. With their altered mutagenic background, there is continual variation in their protein pattern as they mature in the

germinal center (Appendix VIII), and eventually, are released into the general circulation. The collection of these pesticides in body fat indicates that they would be in close proximity to lymphocyte progenitor cells near bone marrow fat stores to induce DNA (gene) changes during early maturation.(11)

Because of the altered pattern of maturation in the lymph node germinal centers, a variety of classifications have been made of lymphoma that may be noted in the general chart outlining the designated clinical conditions (Appendix III). Only recently have we begun to appreciate that by evidence from analysis of the genome, we now have specific gene patterns that can be followed in the mature cells response to external toxic stimuli. As noted on Appendix IX, one sees that three types of lymphoma have specific alterations in their gene pattern which will allow the diagnoses to be made by gene studies rather than by clinical judgment and morphological appearance. The evidence indicates that the abnormal lymphocyte is altered through many mutagenic pathways as it matures in the germinal center of the lymph node, and then, dependent on their gene pattern, it is released. With the disorder with the B-cell malignancy called Hodgkin's disease (HD), this pattern is also distinctive that allows for the clinical diagnosis to be made. Although the published gene assay for non-Hodgkin's lymphoma is incomplete, the gene-disease association for all lymphoid abnormalities may be anticipated in future studies.

Because of the malignant nature of these precursors early lymphocytes, there is continued alteration and proliferation of unstable abnormal patterns in the gene structure as they persist in the body over a period of months or years. Hence, one may note among these four plaintiffs here that the initial pathologic diagnosis of two patients was changed as they were observed over a period of time. L. Garza changed from follicular lymphoma to large B-cell lymphoma; J. Solis from diffuse T-cell lymphoma to small cleaved B-cell follicular lymphoma. These clinical observations have repeatedly been made to emphasize that non-Hodgkin's lymphoma, as a group, are not stable diseases, but rather, because of the progressive abnormal protein proliferation may terminate with different morphologic patterns, and different expressions of their disease by name and prognosis.(12)(13)(14)(15)

As might be expected, there are abnormal changes of the altered lymphocyte as it matures in the germinal center of the lymph node, and there is opportunity for the lymphocyte to follow different pathways among the multiple germinal centers in a lymph node. Hence, patients can have two different types of a lymph node morphologic appearance of non-Hodgkin's lymphoma.(16)(17) When a lymph node is biopsied, the abnormal proliferation at that site is not necessarily uniform throughout the body's lymph nodes as a malignancy progresses.

Over the past decades, there has been limited information of collecting specific pesticides in relationship to non-Hodgkin's lymphoma in general and more specific sub classifications of the disease. Agricultural workers, for the most part, as

noted by the coworkers in the Hayes-Sammon facility in Mission, Texas, often use mixtures of the chemicals so that the identification of a specific agent cannot be evaluated. However, data on some specific chemical associations with non-Hodgkin's lymphoma have been collected, as noted in the attached listing (Appendix X) of relative risks from the exposure to these agents. In this instance, because of the stability of the pesticides they were selected to differentiate the causal relationship and relative risks that can be estimated from the soil sampling data. Specific causative relationship has been noted with these indicted agents.

The four plaintiffs lived in the vicinity of the HS facility, and had prolonged exposure to pesticides. The chronic exposure to high risk levels of organochlorine pesticides were the cause, with more probability than not, for their onset of non-Hodgkin's lymphoma.

Sincerely yours,

[redacted]

[redacted] Gardner, MD

Attachments: Appendices I through X

References

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(17) Jaffe, E.S. and Wilson, W.H. Gray Zone" Synchronous and Metachronous Lymphoma. Diseases at the interface of Hodgkin's disease and non-Hodgkin's lymphoma, Chapt. 6 in *Non-Hodgkin's Lymphoma* (ed. Mauch, P.M., *et al.*) 2004. Lippincott, Williams & Wilkins. Philadelphia. Table Pg. 72 shows various transformations of non-Hodgkin's lymphoma.

APPENDIX II

Hayes-Sammons Formulae for Dusting

DDT - Solid Cakes - Ground to powder, mixed with clay or other powders to make pesticide = Dust

BHC - Solid Cakes - Ground to powder with clay; mixed with other pesticides, at times, for specific mixtures = Dust

Dieldrin - Solid Particles like corn flakes - Ground to powder for use or mixture = Dust

Chlordane - Liquid mixed with solvent to spray to a powder = Dust

Toxaphene - Waxy Material - mixed with solvent to spray to a powder = Dust

APPENDIX III

B-Cell Malignancies

Revised European-American lymphoma classification from the International Lymphoma Study group

B-Cell neoplasms

Precursor B-cell neoplasms
Precursor B-lymphoblastic leukemia/lymphoma

Peripheral B-cell neoplasms
1. B-Cell CLL/PLL/SLL
2. Lymphoplasmacytoid lymphoma/immunocytoma
3. Mantle cell lymphoma
4. Follicle center lymphoma, follicular
   Provisional cytologic grades: I (small), II (mixed), III (large)
5. Marginal zone B-cell lymphoma
   Extranodal (MALT ± monocytoid B-cells)
   Provisional category: nodal (± monocytoid B-cells)
6. Provisional entity: splenic marginal zone lymphoma
7. Hairy cell leukemia
8. Plasmacytoma/myeloma
9. Diffuse large B-cell lymphoma
10. Burkitt's lymphoma
11. Provisional entity: high-grade B-cell lymphoma, Burkitt-type

T-Cell and putative NK cell neoplasms

Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia

Peripheral T-cell and NK cell neoplasms
1. T-Cell CLL/PLL
2. Large granular lymphocyte leukemia
3. Mycosis fungoides/Sézary syndrome
4. Peripheral T-cell lymphomas, unspecified
   Provisional categories: medium, mixed, large lymphoepithelioid provisional subtypes
   Hepatosplenic γδ T-cell lymphoma
   Subcutaneous panniculitic T-cell lymphoma
5. Adult T-cell lymphoma/leukemia
6. Angioimmunoblastic T-cell lymphoma
7. Angiocentric lymphoma
8. Intestinal T-cell lymphoma (± enteropathy)
9. Anaplastic large cell lymphoma (T/null)
10. Provisional: ALCL Hodgkin's-like

Modified from: Magrath, 1998. The Non-Hodgkin's Lymphoma. 2nd Ed.

APPENDIX IV

	Guadalupe Garza	Irma Gomez	Noellie Morales	Jose Solis
Sex	F	F	F	M
Date of Birth	2/19/43	11/28/47	04/04/32	11/21/30
Date Diagnosis of B-Cell Malignancy	1998	2001	1996	1999
Biopsy Site	Left Axilla Node	Right Inguinel Node	Left Axilla Node	Right Supra-Clavicular Node
Pathologic Classification	Follicular Node	Follicular Germinal Center	Mixed Nodule B-Cell	Diffuse T-Cell Lymphoma
Therapy	FND \Rituxan	FND Interferon	CVD Rituxan	CHOP
Date Recurrence of Tumor	----	2002	2003	2001
Biopsy Site	----	Left Inguinal Node	Right Cervical "B Symptoms"	Right Arm Nodes
Pathological Classification	----	Large B-Cell	Follicular Small B-Cell Hodgkins	Follicular Small B Cleaved Cell
Therapy	----	VAD, CHOP Stem Cell Transplant (8/02)	Radiation FND Fludara	CHOP
Exposure to Pesticides	1943 to Present	1968-2002 Father's Clothing	1969-1974	1968 to Present
Associated Medical Problems	Hysterectomy 1976 Palpitations 1988 Arthritis 1994 GERD 1999 (No drug related exposure.) Carpal Tunnel Syndrome	Miscarriages 1969 & 1970 Hair Dye Age 35-40	Headache 1970 HTN 1980 Diabetes 1998 CABG 2000 Arthritis 2000 Hair Dye Age 40-45	HTN Diabetes Osteoarthritis Basal Cell Carcinoma
Smoking	0	0	0	1 Pk/day-30 yrs.
Alcohol	0	0	0	Social

Group Pesticide Exposure
DDT, Dieldrin, BHC, Toxaphene Chlordane

FND = Fludara, Novaxantrone, Dexamethasone
CVP = Cytoxan, Vincristine, Dexamethasone
VAD = Vincristine, Adriamycin, Dexamethasone
CABG = Coronary Artery Bypass Graft
HTN = Hypertension
GERD = Gastric Esophageal Reflex Disorder
RITUXAN = Monoclonal B-Cell Antibody

APPENDIX V-a

Jose M. Solis

Mr. Solis, a 69 year old Latin American male, noted a mass above the right clavicle (right supraclavicular area) in July, 1999. A surgical biopsy indicated that he had diffuse nonHodgkin's lymphoma, T cell type. Radiologic CT studies demonstrated widespread adenopathy throughout all areas of lymph node patterns. He has a past history of placement of tympanic tubes in his ears in 1998, diffuse osteoarthritis for many years, symptomatic treatment of hypertension, non insulin dependent diabetes mellitus for the past five years, and a thirty year history of smoking. He has not received any previous medications that might be associated with lymphadenopathy. He had a history that one brother died of cancer of the pancreas. The patient received chemotherapy, six courses of CHOP (adriamycin, oncovin, prednisone, and cytoxan). He had marrow suppression which was associated with some fever, but only required one hospital observation to be certain there was no complications of fever aside from his marked neutropenia from chemotherapy.

In May, 2000, he had enlargement of a mass (3 cm) in his right arm which was removed. This was an enlarged lymph node, B cell nonHodgkin's follicular lymphoma, small cleaved cell type. The second biopsy differs from the initial supraclavicular node, and probably is the predominate precursor for his lymphoma from the onset. Radiologic CT scan revealed diffuse adenopathy to indicate widespread lymph node involvement in all lymphoid areas. These areas were treated again with six courses of CHOP. Thereafter, he received upper and lower mantle-abdominal radiation. A nodule on the right ear auricle was removed in May, 2002,

and was a follicular lymphoma lesion. A nodular lesion on the chin was excised in 2003 that was basal cell carcinoma. He has continued to be followed by his local physician for control of his diabetes mellitus, hypertension, and osteoarthritis with no significant clinical progression of his non-Hodgkin's lymphoma.

APPENDIX V-b

Guadalupe Garza

Following the demonstration of lymph node enlargement in the left axillary tail on a mammogram study in August, 1998, Guadalupe Garza, age 58, had a lymph node biopsy which revealed that she had a B-cell follicular lymphoma. Radiologic studies revealed a diffuse adenopathy in the cervical, axilla, anterior medial sternal region, and in the periaortic area. She was started in a program of fludara, novaxantrone, and dexamethasone (FND). This was given from January, 1999 through May, 1999 at biweekly infusions. She tolerated the chemotherapy quite satisfactorily without bone marrow depression. Thereafter, she received four weekly doses of Rituxan without complications. Throughout this program, she was considered to have Stage IVA disease with evidence of enlarged lymph nodes and malignancy both above and below the diaphragm. On completion of this therapy, radiologic studies in the Fall of 1999 revealed decrease in the lymph nodes, but more importantly, stability without any change in their pattern.

Following her program of FND and Rituxan, she was then started on a two year maintenance program of parenteral alpha-interferon; 5 million units, three times weekly. She has been followed by the Oncology Group until the present time without evidence of recurrence. She does complain of some numbness in her upper extremities, which may be related to the interferon therapy, although she will be followed to exclude carpal tunnel syndrome.

During these intervals, the patient has had skeletal complications, and has had consultations with the Orthopedic Surgical Group. For the most part, these have been

defined as osteoarthritis, possibly related to increased stress on weight bearing joints. She has also sought advice regarding numbness of her hands, and this has been considered to be a form of carpal tunnel syndrome. Analgesic and local therapy has been helpful and no surgical intervention has been done.

With a Stage IVA classification associated with diffuse adenopathy throughout the lymphatics, the patient is considered, despite her long stable interval, to be in remission, rather than cured. From her past history, there is evidence of heart disease in her parents. No evidence of malignancy associated a genetic pattern. The patient is a nonsmoker, and does not use alcohol socially.

APPENDIX V-c

Irma Gomez

Mrs. Irma Gomez is a 53 year old kindergarten teacher who saw a physician because of swelling in the right thigh in December, 2000. The examination revealed no deep vein tenderness, but there was a palpable right inguinal lymph node which was biopsied. The tissue study revealed a nonHodgkin's B-cell lymphoma, follicular center cell lymphocytic Type Grade 1. A CT radiologic pelvic scan revealed pelvic abdominal adenopathy. There was no evidence of family history to suggest hereditary malignant patterns. The patient was referred to M.D. Anderson for suggested therapy. Bone marrow studies revealed increased lymphoid infiltration. A program of systemic chemotherapy using Fludara, dexamethasone, and Novaxantrone (FND) was initiated. The 10, 3-week cycles of the medication was well tolerated with rapid improvement in the leg swelling. She was observed for four months, and there was no residual evidence of the diffuse lymphoma noted by the CT body scanning with radioactive gallium in May, 2001. This therapy was continued through the rest of 2001. The patient had some episodes of neutropenic fever without complications from the chemotherapy. Thereafter, she was placed on alpha-interferon with plans that she would receive the medication every two weeks for one year as a consolidation program for her suppressed lymphoma.

She initiated this therapy (interferon), and after two months, she had evidence of an enlarged left inguinal lymph node. This was biopsied, and upon examination, was classified as a large B-cell non-Hodgkin's lymphoma. This suggested that the initial biopsy of a follicular lymphoma had a transformation of the cell type to a more active malignant lymphoma. Consideration for a bone marrow stem cell transplant

was reviewed, and she was placed on a program of vincristine, adriamycin, and dexamethasone (VAD) in March, 2002. She had transient complications of neutropenic fever from the chemotherapy that responded to antibiotic therapy. The recurrent left inguinal lesion responded to the chemotherapy, and the patient had less discomfort from the swelling. The concept of stem cell transfusion was discussed with the patient, outlining the risk of mortality (15%-20%), as well as infection and chronic graft vs. host disease (GVH). A search was made to evaluate family members and the National Registry for compatible stem cell donors. In April, 2002, she was placed in a more intensive program of rituxan and CHOP (cytoxan, adriamycin, oncovin, and prednisone). There was no evidence of bone marrow involvement, and a colonoscopy was done to remove a small adenoma polyp in preparation for the stem cell transplant.

The patient received a HLA compatible stem cell infusion from her sister in August, 2002, and was followed with an immune suppression therapy of tacrolimus, as well as medications to suppress any viral or bacterial infection. She tolerated the transplant with minimal graft reactions with anticipation that these immune suppression drugs would be discontinued in early 2003. In the convalescent period, she was maintained on a large number of medications to control irritable bowel symptoms, viral infections, vitamin deficiencies, and a variety of bacterial infections. One month after the stem cell transfusion, there was radiologic evidence of decreased metabolic tumor activity by infusing radioactive glucose for a PET scan to suggest a successful bone marrow graft of the donor cells. She did have a transient infection with cytomegalic virus, which appeared to respond to specific therapy. Slowly, the immune suppressive medications were withdrawn, and as she has been

followed, she has had no evidence of chronic liver or kidney complications from her toxic medications. Morphologic and immune cellular evidence indicates that she has had a successful transplant with all of the precursors of donor specificity. When seen one year after transplantation, the patient had no medications except hydrocodone for intermittent cough, utilized once or twice a week. It is considered the patient is in a complete remission with a successful bone marrow stem cell transplant, and has remained so to the present time.

APPENDIX V-d

Noelia Morales

In March, 1996, Ms. Noelia Morales, a 63 year old housewife with long standing diabetes mellitus and hypertension, saw her physician for painful swelling in the left lower extremity. This was refractory to the use of diuretics, and other radiologic studies revealed that she did not have deep vein thrombosis, but showed lymphadenopathy in the pelvic area with compression of the iliac vein to cause the leg edema. On careful physical examination, the patient had an enlarged lymph node in the left axilla which was biopsied, and was diagnosed as a mixed nodular nonHodgkin's lymphoma. Review of laboratory and radiology studies classified her as Stage IVA with diffuse adenopathy and bone marrow invasion.

The Oncologist proposed that she be treated with chemotherapy (CVP = cytoxan, vincristine, and prednisone). It was recognized that the patient has associated essential hypertension and diabetes mellitus, and she would be carefully observed with the risk as accentuating her diabetes from the prednisone. With the chemotherapy, she had marked relief of the leg swelling, and much improvement in her appetite and well being, without significant toxic hematologic suppression. The patient continued to be followed by the Oncology Clinic over the following years. She has had some intermittent arthritis treated symptomatically Because of a breast nodule, she had a breast biopsy which was benign. Her diabetes appeared to be moderately controlled by her local physician.

With her persistent hypertension, she had onset of angina pectoris. She was evaluated and found to have atherosclerosis of the coronary arteries, and underwent a

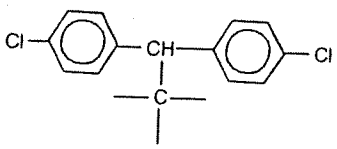
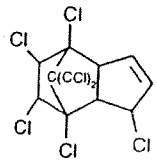
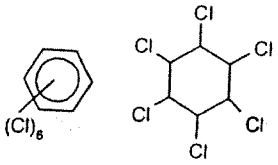
coronary bypass procedure with an arterial venous graft without complications in July, 2000. In October, 2000, Ms. Morales had right lower quadrant pain, and also swelling of left lacrimal gland. A CT scan revealed a right pelvic mass. She received Rituxan antibody therapy for 4 weekly treatments with good resolution of the tumors. Thereafter, with stable diffuse adenopathy, the patient has been followed expectantly.

In early 2003, Mrs. Morales began to have "B" symptoms with weight loss, night sweats, and an enlarging mass in the right frontal cranium with invasion of the orbit. Radiologic CT scan demonstrated increased abdominal adenopathy. A surgical lymph node biopsy from the left groin confirmed that the patient continued to have low grade follicular small cell, nonHodgkin's lymphoma seven years after the original diagnosis. She received right cephalic irradiation and systemic chemotherapy FND (Fludara, Dexamethasone and Novaxantrone) and weekly Rituxan to stabilize her lymphoma again.

She tolerated this program quite well over an interval of three monthly infusions. Thereafter, she received fludara regularly on a weekly basis to be treated for an additional 12 treatments. Studies in March of 2004 indicated a marked reduction in lymph node size to indicate a good response to the chemotherapy program. As anticipated, the patient will have intermittent therapy in the years ahead. Ms. Morales has had a variety of health problems; namely, hypertension with coronary artery disease, osteoarthritis, and diabetes. None of these contributed to her diagnosis of non-Hodgkin's lymphoma; rather, altered immunity from the genesis of her lymphoma may have contributed to the progression of her vascular disease.

APPENDIX VI

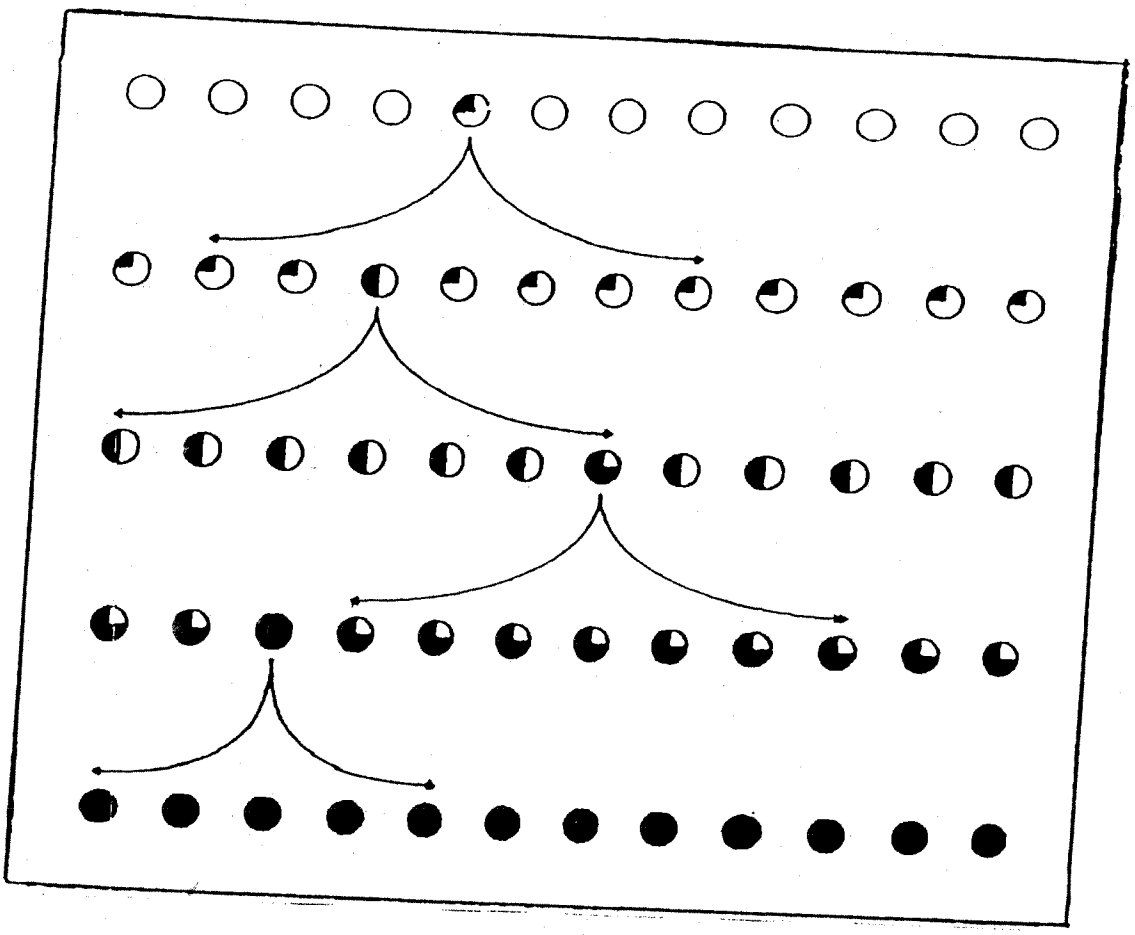
Structural Classification of Organochlorine Insecticides

Dichlorodiphenylethanes		DDT and Derivatives
Cyclodienes		Aldrin - Dieldrin Chlordane Toxaphene
Chlorinated Benzenes Cyclohexanes		HCB

From: *Toxic Effects of Pesticides*, Chap. 22, Casarett and Doull's Toxicology, ed. Klassen, C.D., 5th ed. 1996.

Multiple "Hits" Concept of Marrow Mutagenesis

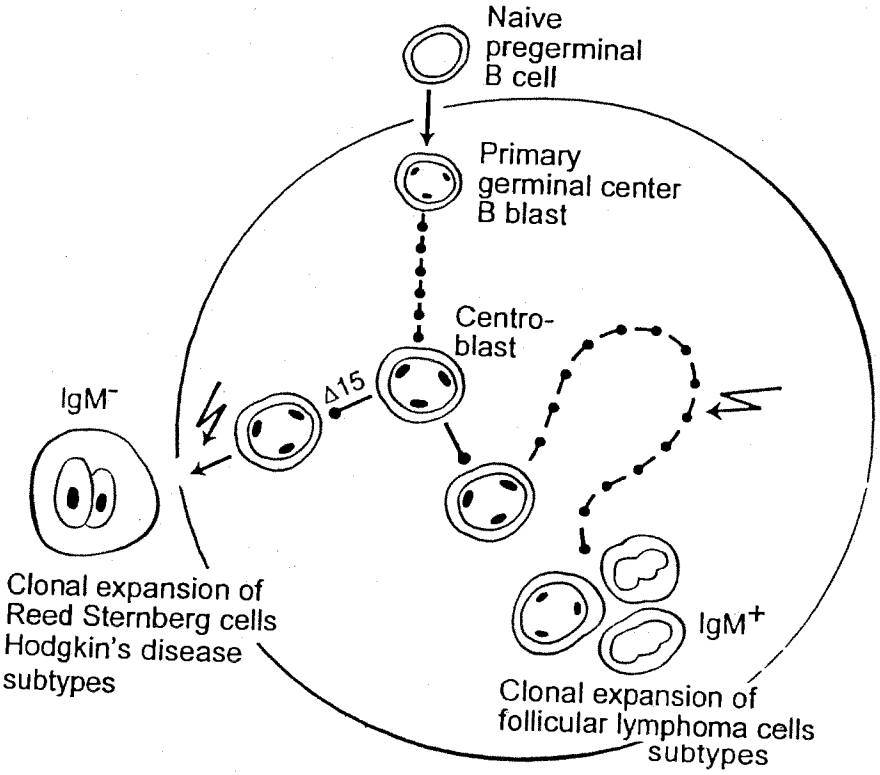
Each "hit" of the toxic exposure adds to the gene alteration to eventually induce a malignant proliferation.



Weinberg, R.A. 1991. Tumor suppressor genes and cancer pathogenesis. *Triangle* 30, 61-86.

APPENDIX VIII

Development in a Lymph Node of Two B-Cell Malignancies (Hodgkin's disease and follicular lymphoma) from the same Germinal Center B-cell precursor with common somatic VH gene (peptide) mutations



From: Marafiati, T., *et al.* (1999). Classical Hodgkin's disease and follicular lymphoma originating from the same germinal center B-cell. Jr. Clin Onc. 17, 2804

APPENDIX IX

Selective diagnosis of non-Hodgkin's lymphoma groups by gene microarrays. Clusters of genes significantly discriminate 3 histologic subtypes with a 96% accuracy.

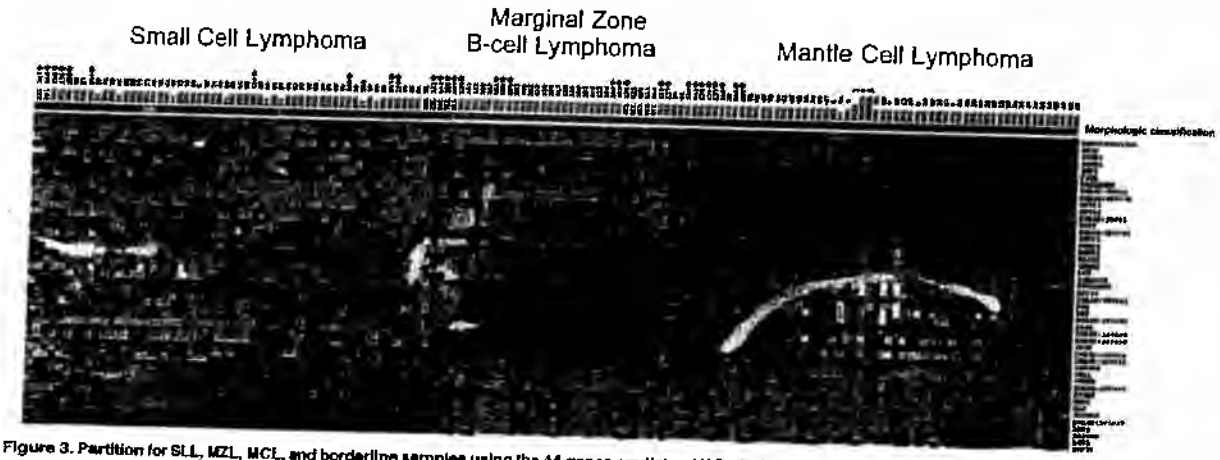


Figure 3. Partition for SLL, MZL, MCL, and borderline samples using the 44-genes predictor. (A) Preliminary group samples were correlated to SLL, MZL, and MCL mean profiles. The horizontal axis represents correlations with the MCL mean profile (R_{MCL}) and the vertical axis represents correlations with the SLL mean profile (R_{SLL}). The SLL samples are represented in orange, the splenic MZL samples in blue, and the MCL samples in pink. Cases reclassified as borderline cases are represented in brown. Three of the 6 cases were hybridized twice. Each axis represents the positive value of one subtype. (B) Gene-expression data of the 44 selected genes used for the diagnostic predictor. All samples, the preliminary group, and the validation group samples were clustered according to the expression data of the 44 genes of the diagnostic predictor. Validation group samples were blind analyzed and are marked with a black dot. Note the small branch on the left side of the dendogram containing 4 unpredictable samples.

From: Thiebelemonti, C., *et al.* (2004). Small lymphocytic lymphoma. Marginal zone B-cell lymphoma and mantle cell lymphoma exhibit distinct gene expression profiles allowing molecular diagnosis. *Blood*, 103, 2727.

γ-BHC

Cantor et al, 1992	OR=2.6 (1.2-5.5) No protection, on crops
McDuffie et al, 2001	OR=2.06 (1.1-4.22)
Schroeder et al, 2001	OR=2.3 (1.3-3.9) for t(14;18) NHL

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