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ANIMAL MODELS
Group Report

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INTRODUCTION

The opportunity to bring together a multidisciplinary group of scientists to consider the topic of animal models and their use in research on depression was unique. This report represents the deliberations of our group over a period of several days and should be considered as complementary to the four data-based papers dealing with details of specific animal model systems.

MODELS — SOME GENERAL CONSIDERATIONS

As an introduction it may be useful to consider in a limited way issues related to some general properties and purposes of models, emphasizing their usefulness in studies relating to the origin of depression. The general issue of animal models is, of course, a large topic that has been reviewed elsewhere, and a detailed discussion of models and the process of modeling need not be considered here.

A Model of Models

We might consider first that there is "the model," which must be considered in proper perspective with what is being modeled, in this case human depression. The need for the model is in part due to the fact that relatively little is known about the social, environmental, and biological basis of the human disorder, and many features of the diagnostic framework are controversial as

well. Models can be used to address a variety of issues systematically, including social, environmental, and biological issues, but it is of utmost importance that models themselves be formulated and used with a clear understanding of the origin of the model, its logical relationship to what is being modeled, and the purpose or goal of research with the model system.

These three concepts can be viewed in a dimensional structure (see Fig. 1). *Origin* in this context refers to the fundamental rationale for establishing a research paradigm in animals ranging from systems designed to test a specific preexisting theory (theory driven) to those that are based on an operation which is known to have behavioral and/or biological efects of importance but for which there is no explanation (operation driven).

The *logical relationship* which the model bears to what is being modeled is a dimension which has two extremes. One end of this dimension is homologous, in which case the model is considered for all practical purposes the same as that which is being modeled, with equivalence of structure, function, and underlying mechanisms based upon a common phylogenetic history in the animal model and what is being modeled. The other end of this logical dimension is analogous, in which case the model may be similar in form or function but is not based upon common underlying mechanisms or a common evolutionary history.

The *purpose* of the model may be to reflect the effect of a restricted set of causal relationships identified in advance (correlative) or to allow the exploration of other facets of a complex biological system, not all features of which may be understood (heuristic). Any particular model may be characterized on all three of these dimensions.

Factor		**Dimensions**
Origin	Theory Driven	Operation Driven
Logical Relationship	Homologous	Analogous
Purpose	Heuristic	Correlative

FIG. 1 — Schematic representation of a dimensional structure of animal model systems.

The terms homology and analogy should perhaps be considered in some depth, as a fundamental understanding of these two concepts is necessary for the proper interpretation of data resulting from animal model systems. Homology assumes both similarity in function and commonality in evolutionary mechanism. The advantage of homologous models is that one can make the assumption that the phenomena being studied in one species is very similar to that in the other species, and that what is learned from, in this case, the model can be directly applied from one species to the other.

Difficulties with homologous models include the fact that it is necessary to establish that the phenomenon being investigated is indeed common across the two species, one of which is being used as a model, and to establish that the phenomenon has not been significantly influenced by processes of speciation subsequent to evolutionary divergence.

Analogy, by comparison, assumes only common function and not common ancestry or mechanisms. An advantage of analogous models is that one can compare functional behaviors in species which have undergone convergent evolution, and the behaviors being compared need not be similar in form or underlying mechanisms, just similar in function. Examples might include precopulatory behavior and certain responses to stress.

The potential disadvantages of analogous models are that the functions being studied may differ in different circumstances across species, and an analogous behavior which serves one purpose in one species may serve multiple functions in another species. Similarly, what is learned about mechanisms in one species may have little relationship to mechanisms underlying similar behaviors in another species.

Some General Advantages of Animal Models

Studies of mechanisms

One clear advantage of animal models is that they permit the direct study of mechanisms and drug effects in a way not possible in man. They can be used, for example, to localize areas of potential central nervous system (CNS) dysfunction, utilizing invasive techniques not appropriate for clinical research. Additionally, they can facilitate studies of in vivo pharmacology in humans. Such studies may be done in man with positron emission tomography (PET) scan techniques, but only if preliminary animal studies identify where one should first look.

A problem in clinical depression is that classification schemes are "dirty," i. e., confusing and unclear. Similarly, many of the antidepressant drugs that are therapeutically efficacious can be seen as "dirty" in terms of having diverse effects possibly unrelated to their main therapeutic effect. If research questions are clearly defined in animals, these two problems may be in part overcome. In this case, "carefully" means asking questions that can be reasonably defined, stemming from the careful definition of possible etiological features that ultimately arise from clinical studies and clinical features amenable to pharmacological modification.

One important advantage of animal model research is that it is much easier to do well-controlled true prospective studies. This is very important for issues having to do with event-related research and questions of vulnerability and outcome. It is both difficult and expensive to incorporate proper prospective designs in clinical paradigms.

The issue of individual variability in response to various stresses (e. g., separation) can also be systematically studied in animal model systems. This issue is of paramount clinical concern, for it is well-known that not all individuals are equally affected by the same experience, stress, or biological and/or psychosocial challenge. Animal models permit systematic assessment of (and control of) biological and/or experiential contributions to such variability in a manner not possible in clinical research paradigms.

Even if one is not particularly concerned with what a particular change in animal behavior looks like phenomenologically, if it responds (in some way) to the same set of drugs that alters human behavior, some clinically useful data on pharmacological behavioral interactions may result. Additionally, certain events, such as separation, may have effects more widerspread in animals than the clinical phenomena they have been designed to model. Thus, they may have heuristic value in more diverse areas.

It is almost certain that there can be no one single animal model of human clinical depression; indeed, it is probable that one model can represent only a portion of the depressive spectrum or syndrome. In fact, the ability to study facets of the syndrome in isolation, e. g., single symptoms, may represent a real advantage.

Our group discussed the importance of considering at all times the ethical issues involved in animal experimentation when studying, developing, or modifying animal models. The fact that animal experimentation is free of

certain ethical issues that apply to human research does not free the experimenter from carefully examining all animal model paradigms with respect to minimizing discomfort and maximizing information obtained.

Studies of developmental determinants

Models can be especially helpful in studying developmental determinants of altered behavior, since many aspects of development can be controlled, including experiences that occur during development. This is an area of considerable theoretical importance when dealing with the affective illnesses, as developmental determinants such as loss have frequently been implicated as having etiological or outcome relevance. Again, these paradigms can only be studied in animal model systems.

There is a close and obvious relationship of such paradigms to life-event research as well. This area, of considerable importance to several areas of medicine in addition to psychiatry (especially depression), can benefit from well-controlled prospective studies and accurate outcome measures that are possible with animal model paradigms.

Of further developmental significance, models, such as separation, may be used to study coping responses and their influence in the development of lifestyles as well as sensitization to later insults.

EXAMPLES OF ANIMAL MODELS USED IN STUDYING DEPRESSION

Four animal model systems that have been most useful to date in studies related to depression have included separation models, drug-induced models, stress, and learned helplessness. Each of these is considered in detail in terms of its historical background and development, how the model actually works, and some of the major findings that have emerged in studies using such models as described in the individual papers in this volume. Thus, they will only be briefly reviewed here. An additional set of models, called non-imitative, will additionally be mentioned, as they may have some relevance to depression.

Separation Models

Studies involving various types of social separation paradigms have been performed in a number of species of animals. While it is probably fair to say that the results of experiments involving nonhuman primates have been most directly relevant to depression, studies in other species have provided important knowledge about the nature of the attachment system whose disruption is presumed to underlie the phenomena seen in separation studies.

Primate research has demonstrated that separation-induced depressive behavior can occur at all ages in response to several types of separation paradigms, including juvenile and adult peer separation, nuclear family separations, and separations of adults from close friends ((4, 16), and see Kraemer et al., this volume). While some adult monkeys' separation-induced depressive reactions remit almost immediately upon reintroduction to social groups, suggesting a time frame quite different from that of human depressive disorders, other separation-induced behavioral depressions have a much slower time course in both development and response to reestablishment of social ties (e.g., (21)).

The depressive behavioral response seen in separated monkey infants is quite similar to the syndrome of "anaclitic depression" described in human children (29): it can be conceptualized as an adaptive mechanism, as well as a maladaptive response to the disruption of an attachment bond. In the former case, the initial protest stage of the two-stage protest-despair or agitation-depression reaction is seen as an adaptive response, similar to a fight-flight type reaction, the purpose of which is to attempt to regain the mother. The second, or despair, reaction is viewed as a manifestation of conservation withdrawal, a behavioral reaction designed to conserve resources and prevent exhaustion (9). Alternatively, the second despair or depressive stage may be viewed as a behavioral and physiological state that may be intrinsically maladaptive with an associated morbidity and mortality. These two interpretations need not be mutually exclusive and may indeed coexist, with a maladaptive outcome of the depressive or despair stage representing a failure of the adaptive conservative withdrawal mechanism.

There is evidence that the behavioral responses to separation in both young and older monkeys, including mother-infant separation, peer separations, and adult separations, may be responsive to tricyclic antidepressant medications (5, 30).

These considerations address the response to separation in terms of biologic response mechanism. It is also necessary to view these responses in terms of their psychological aspects. Situations involving flight-fight (a biological response system) are situations of danger, a psychological concept that the developing organism soon achieves in such situations. Likewise, the corresponding response is soon experienced as anxiety, so that both the situation and the response become psychobiological. Similarly, the original biological conservation-withdrawal response, invoked when the functionally helpless organism can no longer cope actively, soon achieves psychological significance

as an experienced state of painful despair and helplessness, so that the organism henceforth tries to avoid repetitions, e.g., not getting separated again, i.e., reinforcing patterns of closeness. The adaptive functions thus attach to the affects as well: anxiety becomes a signal of danger and dysphoria a signal of impending helplessness, calling forth attempts to cope at all levels of organismic function, i.e., a biopsychosocial response. With such a perspective, it becomes possible to view these psychobiological responses to separation as the core phenomena of anxiety and depression, respectively, and to seek their derivatives in clinical disorders (8). For example, Klein and McGrath (this volume) suggest that panic attacks are based on the core flight-fight separation anxiety response, with an originally adaptive response appearing in maladaptive form because of a lowered threshhold (genetically predisposed?). Similarly, clinical forms of depression may arise maladaptively when the core conservation-withdrawal despair response is inappropriately triggered, also perhaps because of a genetically-disposed lower threshhold. (As we know, it may also be triggered by a repetition of the early object loss.) From a modeling viewpoint, these core separation responses may be studied biologically for clues to the physiology and biochemistry of the clinical disorders.

Drug-induced Models

There are a number of drug-induced models of behavioral depression in animals that have heuristic value and are important from pharmacological viewpoints. These are reviewed by Porsolt (this volume). The best known is reserpine-induced catalepsy, ptosis, hypothermia, and sedation, which is valuable as an initial screen for antidepressant effectiveness. This model, however, does tend to select some compounds that are not antidepressants and may miss some that are (1, 2).

AMPT produces a state of behavioral depression in monkeys at doses that are without other behavioral effects, the mechanism of which apparently is related to the blocking of norepinephrine synthesis. While AMPT appears to potentiate the depressive behavioral response to separation, this model has not been widely used in pharmacological drug testing (12).

A third type of drug-induced model is behavioral depression resulting from withdrawal of amphetamines. This behavioral response is prevented by imipramine, amitriptyline, pargyline, and mianserine (11).

A fourth type is the decreased motor activity induced by clonidine, an effect probably resulting from a decrease in the release of norepinephrine through a presynaptic inhibitory mechanism (24).

Finally, there are the sedation and catalepsy induced by neuroleptics, which may be antagonized by antidepressant drugs (31). Antagonism of neuroleptic effects are not as widely used as reserpine models.

Stress-induced Models

Stress-induced models, considered in detail by Katz (this volume), have a long history. During the past ten to fifteen years such models have been investigated as they may relate to depression. A variety of stresses, including swimming in cold water and electric shock, have led to behavioral changes interpreted as possibly being "depressive" in nature as well as suggesting specific types of interference with learning. Some of these behavioral changes include loss of personal caretaking, apparent motivational changes, and alterations in social behavior. Such stress-induced alterations are frequently responsive to drugs that have been effective in the treatment of depression, such as certain of the MAOI's and tricyclic antidepressants.

Learned Helplessness

A comprehensive review of the history and current status of learned helplessness models and their imputed mechanisms can be found in the paper by Hellhammer (this volume).This interesting behavioral phenomenon, originally described by Seligman (25), has an important historical antecedent in that psychiatrists have long considered the concept of "helplessness" a core phenomenon of depression. This antedated considerably the more formal learned helplessness strategies of the recent past, which are interesting, however, because of their apparent relationship to affective disorders on several levels. Basically the procedure consists of placing animals in situations in which they have no control over the occurrence of repeated aversive events. They seem to learn that there is no relationship between their response and the outcome and develop behavioral deficits characterized by diminished motivation, impaired future learning, and emotional disturbances.

Non-imitative Models

Non-imitative or empirical models are of use primarily in pharmacology as screening procedures and include phenomena such as deficits in passive avoidance learning in bulbectomized rats, muricide behavior in rats, amygdaloid-induced convulsions, and REM sleep changes in cats. These are discussed in greater length by Porsolt (this volume).

USEFULNESS AND LIMITATIONS OF CURRENT MODELS OF DEPRESSION

Separation Models

Separation models have been shown capable of reproducing in animals a behavioral phenomenology very similar to that of human grief following a similar manipulation, and they have demonstrated that a complex set of physiological and immunological changes may accompany this syndrome (22, 23). While there are yet little relevant comparative data in man, the extent to which similar phenomena may exist is testable, and experiments on animals can be designed to elucidate the mechanisms underlying the behavioral and physiological changes.

Separation models have also provided data on the importance of social support, demonstrating how such support may palliate or otherwise influence the response to loss. Separation paradigms are ideally suited to this type of research, for the nature and degree of social support can be controlled.

Additionally, separation work in nonhuman primates supports "by inference" the notion that a psychological state of helplessness is involved in depression.

Finally, separation models have demonstrated the role of the separation experience in sensitizing the organism to later insults.

Drug-induced Models

Despite the inherent limitations of drug-induced models, they have been highly useful, in particular the reserpine model, in the discovery of new antidepressant compounds, mostly of the tricyclic or MAOI type, but also including atypical agents such as bupropion, nomifensine, and viloxazine.

Insofar as one can develop a good drug-induced model of depression, it may also be possible to identify a potentially "depressogenic" drug and thus avoid its utilization in man.

As in other areas, the question of genetic vulnerability of selected animals is likely to be shown important in drug models, as certain genetic subtypes may be more affected by certain drugs than others. At present, genetic selection experiments for special drug susceptibility have not yet been reported, but the model is well suited for such research strategies.

Stress Models

Stress models have made and are making contributions in several areas. They can provide basic physiological information about the various effects of stress in animals and, to the extent to which the phenomena are homologous, in man.

Insofar as stress may be an etiological or aggravating factor in depression (a relationship not yet clear), such models may be able indirectly to tell us something about the origins of depression. There are some stress paradigms in which cortisone does not increase; these strategies may be able indirectly to tell us something about panic attacks that do not show changes in cortisone or norepinephrine. Stress models may prove to be useful as drug-screening paradigms providing evidence of new compounds that may act as antidepressants. Finally, these models are useful for studying the biology of stress per se, a fundamentally important issue, and one that can be independent of depression.

The physiological changes which underlie the altered behaviors in stress models have been, to date, attributed in a large part to alterations in norepinephrine. There is some evidence of genetic vulnerability, in that those animals who are predisposed to lower central norepinephrine levels may be more vulnerable. Further evidence suggests that there are strain differences in the response of animals to forced swimming and in the effects of imipramine on the resulting behavioral syndrome (20). These models are especially amenable to neurochemical and/or endocrinological evaluation and are well suited to genetic studies. Some stressed rats exhibit an increase in the primary adrenocorticoid, corticosterone. This endocrine profile may be analogous to Cushing's disease in humans.

Learned Helplessness

The extent to which learned helplessness paradigms have yet to make direct contributions to our understanding of the origins of depression is controversial. In a sense, our understanding of learned helplessness in animals and man may proceed in parallel, for this is one of the few experimental paradigms created in animals that has subsequently been replicated in humans. Learned helplessness may prove to be helpful in an interactive way, permitting investigation of the uncoupling of the control and predictability factors, with implications in the areas of both cognitive therapy and psychodiagnostic approaches concerning locus of control phenomena in man. To what extent the paradigm will be useful in drug screening is not yet clear. A possible important point of concurrence is that certain depressive patients and animals exhibiting learned helplessness appear to exhibit analgesia with higher pain thresholds. The development of analgesia in animals exhibiting learned helplessness would suggest a parallel to the conservation-withdrawal helpless response of separated animals and point to the studies of common underlying mechanisms (see Other Model Systems, below). The potential for designing experiments to study mechanisms underlying this paradigm is significant.

An important potential contaminant of the general area of learned helplessness is the fact that the term itself is emotion-laden with connotations above and beyond what might be empirically demonstrated, and there are questions as to whether such concepts, at least in regard to man, are culture specific.

In dealing with states such as helplessness, it is important to distinguish between helplessness as a description of an organism's functional status and helplessness as an experienced internal state. Both the conditions and the frames of reference are different, and our ability to assess the internal experience of a nonhuman animal is limited.

Nonetheless, the learned helplessness phenomenon results in both behaviors that can be defined in an objective way as well as evidence of specific pharmacological responsiveness, and thus it is an interesting model with heuristic value intrinsically independent of its relationship to depression.

Non-imitative Models

The non-imitative models have yet to be directly related to clinical depression as we know it. It appears, however, that they may provide a mechanism for investigating the operation of brain systems whose functions have been related to regulation of affective behavior. In this regard, it is interesting that at least three of the non-imitative models, i. e., muricide behavior in rats, amygdaloid convulsions, and the bulbectomy syndrome, implicate limbic system function, in particular the amygdala (6). Altered amygdala activity has also been suggested (although not empirically demonstrated) as being involved in the response to separation in monkeys (indeed, it has been suggested that attachment and affiliative behavior generally is mediated by limbic, especially amygdala, and related orbito-frontal cortical regions (10)), and a small group of depressed patients (who probably have a partial complex seizure disorder) respond to carbamazine (Tegretol). These various data suggest limbic involvement in affective disorders, and thus such models may be heuristically valuable from this standpoint as well. Other animal model systems could be used to specifically test limbic mechanisms in animals or to help design in vivo pharmacological experiments (using PET scanners) in man.

Other Model Systems

While we have not directly considered the area of animal models of circadian systems and other biological rhythms in this report, a great deal of current work has to do with the regulation of biological rhythms. These experiments utilize a variety of animal models and many different species. Fundamental

increases in our understanding of the neurobiology of biological rhythms are emerging from this work.

There is also increasing evidence from a number of laboratories implicating disturbances in the control of biological rhythms as being importantly related to affective disorders. Although the nature of such relationships is not yet clear, it seems likely that further work on mechanisms underlying the regulation of such rhythms performed in animal model systems may be of considerable ultimate clinical utility in the area of depression.

One avenue that can now be pursued with animal models is the attempt to understand the neuro-anatomical pathways involved in specific behavioral changes. In the learned helplessness model, an outline of a proposed pathway is available from the work of Sherman and Petty (26, 27). This pathway suggests that norepinephrine is involved in the hippocampus (and only the hippocampus). A recent study by Johnson et al. (7) looked at the effect of learned helplessness training on α and β receptors in several brain regions and found that training altered β receptors only in the hippocampus, and that neither the α_1 nor α_2 receptor is altered in any other brain region. The hippocampal β receptor density is increased by about 50% after learned helplessness is induced; this increase appears steady for the period of helplessness. Upon treatment with imipramine, the β receptor level comes back to control or pre-training levels. The change in the CNS receptors is parallel with behavioral changes, showing that learned helplessness training can cause reversible CNS alterations. To determine if the receptor system is directly responsible for behavioral changes, an attempt was made to disassociate the receptor changes and behavioral changes temporarily. If animals are allowed to revert from helplessness spontaneously, at the point of behavioral change the β receptor density is still high, suggesting that this system correlates with but does not directly drive the behaviors. Similar work is underway determining the neurochemical substrate of the rather simpler "behavioral despair" model using both pharmacological (19) and neurochemical techniques (17). These are examples of the neurochemical insights which can only come from work on animals.

The learned helplessness model has also shed light on the complex relationships between the opioid system and the hypothalamic-pituitary-adrenal cortex system. The analgesia appears to be based on opioids yet is dependent on corticosterone (13). Further work should help clarify these complex functions of the neuroendocrine systems and their relationships to depression.

FUTURE DIRECTIONS OF ANIMAL MODEL RESEARCH IN DEPRESSION

In this section we consider the general area of future directions for animal model research in depression, including such topics as to what extent it might be reasonable to expect that animal model systems can tell us more about the origin of depression, how experiments might be designed to achieve these goals, and what new models and/or techniques for evaluating or measuring models would be helpful in achieving these aims. Several areas will be considered in turn.

Modeling Core Signs and Symptoms of Depression

Attempts to design models to specifically evaluate core signs and symptoms of depression, as well as eliciting events and functional mechanisms, would be of considerable potential benefit. This is a complicated area insofar as there is general and widespread disagreement on what constitutes the core signs and symptoms of depression (an area in which experts do not agree).

One approach is to break depressive disorders into specific components as was done by Carrol (this volume). After considerable discussion, our group finally made the following list that might be considered as representing core symptoms:

a. General loss of interest
b. Anhedonia
c. Disturbed psychomotor regulation
d. Sadness
e. Sleep disturbances
f. Appetite disturbances
g. Cognitive changes
h. Disturbances of biological rhythms

Obviously such a list can be neither comprehensive nor exhaustive, but it does provide a starting point from which specific animal model experiments can be designed to test to what extent such systems are disturbed and what mechanisms may underlie such disturbances. Experiments designed to evaluate mechanisms underlying such changes may have heuristic import in our consideration of an etiology of depression.

Spontaneous Depression

Most current animal models of depression include behavioral and physiological changes arising in response to some specified intervention or treatment. A

model system in which the event appeared spontaneously would be useful in light of the fact that many clinical depressions appear in such a fashion.

Comparability Studies

It would be most helpful if we better understood what was common among current different animal model systems, especially as regards underlying mechanisms. This would clearly improve the ability to correlate them in a meaningful fashion to human depressive disorders and would facilitate our understanding of similarities and differences in drug responses, for example, across diferent models.

Development of Genetic Susceptibility

Several, if not all, current models of depression could be examined from a genetic standpoint, with attempts being made to selectively breed for greater or lesser responses to the stresses, experiences, or drugs used to induce the modified behaviors. Such genetically-determined differences would be most useful in facilitating our understanding of mechanisms underlying the responses. To the extent that the models are closely related to aspects of human depression, such studies would be directly relevant to our understanding of human mechanisms.

Models of Cyclic or Periodic Affective Disorders

Animal model systems studied to date are notable for the absence of models relevant to bipolar disorders. Models involving intraventricular injection of 6 OH dopamine in rats produce sustained hyperactivity that might in some ways resemble mania, but it is not a cyclic disturbance. Similarly, hyperactivity induced by the simultaneous administration of chlordiazepoxide and amphetamine varies in intensity only with varying drug doses, and not autonomously. A few model systems possibly relevant to this area have been developed utilizing intracranial self-stimulation on an intermittent basis; their feasibility is not clear, however. Indeed, there is some evidence that intracranial self-stimulation may itself act as an antidepressant and terminate or prevent the development of experimental depression (Katz, personal communication). Other experiments could study the effects of modification of circadian rhythms such as the sleep-wakefulness cycle. Preliminary findings in rats, for example, have suggested that selective REM sleep deprivation has similar effects to imipramine in the "behavioral despair" model (18).

Thus, a model system involving spontaneous alteration or rhythmicity of a type that could be related to bipolar disorders (or periodic depression) would be most useful, especially if it included a genetic component.

One possibility for a model of mania stems from the spiraling nature of mania and an old observation of Huxley's that behavior is both self-inhibiting and self-stimulating. What is needed, conceptually, is a method for positive feedback of a hedonically positive behavior, or the elimination of negative feedback.

Utilization of Other Species

Most current models use rodents or, in the case of separation studies, nonhuman primates. While dogs were involved in the original descriptions of learned helplessness, they are currently rarely used as research subjects. They are, however, animals that clearly exhibit what appear to be well-defined affective behaviors, including both sadness and joy. It would be appropriate to evaluate the extent to which other species, including dogs, might serve as model systems relevant to affective disorders.

Another area that could prove fruitful is the study of "depressive resistant" species. Whether such mammalian species exist is unclear, and the utilization of non-mammalian species is fraught with the difficulty that such models would most likely be merely analogous and not homologous, thus their utility as tools for investigating mechanisms in man would be severely compromised. Indeed, there are questions about the degree of homology of attachment systems within mammalian species per se.

New Techniques for Studying Animal Models

Specific suggestions included utilization of PET scan and similar imaging techniques, neuromagnetic recordings, new push-pull cannulas to sample localized brain regions, improved electrochemical methodologies to permit in vivo monitoring of neurotransmitters in unrestrained animals, and possibly the development of more refined and discrete lesioning techniques. Technological advances such as these would greatly facilitate research aimed at defining the basic neurobiological mechanisms that underlie current and future animal model systems.

New Theoretical Perspectives

A theoretical conceptualization of model systems from a somewhat broader perspecitve could prove to be helpful. If, for example, the despair phase seen in separation studies in nonhuman primates were, in fact, to represent an adaptive neurobiologically-based and -mediated evolutionary mechanism, one could anticipate its being released at times inappropriately, thus resulting in syndromes similar to certain depressive disorders.

Data stemming from research on starvation by Southwick (28) as well as more recent studies by Margules (14, 15) on a proposed opioid-related adaptive mechanism called into play on the anticipation of famine suggest that a primitive biological system, perhaps antedating conservation-withdrawal, may be present in higher animals. Many of the symptoms of depression involve changes in appetite and food-related behavior, and in young primates a syndrome very much like the depressive response to separation can be induced by a relatively short period of food deprivation. The relationship between DST response and weight loss in depression remains an area under investigation. It is possible that the role of food intake and regulation of appetite may be more central to depression than is generally realized. Should an underlying basic system such as that described by Margules exist, its inappropriate activation could be related to the onset of depressive disorders.

Models Involving Autonomy

A characteristic feature of many clinical depressions is that, once established, they continue and are not reversed, even if obvious precipitating factors are removed. This process is called autonomy. There has been relatively little evidence for autonomy in most of the animal models of depression described to date, although certain of the persistent motivational deficits in learned helplessness and long-lasting physiological changes seen in separated monkeys may at least indirectly address this issue. It would nonetheless be helpful to have a model system in which this phenomenon is more unequivocally present, both from the standpoint of increasing the validity of available models and of providing a mechanism for investigation of the process of autonomy per se.

Bridging the Communication Gap

One future task should be to bridge the communication gap between psychology and neuroscience, using more systematic approaches in which animal models might play an important role. Such concepts should be built on the basis of our current knowledge in neuropsychology and allow us to generally transfer information from psychology to brain sciences and vice versa. A model of such bridging of the communication gap is discussed by Hellhammer ((3), and this volume).

SUMMARY

In summary, then, while our treatment of animal models as they relate to the origin of depression cannot be considered exhaustive, we hope that it is comprehensive from the standpoint of addressing most of the major contemporary

issues in this area. It is hoped, furthermore, that the discussion of future directions of animal model research in depression will prove to be useful to investigators concerned with these topics, and that it may have a beneficial influence on research in these areas.

REFERENCES

(1) Colpaert, F.C.; Lenaerts, F.M.; Niemegeers, C.J.E.; and Janssen, P.A.J. 1975. A critical study on Ro 4–1284 antagonism in mice. Arch. Int. Pharmacodyn. **215**: 40–90.

(2) Gouret, C.; Mocquet, G.; Coston, A.; and Raynaud, G. 1977. Interaction de divers psychotropes avec cinq effets de la reserpine chez la souris et chez le chat. J. Pharmacol. Paris **8**: 330–350.

(3) Hellhammer, D. 1983. Gehirn und Verhalten. Muenster, FRG: Aschendorff Publishing Co.

(4) Hinde, R.A., and Spencer-Booth, Y. 1971. Effects of brief separation from mother on rhesus monkeys. Science **173**: 111–118.

(5) Hrdina, P.D.; von Kulmiz, P.; and Stretch, R. 1979. Pharmacological modification of experimental depression in infant macaques. Psychopharmacology **64**: 89–93.

(6) Jalfre, M., and Porsolt, R.D. 1982. Antidepressants and the limbic system. **In** Psychopharmacology of the Limbic System, eds. E. Zarifian and M. Trimble. New York: Wiley, in press.

(7) Johnson, J.; Sherman, A.; Petty, F.; Daylor, D.; and Henn, F. 1982. Receptor changes in learned helplessness. Soc. Neurosci. Abst. **8**: 392.

(8) Kaufman, I.C. 1977. Developmental considerations of anxiety and depression: Psychobiological studies in monkeys. **In** Psychoanalysis and Contemporary Science, ed. T. Shapiro, pp. 317–363. New York: International Universities Press.

(9) Kaufman, I.C., and Rosenblum, L. 1967. The reaction to separation in infant monkeys: Anaclitic depression and conservation-withdrawal. Psychosom. Med. **29**: 649–675.

(10) Kling, A.; and Steklis, H.D. 1976. A neural substrate for affiliative behavior in nonhuman primates. Bain Behav. Evol. **13**: 216–238.

(11) Kokkinidis, L.; Zacharko, R.M.; and Predy, P.A. 1980. Post-amphetamine depression of self-stimulation responding from the substantia nigra: reversal by tricyclic antidepressants. Pharmacol. Biochem. Behav. **13**: 379–383.

(12) Kraemer, G.W., and McKinney, W.T. 1979. Interactions of pharmacological agents which alter biogenic amine metabolism and depression. J. Affect. Dis. **1**: 33–54.

(13) MacLennan, A.J.; Drugan, R.C.; Hyson, R.L.; Maier, S.E.; Madden, J.; and Barchas, J.D. 1982. Corticosterone: A critical factor in an opioid form of stress-induced analgesia. Science **215**: 1530–1532.

(14) Margules, D.L. 1979. Beta-endorphin and endoloxone: hormones of the autonomic nervous system for the conservation or expenditure of bodily resources and energy in anticipation of famine or feast. Neurosci. Biobehav. Rev. **3**: 155–162.

(15) Margules, D.L. 1981. Opioid and anti-opioid actions in the survival and reproduction of individuals. **In** Theory in Psychopharmacology, ed. S.J. Cooper, vol. 1, pp. 177–195. New York: Academic Press.

(16) Mineka, S., and Suomi, S.J. 1978. Social separation in monkeys. Psychol. Bull. **85**: 1376–1400.

(17) Miyauchi, T.; Kitada, Y.; and Satoh, S. 1981. Effects of acutely and chronically administered antidepressants on the brain regional 3-methoxy-4-hydroxy-phenylethyleneglycol sulfate in the forced swimming rat. Life Sci. **29**: 1921–1928.

(18) Porsolt, R.D.; Anton, G.; Blavet, N.; and Jalfre, M. 1978. Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur. J. Pharmacol. **47**: 379–391.

(19) Porsolt, R.D.; Bertin, A.; Blavet, N.; Deniel, M.; and Jalfre, M. 1979. Immobility induced by forced swimming in rats: effects of agents which modify central catecholamine and serotonin activity. Eur. J. Pharmacol. **57**: 201–210.

(20) Porsolt, R.D.; Bertin, A.; and Jalfre, M. 1978. Behavioural despair in rats and mice: strain differences and the effects of imipramine. Eur. J. Pharmacol. **51**: 291–294.

(21) Rasmussen, K.L.R., and Reite, M. 1982. Loss-induced depression in an adult macaque monkey. Am. J. Psychiat. **139**: 679–681.

(22) Reite, M.; Harbeck, R.; and Hoffman, A. 1981. Altered cellular immune response following peer separation. Life Sci. **29**: 1133–1136.

(23) Reite, M.; Short, R.; Seiler, C.; and Pauley, J.D. 1981. Attachment, loss, and depression. J. Child Psychol. Psychiat. **22**: 141–169.

(24) Robson, R.D.; Antonaccio, M.J.; Saelens, J.K.; and Liebman, J. 1978. Antagonism by mianserin and classical a-adrenoceptor blocking drugs on some cardiovascular and behavioral effects of clonidine. Eur. J. Pharmacol. **47**: 431–442.

(25) Seligman, M.E.P. 1968. Chronic fear produced by unpredictable electric shock. J. Comp. Physiol. Psychiat. **66**: 402–411.

(26) Sherman, A.D., and Petty, F. 1980. Neurochemical basis of the action of antidepressants on learned helplessness. Behav. Neur. Biol. **30**: 119–134.

(27) Sherman, A.D., and Petty, F. 1982. Additivity of neurochemical changes in learned helplessness and imipramine. Behav. Neur. Biol., in press.

(28) Southwick, C. 1967. Experimental studies of intra-group aggression in rhesus monkeys. Behaviour **28**: 1–28.

(29) Spitz, R.A. 1946. Anaclytic depression. Psychoan. St. **2**: 313–342.

(30) Suomi, S.J.; Seaman, S.F.; Lewis, J.K.; Delizio, R.D.; and McKinney, W.T. 1978. Effects of imipramine treatment on separation-induced social disorders in rhesus monkeys. Arch. Gen. Psychiat. **35**: 321–325.

(31) Zetler, G. 1963. Die antikataleptische Wirksamkeit einiger Antidepressiva (Thymoleptica). Arzneim. Forsch. **13**: 103–109.