Meetings

Behavioral Pharmacology

Behavorial research being conducted at the University of Maryland and at the Institute for Behavioral Research was discussed at the annual meeting of the Behavioral Pharmacology Society in College Park, Maryland, 1 February. As in past meetings, problems in the experimental analysis of behavior were featured rather than drugs themselves. The reasons are clear; if you do not understand and are unable to exercise precise control over a sample of behavior, whatever changes you observe following the administration of a drug are apt to leave you more puzzled than ever.

Since we presume that drugs aimed at modifying behavior act centrally, we might expect that experiments on self-stimulation of the brain would prove illuminating. But simply to plug an electrode into the head and then measure response rate is hardly adequate. The parameters of the stimulus and of the reinforcement schedule that arranges the contingencies between behavior and reinforcement are crucial variables and of comparable importance to the locus of stimulation. Stanley Pliskoff demonstrated the complexity of the reinforcing value of various stimulation intensities. Rats with implanted electrodes were trained to press one lever in an experimental chamber for access to a second lever. Access to the second lever was governed by a variable interval reinforcement schedule. When the second lever became available, the rat was allowed five stimulation-reinforced presses. The amount of current delivered was systematically varied. As the intensity of the reinforcing stimulus increased, rate on the second lever increased to a peak, and then fell with further increases in intensity. Response rate on the first lever, however, continued to increase with each increase in intensity. Such a chaining procedure allows one to separate the side effects of the stimulation from its reinforcing value. Pliskoff also described a procedure, again a two-member chain, for determining an organism's ability to discriminate number of events. Briefly, if a large number of pecks by a pigeon were required to complete the first member, the pigeon would receive food by pecking the left key. If a small number of pecks were required on the first member, a peck on the left key would deliver reinforcement. The number of errors increased as the two numbers approached one another.

Jack D. Findley offered other data relevant to chaining. A chimpanzee was required to press a key several thousand times in order to obtain a food reward. If this large fixed ratio was broken into smaller divisions, each of these being followed by a stimulus correlated with reinforcement (a "conditioned reinforcer"), pauses before beginning to work and during the ratio were much less. By other means, it was shown that the chimpanzee preferred the condition associated with conditioned reinforcement to the other even though the final reward was no different.

Another problem in response chaining was described by John Thomas. A chained schedule is one in which different components of the schedule are identified by different exteroceptive stimuli, such as colored lights. At the end of the last component of the chain, reinforcement is delivered. A tandem schedule, on the other hand, displays no identifying stimuli for the different components. Thomas studied a chained schedule whose three separate components consisted of fixed ratios; that is, the pigeon subjects were required to emit a fixed number of responses to complete one component of the chain and move on to the next (or to reinforcement). He contrasted this performance with a tandem schedule having duplicate requirements but no correlated discriminative stimuli. Chlorpromazine, in increasing doses, increased the ratio of response rates in the chained members to response rates in the tandem members. At high doses, the ratio decreased again. These data will be useful in understanding the processes by which drugs modify the stimulus control of behavior.

On certain types of reinforcement schedules, behavorial chains may arise spontaneously as a result of adventitious reinforcement. Such chains are sometimes observed when a subject must wait a specified interval of time between successive responses of a particular type in order to obtain reinforcement. The interresponse chain is reinforced because it lasts long enough to allow the final member—the required response—to produce reinforcement. William Hodos presented three examples of such chains. One was a monkey that was required to press one lever at least three times in order to be reinforced by a single response on a second lever. As the specified waiting time was lengthened, a greater number of responses were made on the first lever. An experiment with a cat showed that this animal could "count" short tones precisely enough to make a very fine temporal discrimination. A third experiment showed that pigeons emitted great quantities of collateral behavior when time was a critical variable in obtaining rewards. These data should make us cautious in allotting a role to some central "timing" process when we try to account for drug effects on temporally defined reinforcement schedules.

Lewis Gollub presented an empirical study of two measures of the temporal distribution of behavior on fixed-interval schedules. One was the index of curvature developed by Fry, Kelleher, and Cook, and the other was the quarterlife measure developed by Morse and Herrnstein. Since fixed-interval schedules are widely used to evaluate drugs, the methods used to describe alterations in performance are of widespread interest. Gollub concluded that these two measures were so highly correlated that an experimenter could use either under most circumstances. He did point out, however, that the quarterlife measure was somewhat less variable.

The prolonged effects of reserpine on avoidance behavior were discussed by Peter Levinson. A high dose of the drug disrupted the performance of rats,

but the period of disruption seemed to depend on the supplier from which the rats were obtained. This result suggests that a difference in strain or diet may play a role here. Levinson also discussed the difficulties of training rats on avoidance schedules.

Joseph V. Brady (Walter Reed Army Institute of Research) described a different aspect of avoidance behavior. The Walter Reed laboratories have emphasized the chronic features of avoidance behavior and have examined various endocrine and somatic correlates of prolonged exposure. In recent experiments, rhesus monkeys exposed to 72-hour avoidance sessions once per week show, during the first few sessions, high levels of adrenal steroid output and high response rates on the avoidance schedule. With repeated sessions, steroid output falls to or below basal levels and the behavior becomes more efficient. Monkeys subjected to 72-hour avoidance sessions before undergoing ionizing radiation from a source emitting 10,000 r display enhanced radio resistance, and live significantly longer than controls. The elevated steroid levels produced by the avoidance procedure may play a part in this phenomenon.

Roger T. Kelleher (Harvard Medical School) is the new president of the Society and Larry Stein (Wyeth Laboratories) is the new vice president.

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Carbon-14 in Clinical Research

A conference on metabolic studies with carbon-14-labeled substrates and continuous assay of $C^{14}O_2$ in expired air was held at the University of Chicago 25–26 November 1963. These studies are of potential value in clinical research because in man it is seldom feasible to investigate intermediary metabolism in the same detail as in animals where—in addition to blood, excreta, and expired air—organs and tissues are readily available for radiochemical analysis. Continuous assay of expired air yields patterns which give direct information on the rate of respiration of $C^{14}O_2$ formed by the catabolism of substrates labeled in specific positions with carbon-14.

One of the pioneers in this field, Bert Tolbert (Colorado) observed that the basic concept of the method is that catabolic rates are controlled by the dynamics of intermediary metabolism and physiology. If one can measure the rates of respiration of $C^{14}O_2$ from a sufficient variety of labeled substrates it should be possible to define rather clearly and quantitatively the relative importance of the major metabolic pathways in health and disease. In terms of metabolic pathways, the oxidation of most intermediates to carbon dioxide has been well worked out during the past 15 years. In contrast, except in a general way and under quite special conditions, very little is known about the dynamics of intermediary metabolism in the intact subject—the mixing times, pool sizes, turnover rates, and competition between alternative pathways. The development of a body of knowledge on the dynamics of the system and the determination of the dynamics of intermediary metabolism is an essential part of the evolution of the technique that was discussed at the conference.

No formal papers were presented, but there were special discussion periods related to instrumentation, data processing, interpretation of activity-time curves, design of experiments, and radiological safety. A typical instrument system consists of (i) a face mask, helmet, or hood to collect expired air; (ii) a ventilometer; (iii) a radiation detector; and (iv) a carbon dioxide analyzer. For studies of total metabolism an oxygen analyzer is added. A closed system (undiluted expired air collected with a face mask) is suitable for normal subjects and for some patients. An open system with a helmet or a hood is more comfortable for sick or weak subjects, but introduces problems associated with dilution of expired air. Calvin Long (Harvard) reported that air-flow rates of 35 to 40 liters per minute are necessary when working with very sick patients.

The radiation detector in most systems is a flow-through ionization chamber with a vibrating-reed electrometer. A well-calibrated chamber should detect about 0.2 nanocurie (nc) of $C^{14}O_2$ per liter. Don Charleston (Chicago) discussed the Argonne Hospital instrument that uses a 4-π Geiger-Mueller counter which can detect 0.8 nc/liter or 0.5 nc/mmole. Regardless of the type of detector used, all systems are characterized by a large output of information which can only be handled conveniently by machine methods. W. F. Yasdick (Datex Corp.) discussed several methods for analog-digital conversion to make data available for electronic computers. He described in detail the advanced data-logging equipment of the Argonne system. Such installations are costly when they are custom-made, but if investigators could agree on their requirements, less expensive production models would become available.

The curve of radio-activity incorporated into CO_2 recorded during the first several hours after administering a labeled substrate which is oxidizing rapidly (for example, glucose-1-C^{14}), is fairly typical for each intermediate, is quite reproducible in the same subject, and is complex. Its configuration is determined by at least three factors: (i) the behavior of the labeled substrate within its particular metabolic pool, (ii) the rate of intracellular oxidation, and (iii) the kinetics of the carbon dioxide pool through which $C^{14}O_2$ must pass enroute to expired air.

James Robertson (Brookhaven National Laboratory) led off the discussion with a critique of methods that analyze the system as though it consisted of well-mixed, connecting compartments. The explicit solution of this model is a series of exponential terms. Some of the participants considered the results an exercise in curve fitting, and challenged the practice of assigning a physiological or anatomical identification to every or any exponential term. Max Kleiber (Davis) remarked that the final exponential term derived from a curve of decreasing radioactivity is more often a function of the duration of the experiment than of a particular physiological process. In the case of the carbon dioxide pool, LeRoy (Chicago) and Okita (Northwestern) described their application of the theory of indicator-dilution methods advanced by Meier and Zierler [*J. Appl. Physiol.* **6**, 731 (1954)]. The procedure, which has been programmed in Fortran, computes pool size (V), flow (F), and mean transit time ($\bar{t}$). The inputs for this program are digitalized data from continuous assay of expired air obtained during 1 to 2 hours after administration of a dose of $NaHC^{14}O_3$.

The usefulness of information