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An Introduction to Neurobehavioral Toxicology

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The stated objectives of these Target Organ Toxicity Symposia are to review the morphology, physiology, and biochemistry of the particular organ system, describe means used to assess toxicity, evaluate tests used for this assessment, and finally, to propose the application of recent advances to the development of practical test procedures. Basically, the intent is to discuss ways of evaluating the functional integrity of a given organ system.

The subject of a previous symposium in this series was the kidney which may serve as a useful departure point for this discussion. The kidney, like other organ systems, is involved in the organism's homeostatic processes and, of course, its primary role in this regard is to regulate the composition of body fluids. To carry out this function, certain input/output relationships must be maintained. Input to the kidney is provided via the renal artery, and various components of this input (in the form of solute material) are processed in different parts of the kidney. Subsequently, an output is obtained via the ureter, i.e., urine.

There are many useful approaches to the study of renal toxicology, including the morphology, physiology, and biochemistry of the organ. Certainly, another rather obvious approach is to quantitate the functional output of the organ, that is, to measure urinary output. A graduated cylinder or some equivalent is the only equipment required for such an approach. Of course, more elaborate measurements can be made including quantitation of the exact composition of the output. In this case more time and expense are involved, but certainly more information is obtained.

A suggestion to use such a measurement in the study of renal toxicology would in all likelihood be well received by most toxicologists. Unfortunately, suggestions to measure the functional output of the nervous system in toxicology, i.e., behavioral toxicology, are not always as acceptable even though the principles are the same. Hopefully the information contained in the following papers will change this attitude.

Figure 1 is a simplified representation of the nervous system, the target organ of this symposium. Like the kidney, the nervous system serves to maintain homeostasis under certain input/output conditions. Information concerning the external and

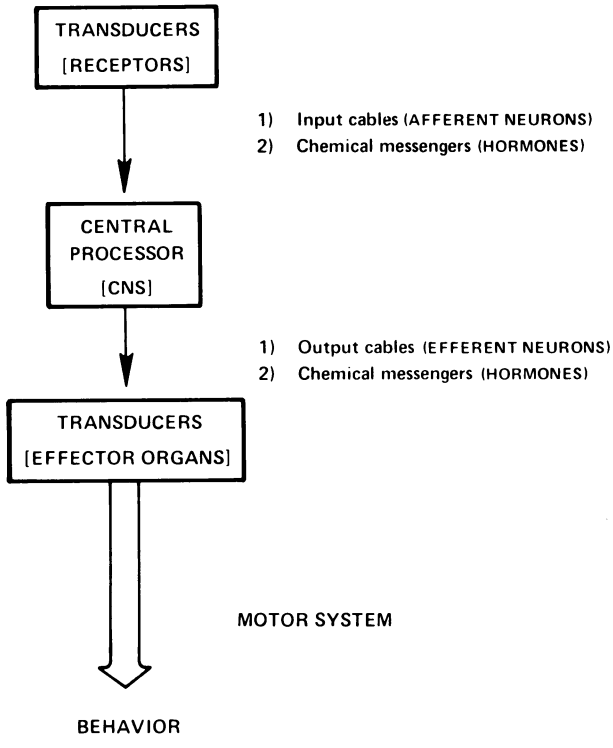

FIGURE 1. Schematic representation of the nervous system showing the various locations which are subject to disruption by toxic agents.

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internal environment is relayed to the CNS either by afferent neurons or by chemical messengers. Processing of this information by the CNS may or may not result in an output. Also, the CNS may generate output spontaneously. In any event, when output is generated which involves the motor system, a measurable behavior occurs. A chemical may act to disrupt these input/output relationships either by directly affecting some level of neuronal organization or by interacting with another organ system and, thus, affecting nervous system function indirectly. Therefore, consideration must be given to the total organism. To qualify as a neurotoxicant, a compound must act directly on the nervous system, but certainly the use of neurobehavioral techniques need not be limited to the study of neurotoxicants. That is, neurobehavioral changes may provide us with an indication of impending toxicity.

Returning for a moment to a consideration of the kidney, there are two equally valid approaches to our urine collection. One approach is to measure urine output in a "free flowing" condition, in which case no attempt is made to manipulate the input/output relationships. A second approach is to manipulate the input to determine how this affects the output. Techniques such as salt loading or water deprivation may be useful here. In our consideration of the functional output of the nervous system, similar approaches are used. In the former approach, an animal is simply placed in an environment, and his behavioral response is quantitated. This approach is often referred to as an ethological approach and will be considered first in our symposium. With the latter approach, the behavior of an animal (output) is brought under experimenter control by manipulating the environment (input). This approach, exemplified mainly by operant conditioning experiments will be considered second in the symposium.

Finally, an important consideration in any discussion of target organ toxicity is the concept of a critical organ. This concept has been widely used to describe the toxicity of heavy metals. The Task Group on Metal Accumulation (*1*) described the concepts of critical organ and critical concentration as follows: "With the accumulation of metal, when undesirable functional changes, reversible or irreversible, occur in the cell it can be said that the *critical concentration* has been reached . . . Analogously, the *critical organ concentration* is defined as the mean concentration in the organ at the time any of its cells reach critical concentration . . . The concept of a *critical organ* refers to that particular organ which first attains its critical concentration of metal. The organ of greatest accumulation or retention is not necessarily the critical organ." These concepts although formulated for heavy metals seem applicable to most toxic materials.

Certainly, the main impetus for toxicological research is to provide useful information for the protection of human health. For the Environmental Protection Agency, these data serve as a basis for regulatory decisions concerning human health. In order to accomplish this task, certain data are needed, most notably the identification of adverse health effects which in turn, requires the determination of dose–response relationships. Ideally, these dose–response relationships would be defined by the concentration of the toxicant at the site of effect, that is, at the target organ itself. Although this is not generally possible in the clinical situation, it is very important in experimental work. Only by determining dose–response relationships can the critical organ be identified.

The practical significance of the critical organ approach is extensively reviewed by Nordberg (*2*). Figure 2 (redrawn from Nordberg) represents a family of theoretical dose–response curves for various target organs. If lead were used as an example, curve *C* would represent the dose–response curve for the kidney. The remaining two curves (*A* and *B*)

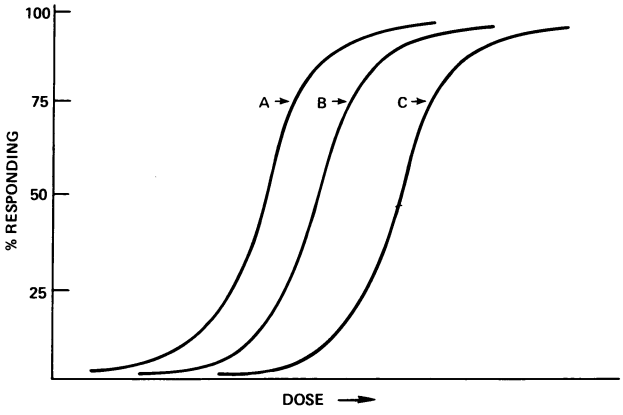

FIGURE 2. A family of hypothetical dose–response curves for various target organs.

would represent the hematopoietic system and the nervous system. Since disruption of heme synthesis is used as a clinical sign of lead exposure, it is of practical importance to know the relative relationship of these two curves. If curve *A*, for example, represents the hematopoietic system, then the use of various enzyme or substrate levels involved in heme synthesis to define a critical effects level is warranted since these changes would occur at exposure levels below those producing effects on the nervous system. If, on the other hand, the dose–response curves are reversed, in which case curve

A represents the nervous system response and curve *B* represents the hematopoietic system, then the critical effects level would be missed if the hematopoietic system is the index of exposure, since a large percentage of the population will have CNS involvement before a significant change occurs in the hematopoietic system. Thus, the strategy for the diagnosis of lead poisoning would require modification.

In this symposium, behavior, representing nervous system output, is presented before the morphology, physiology and biochemistry of the brain. Perhaps this is a case of the cart preceding the horse, but hopefully we will integrate these various endpoints into one functional unit which will carry us forward to a better understanding of neurotoxicology.

REFERENCES

1. Task Group on Metal Accumulation. Accumulation of toxic metals with specific reference to their absorption, excretion and biological half-times. Environ. Physiol. Biochem. 3: 65 (1973).
2. Nordberg, G. F. Effects and Dose–Response Relationships of Toxic Metals. Elsevier, Amsterdam, 1976.