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Pharmacogenetics Helps in Therapeutic Drug Monitoring

By Jimmie L. Valentine and Amanda J. Jenkins

Therapeutic drug monitoring has proven to be an excellent addition to patient care, especially for drugs with such a narrow therapeutic range that toxic effects occur at blood levels close to those needed to achieve a therapeutic effect. Therapeutic monitoring can be used to correlate the observed pharmacological effect(s) with the rate at which drug is removed from the central compartment (systemic circulation) through the processes of metabolism, re-distribution, or elimination. Knowing the blood level permits the patient's dosage to be adjusted based on what is happening in the central compartment.

Digoxin and gentamicin

For example, within its therapeutic range, digoxin should produce the desired effect of increasing the strength of contractility in the failing heart without producing the toxic effect of arrhythmia. Digoxin's therapeutic range is 0.5–2.0 ng/mL. Levels greater than 2.0 ng/mL can cause arrhythmias, while those greater than 3.5 ng/mL can be fatal. The narrow range between therapeutic effectiveness and toxicity has made monitoring extremely valuable for establishing a therapeutic dosing range with digoxin.

Another example is gentamicin, the peak and trough levels of which must be monitored to prevent oto- or nephrotoxicity. A so-called "peak" level is obtained 30 minutes after a dose, and a "trough" level is determined 30 minutes prior to the next dose. For gentamicin, the peak level should be from 6–10 µg/mL, and the trough level should be 0.5–2 µg/mL. For such levels to be meaningful, they should be drawn when the drug is near a steady-state plasma concentration, usually after three or more doses.

The advent of pharmacogenetics, the study of

the effects of genetic factors on the metabolism of a drug, has made possible an understanding of how polymorphisms in an enzyme affecting drug metabolism can affect therapeutic drug monitoring. Polymorphisms can either increase or decrease the amount of measured drug compared with a previously correlated therapeutic level in the general population. An example of both effects would be slow (former case) or fast (latter case) acetylators of the antituberculosis drug isoniazid. The frequency of the phenotypes for acetylation is apparently isolated in certain races or ethnic groups; for example, slow acetylators are found predominantly in Scandinavians and fast acetylators in Japanese. Because of the heterogeneity of races in the United States, upwards of 50% of the population may be slow acetylators. Therapeutic drug monitoring for isoniazid can be particularly valuable in individuals with such phenotypic expression because an effective therapeutic level may require dose adjustment based on levels in the central compartment.

Metabolism systems

Biotransformation of drugs is complex, with many drugs being metabolized by multiple enzyme systems. In general, drug metabolism occurs in a two-step process, termed Phase I and Phase II reactions, as illustrated in Figure 1. Oxidation predominates in Phase I reactions and is facilitated mainly by a super-family of mixed-function mono-oxygenase enzymes termed the cytochromes P450 (abbreviated CYP).

The different cytochromes are divided into families based on their protein and DNA homology. Six of these enzyme families (namely, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and

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Pharmacogenetics and TDM

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CYP3A4) mediate the oxidative metabolism of many drugs.

Phenotypic expression of some of these isozymes has been observed to affect plasma concentrations in a manner similar to that discussed above for isoniazid, although the metabolic products are different. If, however, the patient is taking other drugs concurrently with the drug measured during therapeutic monitoring, drug–drug competition for a CYP isozyme may occur, which can alter the metabolism of the measured drug.

Dextromethorphan

For example, the common over-the-counter cough suppressant dextromethorphan is oxidatively metabolized by CYP2D6. If dextromethorphan is used concurrently with a tricyclic antidepressant, such as amitriptyline, the two drugs will compete for CYP2D6 and thus increase the blood level of amitriptyline. The increase in amitriptyline could be great enough to cause the untoward side effect of drowsiness. The effect on the patient could be dramatic if blood levels of amitriptyline were being regularly monitored and a baseline therapeutic level had been established. A physician who did not know that the patient was taking another CYP2D6-metabolized drug might reduce the amitriptyline dosage. Then when the patient stopped taking the cough suppressant, a sub-therapeutic level of amitriptyline could occur.

Studies now being reported in the scientific literature identify which therapeutic drugs act as substrates for a particular CYP family. For example, tolbutamide, an oral hypoglycemic drug structurally similar to the sulfonamides, is a substrate for CYP2C9. Hydroxytolbutamide is produced as the metabolite in a Phase I reaction. Thus, it would be reasonable to expect that co-administration of a sulfonamide and tolbutamide might alter the metabolic

degradation of the latter due to competitive inhibition of CYP2C9. This effect has been demonstrated by observing the area under the curve for tolbutamide, which increased fivefold when tolbutamide was co-administered with sulfaphenazole, a sulfonamide used to treat tuberculosis.

CYP2C9 appears to be mostly involved in metabolism of polar acidic drugs and can be competitively inhibited by the sulfonamides, tolbutamide, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, phenytoin, selective serotonin reuptake inhibitors, and warfarin. Concurrent administration of any of these drugs with a monitored drug that is metabolized by the same CYP would be expected to alter the observed blood concentrations.

Cisapride

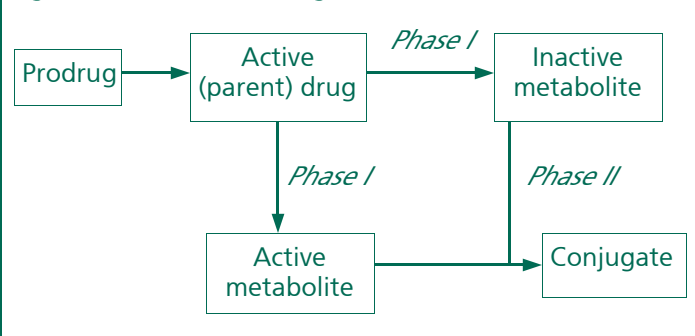
The other major isozyme family, CYP3A4, is responsible for metabolism of about 50% of all therapeutic agents. If the therapeutic drug has a small therapeutic range, the co-administration of another drug metabolized by the same isozyme system may have a deleterious effect. For example, the prokinetic agent, cisapride, used for the treatment of gastrointestinal disorders such as gastro-esophageal reflux, can be affected by other drugs, with potentially dangerous results. When cisapride was co-administered with a macrolide antibiotic like erythromycin, which is also metabolized by CYP3A4, potentially fatal arrhythmias occurred. This anomaly was shown to be due to an increase of unmetabolized cisapride in the blood due to competition between the macrolide antibiotic and cisapride for the CYP3A4 isozyme.

A similar situation of fatal arrhythmias due to the same mechanism was discovered when the antifungal drug, ketoconazole, was ingested concurrently with the nonsedating antihistamine, terfenadine. The increase in terfenadine concentration had unmasked its ability to block fast potassium channels in the heart, resulting in cardiac conduction delays.

Cyclosporine

In transplant patients, the common immunosuppressant cyclosporine is closely monitored using a variety of analytical methods. The reference ranges for effective immune suppression to prevent organ rejection are method-dependent, but in general, trough blood levels greater than 150 ng/mL are considered nephrotoxic. Several therapeutic drugs alter the observed blood levels of cyclosporine, including a number of antimicrobial drugs. For example, rifampicin decreases cyclosporine blood concentra-

Figure 1. Patterns of drug biotransformation



tions below the limit of detection of many assays, whereas, erythromycin, ketoconazole, sulfadimidine, thrimeth-oprim, and fluoroquinolones increase its concentration. Obviously, use of these antimicrobial agents with cyclosporine would require adjusting the cyclosporine dose for optimal immunosuppression.

Phase II metabolism

Phase II metabolism involves some type of conjugation reaction, generally following an initial Phase I transformation. Glucuronide conjugation with the uridine 5'-diphospho-glucuronosyltransferase (UGT) family of enzymes is illustrative. Various isoforms exist for the UGT family, with each isoform exhibiting substrate specificity for different drugs. The multigene superfamily of human UGT includes more than 24 genes and cDNAs. Sixteen are functional and encode full-length proteins; eight of these 16 are encoded by the UGT1A locus (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, and 1A10), and eight are encoded by UGT2 genes (2A1, 2B4, 2B7, 2B10, 2B11, 2B15, 2B17, and 2B28). So far, few drug classes have been characterized for the specific UGT isoform responsible for their transformation.

Zidovudine

Zidovudine (AZT), the drug used to inhibit HIV infection, is metabolized to its inactive glucuronide by UGT, and this conversion can be inhibited by fluconazole, presumably by competitive inhibition. Because fluconazole, an antifungal drug, is important in immune-suppressed patients, the potential for a clinically significant interaction must be considered, although neither drug is typically assessed by therapeutic monitoring. Similar interactions could occur with other drugs that are both competing for glucuronidation with UGT.

With the human genome project nearing completion, it will soon be possible to predict which drug-metabolizing enzymes will be polymorphic. To date, most known drug-metabolizing polymorphisms have been found as a result of clinical observations and unexpected results from therapeutic drug monitoring. Often the laboratorian receives a specimen for therapeutic monitoring without sufficient information about other drugs the patient is receiving. As illustrated above, concurrent administration of drugs competing for the same Phase I or Phase II isozyme can produce changes in observed blood levels. If therapeutic drug monitoring is being used to follow a patient's compliance, as is often the case with anti-convulsants, the introduction of another drug metabolized by the same isozyme might result in altering the dosage based on an increase or decrease relative to the previously established levels.

The goal(s) of therapeutic drug monitoring must be clearly established for a given analyte. For purposes of monitoring compliance, the most important factor may be regular evaluation of any new drugs being taken by the patient. For purposes of monitoring to prevent toxic effects from a narrow therapeutic index, polymorphisms play a more dominant role. A dose that elicits a satisfactory therapeutic response in one patient may produce a toxic response in another because of genetic variations. Therefore, the laboratorian must be vigilant for values that are outside the established therapeutic monitoring range for a given drug. Although such values may indicate patient noncompliance, the alternate explanations of genetic variations or concomitant use of a drug or food competitive with the metabolizing isozyme must also be considered.

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Urine and Vitreous Humor Aid Postmortem Alcohol Testing

By James C. Garriott

Ethyl alcohol is by far the most frequent test performed in postmortem toxicology as well as the most common positive finding. This is certainly to be expected because an estimated 103 million Americans are drinkers and 11 million are heavy drinkers or abusers. In addition, alcohol use is linked with behavioral traits involving aggressive and reckless actions, which significantly increase the risk of death from accident, homicide, and overdose.

The finding of alcohol at autopsy may have legal implications, including workers' compensation insurance settlements as well as civil and criminal actions, because a positive result is assumed to relate to consumption of alcohol, which implies intoxication and impairment around the time of death. It is therefore imperative that an alcohol test result be properly interpreted and substantiated.

In the great majority of autopsy cases, a blood alcohol result, irrespective of the site of the specimen, is a valid indication of the blood alcohol level at the time of death. On the other hand, certain circumstances can contribute to artifactual production of alcohol leading to a positive alcohol result. This is considerably more likely when organs are used for analysis. Factors that should alert the pathologist to the possibility of a false-positive or falsely elevated result include decomposition, traumatic injury with rupture of a body cavity, exposure to extreme temperatures, submersion, extreme blood loss, and contamination due to embalming.

Postmortem production

In the intact body, ethyl alcohol is not formed rapidly postmortem and rarely reaches high levels in blood. One study of 130 autopsy cases in various stages of decomposition found no alcohol in 24 of 30 mildly decomposing bodies. Of the other six, only one had a positive result not attributable to alcohol ingestion prior to death. Of all the cases studied, which included mild to severe decomposition, 23 (17%) had presumed alcohol production postmortem. Nineteen of these positive cases had levels less than .07 g/dL, while four cases had 0.11, 0.12, 0.13, and 0.22 g/dL, respectively. Vitreous humor and urine were used as the criteria for determining the presence of endogenously formed alcohol (1).

A study of 286 autopsy cases found similar results, with postmortem alcohol formed in 19% and the highest level found being 0.07 g/dL (2).

Interpretation

The key to proper interpretation of postmortem alcohol results is simple in most cases. Whereas blood and tissues contain proteins, sugars, and other carbohydrates that can produce alcohol, the urine and vitreous humor do not, except under rare pathological circumstances. Urine may produce alcohol artifactually only in uncontrolled diabetes, kidney disease, and similar circumstances when abnormal glucose and proteins enter the specimen. This production is more likely to occur in urine *in vitro* during storage, however. With both vitreous humor and urine, losses of alcohol can occur during storage if a large headspace is present in the tube.

Vitreous humor has a normal alcohol distribution ratio with blood of 1.27 when distribution is complete (about one hour after the cessation of drinking), and the urine blood ratio is about the same, again after body distribution is complete. During the pre-absorptive phase (soon after ingestion while the alcohol is still being absorbed), both vitreous humor and urine levels may be lower than those in blood. It is extremely unlikely that these specimens would be negative in the face of a positive blood alcohol, however, because alcohol begins entering these specimens with the first pass of blood circulation after drinking. Therefore, a positive blood alcohol with a negative vitreous humor or urine is indicative of postmortem alcohol formation, and thus the blood alcohol result should be interpreted as a negative (a false positive).

Skeletal muscle has also been found to relate closely to the true blood alcohol, and can be used to support alcohol results except after extreme decomposition (3).

In severely decomposed cases with limited availability of fluid specimens, extreme caution should be used in interpreting alcohol findings. If body tissues are positive for alcohol, skeletal muscle is probably the best comparison, because it does not contain as much potential substrate for alcohol production. N-propanol was found to agree closely with postmortem alcohol production in studies of rat corpses (4) and human autopsies (5). The n-propanol should be greater than 10% of the ethanol concentration if decomposition was the source.

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Metal Inhalation Can Result In a Variety of Toxic Effects

By Donald Frederick

Occupational lung disease is one of the ten leading causes of work-related health problems in the United States. Since the advent of the industrial revolution, myriad illnesses have been described as a result of inhalation toxicity. The wide range of illnesses is a result of the great variety of compounds that can be inhaled and cause lung damage and even systemic toxicity.

An important category of toxic compounds, metals can affect individuals through occupational exposure to inorganic dusts and metal aerosols. Inhaled compounds exert their toxicity generally through three mechanisms: irritation, immunological responses, and fibrogenesis.

Direct irritation of the respiratory tract can result in excessive mucus secretion, cough, airway hyper reactivity, pneumonitis, and pulmonary edema. Some agents can cause bronchoconstriction (reflex bronchospasm) by stimulating irritant receptors in the bronchial wall. Others have direct pharmacological action on the bronchi, causing bronchoconstriction that on continuing exposure can produce non-specific bronchial hyper-reactivity. The inflammation caused by chronic exposure can lead to chronic bronchitis even after the exposure ceases, with obstruction to airflow and chronic hypoxia resulting in chronic obstructive pulmonary disease.

Immunologically mediated diseases are usually one of four types. Type I responses are allergenic

(IgE mediated) and produce bronchial edema and occupational asthma. Compounds that can cause these reactions range from cotton dust (known as byssinosis) to high molecular weight biological compounds such as bacterial enzymes. Type II responses are direct cytotoxic reactions such as those seen in hemolytic anemia and are generally not a problem in lung diseases. Type III responses cause inflammation resulting in interstitial infiltrates and granuloma formation. An example is "farmer's lung" from a hypersensitivity reaction to *Micropolyspora faeni*. A wide variety of agents, including fungi, animal proteins, arthropods, chemicals, and bacteria, produce these reactions in many occupational settings. Type IV responses are cell-mediated and may play a role in some occupational asthmas.

Dusts with particle sizes of less than 5 microns provoke a fibrotic or granulomatous response in lung tissues. The severity of the disease produced depends on a wide range of factors, including particle size, chemical composition, shape, intensity and duration of exposure, and a variety of host factors (individual susceptibility, cigarette smoking, underlying disease). In a recent excellent review of the damage produced by toxic agents on the nasal passages, V.J. Feron and coauthors describe the mechanisms of damage to the mucosal linings (1).

Metals do not invoke a single response in humans but cause a variety of the mechanisms outlined. Often the exact mechanism for damage is unknown. The symptoms caused by exposure can be confused with those of secondary infections or underlying disease from other factors. Clinical presentations of lung diseases are usually described as asthma, hypersensitivity pneumonitis, acute bronchitis, chronic bronchitis, pneumoconiosis, or neoplasm. Metals can be involved in the development of these varied diseases depending on the metal and the form of exposure. Some of the toxicity is due to the metal's physical form and properties rather than its chemistry.

Metal fumes

First described in 1822 by Potissier, metal fume fever was a product of very dirty foundries and smelters. As occupational controls become more stringent, fewer cases are seen in countries that adopt exposure standards, although occasional cases are still reported. Fumes from metals such as beryllium, cadmium, mercury, nickel, vanadium, zinc, chromium, and osmium act as irritants to the respiratory mucosal surfaces. Initial leukocytosis can persist for a day after the symptoms subside.

Continued exposure to metal fumes produces

hyperplasia of mucus-producing cells, reduces ciliary transport, and ultimately leads to obstructive changes in the small airways. The resultant chronic bronchitis produces a productive cough and leads to an irreversible decrease in expiratory flow rate with little response to bronchodilators. Symptoms may not be noticed until an acute upper respiratory tract infection occurs in addition to the underlying toxicity. Without a concurrent infection, the disease's progression may be slow, first noticed as dyspnea on exertion. As the first site of exposure, the nasal area can be damaged with loss of olfactory acuity, mucosal ulcers, perforated nasal septum, or sinonasal cancers (2). Recent research is refining our knowledge of the olfactory and trigeminal nerve toxicity associated with inhaled toxicants including metals.

Metal dusts

Particle size is an important factor in a metal dust's effects on lung function. Particles between 5 and 30 microns are deposited in the nasopharyngeal region. Particles between 0.5 and 5 microns are the most dangerous because they reach the alveoli and terminal bronchioles. The flow of nonspherical particles depends on their mass mean aerodynamic diameter.

Once lodged, a particle is removed by the alveolar macrophages. The effectiveness of this clearance depends on the health of the mucociliary system, which can be impaired by a variety of diseases. Pulmonary macrophages phagocytize particles and clear them mostly through the lymph system. Metals such as barium, which have no inherent toxicity, can be cleared safely even in large quantities. Other metals, such as cobalt, produce hard metal disease, even when the dust contains small quantities of the metal. See the section on cobalt for further discussion of hard metal disease.

Oil mists

Oil mists generated during cutting or grinding of metal are composed of three basic types: straight oil (insoluble), oil emulsions (soluble), and synthetic/semi-synthetic. In addition to the oils, additives (many of which are proprietary formulations) are used to improve performance. In some circumstances it may be difficult to separate the toxicity of the metal from the oils or oil additives. Improvements in the oil formulations have resulted in less risk from the oils or other lubricants used in cutting or grinding of metals (3).

Nickel

Although nickel is not mined in the United States, it is a by-product of copper mining and is

mined in Canada, the former U.S.S.R., New Caledonia, and Australia (4). Nickel is the 24th most abundant element in the earth's crust, with soil concentrations from 5–500 ppm. Near refineries, soil concentrations can be up to 53,000 ppm. Nickel leaching from cooking utensils generally exceeds the dietary intake by two to five times, accounting for up to 1 mg per day. Water does not contain significant amounts, usually less than 35 µg/L.

There are very few cases of acute toxicity from nickel and the most serious involve nickel carbonyl. Nickel carbonyl is a colorless volatile liquid that is insoluble in water and soluble in organic solvents. Nickel carbonyl is used in refinery processes involving nickel, in nickel-catalyzed coal gasification, in the catalytic synthesis of alkylmethacrylates, and in the nickel vapor-plating process.

Potentially fatal levels are produced by exposure to a 30-ppm nickel carbonyl vapor for 30 minutes. Patients initially experience acute effects on the lung. If the exposure is severe enough, these symptoms proceed to edema and acute pneumonitis. In addition to the lung problems, systemic toxicity produces gastrointestinal symptoms 12 to 120 hours after exposure. Death may result from the interstitial pneumonitis with cerebral edema and hemorrhage. For less severe cases and in those patients who are allergic to nickel, bronchial asthma has been documented.

Chronic exposure to nickel may produce asthma, but this is only seen in some metal-plating workers. Benign pneumoconiosis has been reported in workers exposed to nickel dust, but usually the dust also contains other metals. Generally, nickel dust's effects on the lungs are minimal.

Although not a subject of this paper, the most common clinical problems involving nickel are allergic skin reactions in people who have nickel hypersensitivity. Renal tubular function impairment has been documented in stainless steel welders, although no glomerular dysfunction was detected.

Chronic exposure during the refining of nickel has produced some evidence of increased risk for upper respiratory cancers, with the potency of various species of cancer varying dramatically. Nasal cancers were increased in workers exposed to impure nickel oxides and nickel sulfides associated with older refining technologies. With newer refinery methods, fewer cases have occurred in recent years. The latency period for the development of the lung and nasal cancers is 13 to 24 years. Exposure to nickel fumes during welding can produce cancer; however, the risk from the cadmium in the fumes is much higher. Research is continuing into the mechanisms involved in nickel carcinogenesis (5).

Lead aerosols

According to the Occupational Safety and Health Administration, lead overexposure is a leading cause of workplace illness and one of the most common overexposures found in industry. It has been estimated that 90% of lead aerosols are in the fine fraction with diameters less than 2.5 microns. During construction work on a house where lead has been used, re-suspended dust usually ranges from 1–5 microns. Lead deposits in the alveolar region are almost 100% absorbed, whereas oral ingestion probably leads only to 10–30% absorption. Inhaled lead dust, therefore, is a major concern in the overall toxicity of lead. In a recent review the authors showed that the body load of lead and cadmium may be directly related to male infertility (6).

Aluminum

Aluminum is the most abundant metal in the earth's crust. During the production of aluminum from bauxite ore, several toxicities have been reported. "Potroom" asthma has been recognized since the 1930s with prevalence as high as 39% of aluminum production workers. Parenchymal disease resulting in interstitial fibrosis has been seen worldwide among aluminum production workers and has been reported to occur from exposure to refined aluminum powder used in the manufacture of pyrotechnics (7). Other exposures have occurred in the manufacture of aluminum oxide abrasives, resulting in interstitial fibrosis with honeycombing.

Although intestinal absorption of aluminum is the more significant route of exposure in humans, inhalation remains a problem in some occupations. There is some evidence indicating that inhaled aluminum is transported from the nasal cavity to the brain via the olfactory system. Once in the brain, aluminum accumulates and causes several neurological manifestations. Some researchers believe there is a connection with the brain's aluminum and the development of Alzheimer's disease, although this link is still controversial.

Beryllium

Beryllium is the fourth lightest element, with low density, a high melting point, and high tensile strength, which has led to its incorporation in many high technology applications. Chronic exposure to beryllium during the mining and production of metal alloys and salts has led to "chronic beryllium disease" (CBD). The disease is a granulomatous disorder that affects the lungs, lymphatics, and skin. The reduction of beryllium levels in the workplace has resulted in reduction of acute pneumonitis, but chronic problems affect 2–6% of the workforce. Indi-

viduals respond in three ways. Some workers show no evidence of immune response and are disease-free. Some become sensitized to beryllium but do not have evidence of CBD. Those affected with CBD have a granulomatous or mononuclear cell infiltration of the lung. Beryllium appears to act as an antigen, probably through a beryllium-hapten complex, and reacts with CD4 T-cells.

Cadmium

Cadmium has a low boiling point and high vapor pressure, so it readily produces toxic fumes during production processes. Acute inhalation can cause a chemical pneumonitis and pulmonary edema and within 24 hours workers develop shortness of breath, fever, and fatigue that can progress to pulmonary edema and death. Chronic exposure often leads to emphysema and pulmonary fibrosis, although the mechanisms are not clear. Smoking confounds human studies because cigarettes contain about 2 micrograms of cadmium. Cadmium's half life in humans exceeds 10 years, increasing lung cancer risk (8).

Cobalt

Cobalt is combined with metals such as titanium, molybdenum, or chromium to form hard alloys. Because the matrix is hard, with high melting temperatures, these metals are suitable for use in drills and grinding tools. The dusts produced by these metals cause both obstructive and parenchymal disorders. Clinical symptoms include cough, exertional dyspnea, and weight loss. Long-term exposure leads to interstitial fibrosis. The presence of either a desquamative interstitial pneumonitis or giant cell interstitial pneumonitis is typical of the pathological findings. The mechanism of hard metal disease is unknown, although research indicates that some genetic subgroups are more susceptible to the disease. In addition, because cobalt is most often used with other metals, the combinations may be important in their toxicity. Indeed, cobalt/tungsten carbide combinations are known to be more toxic than cobalt alone.

Research

Research into the area of functional genomics is attempting to define some of the underlying features that control the susceptibility of some individuals to the effects of metals on the pulmonary tree (9). Genes connected with oxidative stress, anti-proteolytic function, and repair of the extra cellular matrix are being examined in mouse models as candidates for differential expression in susceptible individuals. These studies are specifically looking at fine particulate nickel sulfate. Beryllium's interaction with T-helper cells and cytokines is also being studied as part of research on the role of genetic polymorphisms that regulate

these cytokines, which might explain the large inter-individual differences in responses to the metal.

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For information, visit www.aacc.org/abcc or contact ABCC at (202) 835-8727.

CAT and SAT Joint Meeting

The California Association of Toxicologists (CAT) and the Southwestern Association of Toxicologists (SAT) will host a joint meeting in Albuquerque, New Mexico, May 2-3, 2003. The meeting will include a full-day workshop on interpretation of antemortem and postmortem toxicology results.

For information, visit the CAT website at www.cal-tox.org or contact Sarah Kerrigan at (505) 841-2562 or skerrigan@sld.state.nm.us.

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