NEUROTRANSMITTER BALANCES
REGULATING BEHAVIOR
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Editors

Edward F. Domino
Department of Pharmacology
University of Michigan
Ann Arbor, Michigan 48104
and
Lafayette Clinic
Detroit, Michigan 48207

and

John M. Davis
Department of Psychiatry
University of Chicago
Chicago, Illinois 60637
and
Illinois State Psychiatric Institute
University of Chicago
Chicago, Illinois 60612

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PREFACE

The origin of this book was a Study Group session of the American College of Neuropsychopharmacology (ACNP) at its annual meeting in San Diego, December 4 to 7, 1973. The ACNP Program Committee for that year approved a session on Neurotransmitters and Autocoid Balances Regulating Behavior. At the time, only abstracts were requested of the participants and these were subsequently published in Psychopharmacology Bulletin, volume 10, number 3, July, 1974 as part of the Abridged Proceedings of the Twelfth Annual Meeting of the ACNP. However, the meeting generated sufficient enthusiasm among the participants that the majority decided to prepare more detailed manuscripts covering their verbal material for this volume. Inasmuch as the ambitious plan to cover both neurotransmitter and autocoid balances was not achieved, the autocoids were dropped and the result is the present title. Two major sessions were held. The first dealt with chemical balances in the brain systems of reward, and the second with neurotransmitter balances in mental illness. Although a few manuscripts were submitted in early 1974, the majority were completed by mid-1975. In a real sense most of the papers record the most recent observations and concepts.

Many of us have become so preoccupied with identifying the behavioral role of a single putative neurotransmitter that we have forgotten the concepts of earlier researchers, such as Hess, who emphasized the antagonistic roles of the ergotropic and tropotropic systems. The trend for looking for complex interactions among neurotransmitters is again becoming more popular. Surely, it will lead to a better understanding of the brain, its chemical mechanisms and its function — behavior.

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Edward F. Domino

John M. Davis

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CONTRIBUTORS

George R. Breese, Ph.D.
Departments of Pharmacology
and Psychiatry
University of North Carolina
Chapel Hill, North Carolina 27514

Barrett R. Cooper, Ph.D.
Departments of Pharmacology
and Psychiatry
University of North Carolina
Chapel Hill, North Carolina 27514

John M. Davis, M.D., Ph.D.
Department of Psychiatry
University of Chicago 60637
Chicago, Illinois
and
Illinois State Psychiatric Institute
1601 W. Taylor Street
Chicago, Illinois 60612

Peter B. Dew, Ph.D.
Laboratory of Psychobiology
Harvard Medical School
Boston, Massachusetts 02115

Edward F. Domino, M.D.
Department of Pharmacology
University of Michigan
Ann Arbor, Michigan 48104
and
Laboratory of Pharmacology
The Lafayette Clinic
951 E. Lafayette
Detroit, Michigan 48207

William E. Fann, M.D.
Department of Psychiatry
Baylor University Medical Center
Houston, Texas 77025
Samuel Gershon, M.D.
Department of Psychiatry
New York University Medical School
550 First Avenue
New York, New York 10016

Murray Glusman, M.D.
Columbia University
New York, New York 10032
and
Department of Mental Hygiene
New York State Psychiatric Institute
New York, New York 10032

David S. Janowsky, M.D.
Department of Psychiatry
University of California at San Diego
La Jolla, California 92037

Dennis D. Kelly, Ph.D.
Department of Psychiatry
Columbia University
New York, New York 10032
and
New York State Psychiatric Institute
New York, New York 10032

C. Raymond Lake, M.D., Ph.D.
Department of Psychiatry
Duke University Medical School
P.O. Box 3812
Durham, North Carolina 27710

Lewis R. Mandel, Ph.D.
Department of Biochemistry
Merck Institute for Therapeutic Research
Rahway, New Jersey 07065

Steven Matthysse, Ph.D.
Department of Psychiatry
Harvard Medical School
Boston, Massachusetts 02124
Based on their studies of brain stimulation in animals, Stein and Wise (1971) and Wise and Stein (1973) have proposed an interesting biochemical theory concerning the etiology of schizophrenia. They point to the accumulation of research in the past two decades that suggests the existence of two neural systems in the brain, one associated with reward and the other with punishment. The notion of the "reward system" is based on the demonstration that electrical stimulation of certain regions of the brain can serve as a positive reinforcement, a phenomenon first discovered by Olds and Milner (1954). The "punishment system" is based on the demonstration by Delgado et al. (1954) that electrical stimulation of certain brain regions in animals is aversive. The reward system, according to the authors, is mainly noradrenergic (Stein, 1971) whereas the punishment system is cholinergic and perhaps serotonergic as well.

Stein and Wise (1971) have proposed that the cause of schizophrenia in man is due to damage to the noradrenergic reward system by the formation of endogenous 6-hydroxydopamine (6-OHDA) as the result of a genetically determined enzymatic error. They note that systematic family studies and studies of adopted children have established the importance of genetic factors in the development of schizophrenia beyond any real doubt (Heston, 1970). The hereditary transmission of schizophrenia involves transmission of a biochemical abnormality, the result of a pathological gene; this results in an enzymatic derangement which permits the formation of 6-OHDA. It was proposed that by some error of enzymatic regulation of norepinephrine metabolism, excessive amounts of dopamine may accumulate in the noradrenergic vesicles and be transformed to 6-OHDA by an auto-oxidative process or an enzymatic reaction. They suggested the possibility that dopamine-β-hydroxylase might be involved in the enzymatic error (Stein et al., 1972). It was also speculated that small amounts of dopamine o-quinone
(DOQ) may be formed from dopamine by dopamine-β-hydroxylase and 6-OHDA is formed from the DOQ.

Basic to the Stein and Wise hypothesis is Sandor Rado's psychoanalytic concept which attributes the fundamental defect in schizophrenia to an innate deficiency in the organizing action of pleasure or an "integrative pleasure deficiency" (Rado, 1953; Rado et al., 1956).

Because of the importance attached to Rado's formulations, it would seem useful to review his concepts concerning pleasure and pain, examining their origins and reviewing his formulations on schizophrenia and psychopathology.

Sandor Rado was born in Hungary in 1890. He entered the University of Budapest in 1907, planning at first to study political science and law but after reading a paper by Ferenczi entitled "Analysis of the Soul" he became intensely interested in psychoanalysis and decided that after completing his doctorate in political science he would study medicine, then psychiatry, and devote himself completely to psychoanalysis. After completing his medical studies, he undertook training in psychoanalysis and was analyzed by Karl Abraham, then Director of the Berlin Psychoanalytic Institute (Jameson and Klein, 1969). Rado soon became active in psychoanalytic circles. He became a close friend of Ferenczi and in 1924 at Freud's invitation he became the executive director of the two official psychoanalytic journals: Internationale Zeitschrift für Psychoanalyse and Imago, Zeitschrift für Anwendung der Psychoanalyse auf die Natur und Geisteswissenschaften (Rado, 1948). In 1930 he came to the United States at the invitation of the New York Psychoanalytic Society to help set up the New York Psychoanalytic Institute on the model of the Berlin Psychoanalytic Institute. Rado had a close working relationship with Freud but a rift developed which at first may have been personal but by 1939 Rado was voicing some sharp theoretical differences with Freud's theory of instincts or libido theory. He announced that the factual findings of psychoanalysis must be separated from what he regarded as a kind of Freudian mysticism. In keeping with his view that psychoanalysis should be part of medicine he claimed that it was necessary to build a conceptual frame of reference based on biology.

Rado's comments generated considerable opposition in psychoanalytic circles and 1941 he resigned his position as Director of the New York Psychoanalytic Institute. Soon thereafter, he made a great step toward achieving one of his fondest and most cherished ambitions which was to identify psychoanalysis with medicine. In 1944 he organized the Columbia University Psychoanalytic Clinic for Training
and Research within the structure of the Columbia University College of Physicians and Surgeons and as part of the Department of Psychiatry.

Since the psychoanalytic movement in Europe had evolved outside university settings, Rado's achievement in having a psychoanalytic training center established under the auspices of Columbia University was an unusual accomplishment and he was extremely proud of it, feeling that the university affiliation was a sign of medical, scientific and intellectual acceptance. A course of instruction was organized and in addition to Rado's own lectures on adaptational psychodynamics, the term he adopted for his views on psychoanalytic theory, lectures were given on Freud's writings and, at Rado's insistence, some rather unusual courses were included in the curriculum; neurophysiology, taught by Harry Grundfest; neurochemistry, by Heinrich Waelsch; clinical psychiatry, by Paul Hoch; genetics in psychiatry, by Franz Kallmann; and neuropathology, by Armando Ferraro (Rado, 1948).

These courses reflected his own deep interest and respect for the biological sciences. Nevertheless, he had no real working acquaintance with any of the scientific disciplines.

I was privileged to be one of Rado's last students at Columbia before his retirement - and to be taught by him was a most interesting and memorable experience. Rado was a man of short physical stature, but this was more than counterbalanced by his intellectual stature. He had a vast amount of energy, a tremendous enthusiasm for his topic; he was intellectually very gifted, and he enjoyed enormously dealing with concepts, theories, and abstractions on a grand scale. He was a witty man and at times caustic, and he applied a blend of the two with enormous zest and devastating effect to one of his favorite tasks, which was demolishing Freudian libido theory. He felt that the important role that Freud assigned to instincts as motivating forces in behavior was utter nonsense and that libido theory had evolved into an obscure blend of animism and mysticism - totally removed from science and logic.

To underscore his point, he would recount to his students, with relish and delight, Hans Christian Andersen's story of the Emperor's New Clothes (Andersen, 1945). The Emperor, who was excessively fond of fine clothing, was convinced by a pair of fraudulent weavers that they could create for him the most unimaginably fine and magnificent clothes. Not only was the fabric beautiful beyond belief - it had the extraordinary property of being invisible to anyone who was impossibly stupid or otherwise unworthy of his office.
Taken in by the story, the Emperor, for a handsome sum, engaged the weavers to make him these remarkable new clothes. The weavers set to work pretending to weave the fabric which was invisible because it was non-existent. The Emperor and his courtiers praised the remarkable beauty of the "cloth," distrusting the evidence of their eyes and senses, and not daring to confess they could see nothing at all. Such an admission, after all, would be tantamount to a confession of stupidity or incompetence or both. Eventually, when the remarkable clothes were finished, the Emperor, clad only in the non-existent, imaginary garments displayed them in a grand parade before his assembled subjects. The spectators gasped and marveled at their beauty, none daring to admit they could see no clothes until a little child cried that the Emperor had nothing on. From person to person the child's words swept until at last the great hoax was exposed and all the spectators roared that the Emperor was without clothes.

Rado no doubt saw himself as the heroic child who, by trusting his mind and senses, exposed a great hoax, revealing libido theory to be devoid of substance and nothing more than an elaborate figment of the imagination.

Having rejected Freudian instincts as the prime motivating forces of behavior, he was faced with the necessity of finding some logical and scientifically rational alternative. What he did was to formulate his conceptual scheme "Adaptational Psychodynamics" (Rado, 1956). To do this he turned to some great scientific contributions and to some important philosophical ideas.

Rado was fascinated by science, but not on the level of the grubby details of the laboratory bench; his interest was in the great scientific theories and generalizations - he was attracted by the clear logic, the rationality, and the authority of science. Thus, although he knew little about neurology, he was a great admirer of Hughlings Jackson's notions of hierarchical levels in the nervous system (Jackson, 1958); he knew little about physiology, but he was fascinated with Walter Cannon's interest in fear and rage (Cannon, 1953), and Cannon's ideas on homeostasis (Cannon, 1939); he knew little of biology, but he was intimately concerned with Darwin and evolution (Darwin, 1950, 1955). His fascination with science was not an idle one; he incorporated Jackson's ideas as well as Darwin's and Cannon's into his own formulations.

Rado was also greatly interested in philosophy; he had his Ph.D. in Political Science and he was quite familiar with a group of philosophers who were as important for their ideas on politics as for their contributions to
philosophy. Among them were Jeremy Bentham (1748-1832) and his school who derived their major philosophical orientation - which came to be called "Utilitarianism" - from Locke, Hartley and Helvétius. Bentham and his followers, who included James Mill and his son, John Stuart Mill, became the leaders of British radicalism. Eventually their school - the Philosophical Radicals - gave rise to Socialism and Darwinism.

Bentham, who was interested in ethics and politics (Bentham, 1939), based his philosophy on two principles: the association principle and the greatest happiness principle. The association principle was derived from a predecessor, Hartley, but Bentham made it a basic principle of psychology, recognizing the association of ideas and language, as well as the association of ideas and ideas (Russell, 1945).

Bentham's goal was to establish a legal code and a social system that would make men virtuous. To define virtue he had to introduce his greatest happiness principle, maintaining that what is good is pleasure or happiness and what is bad is pain. "Therefore, one state of affairs is better than another if it involves a greater balance of pleasure over pain, or a smaller balance of pain over pleasure. The best possible state of affairs is the one involving the greatest balance of pleasure over pain (Russell, 1945, p. 775)."

Bentham and his followers applied their doctrines to practical politics and the Benthamites had a great influence on British legislation and policy in the middle of the nineteenth century.

Like Bentham and the utilitarians, Rado placed major emphasis on pleasure and pain. Bentham, however, was concerned with guiding principles in the political sphere; Rado made pleasure and pain the cornerstones of organismic behavior. He proposed what he called a "central integrative apparatus" (in the psychocerebral system or mind) and, in line with Hughlings Jackson's notion of hierarchical levels of organization in the brain (Jackson, 1958), derived as a result of evolution, Rado proposed a somewhat similar arrangement for the "central integrative apparatus" with four major subdivisions or levels arranged around a common axis (Rado, 1964). The oldest and most primitive level, the level of hedonic self-regulation, is seen phylogenetically in protozoa and it entails the self-regulatory system which makes the organism move toward a source of pleasure and away from a source of pain. He felt that the organism's systemic requirements generate various tensions, urges and needs which prompt the organism to action to supply the
various needs. The organism then in its contact with the environment is guided by responses of pleasure and pain. Pleasure becomes a reward for successful performance and memory of pleasure prompts repetition of the successful activity. Conversely, pain becomes punishment for failure and memory of pain deters the organism from repeating injurious activity. The next higher level in the remaining hierarchical levels of the psychodynamic cerebral system is the "preverbal level of brute emotion" which is dominated by two classes of emotions: The welfare emotions - such as pleasurable desire, joy, affection, love and pride; these are all variants of pleasure. Then there are the emergency emotions - agony, fear, rage, retroflexed rage, guilty fear, and guilty rage - all related to the experience or expectation of pain. The emergency emotions, in line with Cannon's ideas, prepare the organism for flight or combat and take precedence over all other motivations.

The next higher level is emotional thought and finally the highest level is unemotional thought. The emotional thought level culminates in religion, art, and aesthetic pleasure; unemotional thought in science, technology and wisdom.

Hedonic self-regulation involves all the phases of organization from the lowest to the highest. So that just as the infant operates on the basis of primitive pleasure and pain, so the highest levels of an adult's intellectual activities entail expectations of delayed reward instead of immediate reward - or expected disapproval instead of immediate pain as on the lower levels.

The organism's awareness of itself develops via proprioceptive sensations. Thus, an infant in becoming aware of his own muscular activity develops an awareness of himself as the one who acts. Self-awareness develops from the "action-self" which is the organism's highest decision-making unit. The "action-self" occupies a central position in each of the hierarchical levels (Rado, 1964).

Rado accepted Kallmann's suggestion of a genetic basis for schizophrenia (Kallmann, 1938). The schizophrenic genotype, that is, an individual with a genetic predisposition to schizophrenia, he felt manifested a particular kind of psychodynamic picture which he called the schizotypal organization. Thus, Rado (1953) said: "In the schizotypes the machinery of psychodynamic integration is strikingly inadequate, because one of its essential components, the organizing action of pleasure - its motivational strength - is innately defective [p. 411]." His phrase for this crucial defect was "integrative pleasure deficiency." Sometimes, patients recognize this and will say about themselves...
that they are incapable of giving and sharing love.

The basic difficulty in the inadequacy of the welfare emotions creates major problems. The welfare emotions counterbalance the emergency emotions and since in schizotypes the welfare emotions are weak or inadequate, this causes an emotional imbalance so that the emergency emotions tend to grow excessive and schizotypes show unusually intense fear and unusually intense rage. The deficiency in the integrative aspects of pleasure impairs the individual's development of the "action-self." Thus, Rado (1953) commented: "pleasure is the tie that really binds [p. 411]," and, therefore, an action-self without the strong integrative aspect of pleasure is weak and prone to break under stress. The weakness of the action-self is evidenced by the patient's oversensitivity and profound insecurity about himself, his body and his environment. The impaired capacity for pleasure and love prevents healthy sexual function. The sexual organization lacks genuine love and tenderness and is prone to fragmentation. The individual evolves a scarcity economy of pleasure and a security pattern marked by compensatory dependence. Sometimes behavior which is ordinarily handled simply and automatically on the basis of pleasurable feeling is carried out by unemotional thought (Rado, 1953). In similar fashion, Rado derived many aspects of schizophrenic behavior from the basic weakness in pleasure or the welfare emotions.

Rado's views on adaptional psychodynamics and schizophrenia are important and worth serious examination. He extended the views on pleasure and pain of the Utilitarian School of philosophers from the social and political sphere to the psychological sphere. Then, utilizing the scientific contributions of Hughlings Jackson, Darwin and Walter Cannon, he synthesized a psychological system to explain human behavior, both normal and disordered. It is interesting that despite his great concern with scientific contributions in many fields, he tended to overlook the contributions of modern psychology. He made no mention of C. Lloyd Morgan or Thorndike and took little or no notice of Watson, Pavlov, Skinner, Hull, Spence, Hebb, Neal Miller or the ethologists. His concern was with subjective, introspective phenomena in man and he had little interest in the powerful trends in psychology that dismissed subjective phenomena and focused on behaviorism. There could be little attraction for Rado in the credo expressed by Watson (1913):

Psychology as the behaviorist views it is a purely objective experimental branch of natural science. Its theoretical goal is the prediction
and control of behavior. Introspection forms no essential part of its methods, nor is the scientific value of its data dependent upon the readiness with which they lend themselves to interpretation in terms of consciousness... [p. 158]. The time seems to have come when psychology must discard all reference to consciousness; when it need no longer delude itself into thinking that is is making mental states the object of observation...[p. 163]. Psychology, as the behaviorist views it, is a purely objective, experimental branch of natural science which needs introspection as little as do the sciences of chemistry and physics [p. 176].

Also, despite his great interest in science and the philosophy of science - he referred repeatedly to Mach, Poincaré, Nernst, Reichenbach, v. Mises, Bridgman and Woodger - he made little use of scientific method. He was not concerned with systematic observation, acquisition of data, experimental manipulation and hypothesis testing - in short with the indispensable procedures and tools of the empirical scientist. Thus, the principles he derived and the theories he propounded, reasonable and rational as they were, were basically speculations which lacked an empirical base in the subject they dealt with. It is interesting too, that for all of Rado's criticism of Freud and for all of Rado's interest in science, Freud made significant efforts to build his ideas on an empirical foundation, utilizing data from case histories, dream material, and free associations; whereas Rado made no such effort. Rado's relationship to science was in a sense, second hand; he worked with the principles and generalizations that others had derived in various fields and used them as the basis for a set of theoretical constructs dealing with psychopathology. Rado's tools were the philosopher's tools, the power of his own intellect and an admirable ability to reason logically and clearly. With those tools he built an important set of theories concerning human behavior and psychopathology.

The question to be asked now is how relevant are these concepts to brain stimulation? Stein and Wise have felt that they are extremely relevant, even constructing a theory concerning the biochemical disturbance in schizophrenia which relates directly to Rado's concepts. It should be pointed out that Rado's ideas cannot enhance the validity of Stein and Wise's hypothesis because Rado's notions, as indicated in detail above, are in the final analysis, speculations rooted in philosophical notions and thus
far they are unsupported by scientific data or evidence. Stein and Wise's theory provides an interesting extension and elaboration of Rado's theory, but a theory based upon a theory is a tenuous creation at best. Still, no matter how insubstantial the grounds on which a theory rests, there is no logical reason why it may not prove to be correct, and if not correct it may nevertheless stimulate important research and lead to valuable discoveries. Stein and Wise have pointed out that the neural pathways involved in self-stimulation appear to be chiefly noradrenergic whereas the "punishment" system appears to be at least partly serotonergic. They suggest that the pathways involved in self-stimulation constitute the chief reward or pleasure system of the brain and that damage to the noradrenergic terminals of this system via the endogenous formation of 6-OHDA produced by DOQ results in impairment of the pleasure system of the brain, loss of its integrative action, and production of schizophrenia in accordance with Rado's hypothesis. Most recently, Wise and Stein (1973, 1975) have reported that, in line with their hypothesis, dopamine-β-hydroxylase activity is significantly reduced in the brains of schizophrenic patients compared to normals.

Ultimately, the validity of this hypothesis must be established on biochemical grounds; nevertheless, from the standpoint of Rado's concepts, some questions must be clarified.

The obvious and inescapable problem which arises in attempting to relate Stein and Wise's brain stimulation studies with Rado's psychoanalytic concepts is the problem of anthropomorphization. Rado quite clearly pointed out that we know about subjective feeling states via communicated introspection (Rado, 1962):

Although introspection is a private operation of one individual, he can communicate the products of this operation to a participant observer. If, for instance, a patient tells me that he is 'happy' or 'angry' or 'afraid,' I understand what he means because I have experienced these feelings myself and have learned to associate the feelings with words. In order to understand communicated introspection, each of us must use his own introspection as a model, a mediating referent [p. 154].

Communicated introspection is obviously out of the question in animal studies. To obviate the problem of anthropomorphization, the "reward system" and the "punishment system" were defined operationally. Unlike other systems
which have clearly defined functional, neuroanatomical and neurophysiological relationships such as the visual system, the auditory system, the somatosensory system and the motor system, the "reward" and "punishment" systems owe their existence to operational definitions. Operational definitions may be very useful for experimental purposes; they may be of great help in studying various aspects of self-stimulation, or the aversive properties of intracranial stimulation; they guard against the temptation for egregious anthropomorphization; but they leave unanswered the functional significance of the operationally defined systems. Further, too, the relationship of the operationally defined system to known, conventional systems may be confusing and overlapping. For example, if an animal finds stimulation of a given site aversive and works to avoid or escape the stimulus, we are evidently justified in including the locus in the "punishment system." But an animal will find electrical stimulation of the cornea or tooth-pulp aversive. By our operational definition the cornea and tooth-pulp would be included in the "punishment system," although the cornea is, of course, part of the visual system and teeth are primarily involved in feeding and attack or defense. Pain can be elicited from almost any bodily region and there is a considerable body of information concerning the psychological neuroanatomical and neurophysiological aspects of pain; but the relationship between the conventional pain system and the "punishment system" is unclear and confusing. Does the punishment system exist as a separate entity? Does it overlap the pain system, or is it merely an operationally defined portion of centrally coursing pain pathways?

The "reward system" poses similar problems. The discovery of the phenomenon of self-stimulation by Olds and Milner in 1954 initiated a flood of investigations. The phenomenon has been replicated in numerous species and a great deal of information has been gathered concerning the rewarding properties of brain stimulation. Still, the fundamental significance of the "reward system" is far from clear. Almost all of the information available concerning the "reward system" comes from animal studies and again we are confronted with the problem of anthropomorphization. Some limited information has been gleaned from depth-electrode studies in humans by a handful of investigators, but that information is incomplete and inconclusive. Ethical, moral and legal sanctions against human experimentation make it difficult, if not impossible, to determine the significance of the "reward system" in man.

The questions that must be answered concerning the
"reward system" are: First, what significance does the system have for the subjective emotional experience of pleasure in man? Then, to what extent is the "system" a system in the conventional sense, in that it constitutes an anatomically and physiologically related entity whose function is to subserve all pleasure, whether it be from ingestion of food, sex, pleasure of achievement, etc.? Also, is the system so interrelated and unified structurally that it can be destroyed by anatomical or chemical means, and, if destroyed, will a person so afflicted manifest partial or even complete inability to experience pleasure from any and all sources?

The information available to date in man—well reviewed by Valenstein (1973)—is too fragmentary to answer these questions. What we know comes largely from the observations by Heath and his associates at Tulane (Heath and Mickle, 1960; Bishop et al., 1963; Heath, 1963, 1964, 1972; Heath et al., 1968), Sem-Jacobsen and Torkildsen (1960), Sem-Jacobsen (1968), and Bechterewa (1969). Brain stimulation at some sites in humans evidently can produce feelings of well-being or pleasure. One of Heath's patients had attempted suicide, but shortly after the attempt when an electrode in his septal region was stimulated he announced that he felt good although it was difficult for him to explain why he felt good (Valenstein, 1973). A woman with intractable pain said that the stimulus made her feel fine and energetic. In some instances patients may have experienced sexual orgasms during brain stimulation. These may or may not have been secondary to sensations in the genitalia produced by the stimulus. Humans may self-stimulate but for unexpected reasons. One of Heath's patients kept trying to recall a memory vaguely elicited by the stimulus. Heath (1963) reported:

The button most frequently pushed provided a stimulus to the centromedian thalamus. This stimulus did not, however, induce the most pleasurable response; in fact, it induced irritability. The subject reported that he was almost able to recall a memory during this stimulation, but he could not quite grasp it. The frequent self-stimulations were an endeavor to bring this elusive memory into clear focus [p. 573, 574].

Sem-Jacobsen (1968) described similar reasons for self-stimulation with the patients trying to clarify the nature of a fleeting or puzzling sensation. He commented:

An emotional reward often has been designated as an explanation or motivation for self-
stimulation; an unpleasant response is thought to cause the patient to avoid stimulation. In humans, however, other incentives are also very strong and can sometimes be more potent than the simple pleasure received. The reasons given by patients for continuing self-stimulation seem as complex as man himself. In man, curiosity is probably the most dominant causative factor in initiating self-stimulation [p. 54].

He noted too, that a pleasurable response is at times secondary to muscular contractions in the region of the genitals. Thus, Sem-Jacobsen and Torkildsen (1960) observed: In secluded patients it is difficult to evaluate whether the change in mood is a result of central stimulation or a central effect of peripheral reactions to the stimulus. For instance, one patient laughed with joy in response to each stimulation. After several days with stimulation we learned what really took place. The stimulus evoked a fluttering in a muscle group in the pelvis which tickled the patient and she responded with joy and laughter [p. 284].

Bechterewa (1969) reported several instances in which brain stimulation in patients produced pleasurable, erotic sensations and in one woman they led to orgasm (p. 165). Self-stimulation has been reported in humans but great care is required in interpreting the response. Thus, Bishop et al. (1963) and Brazier (1964) noted instances in which patients continued to "self-stimulate" for long periods even after the current had been turned off. Bishop et al.'s patient was a catatonic schizophrenic with marked perseverative behavior. His perseverative tendency included lever-pressing in the self-stimulation study, complicating the study greatly because he lever-pressed with current on or off.

Clearly, much more needs to be known about both the "reward system" and "punishment system" in man before we can understand their significance. But even if we were to assume with Stein and Wise that there did indeed exist a unified reward or pleasure system in the brain, what evidence would we have that impairment of the system is a central factor in schizophrenia? Rado emphasized anhedonia in schizophrenia and made it a basic feature of that disorder. But Rado did not base his conclusions on systemically collected empirical data; his collected papers include only one clinical investigation (Rado et al., 1956) which con-
sisted of a preliminary report of an elaborate, diffuse, clinical study that was never completed and which in no way proved his contention that anhedonia is a crucial element in schizophrenia. Rado himself cited Bleuler as authority for the importance of anhedonia in schizophrenia:

Beginning with Bleuler, clinical observers have repeatedly listed 'anhedonia' and 'pro-prioceptive disorder' among the symptoms of schizophrenia. In contradistinction, the aforesaid inherited defects are viewed here not merely as symptoms, but as the two central axes of an organization sui generis (Rado et al., 1956, p. 226).

But Bleuler made no mention of anhedonia; he stressed disturbance of affect. The schizophrenic may, of course, be anhedonic; flattening of affect is a common enough feature in schizophrenia, but flattening of affect encompasses much more and is a broader and more inclusive disturbance than anhedonia. It is, of course, by no means uncommon to find schizophrenics who are quite capable of experiencing pleasure, although the pleasure may be strikingly inappropriate to the circumstances which elicit it.

Thus, for example, Bleuler (1950) stated:

Especially conspicuous in schizophrenics is the frequently encountered parathymia. The patients are able to react to sad news with cheerfulness or even with laughter. These patients will often become sad, or even more frequently, irritated by events to which others would react with indifference or with pleasure...In the fields of taste and smell, the parathymic disturbance can often be very prominent...A catatonic whom I asked why he drank his own urine, answered with a blissfully entranced expression, 'Herr Direktor, if you should taste it but once, you would never want to drink anything else' [p. 52].

Clearly the patient cited by Bleuler was capable of experiencing pleasure; he was not at all anhedonic but his pleasure, to say the least, was grossly unusual and highly inappropriate.

Actually, anhedonia is not a very common term; it is not listed in the Oxford English Dictionary (1961) or the American Heritage Dictionary (1973), nor can it be found in the indexes of such widely used texts of psychiatry as Kolb's (Noyes' Modern Clinical Psychiatry, 1968), Freedman and Kaplan's (Comprehensive Textbook of Psychiatry, 1967), or Arieti's (American Handbook of Psychiatry, 1974). But
it is listed in Webster's Third New International Dictionary (1968) where it is defined as "1. Insensitiveness to pleasure. 2. Incapacity for experiencing happiness." It is a curious thing that the term never achieved wide popularity in psychiatry and when it is mentioned, as in Meehl (1962) it tends to be related to Rado and his theory concerning schizophrenia. It is odd, too, that the term anhedonia is generally not applied to depressive states although it would seem to be eminently applicable to depressed patients. To be depressed and to be able to experience pleasure is virtually a contradiction in terms. Only when the depressed patient begins to recover does he regain his capacity to experience happiness, but while he is depressed and for the duration of his depression he is by definition anhedonic, and the term is as applicable to him as to any schizophrenic.

To consider another point, Rado pointed out that pleasure and the welfare emotions counterbalance the pain-connected emergency emotions; hence:

In the schizotypes, motivational weakness of the welfare emotions causes an emotional disbalance; without this adequate tempering influence the emergency emotions tend to grow excessive in motivational strength and integrative scope [Rado, 1953, p. 411].

Thus, the schizotypes show greatly exaggerated fear and rage responses.

As for fear and rage responses, Reis, Gunne and their associates (Reis et al., 1967; Gunne, 1969) have obtained evidence in cats indicating that the central mechanisms mediating rage responses produced either by brain stimulation or high decerebration involve noradrenergic pathways. Hence, impairment of noradrenergic nerve terminals should interfere with fear and rage, reducing the emergency emotions as well as pleasure and the welfare emotions. If the motivational weakness due to impairment of the emergency emotions is added to the motivational weakness of the welfare emotions the expected clinical picture resulting from impairment of noradrenergic pathways should show a striking loss of motivation. Since there is also evidence that feeding behavior is noradrenergically mediated (Leibowitz, 1974) there should be loss of appetite as well. Loss of interest in sex should be included too since Stein (1971) suggested that sexual activity is included in the reward system. He commented:

Briefly, electrical stimulation of the medial forebrain bundle serves as a powerful reward and also elicits species-typical consummatory
responses, such as feeding and copulation, which produce pleasure and permit satisfaction of basic needs [p. 346].

From the above, the clinical picture to be expected from damage to the noradrenergic nerve terminals should include among its key features loss of pleasurable responses or impaired gratification, reduced fear and rage, impaired motivation, impaired appetite and loss of interest in sex. This constellation of symptoms corresponds much more closely with the most prominent features of depressive states than with those of schizophrenia.

Beck (1967) in a study of 966 psychiatric patients found some degree of sadness or unhappiness in 88 per cent of severely depressed patients compared with 23 per cent of non-depressed patients.

Loss of gratification was the most prominent complaint. He reported:

The loss of gratification is such a pervasive process among depressives that many patients regard it as the central feature of their illness. In our series, 92 per cent of the severely depressed patients reported at least partial loss of satisfaction; this was the most common symptom among the depressed group as a whole [p. 18].

Loss of positive motivation was found in 86 per cent of Beck's severely depressed patients and in 65 per cent of the mildly depressed ones.

The loss of positive motivation is often a striking feature of depression. The patient may have a major problem in mobilizing himself to perform even the most elemental and vital tasks as eating, elimination, or taking medication to relieve his distress [p. 27].

Anorexia is also one of the most common features of depression. It was found in 72 per cent of severely depressed patients compared to 21 per cent of non-depressed patients. "For many patients loss of appetite is often the first sign of an incipient depression and return of appetite may be the first sign that it is beginning to lift [Beck, 1967, p. 33]." Lastly, there was some loss of interest in sex either autoerotic or heterosexual in 61 per cent of the depressed patients and only 27 per cent of non-depressed patients. In severely depressed patients "Any responsiveness to sexual stimuli is lost and the patients may have a pronounced aversion for sex [Beck, 1967, p. 35]."

Aggression bears a somewhat special relationship to depression. On a hospital ward the severely depressed patient
is not an assaultive, violent, combative individual; he can barely mobilize himself to carry on the everyday tasks of getting dressed, washing, eating, etc. Thus, during severe depressive states aggressive behavior is decreased and the depressed patient is a most unaggressive individual. However, as the patient begins to recover from his depression, aggressive behavior may appear as violence directed against the self in suicide, or as suicide combined with homicide, in which the patient may destroy himself and one or more members of his immediate family; e.g., a husband may not only kill himself, but his wife and children as well, whom he may regard as extensions of himself.

All in all, a strong case can be made that there is a better fit between Stein and Wise's hypothesis with depression than with schizophrenia. There is, of course, a considerable body of evidence implicating noradrenergic mechanisms in depressive states; much of this information has been summarized by Schildkraut (1965), Schildkraut et al. (1965), and Schildkraut and Kety (1967) as part of the catecholamine hypothesis of affective disorders. Stein and Wise's notions may be regarded as a further theoretical contribution to the catecholamines hypothesis. A particularly valuable addition to the hypothesis may be their suggestion (Stein et al., 1972) that after damage to the noradrenergic nerve terminals denervation supersensitivity to norepinephrine may develop. The development of denervation supersensitivity provides a most interesting possibility for explaining the cyclical nature of some affective disorders, e.g., manic-depressive states.

Clearly, we still have not achieved a reasonable hypothesis for the neurochemical basis of schizophrenia. The dopamine hypothesis for the etiology of schizophrenia elaborated by Snyder (1974) and Matthysse (1973), based on findings by Carlsson and Lindqvist (1963) has generated a good deal of interest among investigators in psychiatry. By and large, it seems more defensible than Stein and Wise's hypothesis. Nevertheless, its validity is far from established.

The catecholamine hypothesis for the affective disorders, the Stein and Wise hypothesis and the dopamine hypothesis for schizophrenia may all have their shortcomings; it is heartening, nevertheless, to note that with the rapid expansion of research in the neurosciences we are acquiring sufficiently detailed information concerning brain function to develop increasingly sophisticated and meaningful theories concerning the etiology of some major psychiatric disorders. Not very long ago the possibility of relating the etiology of schizophrenia and the affective disorders to
the brain seemed unattainably remote. Currently, as re-
search in psychopharmacology moves with increasing direc-
tion and sophistication to the level of the neurotrans-
mitters, there are occasional clues that we may be moving
in the right direction and that we may find the answers to
the etiology of schizophrenia and the affective disorders
in the not too distant future.

To conclude, Rado would have been immensely pleased to
know that his formulations were sufficiently relevant to
provide physiologists and biochemists with important clues
for research in schizophrenia. Since he was an excellent
logician he would have recognized that building a theory on
a theory is a precarious venture at best. Nevertheless, as
he maintained again and again to his students - theories
are not dogma; they are made to be broken; what is import-
ant about a theory is that it makes new advances possible
and that it stimulates new research. And that, of course,
is what Rado's own concepts and Stein and Wise's ideas
seem to be doing.

Little has been said about Freud in this presentation
because of the problem of relating Freudian psychoanalytic
to brain physiology. Rado (1962) saw the difficulty
clearly and elucidated it in the following manner:

Freud, the pioneer, took no time out for
methodological considerations. He did not
realize, nor did anyone else for quite some
time, that during the development of his
basic theory of the structure and function
of the mind he gradually switched from a
mechanistic to an animistic conceptual
scheme. The shift began in 1905, with the
introduction of his Theory of Instincts
(the Libido theory, subsequently elaborated
into the Theory of Eros and the death
instincts), and climaxed, in the 1920s, in
the transformation of the concept of
'mental apparatus' into the tripartite struc-
tural notion of superego, ego and id. Brain
physiology, like all physiology, is mechan-
istic. While Freud's originally mechanistic
theory offered hope for correlation with
brain physiology, his later animistic notions
did not. Consequently, psychoanalysis became
separated from human biology. In the last
two decades, more and more people have felt
that psychoanalysis was 'on the loose.'
Instead of examining the question why,
some writers suggested that psychoanalytic
theory be viewed and cultivated as a social science.

Ancient man was animistic. Analyzing his sensory experience in the relation of cause and effect, he attributed natural events to the action of man-like creatures hiding behind them. In the early nineteenth century vitalistic biology—thinly disguised animism—traced human behavior to the action of vital spirits hiding in the ventricles of the brain. Instinct, superego, ego and id are these old vital spirits reintroduced into psychoanalytic theory; the core of each is a miniature personage. To explain *homo* by making him appear as an organization of *homunculi* is a classical instance of the well-known logical fallacy of *petitio principii*; no wonder, animistic (vitalistic) theories have proved unworkable. The life sciences have become what they now are by advancing from the animistic to the mechanistic model [p. 179-180].

To some extent Freud's problem may have been the fact that he began his career as a neurologist. Knowing more about the brain than Rado and seeing it through the eyes of a nineteenth century neurologist, he viewed the task of relating psychiatric disturbances to the chemistry and physiology of the brain as being so far removed as to be almost hopelessly in the future. Thus, he went on to develop psychoanalysis, libido theory and a frame of reference which is very difficult to relate to modern neurophysiology and neurochemistry.

Freud, nevertheless, always felt that the answers to mental illness would eventually come from the laboratories of the neuroscientists. Thus, he said:

*The future may teach us to exercise a direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind. It may be that there are other undreamed-of possibilities of therapy. But for the moment we have nothing better at our disposal than the technique of psychoanalysis, and for that reason, in spite of its limitations, it is not to be despised* [Freud, 1949, p. 79].
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Using neuronal models, I would like to suggest some of the ways in which transmitter balance might be brought about in the nervous system. These "lollipop neuron" models should not be taken too literally, in view of the complexity of the real nervous system, but they will serve their purpose if they alert us to the variety of possibilities for transmitter balance.

Our conceptual formulation of transmitter balance has gone beyond the classical ergotropic - trophotropic notions because we are no longer constrained to think of transmitters only as forces that can push in opposite directions. For example, stabilization of one transmitter system by another is a possibility illustrated in this circuit.

If we assume that the noradrenergic input is excitatory but insufficient by itself to fire the output neuron, its efficacy will depend on the fluctuations in membrane potential. If the other excitatory and inhibitory inputs to this neuron shown in the figure both fire at a high rate,
the average membrane potential may not change, but the fluctuations will diminish (because of the statistical law of large numbers). Increased serotonin activity would, therefore, stabilize the effector pathway of this system against deviations in noradrenergic firing rate. Such a circuit could account for the relationships postulated by Kety between these transmitters in the modulation of affect; serotonin depletion permits mood swings but noradrenaline level controls their direction.

Alternatively, the relationship between serotonin and noradrenaline in the control of affect could be accounted for by a feedback circuit like this:

The overall action of the feedback control pathway is inhibitory, because \((-1)^3\) is negative. Serotonin would serve to stabilize the noradrenergic system against fluctuations but it might not directly influence the level of effector activity. A serotonin blocker, for example, would disinhibit the interneuron but its increased firing rate might not be passed on to the noradrenaline cell as inhibition because of the blockade of the second serotonin synapse. Conversely, an agent which facilitates serotonin actions would decrease the firing rate of the interneuron but potentiate the postsynaptic effect of its impulses on the noradrenergic neuron. These effects might cancel each other out. The stability of the feedback system against changes in activity of the noradrenaline cell would, however, be increased by agents which potentiate serotonin and be decreased by serotonin blockers.
The data presented on acetylcholine effects raises the interesting question of symmetry in the cholinergic system. According to Domino's experiments, acetylcholine agonists and antagonists act symmetrically with respect to self-stimulation behavior; physostigmine suppresses self-stimulation, anticholinergics facilitate it. On the other hand, with respect to mood, they seem to act asymmetrically: physostigmine acts as a depressant (Janowsky) but pure anticholinergics are not considered to be mood-elevating. This situation is similar to release of luteinizing hormone. According to McCann, atropine blocks LH release but carbachol does not release LH effectively. In contrast, the noradrenaline system seems generally to exhibit symmetry between agonists and antagonists. The lack of symmetry might be accounted for by postulating that there are cholinergic neurons involved in the control of mood which have low spontaneous activity. Facilitating agents would then have wide scope for their actions whereas inhibiting agents could only reduce the activity a small amount. The opposite assumption, high spontaneous activity with maximal receptor stimulation, would have to be assumed to prevail in the luteinizing hormone system.

Finally, I would like to suggest a model of dopaminergic-cholinergic interaction which may account for some of the more puzzling aspects of the pharmacology of schizophrenia. Davis and Janowsky have observed that physostigmine antagonizes methylphenidate-induced exacerbation of schizophrenia. On the other hand, physostigmine is not a therapeutic agent for naturally-occurring schizophrenia, and anticholinergics do not interfere with the therapeutic effects of phenothiazines. The absence of symmetry in these effects of cholinergic drugs is hard to reconcile with a simple "push-pull" balance theory. The following model, based on a mixture of the principles discussed above, does account for these observations. The overall effect of the feedback loop is inhibitory, as discussed before. Let us suppose that the pathological defect in schizophrenia is tonic hyperpolarization of the cholinergic interneuron so that it does not discharge. The cause could be a disturbed excitatory-inhibitory balance of other afferents to the interneuron not indicated in the diagram, or some defect in the interneuron itself. Using this model, we can account for the asymmetries in dopaminergic-cholinergic balance in the following way.

Physostigmine potentiates the action of acetylcholine, but in the schizophrenic there is nothing to potentiate, since the interneuron is silent. Methylphenidate inhibits the dopamine-receptive neuron, and therefore indirectly
excites the cholinergic interneuron. After methylphenidate treatment, therefore, the situation has changed and the interneuron is firing, so physostigmine can potentiate its inhibitory control of the dopaminergic neuron. Phenothiazines excite the dopamine-receptive neuron by blocking inhibitory synaptic input, and therefore indirectly inhibit the cholinergic interneuron. The interneuron was not firing before the inhibition, so it is certainly not firing now; therefore, anticholinergics have nothing to block.

Peripheral receptors could be blocked with N-methylscopolamine, although central muscarinic receptors would be affected nonselectively. It has recently been reported that atropine, locally injected into the substantia nigra, increases neostriatal dopamine turnover, in contrast with its effects when administered systemically (Javoy et al., 1974). This observation is in accord with the model. It is possible to design a single circuit which is consistent with the local and systemic effects of atropine on dopamine turnover, the blocking effect of GABA antagonists on feedback inhibition, and the observations on "balance" discussed above. The feedback loop would have to be rather complex, containing two cholinergic neurons and one GABA neuron. The first cholinergic neuron would receive inhibitory dopaminergic input and would inhibit the second cholinergic neuron. The second cholinergic neuron would project downward, making excitatory connections with gabaminergic cells, which finally would inhibit the ascending dopamine neurons. The
feedback properties of this system depend on several un­
known parameters, but if the values are chosen appropriate­
ly, the observations referred to can be accounted for. De­
finitive modelling, of course, must await further neuro­
anatomical–neurochemical exploration of the descending path­
way.

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