Glutathione, Prostate Cancer and PCBs

One important clue to the cause of prostate cancer emerged in a comparison of prostate cancer cells and healthy ones. William Nelson, M.D., of the Johns Hopkins University School of Medicine, Baltimore, Md., discovered a genetic defect in prostate cancer cell samples from 88 of 91 men. This defect prevents the body from producing glutathione S-transferase (GST), an enzyme needed by the liver to detoxify harmful chemicals. The defect was not found in cells from healthy men. "GSTs have been proposed to play a critical role in defending normal cells against ..carcinogens...a possible prostate cancer prevention strategy might be the therapeutic augmentation of GST activity by using GST inducers," Nelson wrote in Proceedings of the National Academy of Sciences of the USA (Nov. 22, 1994;91: 11733-7).

PCBs have been found to alter levels of glutathione compounds in experiments, which may change a man's resistance to prostate cancer.

Summary of Results

(Each entry represents one finding in the 22 studies,, unless otherwise noted. Some studies had multiple findings.)

- Glutathione-s- transferases (GSTs) are a family of detoxification enzymes which catalyze the conjugation of a wide variety of endogenous and exogenous toxins with glutathione
- PCBs enhanced lipid oxidation and decreased glutathione peroxidase activity
- PCBs increased activities of glutathione reductase and glutathione S-transferase (GST)
- the overall activities of glutathione-peroxidases were significantly depressed in mice treated with both PCBs and iron
- Glutathione S-transferase (GST) plays an important role in detoxification mechanisms by catalyzing the conjugation of reduced glutathione (GSH) with toxins possessing electrophilic centers.
- PCBs significantly induced GST activity in all strains, with significant differences in inducibility among the strains
- GSH levels were unaffected by treatment with PCBs
- PCBs may form conjugates with glutathione
- PCBs made possible the depletion of liver glutathione and elevation of serum transaminases by bromobenzene
- Methylmercury did not counteract the effect of PCB on liver glutathione
- there is indirect evidence for the formation of conjugates between PCBs and GSH.
- Treatment with either PCB-126 or dioxin significantly increased the volume fraction of GST-P positive foci in initiated rat livers

- PCB-126 and dioxin reduce connexin expression in the plasma membranes of cells outside the GST-P positive foci
- Connexin expression alterations in the liver may serve as markers for tumor promotion.
- PCBs reduce glutathione peroxidase (GPx) activity in the liver
- glutathione (GSH) and the activities of GSH reductase (GR) and gamma-glutamyl transpeptidase (gamma-GTP) were decreased
- glutathione content in the liver was increased slightly by the halogenated aromatic hydrocarbons [including PCBs].
- Vitamin A [retinal] and Vitamin E [alpha-tocopherol] content was decreased by PCBs
- Glutathione-S-transferase (GST) activity was induced in the liver by PCBs
- PCBs produce long-lasting oxidative stress in the liver PCBs increased AHH and 7-EOD enzyme activities 100- to 200-fold in the prostate
- glutathione-S-transferase (GST) activities were not affected
- sensitivity of prostatic AHH to certain inducers and the capacity of the prostate to produce mutagenic metabolites might be of importance for initiation of prostatic cancer by environmental factors
- One study observed an excess of prostate cancer correlated with level of exposure to dichloromethane
- Two dose-dependent alternative pathways involving cytochrome P450 and glutathione S-transferases are responsible for the metabolism of dichloromethane in human and rodent cells
- mechanistic studies have established a link between glutathione S-transferase- mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice [certain PCBs increase glutathione S-transferase, which may increase dichloromethane cancer effect]
- some people inherit metabolic systems which make them more susceptible to cancer and environmental toxins
- certain levels of glutathione S-transferase may increase cancer susceptibility
- prostate cancer has a paradoxical response to antiandrogens
- differences in human glutathione transferases are studied for genetic susceptibilities to toxins [such as PCBs]
- genetic differences in levels of glutathione transferase may indicate prostate cancer susceptibility
- It is likely that endogenous environments and/or exogenous exposures [such as PCB exposure] play a significant role in modifying the effects of genes in prostate cancer risk
- metabolic activation and detoxification pathways are a major source of inter-individual variation in susceptibility to cancer

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Studies of PCBs and Glutathione

The following 15 studies describe the potential link between glutathione and prostate cancer, and PCB impacts on glutathione levels. This is not a complete list of all studies on this topic. For more, visit theTOXNET database operated by the National Library of Medicine (the source of these abstracts). Keep in mind that these studies are not all equal in size or quality. Some were

published in peer-reviewed journals, while others were simply presented at conferences. A few are duplicates by the same author (one conference-based, another published) but we presented both because the descriptions were slightly different.

Study #1

- Glutathione-s- transferases (GSTs) are a family of detoxification enzymes which catalyze the conjugation of a wide variety of endogenous and exogenous toxins with glutathione

Prostate cancer is currently the most commonly diagnosed cancer in American men. Early diagnosis through accurate screening techniques will significantly contribute to the successful management and eventual eradication of this disease. Currently, serum PSA determination remains the cornerstone of prostate cancer screening. However, more accurate screening to better differentiate patients with benign disease from those with prostatic cancer will alleviate the unnecessary surgical procedures with a significant impact on patient morbidity and health care costs. Glutathione-s- transferases (GSTs) are a family of detoxification enzymes which catalyze the conjugation of a wide variety of endogenous and exogenous toxins with glutathione. (Ross, 2001)

Study #2

- PCBs enhanced lipid oxidation and decreased glutathione peroxidase activity
- PCBs increased activities of glutathione reductase and glutathione S-transferase (GST)

To clarify the mechanism of lipid peroxide formation in polychlorinated biphenyls (PCB)-poisoned rats, the following 2 experiments were carried out. Rats were separated into 3 groups. Group 1 was fed a normal diet, group 2 was fed a PCB-supplemented diet and group 3 was fed a DDT-supplemented diet. After 5 mo., the rats were killed. The thiobarbituric acid (TBA) values in livers of the PCB- and DDT-exposed rats had increased. The activity of catalase was increased in the PCB-fed rats but decreased after the administration of DDT. The glutathione peroxidase activity was decreased only in the PCB-administered rats. PCB and DDT enhanced lipid oxidation. The decrease in glutathione peroxidase was probably the major reason for the increase of lipid oxidation in PCB-poisoned rats. The mechanism of lipid peroxidate production in DDT-poisoned rats could have been different from the case of PCB poisoning. Rats were also separated into 2 groups. To 1 group, normal diet was given and to the other group PCB-supplemented diet was given. After 1 mo., the rats were killed. In PCB-exposed rats, activities of glutathione reductase and glutathione S-transferase were increased. The increase in glutatione reductase could have been a compensation for a decrease in glutathione peroxidase. PCB was probably metabolized to make glutathione conjugates by the action of glutathione S-transferase. (Kamohara et al, 1984)

Study #3

- the overall activities of glutathione-peroxidases were significantly depressed in mice treated with both PCBs and iron

The effect of iron (7439896) on the activities of cytochrome-P450 isoenzymes stimulated by Aroclor-1254 (27323188) was examined in this study. Male C57BL/10ScSn-mice were injected with an iron/dextran or dextran dose of 600mg/kg. For up to 8 weeks after injection, experimental mice were fed a diet containing 0.01% Aroclor-1254. Mice were then sacrificed and the liver tissue was analyzed. By 5 weeks, the uroporphyrin content in the livers of mice treated with both iron and Aroclor-1254 was 630+/-72 nanomoles per gram (nmol/g), while that in mice treated with just Aroclor-1254 was significantly less, only 42+/-24nmol/g. After 2 weeks, ethoxyresorufin-deethylase (EROD) activity was significantly higher in the microsomal and nuclear fractions in mice treated with Aroclor-1254 than in controls. Pretreatment with iron further enhanced EROD activity in the nuclear fraction. Pretreatment with iron did not enhance the pentoxyresorufin (PROD) and benzyloxyresorufin (BROD) activities stimulated by Aroclor-1254. By 5 weeks of Aroclor-1254 treatment, the quantities of EROD, PROD, and BROD were significantly diminished. In both the microsomal and nuclear fractions, chemiluminescence (CL) increased significantly after treatment with Aroclor-1254, and was further enhanced in the microsomal fraction by the presence of iron. Overall, the CL response correlated with isoenzyme activity. Using 1,2-dichloro-4-nitrobenzene as a substrate, the activity of cytosolic glutathione-S-transferase (cGST) increased after 4 weeks of Aroclor-1254 treatment. In mice pretreated with iron, the increased cGST activity was evident in a larger proportion of the liver. However, the overall activities of glutathione-peroxidases were significantly depressed in mice treated with both Aroclor-1254 and iron. The authors conclude that iron pretreatment enhances the activities of cytochrome-P450 isoenzymes and cGST induced by Aroclor-1254. (Madra et al, 1996)

Study #4

- Glutathione S-transferase (GST) plays an important role in detoxification mechanisms by catalyzing the conjugation of reduced glutathione (GSH) with toxins possessing electrophilic centers.
- PCBs significantly induced GST activity in all strains, with significant differences in inducibility among the strains
- GSH levels were unaffected by treatment with PCBs

The activities of hepatic glutathione-S-transferases (GST), glutathione-peroxidase (GPx), and glutathione-reductase (GR), both constitutive and Aroclor-1254 (11097691) induced, were determined in twelve strains of inbred male mice. Glutathione S-transferases play an important role in detoxification mechanisms by catalyzing the conjugation of reduced glutathione (GSH) with toxins possessing electrophilic centers. Mice were randomly divided into two groups, with four mice from each strain in each group. The treatment group received a single intraperitoneal injection of Aroclor-1254 (500mg/kg) in corn-oil, and the control group received corn-oil only. After 5 days, the animals were sacrificed and liver homogenates prepared. Hepatic GST, GPx, and GR activities were determined, as was the level of cytosolic GSH. Aroclor-1254 significantly induced GST activity in all strains, with significant differences in inducibility among the strains. Aroclor-1254 also significantly induced GR activity and significantly decreased GPx activity in all strains. GSH levels were unaffected by treatment with Aroclor-1254. Constitutive GST activities and inducibility showed larger strain differences. (Makary et al, 1988)

Study #5

- PCBs may form conjugates with glutathione

A new sulfur (7704349) containing derivative was found in the partial metabolism of polychlorinated biphenyls (PCBs). The inhibition of some organic substances in the accumulation of PCBs was tested with liver homogenates of ICR-mice or Wistar-King-rats. Reduced glutathione (70188) (GSH), mannitol (69658), arabinose (147819), and the acid hydrolysate of pectin (8047390) were used in reaction mixtures containing PCBs. The hydrolysate of the water soluble fraction and residual PCBs were determined. Single samples of individual PCBs were used in reaction mixtures with the liver homogenates from mice and GSH, arabinose, or mannitol. Thin layer and gas/liquid chromatography were used to characterize metabolites. Metabolites in feces of rats and mice were also examined. In the reaction of the tested organic materials with PCBs in the rat liver system, the formation of a conjugate of PCBs was suggested. A new sulfur derivative of PCBs, polychloro-mercaptobiphenyl, was found as one of the metabolic byproducts in the in-vitro reactions. The alkali hydrolysate of another metabolite was regarded as the conjugate of PCBs with GSH or other sulfur containing biological substances. The same product was found in the feces of rats and mice. The author concludes that the new product supports the possibility of conjugate formation with PCBs and glutathione. (Kurachi, 1983)

Study #6

- PCBs made possible the depletion of liver glutathione and elevation of serum transaminases by bromobenzene
- Methylmercury did not counteract the effect of PCB on liver glutathione

Combined effects of polychlorinated biphenyls (PCB) and methylmercury were investigated by assaying activities of hepatic enzymes and measuring the binding of bromobenzene to microsomal protein. Rats were fed normal or PCB-diet (KC-400-KC-500, 1:1, 50 ppm) for 14 days and methylmercuric chloride (10 mg Hg/kg, s.c.) was given once daily for the last 2 days. Inducing effects of PCB on microsomal cytochrome P-450, cytochrome b5, aminopyrine N-demethylase, aniline hydroxylase and p-nitroanisole O-demethylase were counteracted by methylmercury. Glucose 6-phosphatase activity was additively decreased by the combination of PCB and methylmercury. Activity of glucose 6-phosphate dehydrogenase in soluble fraction was increased by PCB but reduced by methylmercury. Toxicity of bromobenzene was enhanced by PCB but the effect of PCB was counteracted by methylmercury. Depletion of liver glutathione and elevation of serum transaminases by bromobenzene were potentiated by PCB. Methylmercury counteracted the effect of PCB on serum transaminases but not on liver glutathione. The amount of bromine covalently bound with liver microsomal protein after an injection of bromobenzene and the radioactivity bound with microsomal protein after in vitro incubation of 14C-bromobenzene with microsomes were fortified by PCB pretreatment but depressed by combining administration of methylmercury. (Takabatake et al, 1980)

Study #7

- there is indirect evidence for the formation of conjugates between PCBs and GSH.

The possibility of conjugate formation by polychlorinated biphenyls (PCBs) with glutathione (70188) was indicated through some metabolites formed in mice and rats. In a reaction mixture with liver homogenates of mice or rats with PCBs gas chromatography/mass spectrometry was used to characterize possible conjugate derivatives. Because of the extreme difficulty of purifying the possible conjugate due to its being only soluble in water and the limited capacity of the analytic method, conjugates of chlorobenzene (108907) and reduced glutathione (GSH) were studied. Metabolites in the urine of rats and mice were identified. A derivative found by gas chromatography/mass spectrometry, an N-acetyl-cysteine derivative, was demonstrated after methylation or acetylation of metabolites. This derivative was considered to be derived from the conjugate of PCBs with GSH, although direct evidence was not available. When chlorobenzene was used, and N-acetyl-cysteinyl-glycine derivative was found and behavior of chlorobenzene was considered quite similar. In urine, other metabolic forms of acetic-acid, lactic-acid, and cysteamine were found, supporting the possibility of a conjugate of PCBs with GSH. The authors conclude that there is indirect evidence for the formation of conjugates between PCBs and GSH. (Kurachi et al, 1983)

Study #8

- Treatment with either PCB-126 or dioxin significantly increased the volume fraction of GST-P positive foci in initiated rat livers
- PCB-126 and dioxin reduce connexin expression in the plasma membranes of cells outside the GST-P positive foci
- Connexin expression alterations in the liver may serve as markers for tumor promotion.

The ability of polychlorinated biphenyl (PCB) congeners and 2,3,7,8-tetrachlorodibenzo-p-dioxin (1746016) (TCDD) to alter connexin expression outside the placental-glutathione-S-transferase (GST-P) positive foci in the liver was examined in this study. Female Sprague-Dawley-rats were initiated with nitrosodiethylamine 24 hours after partial hepatectomies were performed. Five weeks later, the rats were injected with 10 micrograms per kilogram per week (microg/kg/week) of PCB-126 (57465288), 1microg/kg/week of TCDD, or 20,000microg/kg/week of PCB-153 (35065271) for 20 weeks or 10,000microg/kg/week of PCB-118 (31508006) for 52 weeks. Liver samples were stained for connexins and GST-P and were examined microscopically for immunohistochemical changes. The volume fraction of GST-P positive foci was measured. Connexin extracts were examined via Western blot analysis. The levels of connexin-32 (cx32) and connexin-26 (cx26) outside the GST-P positive foci were not altered in rats treated with PCB-153 or PCB-118. However, cx32 and cx26 levels outside the GST-P positive foci were moderately reduced in rats treated with PCB-126 and TCDD, compared to controls. Treatment with each of the PCB congeners and TCDD caused marked reductions in the cx32 and cx26 levels inside the GST-P positive foci. Treatment with either PCB-126 or TCDD significantly increased the volume fraction of GST-P positive foci in initiated rat livers, compared to controls. PCB-153 and PCB-118 were less potent modifiers of hepatic foci. Western blot analysis revealed that cx32 and cx26 levels were reduced following treatment with PCB-126 and TCDD. The down regulation of cx32 and cx26 was apparent in both initiated and uninitiated livers. The authors conclude that PCB-126 and TCDD reduce cx26 and

cx32 expression in the plasma membranes of cells outside the GST-P positive foci. Connexin expression alterations in the liver may serve as markers for tumor promotion. (Bager et al, 1997)

Study #9

- PCBs reduce glutathione peroxidase (GPx) activity in the liver

The alteration in hepatic glutathione peroxidase (GPx) produced by polychlorinated biphenyls (PCBs) was studied in vivo in aryl hydrocarbon (Ah)-responsive C57BL and -less-responsive DBA strains of mice. 3,3',4,4',5-Pentachlorobiphenyl (PCB 126), one of the high-affinity ligands for the Ah receptor, significantly reduced Se-dependent GPx activity in C57BL mice, but not in DBA mice. A reduction in activity in C57BL mice was also observed following treatment with a high dose of 3,3',4,4'-tetrachlorobiphenyl with lesser affinity for the Ah receptor than PCB 126, but not by 2,2',5,5'-tetrachlorobiphenyl, a low-affinity ligand. To assess the effects on GPx in the liver, the content of reduced glutathione (GSH), an obligate co-factor for GPx, and the activity of two enzymes, gamma-glutamyl transpeptidase (gamma-GTP) and glutathione reductase (GR), which play a role in supplying GSH were determined after PCB treatment. The results showed that although the hepatic activity o ga (incomplete abstract) (Hori et al, 1997a)

Study #10

- glutathione (GSH) and the activities of GSH reductase (GR) and gamma-glutamyl transpeptidase (gamma-GTP) were decreased

The effect of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) on hepatic glutathione peroxidase (GPx) redox system was studied in vivo in rats and guinea pigs. PCB 126 treatment caused significant reduction of Se-dependent and -non-dependent GPx activity in rats. In agreement with this, the content of glutathione (GSH) and the activities of GSH reductase (GR) and gamma-glutamyl transpeptidase (gamma-GTP) were also decreased in this species. On the contrary, guinea pig liver Se-non-dependent GPx activity was significantly enhanced by PCB 126 treatment, while no effect on Se-dependent activity was observed. Neither the content of GSH nor the enzyme activities responsible for GSH supply in guinea pig liver was affected by PCB 126. These results suggest that the damage on GPx redox system is, at least, one of mechanisms by which co-planar PCB induces toxicity in rats. However, in guinea pigs, this is not the case, and a different mechanism from the damage on active oxygen quenching system is likely to be involved. (Hori et al, 1997b)

Study #11

- glutathione content in the liver was increased slightly by the halogenated aromatic hydrocarbons [including PCBs].
- Vitamin A [retinal] and Vitamin E [alpha-tocopherol] content was decreased by PCBs
- Glutathione-S-transferase (GST) activity was induced in the liver by PCBs
- PCBs produce long-lasting oxidative stress in the liver

The long term effects of polychlorinated biphenyls (PCBs) and polychlorinated naphthalenes (PCNs) on cytochrome-P450 activities, oxidative stress levels, and on the antioxidant defense system in rat tissues were examined. Clophen-A50 (8068448) was used as the PCB mixture and Halowax-1014 (1335871) was used as the PCN mixture. A single dose of PCBs at 100mg/kg or PCNs at 20mg/kg was given to adult male Sprague-Dawley-rats intraperitoneally. Rats were killed up to 3 months after treatment. Hepatic EROD activity was induced from day one following exposure and was maximally elevated 7 days after injection. The activity was still induced after 3 months of the single dose. An increase in oxidative stress was noted from the first up to day 14 after dosing. The amount of thiobarbituric-acid reactive material was slightly increased in the liver by PCBs and decreased 35% by PCNs at the 14 day time point. Hepatic glutathione content was increased slightly by the halogenated aromatic hydrocarbons. Hepatic retinol and alpha-tocopherol content was decreased by PCBs but not by the PCNs. Glutathione-S-transferase activity was induced in rat liver by PCBs and, to a lesser extent, by PCNs. The authors conclude that PCBs and PCNs produce long lasting oxidative stress in rat liver. (Mantyla et al, 1993)

Study #12

- PCBs increased AHH and 7-EOD enzyme activities 100- to 200-fold in the prostate
- glutathione-S-transferase (GST) activities were not affected
- sensitivity of prostatic AHH to certain inducers and the capacity of the prostate to produce mutagenic metabolites might be of importance for initiation of prostatic cancer by environmental factors

Induction of aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin-O-deethylase (7-EOD) activities as well as of benzo(a)pyrene (BP) metabolite formation in rat prostatic microsomes was demonstrated after treatment with beta-naphthoflavone (BNF). The capacity to convert promutagenic compounds to ultimate mutagenic metabolite in the Ames' Salmonella assay by 5000nvestigated. Male rats were treated with BNF, polychlorinated biphenyls (PCB; Arochlor 1254), phenobarbital (PB) and the vehicle, corn oil. PCB or BNF pretreatment increased the AHH- and 7-EOD activities 100- to 200-fold in the rat prostate 5000upernatant (S-5 fraction). Epoxide hydrolase (EH) and glutathione-S-transferase (GST) activities were not affected while UDP-glucuronosyltransferase (UDP-GT) was increased 2.2- and 2.5-fold by PCB and BNF, respectively. PB did not significantly affect any of the enzyme activities measured. A dose-dependent increase in mutagenic response vs. amount of 5000promutagen (aflatoxin B1 (AFB), 2-aminofluorene (2-AF), BP) was observed. The most pronounced activation was obtained with S-5 fraction from BNF- or PCB-treated rats. The great sensitivity of prostatic AHH to certain inducers and the capacity of the prostate to produce mutagenic metabolites might be of importance for initiation of prostatic cancer by environmental factors. (SODERKVIST et al, 1983)

Study #13

- One study observed an excess of prostate cancer correlated with level of exposure to dichloromethane

- Two dose-dependent alternative pathways involving cytochrome P450 and glutathione S-transferases are responsible for the metabolism of dichloromethane in human and rodent cells
- mechanistic studies have established a link between glutathione S-transferase- mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice [certain PCBs increase glutathione S-transferase, which may increase dichloromethane cancer effect]

Exposure data. Dichloromethane is used principally as a solvent, in paint removers, degreasers and aerosol products, and in the manufacture of foam polymers. Widespread exposure occurs during the production and industrial use of dichloromethane and during the use of a variety of consumer products containing dichloromethane. Substantial losses to the environment lead to ubiquitous low- level exposures from ambient air and water. Human carcinogenicity data. Seven cohort studies have examined the risk of cancer among populations exposed to dichloromethane. Two studies observed an excess of pancreatic cancer, but the three others which reported on this tumour did not. One study observed an excess of liver and biliary tract cancers among longer-term employees. One study observed an excess of prostate cancer that appeared to increase with level of exposure. One study observed an excess of breast cancer and gynaecological cancers among women with the highest likelihood of exposure and another study observed an excess of cervical cancer. With the exception of the prostate cancer excess observed in one study, all the excesses were based on small numbers. No estimates of exposure levels were available for two of the six studies. Three case-control studies have examined the risk of cancer associated with dichloromethane exposure and provided data adequate for evaluation. One observed an association between estimated intensity, probability and duration of exposure and the risk of astrocytic brain tumours. A second, which focused on female breast cancer, observed an elevated risk in the highest exposure category but no association with probability of exposure. The third indicated an increased risk of rectal cancer and possibly lung cancer. For no type of cancer was there a sufficiently consistent elevation of risk across studies to make a causal interpretation credible. Animal carcinogenicity data. Dichloromethane was tested by oral administration in the drinking water in one study in mice and one study in rats, by inhalation exposure in two studies in mice, three studies in rats and one study in hamsters and by intraperitoneal injection in a lung adenoma assay in mice. In the study in mice by oral administration, no increase in tumour incidence was observed. The study in rats by oral administration gave inconclusive results. In the two inhalation studies in mice, increased incidences of benign and malignant lung and liver tumours were observed in both sexes. ln the three inhalation studies in rats, the incidence of benign mammary tumours was increased in one study in females of a strain in which the incidence of spontaneous mammary tumours is low, and the multiplicity was increased in two studies in females of a high-incidence strain. In one study, in males, the incidence of mammary gland adenomas and fibroadenomas was increased. Negative results were obtained in the lung adenoma test in mice and in the inhalation study in hamsters. Other relevant data. Two dose-dependent alternative pathways involving cytochrome P450 and glutathione S-transferases are responsible for the metabolism of dichloromethane in human and rodent cells. Dichloromethane is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems, predominantly in mice, both in vitro and in vivo. It induced sister chromatid exchanges, chromosome breakage and chromosome loss in vitro in human cells. In-vitro results in rodent cells were inconclusive or negative. Dichloromethane induced DNA

single-strand breaks in mammalian cell cultures, but inconclusive or negative effects were reported for induction of gene mutations. It did not induce unscheduled DNA synthesis either in vivo in rodents or in human fibroblast cultures. It was genotoxic in fungi but not in Drosophila in the sex-linked recessive lethal assay. Mechanistic studies have established a link between glutathione S-transferase- mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The glutathione S-transferase responsible for the metabolism of dichloromethane is expressed to significantly greater extents in mouse tissues than in rat, hamster or human tissues. The available data suggest a plausible mechanism for the development of liver and lung tumours which occur in mice but not in rats exposed to dichloromethane. Evaluation. There is inadequate evidence in humans for the carcinogenicity of dichloromethane. There is sufficient evidence in experimental animals for the carcinogenicity of dichloromethane. Overall evaluation. Dichloromethane is possibly carcinogenic to humans (Group 2B). (IARC, 1999)

Study #14

- some people inherit metabolic systems which make them more susceptible to cancer and environmental toxins
- certain levels of glutathione S-transferase may increase cancer susceptibility
- prostate cancer has a paradoxical response to antiandrogens

Hereditary peculiarities in individual responses to environmental chemicals are a common occurrence in human populations. Genetic variation in glutathione S-transferase, CYP1A2, N-acetytransferase, and paraoxonase exemplify the relationship of metabolic variation to individual susceptibility to cancer and other toxicants of environmental origin. Heritable receptor protein variants, a subset of proteins of enormous pharmacogenetic potential that have not thus far been extensively explored from the pharmacogenetic standpoint, are also considered. Examples of interest that are considered include receptor variants associated with retinoic acid resistance in acute promyelocytic leukemia, with paradoxical responses to antiandrogens in prostate cancer, and with retinitis pigmentosa. Additional heritable protein variants of pharmacogenetic interest that result in antibiotic-induced deafness, glucocorticoid-remediable aldosteronism and hypertension, the long-QT syndrome, and beryllium-induced lung disease are also discussed. These traits demonstrate how knowledge of the molecular basis and mechanism of the variant response may contribute to its prevention in sensitive persons as well as to improved therapy for genetically conditioned disorders that arise from environmental chemicals. (Weber, 1995)

Study #15

- differences in human glutathione transferases are studied for genetic susceptibilities to toxins [such as PCBs]

Genotypes responsible for interindividual differences in ability to activate or detoxify genotoxic agents are recognized as biomarkers of susceptibility. Among the most studied genotypes are human glutathione transferases. The relationship of genetic susceptibility to biomarkers of exposure and effects was studied especially in relation to the genetic polymorphism of glutathione S-transferase M1 (GSTM1). For this review papers reporting the effect of GSTM1 genotype on DNA adducts, protein adducts, urine mutagenicity, Comet assay parameters,

chromosomal aberrations, sister chromatid exchanges (SCE), micronuclei, and hypoxanthine-guanine phosphoribosyl transferase mutations were assessed. Subjects in groups occupationally exposed to polycyclic aromatic hydrocarbons, benzidine, pesticides, and 1,3-butadiene were included. As environmentally exposed populations, autopsy donors, coal tar-treated patients, smokers, nonsmokers, mothers, postal workers, and firefighters were followed. From all biomarkers the effect of GSTM1 and N-acetyl transferase 2 was seen in coke oven workers on mutagenicity of urine and of glutathione S-transferase T1 on the chromosomal aberrations in subjects from 1,3-butadiene monomer production units. Effects of genotypes on DNA adducts were found from lung tissue of autopsy donors and from placentas of mothers living in an air-polluted region. The GSTM1 genotype affected mutagenicity of urine in smokers and subjects from polluted regions, protein adducts in smokers, SCE in smokers and nonsmokers, and Comet assay parameters in postal workers. A review of all studies on GSTM1 polymorphisms suggests that research probably has not reached the stage where results can be interpreted to formulate preventive measures. The relationship between genotypes and biomarkers of exposure and effects may provide an important guide to the risk assessment of human exposure to mutagens and carcinogens. (Radim, 1998)

Upcoming Studies

BELL DA. INHERITED CANCER SUSCEPTIBILITY AND RELATION TO GENETIC DAMAGE. Crisp Data Base National Institutes Of Health. Author Address: NIEHS, NIH

- genetic differences in levels of glutathione transferase may indicate prostate cancer susceptibility

Human genetic polymorphisms in metabolic activation and detoxification pathways are a major source of inter-individual variation in susceptibility to cancer. The group has developed genotyping assays for the "at-risk" variants of enzymes that protect against carcinogens in cigarette smoke, diet, industrial processes and environmental pollution. Following testing of over 5000 individuals for these candidate susceptibility genes, it has been found that the frequency of the at-risk genotypes for glutathione transferase M1 (GSTM1), theta 1 (GSTT1), and n-acetyltransferase (NAT1 and NAT2) vary significantly between Asians, Caucasian- and African-Americans. This suggests that some of the ethnic differences in cancer incidence may be due to genetic metabolic differences as well as exposure differences. In ongoing studies with researchers at the NIEHS, National Cancer Institute, Columbia University, University of North Carolina and University of Keele, England, the group is testing the impact of these cancer susceptibility genes in case- control studies of cancer of the bladder, lung, liver, colon, stomach, prostate, breast and the myelodysplastic syndromes. The glutathione transferase theta 1 (GSTTI) gene defect has recently been shown to be an important risk factor in myelodysplastic syndrome (MDS). Risk of liver cancer from exposure to aflatoxin was found to be greater among individuals with a combined GSTM1 and GSTT1 gene defects. A new polymorphism in the NAT1 gene affects arylamine detoxification and is associated with higher levels of DNA adducts. This common NAT1 variant is a significant genetic risk factor in cancer of the bladder, colorectum, and stomach. The group is also developing new methods to assess damage from

carcinogens. These studies seek to integrate environmental and genetic factors in understanding the etiology of human disease.

REBBECK TR. MOLECULAR EPIDEMIOLOGY OF PROSTATE CANCER. Crisp Data Base National Institutes Of Health. Author Address: UNIV OF PENNSYLVANIA, 423 GUARDIAN DR, PHILADELPHIA, PA 19104-6021

- It is likely that endogenous environments and/or exogenous exposures [such as PCB exposure] play a significant role in modifying the effects of genes in prostate cancer risk

Prostate cancer is the most commonly occurring cancer in U.S. men, yet few factors are known to predict which individuals are at increased prostate cancer risk. Prostate cancers often aggregate in families, but do not generally segregate in a Mendelian manner. One explanation for this aggregation without segregation is that predisposition to develop prostate cancer is the result of somatic genetic effects of multiple genes and/or environments acting on an inherited genotype. An understanding of the complex interplay of genetic variability at multiple loci and of environmental agents will facilitate the use of genetic markers to identify individuals at increased risk of prostate cancer. This information could then be used to more effectively apply prostate cancer prevention and control strategies. The objective of the present study is to examine the role of genes that regulate the metabolism of environmental carcinogens in prostate cancer etiology. These genes include cytochromes P450 (e.g. CYP1A1, CYP2D6, and CYP2E1) and the mu or theta classes of the glutathione-S-transferases. Three specific aims are proposed to accomplish this objective. In Specific Aim l, the relationship of each of the candidate genes and the occurrence or age of onset of prostate cancer will be examined. However, it is unlikely that any single gene will be sufficient to account for the complex etiology of prostate cancer. Therefore, the relationship between multiple candidate genes and the occurrence or age of onset of prostate cancer will be examined in Specific Aim 2. It is also likely that endogenous environments and/or exogenous exposures play a significant role in modifying the effects of these genes in prostate cancer risk. Therefore, the interactions of multiple candidate genes, environments, and exposures will be examined in Specific Aim 3. A number of inferences can be made from the information obtained through this study. First, important information about the distribution of alleles at specific candidate genes will be provided. Second, comparisons can be made of the distribution of these alleles among individuals with and without prostate cancer. Differences in these allelic distributions among cancer cases and controls can identify specific single locus or multilocus genotypes that may be biomarkers of prostate cancer risk. Third, interactions of genotypes at multiple loci and environments can provide information about the modification of the effects of these genotypes by specific endogenous environments or exogenous exposures. Finally, before these genes can be used as biomarkers of prostate cancer risk, it will be important to know whether they represent an improvement over other risk factors such as age or family history. The proposed research will study whether prediction of prostate cancer risk is improved by knowledge of candidate genotypes, even after other "traditional" risk factors are known.

BELL DA. GENETIC SUSCEPTIBILITY TO CARCINOGENS. Crisp Data Base National Institutes Of Health. Author Address: NIEHS, NIH

- metabolic activation and detoxification pathways are a major source of inter-individual variation in susceptibility to cancer

Summary of Work: Human genetic polymorphisms in metabolic activation and detoxification pathways are a major source of inter-individual variation in susceptibility to cancer. The group has developed genotyping assays for the "at-risk" variants of enzymes that protect against carcinogens in cigarette smoke, diet, industrial processes and environmental pollution. Following genotyping of over 5000 individuals for these candidate susceptibility genes, it has been found that the frequency of the at-risk genotypes for glutathione transferase M1 (GSTM1), theta 1 (GSTT1), Pi (GSTP1) and n-acetyltransferase (NAT1 and NAT2) vary significantly between Asians, Caucasian- and African-Americans. This suggests that some of the ethnic differences in cancer incidence may be due to genetic metabolic differences as well as exposure differences. In ongoing studies with researchers at the NIEHS, National Cancer Institute, Columbia Univ., Johns Hopkins Univ., Univ. of North Carolina and Univ. of Occupational and Environmental Health, Japan, the group is testing the impact of these cancer susceptibility genes in case-control studies of cancer of the bladder, lung, liver, colon, stomach, prostate, breast and myelodysplastic syndromes. The glutathione transferase M1 (GSTM1) gene defect has recently been shown to be a risk factor among Japanese gastric cancer patients who were also smokers (6). It was found that both genetic and nutritional factors modulate levels of DNA damage observed among heavy smokers (5). It was observed that a vitamin D receptor polymorphism was associated with risk of prostate cancer (7). The presence of the GSTT1 gene was determined to be an crucial factor in dichloromethane metabolism to formaldehyde in human liver(11). These studies seek to integrate environmental and genetic factors in understanding the etiology of human disease.

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