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Table of Contents

EXPERIMENTAL PSYCHOPATHOLOGY IN NONHUMAN PRIMATES [1]

Introduction

Can monkeys be made as mad as men? Phrased more scientifically, can primate models be useful in understanding human psychopathology? If so, how and what are the specific behavioral, neurophysiological, and biochemical changes seen? What rehabilitation methods are effective in reversing each of the abnormal behavior syndromes? These questions now occupy the attention of several investigators and are the key queries with which this chapter will be concerned.

During the last ten years the field of experimental psychopathology in nonhuman primates has undergone considerable development. It is now possible through utilization of specific social and biological induction methods to produce syndromes of abnormal behavior that can be objectively documented and evaluated. If behavioral and biochemical studies whose findings may subsequently be applied to human beings are to be performed, ideally one should use a species as close to man as possible. From this viewpoint the great apes might be the logical choice. However, due to the scarcity and the difficulties and expense of working with large primates in a laboratory much of the work to be reviewed in this paper has utilized only rhesus monkeys as subjects. Also, the life span of monkeys is considerably compressed in comparison to man or the apes, thus facilitating longitudinal studies. However, occasional reference will be made to work employing other species because the issue of species variation, particularly with regard to social behavior, is a critical one.

The interest of most clinicians in the experimental simulation of abnormal behavioral states in nonhumans has ranged from excessive anthropomorphism to indifference to hostility to confusion. The skepticism with which much animal behavioral work has been received lies partly in the history of the field and partly in the attitude of some psychiatrists who refuse to accept animal work as relevant to human disorders. This latter school of thought has been most actively represented by Kubie who states: “Thus the imitation in animals of the emotional states which attend neuroses in man is not the experimental production of the essence of neuroses itself.” Kubie’s contention is that behavior is only the “sign-language” of an underlying symbolic disorder that is the real core of psychopathology. He feels that animals do not have symbolic capacities and, therefore, it is not possible to produce a “true” neurotic or psychotic state in nonhumans. This position is predicated on an assumption about human psychopathology that many would disagree with, namely, that behavior is important only as an indicator of something more important that is the “real” disorder. Others would insist that observations of behavior are the only way to define disorders reliably. Also, the assumption that higher-order primates do not have symbolic capacities is open to serious question.

However, Kubie in his criticisms did focus on an important issue in this field. Various terms have been applied far too loosely to the abnormal behavioral states created in different species. Labels such as “experimental neurosis,” “phobia,” “anxiety,” “behavioral disorder,” “chronic emotional disorder,” “experimental neurasthenia,” and “depression” have been utilized, often without adequate behavioral descriptions. The laxity in labeling has often alienated clinicians who fail to see the similarities between conditions used to produce abnormal behavior in many animal studies and those which are thought to predispose to human psychopathology.

Many criticisms of the field are justified as will be apparent from the historical section of this chapter. However, there is no intrinsic reason why specific forms of human psychopathology cannot be examined at an animal level. It has been pointed out by Seligman and by McKinney and Bunney that the difficulty in moving from a dramatic analogue to animal models has been due in large part to the lack of ground rules or criteria that might validate the model. This will be reviewed following the historical section. Subsequently, a discussion will be presented of some of the more carefully defined syndromes of abnormal behavior in primates, the conditions that produce them, and, in some cases, effective ways to reverse them. The areas to be covered will include: (a) social isolation, (b) the Harlow vertical chamber, (c) experimental “helplessness,” and (d) attachment-behavior and separation studies. An approach to biochemical studies in primate models and data from recently completed studies will be outlined. Finally, a perspective on the field of experimental psychopathology in primates will be presented and possible future directions discussed.

It should be mentioned that this chapter concerns itself only with experimental-laboratory investigations and does not deal with the broad range of important field studies that are available. However, field studies and laboratory studies of primates should be viewed as complementary rather than competitive, with each having inherent advantages and limitations. Admittedly the choice of topics to be discussed is arbitrary, but hopefully they include the ones of most interest to psychiatrists.

Historical Approaches

The first research on animal neuroses originated in the laboratories of Ivan P. Pavlov of Russia. In 1921, he described a method for producing an “experimental neurosis” using a conditioning paradigm. A previously quiet dog, subjected to prolonged classical conditioning, became unable to distinguish between the appearance of a circle as a signal for food and an almost circular ellipse as a signal for no food. He suddenly exhibited extreme and persistent agitation as evidenced by constant struggling and howling.

Pavlov viewed neurosis as a chronic deviation of the higher nervous system, lasting weeks, months, or years. He felt higher nervous activity was manifested chiefly in the system of conditioned positive and negative reflexes to any stimulus and partially in the general behavior of his dogs. A neurosis in Pavlov's paradigm resulted from a collision, in time or space, of the processes of excitation and inhibition, e.g., receiving positive and negative stimuli too close together.

Gantt also used conditioning paradigms to produce what he called "behavior disorders," though it seems clear that he was not able to model specific syndromes so much as to produce a variety of autonomic responses to different conditioning tasks. He produced experimental conflicts by forcing dogs to make difficult differentiations of conditioned signals and studied the effects of this type of conflict on the animal's neurophysiological functioning. He presented detailed, longitudinal histories of dogs made behaviorally abnormal by this method. Pavlov's approach was also extended and modified by Cook in rats, and by Dworkin in dogs and cats.

Liddell made the first observation of experimental neurosis using sheep as subjects. In 1927, Liddell and Bayne reported what they labeled "experimental neurasthenia" in a sheep subjected to an unsignaled doubling of the number of conditioning trials per day. The animal was observed to have become very excited and agitated. Liddell and his group continued to perform experimental-neurosis research on sheep, goats, and pigs using conditioning paradigms. They presented the concept that experimental disorders in animals represented primitive, relatively undifferentiated behavioral states rather than one specific syndrome. This group also performed longitudinal studies of the effects of stressful conditioning paradigms at different developmental stages in the animal's life cycle.

Masserman used motivational conflict situations to induce abnormal behavior first in cats and later in monkeys. Subjects were conditioned to remove food pellets from a box and subsequently, on certain trials, were subjected to a blast of air when they approached the food, thus producing a conflict between hunger and fear. He described "anxiety" in and out of the experimental situation, frequent startle reactions, "phobic" hypersensitivity, "compulsive" patterns of hiding and escape, motor disturbance (restlessness, cataleptoid immobility), regressive automatisms such as licking or preening, and marked behavioral inhibition that, when directed toward food, could lead to self-starvation. Masserman also studied a variety of methods designed to alleviate the abnormal behavior resulting from the motivational conflict induced. The greatest contribution of Masserman's work lay not in its simulation of any particular behavioral state, but in its demonstration that certain psychoanalytic principles can be made operational and tested experimentally. This was no small contribution in its time or even today.

There have been many other experimenters in this area. For instance, Hebb’s description of spontaneous neurosis in chimpanzees was important in terms of its relation to clinical and experimental phenomena. He described what he termed a “phobia” in one case where a chimp suddenly became afraid of large chunks of food. The other case involved naturally occurring episodic depression. Babkin reported that bromides could reset the balance between excitatory and inhibitory processes thought by Pavlov and Gantt to be important in experimental neuroses. Stainbrook called attention to the value of experimentally producing acute behavioral disorders in animals as a method of psychosomatic research and discussed some of the previous work done in several species.

It is not surprising that the field of experimental psychopathology in nonhumans has been of little interest to clinicians. Most of the work described in the previous section used conditioning techniques and terms whose relevance to clinical phenomena were poorly understood. Clinical terms were thrown about far too loosely to describe certain behavioral states in animals. Little attention was paid to the theoretical problems implicit in using nonhumans to study human psychopathology. In the next section this latter issue will be discussed, since it is basic to what follows in the rest of the chapter.

Criteria for Animal Models

The basic controversy that has developed from the above work, as well as from recent data, is whether a laboratory phenomenon in animals can model a form, or forms, of psychopathology in man. The theoretical considerations regarding this general issue have been discussed by Senay," McKinney and Bunney, Harlow and McKinney, Seligman, and Mitchell. The last article also contains an excellent review of abnormal behavior in primates, which readers of this chapter may find useful.

The above authors stated their criteria in different terms, but the content of what each said was very similar. Much of the work previously described in the historical section suffered from a lack of prior criteria by which the syndromes produced could be evaluated. The establishment of such criteria for animal- model research in recent years has been a major advancement and has had considerable heuristic value.

Forms of human psychopathology are not entities that can be studied at an animal level if appropriate criteria have not been previously established. The following criteria have been proposed by several workers as being useful in evaluating nonhuman experimental psychopathology research:

1. The behavioral manifestations of the syndrome being modeled should be similar to those seen in the human condition.

2. These behavioral changes should be able to be objectively detected by independent observers in different laboratories.

3. The behavioral state induced should be persistent and generalizable.

4. Etiological-inducing conditions used in animals should be similar to those present in human psychopathology.

5. Treatment modalities effective in reversing the human disorder should be effective in primates.

6. There must be sufficient reference-control data available.

While these criteria suggest needed research in the creation of models, it should also be remembered that the condition being modeled is often itself poorly defined from a behavioral standpoint. While this point can be used as a rebuttal to critics who demand more preciseness from "models" research than is currently available, it also delineates one of the potential values of animal-model research, i.e., to aid in more clearly defining human syndromes from a behavioral standpoint.

In essence what is being attempted in the creation of experimental models in primates is the production of a syndrome(s) that meets the criteria outlined above. The value of a model system in animals is that it leads itself to more direct manipulation of social and biological variables than is possible in human beings from ethical and/or practical standpoints. This is not to contend that monkeys are humans or vice versa. Obviously, there are differences, but the similarities far outweigh most differences, especially with regard to social development and affectional systems.

In other medical specialties, animals are frequently used as models for some conditions. Psychiatry does not have this tradition. Primate behavioral research has characteristically been the domain of the experimental psychologist, the ethological zoologist, and the anthropologist. Why this has been so has been discussed earlier in this chapter. As will be apparent, however, there are primate behavioral data available that provide a firm base for understanding of clinical phenomena in several areas. For example, experimental work on social isolation of nonhuman primates has documented the short- and long-term effects of insufficient social input early in development, and recent rehabilitation experiments have indicated successful therapeutic approaches. These data have considerable relevance for human psychopathology as well as for the better understanding of the effects of different rearing conditions.

Social Isolation

The technique of social isolation involves rearing animals from birth either in total isolation chambers where they have no social contact with other monkeys or in bare wire cages where their only contact is visual and auditory.

Social isolation is only one of many different rearing conditions that are possible in a controlled laboratory setting. Harlow and Sackett have discussed each of these rearing conditions and their effects on the behavioral development of rhesus monkey subjects. Each method has an influence on the rapidity and/or nature of development of social behavior but, in general, all, except social isolation, can be used to rear socially normal rhesus monkeys. Social isolation early in life produces severe and persistent syndromes of abnormal behavior involving the destruction or severe disruption of the major "affectional systems" as proposed by Harlow.

The mechanisms underlying the dramatic effects of social isolation are poorly understood and there are virtually no data about possible neurophysiological and/or neuroendocrinological substrates of the syndrome. Sackett has summarized the four most frequent explanations thus:

1. Atrophy—Deprivation effects are due to physical atrophy of sensory mechanisms that were mature at birth or shortly thereafter.

2. Developmental failure and potentiation—Environments void of certain critical inputs may produce later deficits because the physiological substrate underlying a response or information processing fails to mature.

3. Learning deficits—Social-deprivation deficits are caused by a failure of the early environment to provide experiences critical for basic perceptual-motor development. A failure to

integrate perceptual and motor responses early in life permanently impairs the ability to adapt to change.

4. Emergence trauma—Deficits are a function of the discrepancy between rearing and testing environments, i.e., the shock of removal from a stimulus-poor environment to a stimulus-rich one.

None of these explanations can be accepted as the chief one.at present because of the absence of data. However, it is known that the emergence-trauma theory is not supportable. Experimenters have tried to alleviate the occurrence of such trauma by adapting the subjects during the isolation period to the test situation to be employed following removal from isolation. No substantial positive effects were apparent. The “adapted” isolates exhibited social behavior generally as incompetent as that of isolates denied this experience.

It is also known, from recent rehabilitation experiments, that a rigid fatalistic, critical- period hypothesis is not true. With appropriate rehabilitative methods, it has been possible to reverse the social deficits that resulted from early isolation.

Social-isolation data are most extensive in rhesus monkey subjects, and these will be summarized below. However, the isolation syndrome has also been studied in dogs, in pigtail monkeys, and in chimpanzees. The measurement techniques differed from study to study in terms of how the effects of early social isolation were documented, and also the specific techniques of isolation varied. Nevertheless, one can make a general statement that, in all species studied thus far, early social isolation has been a powerful method for inducing persistent patterns of abnormal behavior.

In rhesus monkeys, for example, subjects reared in total social isolation for the first six to twelve months of life exhibit, upon emergence from isolation, severe deficits in locomotive, exploratory, and social behavior. The appropriate responses of grooming, play, and other social interactions are minimal in these subjects. They spend the majority of their time engaging in autistic-like self-clasping, stereotyped rocking and huddling, and self-mouthing behavior. One of these isolates is shown in Figure 15-1. Appropriate sexual responses are virtually absent among isolate- reared monkeys, and those females artificially inseminated typically display grossly inadequate maternal behavior, characterized by indifference or brutality toward their infants. In general, aggressive behavior is either self-directed or inappropriately directed. For example, a chronologically mature social isolate will readily attack a neonate, an act rarely initiated by a socially normal monkey, or it may attack a dominant adult male, a blunder that few socially sophisticated monkeys are foolish enough to attempt. Socially isolated rhesus monkeys have also been reported to exhibit hyperphagia and polydipsia as adults.

Figure 15-1.
A typical Isolate rhesus monkey huddling and self-clasping

Several variables are important in the production of the isolation syndrome. The most severe effects are produced when the isolation is total, when it begins at birth, and when it lasts for a minimum of six months. Alteration of any of these factors will produce a less severe and/or a less persistent syndrome.

The isolation syndrome until recently had been considered permanent. No technique that had been tried had been successful in reversing the syndrome, including aversive conditioning-type procedures, frequent social experience with peers, and prevention of the “emergence trauma.” The first successful rehabilitation of social isolates was brought about by “monkey psychiatrists,” a term that refers to chronologically younger, normal monkeys who served as the therapists in the social rehabilitation study. The specific experiment studied six-month isolates and utilized three-month-old, normal female animals as “therapists.” The isolates were allowed to interact with the therapist monkeys two hours per day, three days per week as pairs (one isolate, one therapist) and two days per week in a group of four (two isolates, two therapists) in a playroom.

The isolates’ initial response to both situations was to huddle in a corner, and the therapists’ first response was to approach and cling to the isolates. Within a week in the home cage and two weeks in the playroom the isolates were reciprocating the clinging. Concurrently the therapists were exhibiting elementary play patterns among themselves and attempting to initiate such patterns with the isolates. Within two weeks in the home cage and a month in the playroom the isolates were reciprocating these kinds of behavior. Shortly thereafter the isolates began to initiate play behavior themselves and, correspondingly, their disturbance activity, which originally had accounted for most of their behavioral repertoire, decreased to insignificant levels. By one year of age the isolates were virtually indistinguishable from the therapists in the amount of exploration, locomotion, and kinds of play behavior.

Not only have isolated monkeys responded to social-treatment methods, they have also improved on chlorpromazine. In a recent pilot study, rhesus monkeys subjected to partial social isolation for the first year of life, plus other traumatic experiences involving being immobilized or seeing peers immobilized, exhibited severe patterns of abnormal behavior such as huddling, rocking, self-clasping, retreat to corners away from other animals, and self-mouthing. When they were two and a half years of age, four such subjects were started on chlorpromazine and the dosage adjusted to 7.5 mgm/kgm given once a day by intubation. Within four to eight weeks on this regimen, the “active” self-disturbance behavior such as self-mouthing, clasping, huddling, etc., had decreased significantly and a few social encounters such as play and social exploration occurred in some subjects.

These studies involving attempts to reverse the social isolation syndrome are being extended to one combining chlorpromazine plus social experience as well as the use of other drugs.

In terms of models it is still unclear what human syndrome is being represented by the isolation syndrome. Labels such as “autism,” “schizophrenia,” “psychoses,” “depression,” have been used by some professionals in describing these animals. A cautious approach to labeling is indicated at present. Certainly the behavioral parallels between these isolate monkeys and certain aspects of each of the above syndromes exist, yet several criteria for models presented earlier have not been met or even approached. One criteria that is particularly critical to keep in mind is the comparability of inducing conditions. It is difficult to hypothesize a documentable human analogy to total social isolation except for the few cases of drastic neglect of infants. Partial social isolation, on the other hand, has a clearer analogue in the limited and stereotyped social input to children present in many groups and families. There are virtually no biological data available on isolated monkeys that might help to understand the mechanisms, and help with the definition of the syndrome. It has been said that rehabilitation studies can help the syndrome and within limits this is true. It appears that a socially induced syndrome can be improved by appropriate social therapy and by use of an antipsychotic drug. The social therapy involved gentle physical contact and nonthreatening social interactions. However, did the drug therapy involve chlorpromazine’s antipsychotic properties or did it facilitate social interaction by making the subjects less fearful of each other? Or some combination of the two? Further work is necessary to clarify this issue.

In conclusion, it is known that a syndrome of abnormal behavior can be predictably produced by early social isolation. This syndrome can be well defined behaviorally, but additional investigations are critical in order to clarify the mechanisms involved and the significance of the syndrome itself as a model for human psychopathology.

Harlow Vertical Chamber

The technique of social isolation requires six to twelve months for effective production of severe syndromes of abnormal behavior. Attempts have been made recently to create other social-deprivation methods that might produce psychopathological behavior in a much shorter period of time. Several pilot studies have been conducted at Wisconsin that indicate that confinement in an apparatus called the vertical chamber may also be capable of producing dramatic behavioral changes in rhesus monkeys.

The vertical chambers are illustrated in Figure 15-2. Essentially, they are troughs constructed of stainless steel, open at the top, with sides that slope inward to a rounded bottom that forms one-half of a cylinder. There are smaller chambers for infants and larger ones for older subjects. One inch above the bottom of both chamber types is a wire mesh-floor that allows waste material to drop through to the pit bottom. Holes drilled in the bottom permit urine collection while the monkey is in the chamber. The chamber is equipped with a food box and a water-bottle holder and is covered by a pyramidal top designed to discourage confined subjects from hanging from the upper part of the trough. While in the chamber a subject would have no tactual or visual contact with other monkeys. Depending on the placement of the chamber in the laboratory, he could or could not have auditory contact.

Figure 15-2.
Vertical chamber apparatus with an attached living cage.

In an exploratory study, four individually reared subjects with an age range of six to thirteen months were placed in single chambers for a period of thirty days. Figure 15-3 illustrates some of the kinds of home cage behavior prior to chamber isolation and for two months following removal. It is obvious that their behavior patterns after removal from the chamber were drastically altered, with marked increases in self-clasping, rocking, huddling, and marked decreases in locomotion and environmental exploration.

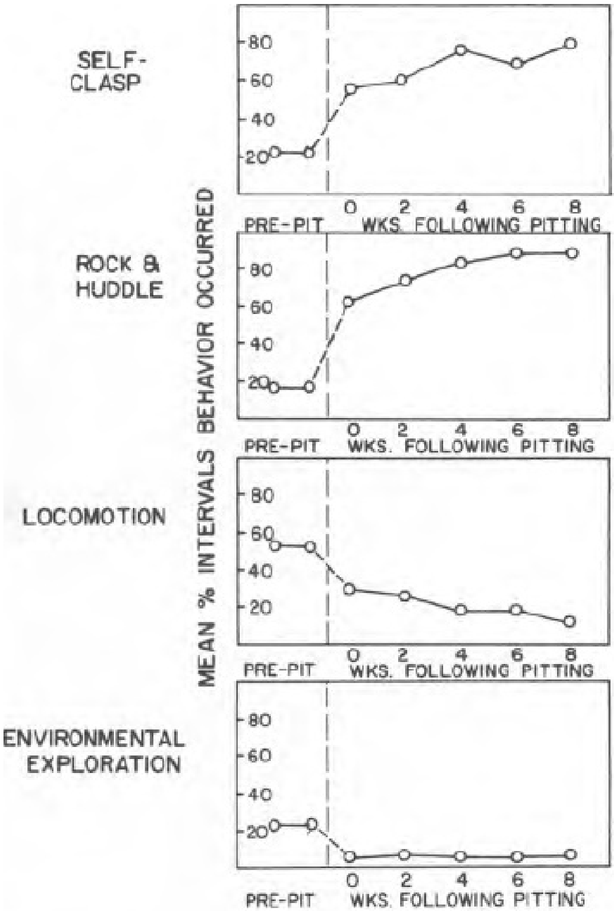


Figure 15-3.
Effect of thirty days of vertical chamber confinement on selected behaviors of four rhesus monkeys (age six to thirteen months).

This pilot study suggested that the vertical chamber had potential for the rapid production of psychopathological behavior in monkeys. Total social isolation from birth to three months results in only transient behavioral disturbance. Also, the effectiveness of social isolation decreases even more if not initiated at or shortly after birth. In contrast, vertical chamber confinement of only thirty days duration produced disturbances even in subjects six to thirteen months old at the time of confinement. Two of the animals were able to be followed for almost a year after removal and little recovery was evident. However, additional long-term studies are necessary to assess the effects of early chambering.

In a second study four monkeys forty-five days of age were placed in individual vertical chambers for six weeks. Upon emergence they were three months of age. Subsequently they were housed individually, but given social experience three days a week in a playroom with equal-aged monkeys. Figure 15-4 shows the animals four days following removal from the chambers. Figure 15-5 shows the same monkeys four months later. The persistence of the behavioral effects was also seen in the monkeys' home cage and playroom behavior eight months later when the animals were eleven months of age. Self-mouthing, self-clasping, and huddling dominated the chambered monkeys' activity, but were virtually nonexistent in control subjects. The reverse was true regarding locomotive and exploratory behavior. Most striking was the almost total absence of any socially directed behavior in the chambered animals despite the fact that they had been given extensive social experience from four months of age. Other groups are currently being tested to see if the data from the pilot experiment described above can be replicated.

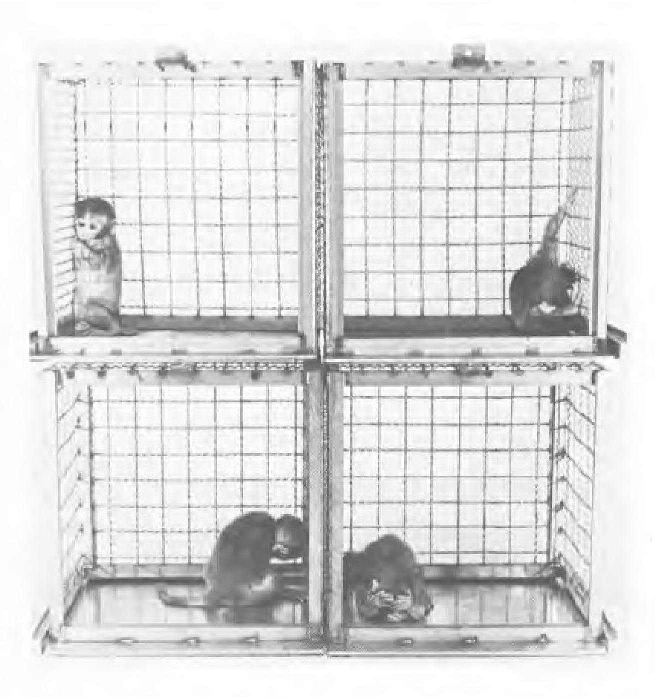


Figure 15-4.
Four rhesus monkeys immediately after six weeks of vertical chamber confinement.

A third study combined peer separation, to be described in a later section (p. 325), with vertical chamber confinement. Infants were paired with each other as a group of four from birth to three months, then separated from each other a total of twenty times, four days for each separation in exactly the same sequence as the multiple-infant-separation study to be discussed later.

The difference in the current study was that during the separation phase the infants were housed in vertical chambers rather than individual cages. Upon reunion, the chambered monkeys showed significantly lower levels of social clinging and higher levels of self-clasping than the cage- separated monkeys. In other words, they did not reattach to each other as the animals housed in standard laboratory cages during separation did. These data are the only suggestion from the Wisconsin laboratory that it might be possible to produce Bowlby’s “detachment” stage in monkeys. Mitchell has also observed a phenomenon resembling detachment when infant rhesus monkeys are reunited with their mothers. In any event, it is apparent that chamber confinement coupled with separation produced effects beyond those produced by either procedure alone.

Figure 15-5.
Four rhesus monkeys four months after six weeks of vertical chamber confinement.

When the vertical chamber studies were extended beyond infants to juvenile-age rhesus monkeys three years old, a very different effect was observed. Such subjects when confined to vertical chambers for as long as eighty days exhibited, upon removal, significant decreases in locomotion and activity levels, and significant increases in contact clinging and passivity as illustrated in Figure 15-6. Such behavior is clearly inappropriate for three-year-old monkeys and seems more typical of monkeys at an earlier stage of development. Thus, as will also be seen in the separation studies, age or developmental stage is a critical variable in determining a subject's response to chambering.

There is considerable question as to what the behavioral changes induced by vertical- chamber confinement represent. There was an initial hope that the chambers could be used to create feelings of "helplessness and hopelessness." This may or may not prove to be the mechanism involved in this severe form of environmental deprivation. That such a state can be created in nonhumans is indicated by Seligman's work to be discussed in the next section. However, based on currently available data, the vertical chamber seems to be an effective means of producing severe and persistent psychopathology in rhesus monkeys. The roles of environmental deprivation, and such parameters as chamber shape, chamber construction, decreased mobility, duration of confinement, and prior social experience are largely unknown, and studies investigating these factors have been initiated.

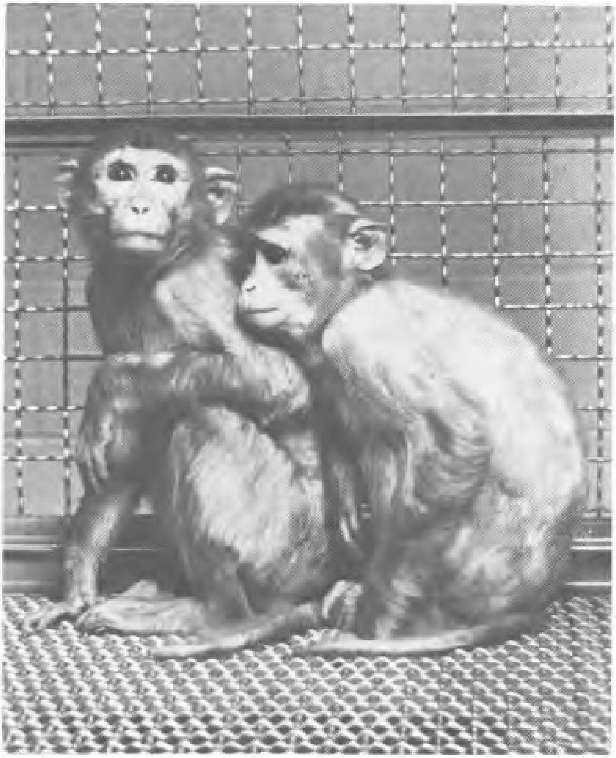


Figure 15-6.
Three-year-old rhesus monkeys clinging to each other after eight days of vertical-chamber confinement.

Learned Helplessness

Seligman et al. use the term “learned helplessness” to describe the interference with adaptive responding produced by inescapable shock. Most of their work has been conducted with dogs, but they note that a similar phenomenon can be observed in rats, cats, dogs, fish, mice, and men.

In the paradigm used to produce learned helplessness, subjects were first given a series of sixty-four unsignaled, inescapable electric shocks. The shocks occurred randomly. Twenty-four hours later the subjects were given ten trials of signaled, escape-avoidance training. During this phase, if the subjects jumped a barrier when the conditioned stimulus was presented, they avoided shock; failure to jump led to a shock that continued until the subjects jumped the barrier.

Learned helplessness is an operational concept used to describe subjects that have had experience with uncontrollable shock and failed to initiate responses to escape shock or were much slower in making responses than naive dogs. Also, if the subject did happen to make a response that turned off shock, it had more trouble than a naive subject in learning that responding was effective. In other words, after an initial experience in which responding could not control reinforcers (uncontrollable shock) the animals ceased to respond even when responding could now control reinforcers.

Such a model for learned helplessness has been suggested as another type of animal model for certain aspects of human depression by those who would see at least reactive depression, especially the passivity components, as having its roots in loss of control over reinforcers, e.g., gratification and alleviation of suffering. In this model, experimental helplessness is cured by letting the animal make repeated responses that turn off the shock. The analogy to depression is that one of the important features in the treatment of depressed patients is changing the patient's perception of himself as hopeless to one in which he believes that he has control over his environment.

Separation Studies

Separation experiences, i.e., object losses, are thought to precede the development of severe depression as well as other forms of psychopathology in human beings.' The theories that postulate the importance of separation are largely based on retrospective studies that start with a population of clinically depressed people who have undergone separation. There is little understanding of the mechanisms underlying the apparent close connection between separation and depression, though the terms "separation" and "object loss" have themselves become well- accepted phrases among clinicians. Such phrases have been used to describe many diverse states, ranging from an infant's response to separation from his mother to an adult's loss of self-esteem when certain defense mechanisms are no longer effective or when life-threatening illnesses confront him. Unfortunately, separation is becoming a greatly overused term in the sense that its usage has far outstripped our basic understanding of its meaning. Separation is certainly more than just an event and needs to be defined in terms of many parameters. If this is not done, there exists the risk that the term will continue to be used so broadly and loosely as to become meaningless. Many variables determine a response to separation and these need identification and study before the connection between what is called separation and depression can be understood. Also, depression may not be the only response to separation, or if it is, then depression may manifest itself differently depending on many factors that almost certainly include genetic and neurochemical ones, prior experience of separations, the conditions surrounding separation, and age to mention only a few.

It is in the area of clarifying the mechanisms underlying separation that primate models have perhaps been most useful thus far. Rhesus monkeys develop strong affectional systems and form close social bonds, factors that have facilitated the study of separation and depression. It was thought initially that these bonds were so strong that they could be manipulated to produce dramatic changes in behavior. Results thus far have confirmed this initial belief.

The issue of mother-child separation, and the mechanisms underlying the disturbance it produces in the human infant, have been discussed by Bowlby.' In his writing concerning separation, grief, and mourning in children and infants, he outlined six theories of separation and concluded that separation anxiety results from activation of the “component instinctual response systems” that form the base of the infant’s attachment. He described three stages of the human child’s response to separation: protest, despair, and detachment. The protest stemmed from anxiety; the despair from grief; the detachment from defensive reactions. Bowlby’s theories, based on studies of the separation reactions of human infants, have provided a major portion of the theoretical underpinnings of the mother- infant separation work in primates. Also of key importance in stimulating the experimental work were the observations of Spitz on hospitalized young infants, who had been separated from their mothers. This reaction he termed “anaclitic depression.” Many infant monkeys undergoing maternal separation stimulate the anaclitic depressive syndromes seen in human infants.

The major separation studies to be described are outlined in Table 15-1.

Mother-Infant Separation Studies

A number of informal separation studies were conducted at the Wisconsin Primate Laboratory in the late fifties on thirty- to ninety-day- old rhesus infants raised with their own mothers. It was noticed that separation ranging from a few hours to a few days in duration resulted in acute disturbance for both mother and infant during separation and a marked increase in maternal protectiveness following reunion. In one case the mother, after a three day separation, kept her infant literally within reach for a period of more than a month. These observations precipitated a more formal study of mother-infant separation, which was reported in 1962 by Seay, Hansen and Harlow.

Table 15-1. Major Separation Studies in Monkeys

INVESTIGATORS	SPECIES	TYPE OF SEPARATION	AGE OF SUBJECTS	SEPARATION TECHNIQUE	LENGTH OF SEPARATION
Seay, Hansen, Harlow	*Macaca mulatto*	Mother-infant	6 months	Removal of infant	3 weeks
Seay, Harlow	*Macaca mulatto*	Mother-infant	7 months	Removal of infant	2 weeks
Jensen, Toleman	*Macaca nemestrina*	Mother-infant	6 months	Removal of infant	1 hour
Kaufman, Rosenblum	*Macaca nemestrina*	Mother-infant	5 months	Removal of mother from group- living situation	4 weeks
Kaufman, Rosenblum	*Macaca radiata*	Mother-infant	5 months	Removal of mother from group- living situation	4 weeks
Hinde	*Macaca mulatto*	Mother-infant	8 months	Removal of mother from infant's sight	6 days
Suomi, Domek, Harlow	*Macaca mulatto*	Peer	3 months	Peers repetitively removed from each other and individually housed	4 days

Mitchell, Abrams, Lindburg	*Macaca mulatto*	Mother-infant	2 months 3-h mo. 5 months	Removal of infant individual housing	48 hours	[illegible]
Preston, Baker, Seay	*Erythrocebus patas*	Mother-infant	7 months	Removal of mother/infants housed together	3 weeks	[illegible]
McKinney, Suomi, Harlow	*Macaca mulatto*	Peer	3 years	Peers repetitively removed from each other and individually housed	14 days	[illegible]

The technique employed in the initial separations at Wisconsin involved the use of the playpen apparatus shown in Figure 15-7. This apparatus allowed mother-infant pairs to live together in each of four corner units with a central play area that the infants, but not the mothers, could enter via an opening in each living unit. Separation was accomplished by merely closing off this opening while the infants were in the central part, so that they could not return to their mothers. Plexiglas paneling was used to permit continued visual and auditory contact, wire mesh paneling that in addition permits tactual contact, or Masonite that allowed only auditory communication.

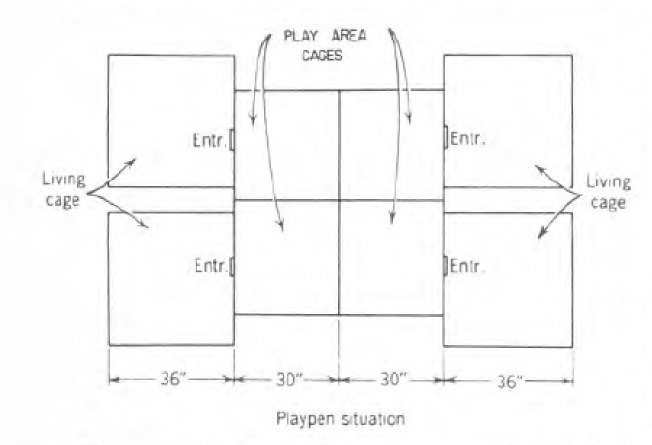


Figure 15-7.
Playpen apparatus used for mother- infant separation studies.

In the original study, four infants and four mothers served as subjects. Two of the infants underwent maternal separation at 169 and 170 days of age and two at 206 and 207 days of age. The experiment was divided into three time blocks of three weeks each: pre-separation period, separation period, and post-separation period. In this study Plexiglas dividers were used and thus the infants could continue to see and hear all mothers. Detailed behavioral observations were made each day. The initial reaction of all mothers and all infants after separation indicated a high degree of emotional disturbance. Immediately after separation the infants' behavior included disoriented scampering, high-pitched screeching, cooing vocalizations, and huddling up against the barrier in close proximity to their mother. The mothers displayed an increase in barking vocalizations and in threats directed toward the experimenter, but the mothers' emotional response appeared to be both less intense and of shorter duration than that of the infants. Later during the separation period most complex forms of infant-to-infant social behavior exhibited a drastic decrease in frequency of occurrence. For instance, noncontact play was for all practical purposes obliterated. Threats, approaches, and withdrawals also decreased. During the post separation period infant- mother clinging and mother-infant cradling rose significantly and infant-mother, nonspecific contact showed a significant decrease in three of the four infants. Interestingly, one of the infants showed a significant decrease in support contact, nipple contact, and nonspecific contact during post-separation as compared to pre-separation. This initial investigation demonstrated that separating a rhesus monkey from its mother had striking behavioral effects, but with individual variation in terms of the nature of the response. In general, the sequence of stages seemed to parallel the "protest" and "despair" stages of Bowlby and to provide a powerful animal analogue for anaclitic depression. These stages are illustrated in Figure 15-8. It is possible that the animal that did not reattach was exhibiting something analogous to the "detachment" stage, but this was uncertain.

Another study by Seay and Harlow used eight rhesus mother-infant pairs separated at about 207 days of age. In contrast to the above study, Masonite paneling was used during the separation phase and the infants were not able to see any of the mothers. Behavioral changes were similar to those already described; however, the reaction seemed more severe when the infants could see their mothers than when they could not.

Jensen and Toleman, in one of the earliest separation studies, observed the short-term effects of separation of mother-infant monkey pairs *(Macaca nemestrina)* for less than one hour and found that the infants screamed almost continuously during the separation. The mothers attacked their own cages and tried to escape. On return of the infant there was a striking increase in the intensity of the mother- infant relationship. This study demonstrated that even extremely short-term separations had severe effects on both mothers and infants.

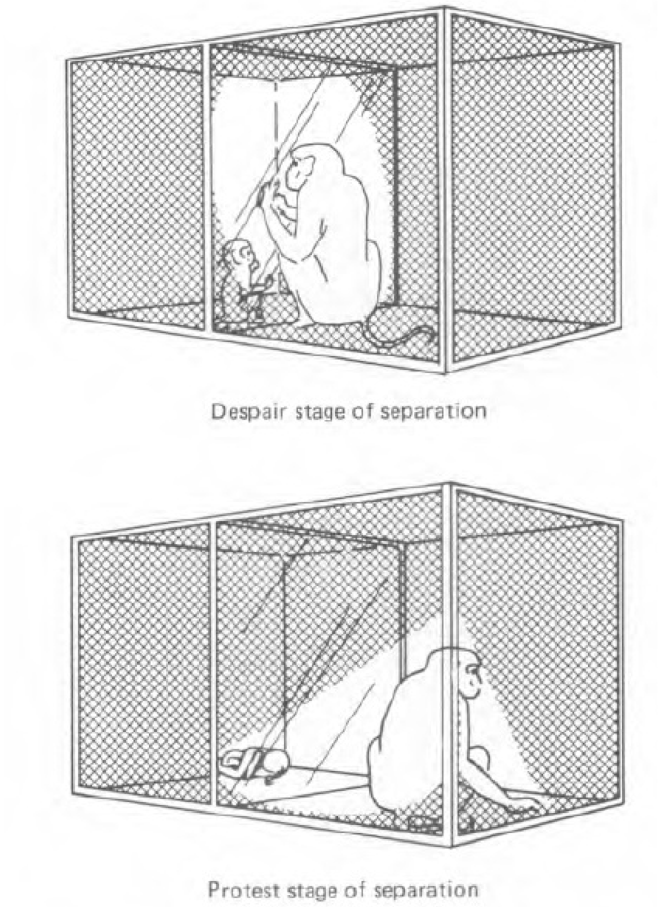


Figure 15-8.
Protest-despair reaction shown by rhesus infants following separation from mother.

In a series of studies Kaufman and Rosenblum compared the separation reactions of infant pigtail monkeys *(Macaca nemestrina*) and infant bonnet macaques *(Macaca radiata*). Their separation studies differed in several key ways from those previously described. In all their studies, subjects lived in groups consisting of several adult females, at least one adult male, and some adolescents. Separation was accomplished by removing a mother from the group, with her infant being left with the remaining members of the group. Separation from the mother in the pigtail infant study was done at age four to six months. The length of the separation was four weeks, after which the mother was brought back into the group. Reunion data were taken for three months.

Before separation bonnet groups were observed to spend long periods of time in passive contact with each other, in contrast to pigtails who did not make much physical contact except to engage in active social interactions like grooming, aggression, etc. Bonnet females even maintained their high degree of passive contact with other adult bonnets despite the birth and continued presence of their developing infants. In other words, bonnet mothers immediately returned to close contact with other females after delivery. Pigtail mothers, by contrast, were very reluctant to engage socially with others immediately following the birth of their offspring. As a result, bonnet infants spent time during the first months interacting with other adults in addition to their own mother. Pigtail infants spent almost all their time with their own mother.

During separation, i.e., removal of the mother from the group living situation, three of the four pigtail infants manifested similar reactions, which Kaufman and Rosenblum term “agitation,” “depression,” and “recovery.” One of the four infants displayed only the first and third stage. The agitation state (“protest”) was characterized by frantic searching movements, frequent cooing and loud screeching, and sporadic brief bursts of play activity. After twenty four to thirty-six hours the pattern changed. The pigtail infants sat hunched over with head down between legs, were inactive, and exhibited social withdrawal, retardation of movement, and sagging facial musculature. After five to six days the depressive phase (“despair”) began to lift, and over the next twenty-four days there was recovery alternating with other depressive periods. Upon reunion of pigtail infants with their mothers, there was a reassertion of the dyadic mother- infant relationship marked by clinging by the infant, protective enclosure by the mother, and increased nipple contact (“recovery”).

In contrast, when bonnet infants of comparable age had their mothers removed they exhibited nothing resembling the depression described above. It was found that there were increased interactions with other adults in the case of the bonnet macaques, and this seemed to provide adequate substitution for the mother during her absence. For example, each of the five infants in one study achieved sustained ventral-ventral contact with other adults during separation. Such contacts were never observed in the pigtail infants. In summary, the gregarious quality of group interaction in bonnets that manifested itself during the development of infants with their real mothers became even more evident when the mothers were removed.

These studies were important in terms of the different methodology used to accomplish separation, i.e., removal of the mother from a group living situation. They also highlighted the importance of cross-species studies with regard to the nature of maternal attachment, group attachment, and the effects of separation.

Hinde’s group focused its attention on the short- and long-term effects of short separations of rhesus macaques. The animals they studied lived in groups that consisted of a male, two to three females, and their young. Separation was accomplished by removing the mother from the infant’s sight. The age of the infants at the time of the original separation was thirty to thirty-two weeks. The length of separation was six days. The infants responded to removal of the mother with behavior similar to that described above for the pigtail infants. They initially exhibited “whoo” calls and were hyperactive. Then there followed a period of “depression,” including hunched posture, decreased activity, and social withdrawal. Upon reunion three of the four infants returned to the pre-separation level of activity within a week, but the fourth showed less activity up to four weeks afterwards. It was also noted that the less an infant had been in contact with his mother before separation, the less clinging he displayed on return and the more quickly he returned to behavior similar to that seen before separation. This study demonstrated that the nature of the pre-separation relationship affected the severity of the reaction to a six-day removal of the mother.

Several other aspects of early separation were studied by Hinde. He theorized that the length of separation was an important variable. Infants who had only a six-day separation experience displayed less depression of activity and recovered from it more rapidly than infants who had a thirteen-day separation or two separate six-day separation experiences. Hinde attempted to describe the source of individual variation among infants in terms of their reaction to separation and concluded that they resulted from differences in the nature of the mother-infant relationship itself.

These same infants were retested when they were twelve and thirty months old—that is, five months and two years after the original separation—to determine if there were any long-term consequences of the early separation experience. It was found that previously separated infants when confronted with strange objects in a strange cage were less likely to approach them than controls, particularly infants with two earlier separation experiences. Thus, the effects of a mere six-day absence from the mother were clearly discernible five months later. When tested two years later, the differences were less marked; however, the previously separated infants were significantly less active than the controls.

Mitchell et al. have studied the effects of forty-eight hour separations of *Macaca muatta* (rhesus monkeys) infants from their mother at three different age periods: two months, three and a half months, and five months. At all ages the infants exhibited signs of protest and despair even with such a short separation period. This same group also reported that six of twenty-four infants used in their study showed signs of “detachment” when reunited with their mothers. That is, the mother would try to retrieve the infants as usual, but the infants would screech and run away before finally establishing any ventral contact despite persistent efforts of the mothers to do so.

Preston et al. have extended the research on mother-infant separation to a non-macaque species *(Erythrocebus patas).* The subjects were six infant patas monkeys who underwent separation from their mothers when they were approximately seven months of age. During the three-week separation each was individually housed, except for one hour a day when the six of them were permitted access to each other. Thus, the infants underwent maternal separation, but had the opportunity to interact with each other during the separation period.

The immediate reaction to removal of their mother was reported to include frequent and intense cooing, frantic searching about, and wide-eyed scanning of the room. The reaction was most intense during only the first half hour, though they continued with high levels of visual searching for several days. The infants also stayed in close proximity to each other and their usual behavior, e.g., play, fell to low levels immediately after removal from the mother, though the infants were reported to have remained "alert." Immediately on reunion, infant-mother non-ventral gross contact and oral manipulation rose significantly. Mother-infant approaches—lip smacks and grooming—increased significantly but were short-lived. For example, four infants began peer play within fifteen minutes of their mothers' return.

Without doubt the mother-infant social relationship has received considerable attention. Mother-infant separation studies have been done many times with several species. The reactions of rhesus infants, at least, is surprisingly predictable, though there is certainly individual variation. Severance of the mother- infant bond in rhesus monkeys results in the development of a behavioral picture very similar to anaclitic depression. In some ways this may be a prototype for other depressions, and, if so, a variety of social, biochemical, and rehabilitative studies could be usefully undertaken. For example, are there any brain amine changes that occur coincident with this severe depressive syndrome? Is it reversible or preventable with antidepressants and/or tranquilizers? Are there any psychophysiological correlates? In part the usefulness of a model lies in these kinds of studies that may help elucidate the mechanisms underlying the abnormal behavioral state produced.

Peer Separation

The technique of peer separation has several advantages that make it a useful complement to mother-infant separation studies. In the case of peers, one is truly manipulating affectional bonds, and the separation reaction, when it occurs, can be viewed more as an emotional reaction than a survival or adaptive response. Although mother-infant separation disrupts an affectional bond, it is complicated by the infant's dependence on the mother in terms of survival. The ensuing response upon separation has been frequently viewed as the infant's attempt at adaptation for survival. There are also certain obvious practical advantages in terms of the comparative manpower required to effect the two kinds of separations. Also, from a research standpoint there was a serious question about the effects of disrupting peer bonds. Recent studies at Wisconsin indicate that severe reactions can indeed be elicited via separation from objects other than the mother.

In the initial peer separation study, infant rhesus monkeys, reared together from birth in a large living cage but without mothers as illustrated in Figure 15-9, exhibited a very marked reaction when separated from each other at three months of age. Separation was accomplished by placing each of four subjects individually in small cages for four days, then returning them to their home cage as a group for three days. This four-day separation, three-day reunion cycle was repeated weekly a total of twenty times, except for one six-week break between the twelfth and thirteenth separations. To each separation the animals exhibited a pro- test-despair reaction, with no adaptation to successive separations. High levels of infant- infant clinging characterized the seventy-two hours a week of reunion.

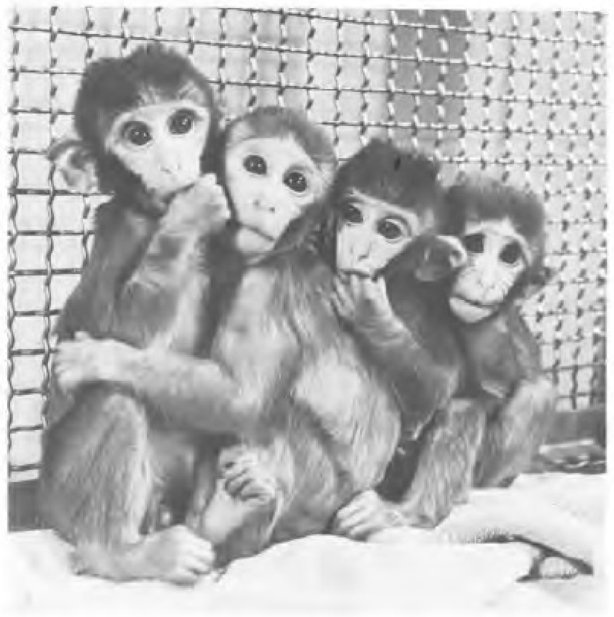


Figure 15-9.
Four “together-together” peers prior to undergoing peer separations.

That age is an important factor in determining the form that separation reactions take is indicated in the following peer-separation study. Male rhesus monkeys three years of age were studied before, during, and after a series of four separations from equal-aged peers with which they had formed close social bonds. Each separation lasted two weeks and was followed by a one-week reunion period during which the animals were housed together as a group of four. During each separation there were significant increases in locomotion and environmental exploration and decreases in passivity. Thus, the protest stage was evident; however, there was no suggestion of a “despair” stage as reported in younger monkeys.

An overview would indicate that separation studies thus far provide the best model for certain aspects of a specific syndrome—depression. More specifically the case for a monkey analogue for human anaclitic depression seems strong in the instance of mother- infant separation. The model is becoming sufficiently well-defined behaviorally so that brain-biochemical studies, psychophysiological studies, and both social- and biological-rehabilitative approaches can be tried as previously mentioned.

Great caution should be exercised however in viewing anaclitic depression as a prototype or model for all depression. That is why separation studies have recently been extended to older subjects. In contrast to the biphasic protest-despair reaction exhibited by younger monkeys upon separation, three year olds exhibit a uniphasic (protest) response without any evidence of despair. Theories about separation and depression that fail to take into consideration the age of the organism as a factor in determining response to separation are thus incomplete.

Efforts to produce a despair-like state in older subjects is continuing, and the reactions of several more age groups to separation experiences need to be determined. Also, the possible role of early separation experiences in predisposing a subject to more severe reactions to separations later in life is being pursued in monkeys.

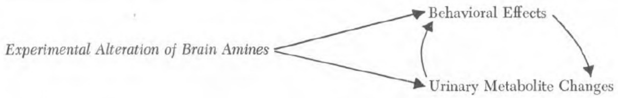
An Approach to Biochemical Studies in Primate Models

One of the reasons for creating primate models for behavioral disorders is to be able to do direct biochemical studies. It is hoped to study rhesus monkey subjects with induced syndromes of psychopathology by directly examining the relationship between brain neurotransmitters and the abnormal behaviors exhibited. This area of research is in its infancy and, therefore, this discussion is largely an outline of approaches now being used in primate models in order to examine the critical relationships among brain, behavior, and peripheral metabolism.

The following general approaches are proposed to illustrate how primate models might have value in our understanding of the biological substrates of abnormal behavior. They are outlined in Table 15-2.

Work in all these areas is currently underway. Despite external pressures to do so, it would have been premature to engage in biochemical studies until the behavioral aspects of primate models had been sufficiently well established, since the weakest link in most behavioral-biochemical research has been the behavioral aspect. It is also important to consider how to combine a social experiment, where animals either have to live or be tested together in groups and, simultaneously, have biological specimens collected. For instance, in several studies examining the relationship between brain biogenic amines and primate social behavior, the animals lived together in small groups. Urine collection was accomplished by pulling an animal from the group and putting him in a restraining chair. This technique seems less than desirable since there are considerable data that indicate severe and persistent effects on primate-group and individual social behavior following removal and reintroduction of members. If group social behavior is used as the major index of drug effect, a hopelessly confused situation ensues.

TABLE 15-2. **Use of Primate Models for Biological Studies**



1. Reserpine
2. α methyl-paratyrosine (AMPT)
3. Para-chlorophenylalanine (PCPA)
4. 6-hydroxydopamine
5. Others

Social Induction of Syndromes of Abnormal Behavior

Techniques	*Some Possible Studies*
Social Isolation	Brain Biogenic Amine Levels and Turnover
Separation	Urinary Amine Metabolite Excretion
Vertical Chamber Confinement	Steroids (Plasma and Urine)
	Cyclic AMP
	Others

Biological Rehabilitation

Induction Techniques	*Treatment Methods*
Social Isolation	Phenothiazines
Separation	Minor Tranquilizers
Vertical Chamber Confinement	Antidepressants
Learned Helplessness	Precursors
	Lithium
	Electroshock

One technique recently developed involves the use of special monkey metabolism cages where subjects can live individually and have urine collected by simply changing the type of pan beneath the cage. The subjects are adapted to a specifically designed playroom where group social testing is done. At least one twenty-four-to-forty-eight hour period each week is reserved for urine collection without social testing. Thus, a complete urine collection can be obtained while still getting meaningful group social data on the other days. This problem illustrates the difficulty of doing combined social and biological studies in nonhuman primates, yet this area is being continually developed and may prove to be a very productive area in the next several years as far as development and evaluation of primate models are concerned.

Experimental Alteration of Brain Amine Levels

This approach was suggested in 1969 as a method to evaluate the probable importance of biogenic amine metabolism in behavioral disorders, more specifically, depression. The methodology involves selected depletion of one or more of the biogenic amines and careful observations of the resultant behavioral changes in monkey subjects. In a broader sense this approach may permit one to learn more about the role of the monoamines—serotonin, dopamine, and norepinephrine—in the regulation of a variety of activities, e.g., appetite, temperature, sleep, alertness, motor function.

The first study using depletion techniques in monkeys involved the administration of reserpine to rhesus monkeys. Over the years the reserpinized rat has been hailed as an animal model of depression. Despite many biochemical advances that have resulted from studies of rats and cats given reserpine, the suggestion that the behavioral changes seen might model depression is open to serious question. Careful behavioral measures have not usually been included in such studies, especially measures of social interaction. A comparative study in monkeys, where more extensive social data could be obtained, was thus deemed desirable. Reserpine was administered once daily for eighty-one days by nasogastric intubation in a dosage of 4 mgm/kgm to three rhesus monkeys. The subjects were tested both in their home cages and in a playroom with three control subjects who had been given a placebo by nasogastric intubation. Reserpine caused significant decreases in locomotion and visual exploration and increases in huddling and posturing. A reserpinized rhesus monkey is illustrated in Figure 15-10. The reserpine monkeys were not asleep, just extremely inactive, and would respond to social stimulation, though they would not initiate any kinds of social behavior.

Reserpine, however, is a very nonspecific drug since it reduces levels of catecholamines and indoleamines in both the brain and periphery. There are agents that are more specific and there has been some limited experience with them in primate models.

Alpha-methyl-paratyrosine (AMPT) is known to inhibit the enzyme tyrosine hydroxylase thereby blocking norepinephrine synthesis. It has been given to two species of monkeys in two separate experiments.

In one study four rhesus monkeys were given AMPT in a dosage of 250 mgm/kgm and their social behavior was compared with four control subjects given a placebo. Both groups were tested in their home cages and in a playroom setting where social interaction was possible. AMPT-treated monkeys became inactive as exhibited by decreased locomotion, increased passivity, increased huddling, and a decrease in all initiated social behavior. Redmond et al. have reported similar findings in stump tail monkeys *(Macaca speciosa).* The latter research group has also attempted unsuccessfully to reverse the AMPT behavioral syndrome with L-Dopa or with DL,3,4-treodihydroxyphenylserine (DOPS), a compound that penetrates the blood-brain barrier and is decarboxylated directly to L-norepinephrine.

On the other hand para-chlorophenylalamine (PCPA), an inhibitor of serotonin synthesis, has been found by Redmond et al., as well as McKinney et al. to have little or no effect on the social behavior of monkeys despite very high-dose levels (up to 800 mgm/kgm). These results contrast sharply with the reported aphrodisiac quality and the increased aggression reported as a result of PCPA administration to rats and cats.

Figure 15-10.
Typical reaction of two-year-old rhesus monkey to daily reserpine (5.0 mgm/kgm) administration.

Both AMPT and PCPA have peripheral as well as central effects that are undesirable if one wants to study the relationship between brain amine depletion and behavior. In the spring of 1971, Wisconsin researchers, in collaboration with Drs. Breese, Prange, Howard, and Lipton of the University of North Carolina, began to study the effects of intraventricular 6-hydroxydopamine on the social behavior and on urinary amine metabolites in rhesus- monkey subjects.8 This study was preceded by considerable work in rats concerning the neuropharmacology of 6-hydroxydopamine. This work had shown it to be a compound that selectively destroyed central noradrenergic neurons without affecting the serotonergic system or peripheral noradrenergic system when given centrally. The goal has been to produce, experimentally, the defect postulated to be important in human depression, namely a central noradrenergic depletion, and to study the effect of this depletion on social behavior and on urinary metabolites. There have also been recent studies,55,82 of the effects of 6-hydroxydopamine in three *Macaca speciosa* (stumptail) monkeys on their social behavior and on urinary metabolite excretion patterns.

Preliminary reports of the behavioral changes observed following central noradrenergic depletion with 6-hydroxydopamine in both studies consist of decreased activity, decreased alertness, and a decrease in all initiated social behaviors. A monkey given intra- ventricular 6-hydroxydopamine is illustrated in Figure 15-11. The preliminary nature of these findings is emphasized because the number of subjects studied is still small and there remain many problems in terms of drug toxicity that must be solved before conclusions can be drawn.

An added dimension of the 6-hydroxydopamine studies, which may prove useful, are urinary studies. Many workers have long looked for a urinary marker that would reflect human brain metabolism, since urine is the easiest body fluid to collect in humans. A variety of metabolites including VMA, normetanephrine, and metanephrine have been shown to reflect mostly peripheral metabolism. Three-methoxy, 4-hydroxyphenylglycol (MHPG) has been postulated to be the only urinary metabolite that can be used, even in part, as a measure of brain metabolism.56,57 In the case of the monkeys referred to in the above studies, when brain norepinephrine was depleted this change tended to be reflected in a decrease in urinary MHPG. However, there was great individual variation and large numbers of subjects will be necessary to fully document the nature of this relationship. There was no change in any of the other urinary metabolites coincident with lowered brain norepinephrine. The use of primate models represents a new approach, but one which may prove increasingly useful in elucidating the biochemical mechanisms underlying depression and, in particular, the relationship between brain and peripheral metabolism.

Socially Induced Syndromes of Psychopathology

The major social-induction techniques that are currently available are social isolation,

separation, and vertical-chamber confinement, all of which have been previously described in this chapter. The biochemical effects of each of these induction techniques can now be systematically studied and this research is currently underway. Included are urinary studies, plasma studies, and brain-tissue studies of monkeys who exhibit syndromes of abnormal behavior induced by social means. Steroid metabolism, catecholamine, indoleamine, and cholinergic substrates of these behavioral syndromes are being studied in an effort to relate social stress to specific biological changes.

Figure 15-11.
Social withdrawal and huddling posture of rhesus monkeys following intraventricular administration of 6-hydroxydopamine.

Biological Reversal of Abnormal Behavior

In this phase of research with primate models, after a syndrome is induced, either socially or biologically, rehabilitative methods are being employed to reverse the abnormal behaviors. In this regard, a study using chlorpromazine was summarized earlier in the chapter. As far as psychopharmacology is concerned, primate models have the potential for eventually providing a better method of pre-clinical psychotic or antidepressant drug trials than is now available. Also important, however, are the possible implications for a better understanding of the psychopathological state being treated.

Somewhat outside the scope of this chapter, but of importance, is the recent work using monkeys to study the effects of methamphetamine and “speed” usage, the recent use of the chimpanzee as an animal model for alcoholism, and the use of primates to study heroin addiction. In these areas the primate models may also provide key breakthroughs in our understanding of the disease state being modeled.

Perspectives

Experimental psychopathology in nonhuman primates is at the same time a new and an old field. Historically it has suffered from a too loose use of clinical terms without adequate behavioral descriptions and the exclusive use of conditioning techniques. As a result clinicians have been uninterested in the field. This lack of interest is surely overdetermined, but hopefully it is changing somewhat as the field itself matures and psychiatrists become increasingly aware of the potential relevance of many fields of inquiry.

The major areas of interest for psychiatrists in primate models probably include the development of kinds of attachment behavior, the effects of social isolation, separation studies, the possible experimental simulation of learned helplessness, and various biological approaches being developed. It is in these areas that work has been and is being conducted that has potential clinical usefulness. Investigators may be close to developing a viable animal model for depression that may facilitate a more comprehensive understanding of this particular syndrome and enable studies to be done that are currently impossible to perform utilizing human beings. The rest of medicine has long used nonhuman primates to advance knowledge about their fields and there is no logical reason why psychiatry should not do the same.

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Notes

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