

Methods of Clinical Surveillance: Effects on Liver and Other Organs

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ABSTRACT

The methods used for clinical surveillance of organ system injury by mixtures of environmental chemicals are not specific. The organs most commonly injured by such agents are those involved in absorption, detoxification, and excretion of chemicals. Therefore, lung, liver, and kidney injury are clearly the most frequently recognized. However, every organ system may be involved, including the brain, the reproductive system, the haematopoietic system, and the gastrointestinal tract. This chapter reviews methods available for surveillance by clinical examination and laboratory studies. Indirect techniques for analysis of the impact of chemical agents are reviewed. These include mutagenicity studies and measures of chromosomal damage in circulating blood cells. The use of isolated hepatocytes for surveillance is also reviewed. More direct measures of injury in humans with special emphasis on the liver are discussed. The liver is extremely sensitive to many chemical environmental agents. Although many changes in liver histology and liver function may be detected, in no situation are these more than characteristic. A variety of other disease states and physiological changes can mimic those produced by environmental chemicals. A brief review of surveillance mechanisms for injury to the testes, kidney, and the central nervous system is presented.

1 INTRODUCTION

The need for adequate screening methods to detect human organ system injury from environmental chemicals has become increasingly apparent as the number of chemical compounds added to the environment has rapidly increased in recent years. The recognition that single, isolated exposures to high levels of potentially toxic agents represent only a small part of the total biological impact on the environment has added to the urgency of developing methods directly applicable to human abnormalities and disease. The complexity of the problem of developing techniques to recognize injury in humans is further magnified by the

important interactions between various chemicals and such additional factors as diet and exposure to substances such as cigarette smoke, coffee, tea, and other natural products ordinarily not considered a part of the toxic chemical environment. Nevertheless, the latter elements and their metabolic effects may be critical in the determination of biological changes in humans. The ubiquitous exposure to such natural products virtually mandates that studies and observations in humans will be necessary to supplement those obtained from animal, bacterial, or cell culture techniques for measuring chemical injury. Although some of the latter techniques will be discussed in this review, the major emphasis will be directed toward existing, promising or desirable techniques that measure biological changes induced by mixtures of chemicals and other products in the environment of man.

Chemicals, either in isolation or in mixtures, may have adverse effects on virtually all the major vital organs including brain, liver, kidney, lung, heart, and skin. However, the majority of recognized chemical agents that cause toxicity will alter liver metabolism or structure either as a consequence of their own metabolism or by direct injury. It is this area that will be emphasized in this review, although it is clearly recognized that many agents or mixtures will have a major impact on other human organs (e.g. asbestos, silica, copper, etc.) either in addition to producing liver changes or with no significant changes in this organ.

2 AN EVALUATION OF SCREENING METHODS FOR TOXIC CHEMICALS

2.1 Indirect Techniques

2.1.1 *Animal Studies*

It is obvious that utilization of non-human experimental systems would be ideal in the screening of potentially toxic individual chemicals and chemical mixtures. In fact, such techniques are widely used and form an important part of the effort to screen all new and established compounds known in the environment. If such screening were widely available, inexpensive, predictable, and capable of reproducing the nutritional, biochemical, and dosimetry aspects of toxic exposure in man, there would be little need for screening human populations or epidemiological surveys, since no humans would presumably be exposed to chemicals in situations known to produce toxicity in non-human studies. Unfortunately, none of the existing experimental animal models can predict, with absolute assurance, chemical injury in man. This is even more obvious for mixtures of chemicals or chemical and natural product interactions where substantial differences in duration of exposure, route of ingestion, biological distribution, and host metabolism exist between individuals as well as between

the test animals and man. Species differences in chemical metabolism and catabolism are magnified by the occurrence of multiple chemical exposures. Nonetheless, exposure of various animal species to single chemicals by various routes and over a large dosage range provides basic information about overt and potentially toxic individual compounds. Some authors believe that such single chemical testing is the best initial procedure in evaluating chemical mixtures for potential human toxicity (Neal, 1983). Toxicity may be assessed in such models by appropriate monitoring of organ functions (for liver, see below) and by histological examination of tissues for evidence of cell injury or diagnostic changes.

2.1.2 Mutagenicity Testing

Within the general framework of non-human methods for assessment of potentially toxic chemical mixtures are the various microbiological screening tests. Also available are various other mutagenic tests, including measurement of protein adducts, thioether formation, and chromosomal aberrations in animal models of toxicity. Many of these same methods may also be used in screening exposed human populations. The basic premise of mutagenicity testing is the measurement of changes in genetic material by chemicals which are electrophiles or converted to electrophilic intermediates during catabolism (Sorsa *et al.*, 1982).

Some chemicals exert effects by non-covalent associations with nucleic acids or by indirect interference with genetic material, for example by disturbing the normal segregation of chromosomes during cell division. Obviously, the rate of electrophile formation may be critical for some agents, whereas the concentration of the cellular nucleophile may be important in other situations. Various different types of attack on genetic material are now recognized and will not be reviewed here.

Of importance is the availability of techniques to monitor the results of these interactions in animal models and their use as predictors of potential human effects. Thioethers are formed as a consequence of the detoxification of alkylating agents, for example during conjugation with glutathione by enzymes of the glutathione-*S*-transferase class. The ultimate metabolism of these conjugates results in formation of mercapturic acid, sulphoxides, sulphones, and other compounds. Techniques have been developed to measure these compounds in the urine of animals and man. Such methods have been used in humans to detect changes in the urine of smokers and some industrial workers in comparison with appropriate controls (Vainio *et al.*, 1978).

Alkylated proteins (alkylation of amino acids) may also be measured in the blood as an indirect measure of simultaneous nucleic acid alkylation. Some compounds react directly (e.g. ethylene oxide), whereas others must be metabolized to more reactive agents. Ethylene and vinyl chloride are examples of the latter. Alkylation of haemoglobin is another technique used to measure

protein adduct formation in the blood of either experimental animals or exposed humans.

Direct measure of the mutagenicity of urine from animals or exposed humans by application to microbiological systems also has been widely used. Urine must be concentrated for these studies, and the direct toxicity of the urine on bacteria is often a problem with this technique. Many mutagenic compounds are excreted in conjugated or inactive form and must be deconjugated prior to testing. Although these tests are not specific for chemical agents, this has been suggested as an advantage in dealing with exposures to complex chemical mixtures among workers with various life-styles which expose them to other mutagenic substances (Falck *et al.*, 1980). This technique has identified workers in the rubber industry exposed to excessive mutagens in the environment although the precise interaction of the various chemicals and other natural products has not been clarified.

2.1.3 Other Measures of Chromosomal Damage

Other *in vitro* techniques using animal or human materials are available. For example, structural chromosome observations may be measured in peripheral blood lymphocytes, a technique useful in humans exposed to ionizing radiation. Cytogenetic monitoring of lymphocytes from exposed populations is also feasible, but careful selection of appropriate 'non-exposed' controls is necessary. However, in cases of industrial exposures it would be possible to test prospectively the same individual before and after exposure to specific chemical mixtures in the workplace, thus avoiding the difficulties of a suitable control population. However, such factors as ethanol consumption, cigarette smoking, drug exposures, etc., must be considered before incriminating environmental chemicals as the cause of any observed changes.

Sister chromatid exchanges are a measure of rearrangements in the DNA helices. This technique is relatively simple and may provide the best cytogenetic marker for exposure to hazardous chemicals (Perry, 1980). To date, this technique has been most widely used in measuring the effects of chemotherapy in humans. However, industrial chemical exposures could be monitored, provided adequate evaluation of 'life-style' factors are considered in the final analysis. Widespread screening with this method has apparently not been reported.

In the studies conducted so far, the various cytogenetic tests, including direct observation of structural chromosome changes, have yielded conflicting results. This does not necessarily mean that one test is superior to or even more sensitive than another, but could simply reflect the likelihood that the current tests reflect a variety of different types of chromosomal injury. Certainly, a single negative test does not exclude a risk of potential chromosomal damage by any environmental agent or mixture.

Finally, it should be noted that the relationship of chromosomal injuries in

man to cancer is not yet established on an individual basis, although there is epidemiological evidence for increased incidence among exposed populations. The importance of this possible association makes it important that cytogenetic testing be improved, verified, simplified, and much more widely applied in human studies of various exposed populations.

If such studies were readily available, industrial monitoring for mutagenic exposures would be greatly simplified and high-risk situations could more readily be identified and avoided. Certainly such measures of biological effect seem more useful than simple quantitative monitoring of chemical exposure in the environment as a mechanism to identify individuals or groups with a high risk of chromosomal alterations.

2.1.4 The Use of Isolated Hepatocytes in Toxicity Assessment

Techniques have been developed to maintain isolated hepatocytes in monolayer cell culture for periods up to 10–14 days. By manipulation of the environment and media, various characteristic functions of the hepatocyte may be maintained during this period (Guzelian *et al.*, 1979). Detailed descriptions of the morphology and function of these cells have appeared during the past five years. These monolayer preparations have been used to study the effects of individual chemicals or mixtures of agents on the hepatocyte (Klaassen and Stacey, 1982).

The monolayer cells are useful in studies of uptake, metabolism, excretion, and interaction with other agents. Moreover, changes in morphology may be assessed simultaneously. The binding of chemicals to intracellular macromolecules may also be assessed. While such techniques are not strictly useful as chemical screening methods, they offer information *in vitro* in predicting which agents or combinations of agents are most likely to require careful monitoring in exposed populations.

Finally, it is technically feasible to use human liver obtained at biopsy for preparation of monolayers. Again, this would not be a practical screening procedure in large populations, but might help confirm that alterations detected in monolayer systems derived from animals apply to human cells as well.

2.2 Effects of Multiple Chemical Exposures on the Mixed Function Oxidase System in Humans

Most chemicals to which man is exposed undergo biotransformation, predominantly, but not exclusively, in the liver. This process renders many of the lipophilic environmental agents more soluble in the aqueous milieu of urine and bile where they are excreted.

The endoplasmic reticulum of the hepatocyte is the major site for this biotransformation, which is mediated by a group of haemoprotein isozymes. Cytochrome P-450 is the most widely studied of these haemoproteins. For some

chemicals, the biotransformation reaction results in the formation of inactive metabolites. More often, metabolism produces a mixture of potentially toxic, oxygenated compounds, which may interact chemically with proteins, nucleic acids or other cellular macromolecules. Many of these toxic intermediates are rendered harmless by various conjugation reactions which produce inactive water-soluble products. It is obvious that factors which accelerate oxygenation by inducing haemoprotein enzymes or which reduce the conjugation mechanism within the hepatocyte may profoundly alter the potential toxicity of many environmental agents. Since exposure to environmental chemicals is one known cause for such changes in biotransformation reactions, it is not surprising that human exposure to one chemical can produce profound changes in the toxicity of simultaneous or subsequent exposures to different agents. For example, many of the inducers of cytochrome P-450 are environmental compounds, including drugs, natural agents, and various pollutants (Snyder and Remmer, 1979). This effect is prompt, dose related, and usually rapidly reversible. However, it may have profound effects on the toxicity of another agent to which an individual is simultaneously exposed.

Similarly, there are dietary and chemical exposures that may reduce the rate of conjugation with glutathione or glucuronide. Inhibition of these processes could also increase the toxicity of intermediate compounds produced during environmental chemical exposure.

One of the best studied examples of mixed chemical interactions in man and experimental animals has come from work describing the toxic interaction of various alcohols with chloroform or carbon tetrachloride. In this situation, alcohols which are metabolized to ketones substantially increase the risk of toxicity from several haloalkanes. This effect seems to occur by increasing the bioactivation of the haloalkanes and not merely by increasing cytochrome P-450. The ketones may also increase the reaction of oxidized intermediates with key cellular macromolecules.

Since the complex interaction between diet, natural agents, liver disease, hereditary variations in biotransformation reactions and exposures to various environmental agents is extremely difficult to predict, measurement of the overall rate of these reactions by indirect methods has been attempted.

2.2.1 Enzyme Changes

Direct measure of hepatic cytochrome P-450 and other haemoproteins is well described for experimental animals and is also feasible in humans. Direct surgical or needle biopsy would be required for human studies and is not practical on either ethical or practical grounds. Therefore, indirect measures *in vivo* have been proposed. Chemicals and natural products that increase the haemoprotein enzymes usually induce the formation of endoplasmic reticulum and other enzyme

systems associated with this organelle. One example is serum γ -glutamyl-transpeptidase which is commonly increased by chemical exposures. Unfortunately, this enzyme is present in other hepatocyte organelles and is frequently increased during drug ingestion as well as by ethanol or a large variety of unrelated liver diseases. Thus, an elevation of this enzyme is non-specific and not very helpful in evaluating an increase in the overall mixed function oxidase system in the liver of humans.

2.2.2 Drug Clearance Studies

Of much greater utility are measures of the rate of disappearance of agents which are metabolized by the cytochrome P-450 system. Drugs are utilized which are easily measured in blood or other body fluids. The rate of clearance of the drug or the detection of radioactive metabolic products has been used as a measure of the rate of chemical metabolism *in vivo*. The rate of metabolism is directly correlated with the activity of the total hepatic mixed function oxidase.

One such commonly used agent is antipyrine (Vesell, 1979). This drug is administered orally and its rate of disappearance from saliva offers a simple and safe but indirect measure of mixed function oxidation *in vivo*. Although ethanol does not significantly alter antipyrine clearance, other factors such as diet or the ingestion of coffee or tea may produce changes (Conney *et al.*, 1980).

An example of the use of antipyrine clearance is the work of Dossing (1982). He showed that workers exposed to certain chemical mixtures, such as insecticides and herbicides, had accelerated antipyrine clearance, whereas workers exposed to other agents (paint and solvents) actually showed a reduced clearance. In the absence of confounding factors, this observation implies that various chemicals in combination may either increase or decrease the overall rate of mixed function oxidation in man.

Other agents have been used for such studies of clearance, including aminopyrine (Hepner and Vesell, 1974). Such clearance tests offer simple and reproducible techniques to measure an important effect of chemical exposure. Improved methods of analysis, description of limitations or confounding factors, and greater experience with normal and diseased humans will be necessary before such techniques can be routinely applied to any large population for screening purposes (Bircher, 1983).

2.2.3 Urinary Excretion Products

The urinary excretion of D-glucaric acid in man has been reported to be increased following administration of phenobarbitol. The D-glucaric acid is derived from glucuronate by action of mixed function oxidase enzymes located in the endoplasmic reticulum. The excretion of D-glucaric acid is also increased in workers exposed to pesticides (Hunter *et al.*, 1972). The simple measure of this compound in the urine has been taken as an indirect measure of hepatic

biotransformation capacity in man. However, the method is susceptible to a number of major technical difficulties and is not widely used.

Similarly, other endogenous products of hepatic mixed function oxidase reactions have been measured in the urine of man and experimental animals. The excretion of 6 β -hydroxycortisol, a product of endogenous sterol metabolism, may also reflect the rate of bio-oxidative reactions in the endoplasmic reticulum.

Further study of the excretion of such endogenous products could provide more information regarding their reliability as measures of mixed function oxidase reactions *in vivo*, if methodological difficulties can be overcome. The obvious safety and convenience make them especially attractive for further application as screening measures in large population groups.

2.2.4 Direct Measure of Cytochrome P-450 and Other Haemoproteins

It is theoretically possible to determine the level of most of the important biotransformation reactions in the liver of humans. Although this has been partially accomplished, the risk of liver biopsy in humans cannot be justified for such measurements alone. If histological material is needed because of evidence of liver injury or disease, such measurements might have utility. Thus, despite their obvious directness in measuring effects of chemicals on human hepatic mixed function oxidase, such methods could not be applied to large population groups or as a screening technique.

Similarly, study of the hepatocyte organelles by electron microscopy will remain a method which is useful only for limited studies in heavily exposed humans with obvious clinical evidence of hepatic toxicity.

2.3 Direct Clinical Measures of Hepatocyte Injury

2.3.1 Enzyme Release

One of the earliest changes to occur in the case of liver injury, regardless of type, is the release of intracellular enzymes into the blood. Some of these enzymes are found predominately in hepatocytes, e.g. aspartate aminotransferase (AST) and alanine aminotransferase (ALT), whereas others are predominately released from cholangiolar and ductular cells of the liver (e.g. alkaline phosphatase and 5'-nucleotidase). The measurement of these enzymes in blood is regularly used to detect liver injury and the methods are widely available as inexpensive screening tests.

ALT is relatively specific for liver injury, whereas the other two enzymes may be elevated by injury to other organs. AST may be released from a variety of injured tissues, including muscle, brain, pancreas, and heart. Therefore, acute injury to these other organs must be excluded prior to considering an elevation as an indication of liver injury. However, for most environmental agents, significant

damage to cells in other tissues containing AST is uncommon. In the case of alkaline phosphatase, bone and placenta are common other sources of enzyme release. However, isozyme fractionation is possible which can specifically identify the liver isozyme, if necessary.

Both ALT and AST have been used to monitor the hepatotoxic effects of insecticides in man (Curtis and Mehendale, 1980). Unfortunately, neither is specific for environmental chemical injury to the liver, and these tests are commonly abnormal in alcoholics, in patients ingesting various drugs, and in patients with acute or chronic liver diseases. Also, there are recognized examples of drugs (e.g. methotrexate) which may cause serious liver injury in man with little or no alteration in these enzyme levels. Thus, these determinations are useful as crude screening methods to detect liver injury, but positive results must be interpreted with caution, and negative findings do not completely exclude hepatotoxicity. Other enzymes released from injured hepatocytes can be detected in serum following various forms of liver injury, and may provide information regarding specific organelle injury (Zimmerman, 1982).

Other liver function determinations have been proposed for evaluation of hepatic injury due to drugs or chemicals. Perhaps the most specific and sensitive is the serum bile acid level. Bile acids are formed in hepatocytes, excreted into the biliary tree largely in a conjugated form, and then reabsorbed from the intestine following bacterial deconjugation. Serum free bile acid levels rise in any injury which reduces the capacity of hepatocytes to remove them from blood and re-excrete the bile acids into bile. Studies in patients with known liver diseases have shown a good correlation between serum bile acid levels and early hepatic injury. However, this determination has not been used widely in toxicological screening, although methods have been simplified so that such testing in man is feasible (Table 1) (Guzelian, 1983).

Other standard liver function tests, including serum bilirubin, albumin, prothrombin time, and cholesterol, are useful only in the detection of moderate to severe liver injury and probably are impractical as screening methods to specifically evaluate early evidence of organ damage due to chemicals. Alterations in these tests may be expected with severe injury, such as that noted with heavy carbon tetrachloride exposure.

2.3.2 Morphological Changes in Liver Biopsy

Detection of hepatocyte injury by direct light or electron microscopic examination of liver tissue obtained from humans exposed to toxins would be a very sensitive technique for the determination of toxic liver injury. The response of the liver to injury, whether due to chemicals, infections (e.g. viral hepatitis) or metabolic change (e.g. obesity, diabetes), is rather limited; therefore, interpretation of findings is often difficult. For example, hepatocyte infiltration with fat is commonly seen in obesity, diabetes, alcoholism, and in patients given tetracycline

Table 1 Screening tests of liver function

Test	Abnormality	Sensitive	Liver-specific
Aspartate aminotransferase (AST) (SGOT)	Hepatocyte necrosis	Yes	No
Alanine aminotransferase (ALT) (SGPT)	Hepatocyte necrosis	Yes	Yes
Alkaline phosphatase	Biliary obstruction Infiltrative diseases	Yes	No
Bilirubin	Biliary obstruction	No	No
γ -Glutamyltranspeptidase (GGTP)	Biliary obstruction Hepatocellular necrosis Ethanol Microsome induction	Yes	No
Serum bile acids	Biliary obstruction Hepatocellular necrosis Extrahepatic shunts	Yes	Yes
Aminopyrine breath test	Microsome induction Functional liver mass	No	No
Urinary glucaric acid	Microsome induction	No	No
Urinary 6β -hydroxycortisol	Microsome induction	No	No
α -Foetoprotein	Hepatoma	Yes	No

From Guzelian (1983). *Reproduced by permission of Environmental Health Perspectives.*

or exposed to carbon tetrachloride. Such a diversity of aetiological causes of a simple histological and biochemical change makes interpretation of fatty infiltration most difficult.

Similar complexity would be expected in situations where hypertrophy of the endoplasmic reticulum was detected, or in cases of isolated hepatocyte necrosis (so-called 'focal hepatitis'). However, such findings, if consistently observed in a population exposed regularly to specific chemical mixtures, would be convincing in indicating a cause and effect relationship. In contrast, isolated findings in a potentially exposed population would be most difficult to interpret. These types of histological change are thought to be fully reversible in most instances, although this has not been carefully evaluated for toxin exposures.

Perhaps of greater interest would be the findings of massive or submassive necrosis, fibrosis, or changes considered to be premalignant. Chemicals known to cause malignancy may also cause dilation of the sinusoids, peliosis hepatitis, neoplastic nodules, or adenomas.

These dramatic changes in the liver of humans exposed to mixtures of chemicals would be convincing evidence of serious hepatotoxicity. Most often, such changes would be preceded by serum enzyme changes, but this is not always the case, for example in patients treated for long periods with methotrexate.

Hence, under unusual circumstances, liver biopsy may be the only way to detect serious but occult liver injury. Unfortunately, under most conditions, liver biopsy for histological study would not be suitable as a routine screening test because of the potential risk of complication. However, biopsy could be used as a confirmatory test selected because of biochemical changes detected in an exposed group. Liver biopsy itself carries a very small risk of mortality ($< 0.1\%$) and morbidity (1–5%).

2.3.3 Direct Determination of Chemicals or Metals in Liver

It is possible to detect chemical agents as adducts in small amounts of material obtained by liver biopsy (Poirier *et al.*, 1980). Such determinations might be useful in correlating specific histological changes observed on biopsy with specific chemical exposures. However, they could not be used as screening techniques in view of the difficulty and risk in obtaining liver biopsies from large groups of exposed individuals.

Of more promise is the possible detection of agents such as cadmium by non-invasive methods including neutron irradiation or nuclear magnetic resonance tomography (Al-Hiti *et al.*, 1979; Smith *et al.*, 1981). The widespread availability of such techniques in clinical medicine during the next decade may make such methods practical as screening methods for certain chemical agents.

2.4 Other Organ Systems

The liver is one of the most sensitive organs to chemical injury because of its critical role in uptake, metabolism, and the biotransformation of a large number of endogenous and exogenous compounds. However, injuries to other organs, including lung, kidney, brain, testes, ovary, and skin, are well described. The availability of useful clinical screening techniques for these organs is more limited and their use in detection of injury to chemical agents has not been extensive. A brief review of some methods for kidney, testes, and nervous system injuries is presented.

2.4.1 The Kidney

The major clinical methods for detecting kidney injury include: (1) determination of substances which accumulate in blood because of failure of renal excretion (e.g. creatinine, urea, and uric acid); (2) measurement of changes in the urine formed (e.g. reduced urine osmolarity, increased urine protein or altered pH); and (3) changes in serum electrolytes regulated by renal function.

Each of these measurements is practical as a screening test for renal injury due to chemical exposures, but none is specific (Wedeen, 1983). Virtually any form of kidney injury will cause changes in one or more of these renal tests. In addition,

none of them is sensitive to early changes in function. For example, it is known that more than 50 % of renal function must be destroyed before significant elevations in serum creatinine or urea occur.

More sensitive tests, including clearance determinations, have been proposed to detect subtle renal injury due to drugs or chemicals (Wedeen, 1983). Small changes in filtration, secretion, or tubular reabsorption may be detected by the measurement of urine amino acid content or excretion of such compounds as β_2 -microglobulin.

Finally, newer techniques used to measure metal deposition in liver may also be applicable to the kidney. The use of nuclear magnetic resonance techniques for detection is a new and currently unproven methodology which offers great promise.

Histological study of the kidney is feasible, as it is for liver. Again, the changes of interstitial nephritis or glomerulonephritis are non-specific and may be related to multiple aetiological factors, including chemical exposures (Beirne, 1972). One example of the latter is the well-described association of interstitial injury with heavy and long-term exposure to acetaminophen. It is not possible to attribute changes to environmental chemicals without careful consideration of the effects of simultaneous drug ingestion which is commonplace in some industries.

The role of pollutants as potential sensitizing agents in promoting renal injury by other organic compounds has been described and is of significant importance in multichemical industrial or environmental exposures (Kluwe and Hook, 1980).

2.4.2 Testes

Damage to human sperm may be detected by various screening tests, including sperm counts, measures of sperm motility, and studies of sperm morphology. Cytologic studies appear to be the most sensitive and have been used to detect changes that produce injury (Wyrobek, 1983).

Unfortunately, both disease and human habits (e.g. alcohol, tobacco, and marijuana) profoundly affect sperm function and morphology. Thus, any studies used in screening exposed populations must consider such factors in correlating changes with specific agents.

Finally, the exact relationship of the various measures of sperm function to fertility and birth defects requires further studies.

2.4.3 Central and Peripheral Nervous System

Injury to various components of the nervous system is a well-recognized consequence of toxin exposure. The peripheral nerves, spinal cord, cerebrum, and cerebellum are most sensitive to injury (Spencer and Schaumburg, 1980).

Screening tests for potential neurotoxins must be viewed as less than satisfactory, though it may well be that intensive work and research will lead to

development of useful and relatively reliable methods for clinical surveillance. Physical examination and electrophysiological and neuropsychological tests are the methods most commonly used (Schaumburg *et al.*, 1983). Peripheral nerve dysfunction can be evaluated by nerve conduction velocity and studies of evoked potential. These studies are difficult to perform and evaluate and require considerable expertise. Their use as screening tests requires great care.

Behavioural and cognitive disturbances may be detected by standard psychological tests modified for rapid screening. Changes have been reported in exposed populations (Lindstrom, 1980). It would be most useful if appropriate screening tests could be designed based on experimental results in animal models of toxin exposure.

The nervous system, both central and peripheral, is a target for environmental chemical injury. Although the neurologist begins with a consideration of symptoms and signs, the neurological history and conventional examination are useful but have limited application for the surveillance of a population for effects of a neurotoxin. This limitation results from the extremely variable effect of neurotoxins. For example, some have effects on the sensory system, others on peripheral nerves, and still others on cortical neurones and structures. In addition, subacute or chronic effects are subtle or non-specific in their clinical manifestations. In this complex of variable and broad ranges of clinical effects, the available screening techniques are very limited in their capacity to resolve and discriminate between various chemical agents. A list of the screening procedures which have been employed is provided in Table 2.

Undoubtedly, the effects that are most readily distinguished are those involving the peripheral nervous system. These manifest paraesthesias and distal weakness of a rather distinctive form. In addition, quantitative examination of nerve conduction and velocity is possible and these studies may demonstrate the presence of denervation. Finally, psychometric tests appear to be extremely promising as screening methods. Their use will be increased by further development and validation in clinical studies. Improvements in all of these tests are necessary to make screening for neurological injury practical and reliable (Valciukas and Lilis, 1980; Xintaras and Burg, 1980).

Table 2 Commonly used tests for population surveillance for neurotoxins

Clinical history (may include use of questionnaire)
Neurological examination
Electroencephalography
Cortical evoked potentials
Electromyography
Electroneurography (determination of nerve conduction velocity)
Electrooculography
Psychometric testing
Audiometry

3 SUMMARY

There are a number of useful screening tests which will detect organ system damage by chemicals in man. Unfortunately, for most organs and chemicals, these changes are non-specific. Thus, correct interpretation of abnormalities in laboratory tests, morphology or clinical examination requires substantial information regarding unrelated diseases, habits, drug ingestion, and diet in exposed populations.

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