NEUROTRANSMITTER BALANCES
REGULATING BEHAVIOR

Edited by
E. F. Domino and J. M. Davis

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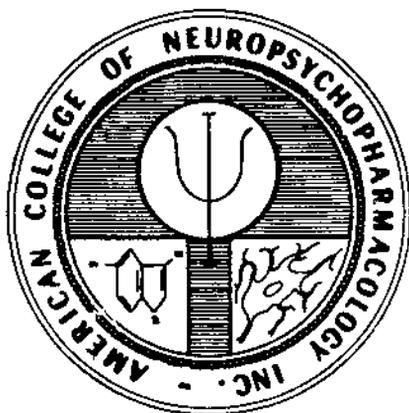
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The origin of this book was a Study Group session of
the American College of Neuropsychopharmacology (ACNP) at
its annual meeting in San Diego, December 4 to 7, 1973.
The ACNP Program Committee for that year approved a session
on Neurotransmitters and Autocoid Balances Regulating Be-
havior. At the time, only abstracts were requested of the
participants and these were subsequently published in Psy-
chopharmacology 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 suf-
ficient 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 ob-
servations 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.

The efforts of Mrs. Ellen Howard in typing the final
manuscripts are gratefully acknowledged.

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PSYCHOANALYTIC CONCEPTS AND BRAIN STIMULATION:
A CONSIDERATION OF RELEVANCE

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Based on their studies of brain stimulation in animals,
Stein and Wise (1971) and Wise and Stein (1973) have pro-
posed an interesting biochemical theory concerning the
etiology of schizophrenia. They point to the accumulation
of research in the past two decades that suggests the exis-
tence 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 elec-
trical stimulation of certain regions of the brain can
serve as a positive reinforcement, a phenomenon first dis-
covered 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 punish-
ment 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-hydroxydopa-
mine (6-OHDA) as the result of a genetically determined en-
zymatic error. They note that systematic family studies and
studies of adopted children have established the importance
of genetic factors in the development of schizophrenia be-
yond any real doubt (Heston, 1970). The hereditary trans-
mission of schizophrenia involves transmission of a bio-
chemical 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, ex-
cessive amounts of dopamine may accumulate in the norad-
renergic 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 in-
volved in the enzymatic error (Stein et al., 1972). It was
also speculated that small amounts of dopamine o-quinone

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(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 Zeitschrit 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, en-
gaged 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 spec-
tators 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 ex-
posed 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, re-
vealing libido theory to be devoid of substance and nothing
more than an elaborate figment of the imagination.

Having rejected Freudian instincts as the prime motiva-
ting forces of behavior, he was faced with the necessity
of finding some logical and scientifically rational alter-
native. 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 Jack-
son'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 in-
timately 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 or-
ientation - which came to be called "Utilitarianism" -
from Locke, Hartley and Helvétius.   Bentham and his follow-
ers, 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 Social-
ism 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 prin-
ciple.   The association principle was derived from a pre-
decessor, Hartley, but Bentham made it a basic prin-
ciple 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, main-
taining 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 influ-
ence on British legislation and policy in the middle of the
nineteenth century.

Like Bentham and the utilitarians, Rado placed major em-
phasis on pleasure and pain.   Bentham, however, was con-
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 integra-
tive 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 phylogeneti-
cally 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 in-
jurious 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 expec-
tation 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 or-
ganization 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 ac-
tivities entail expectations of delayed reward instead of
immediate reward - or expected disapproval instead of im-
mediate pain as on the lower levels.

The organism's awareness of itself develops via proprio-
ceptive 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 gen-
otype, that is, an individual with a genetic predisposition
to schizophrenia, he felt manifested a particular kind of
psychodynamic picture which he called the schizotypal or-
ganization. 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 cru-
cial defect was "integrative pleasure deficiency." Some-
times, 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, introspectional 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 con-
sciousness; 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 associa-
tions; whereas Rado made no such effort. Rado's relation-
ship 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 schizo-
phrenia 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 no-
tions, as indicated in detail above, are in the final anal-
ysis, 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 seroton-
ergic. 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 pro-
duced by DOQ results in impairment of the pleasure system
of the brain, loss of its integrative action, and produc-
tion 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 schizo-
phrenic patients compared to normals.

Ultimately, the validity of this hypothesis must be es-
tablished on biochemical grounds; nevertheless, from the
standpoint of Rado's concepts, some questions must be clar-
ified.

The obvious and inescapable problem which arises in at-
tempting to relate Stein and Wise's brain stimulation stud-
ies 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 opera-
> tion of one individual, he can communicate
> the products of this operation to a partici-
> pant 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 refer-
> ent [p. 154].

Communicated introspection is obviously out of the ques-
tion in animal studies. To obviate the problem of anthro-
pomorphization, 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 ex-
istence to operational definitions. Operational defini-
tions 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 egre-
gious anthropomorphizarion; but they leave unanswered the
functional significance of the operationally defined sy-
stems. Further, too, the relationship of the operationally
defined system to known, conventional systems may be confu-
sing and overlapping. For example, if an animal finds stim-
ulation of a given site aversive and works to avoid or es-
cape 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 sy-
stem 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 con-
cerning the psychological neuroanatomical and neurophysio-
logical aspects of pain; but the relationship between the
conventional pain system and the "punishment system" is un-
clear 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 discov-
ery 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. Al-
most all of the information available concerning the "re-
ward 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 structur-
ally that it can be destroyed by anatomical or chemical
means, and, if destroyed, will a person so afflicted mani-
fest 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 observa-
tions 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 stimu-
lation at some sites in humans evidently can produce feel-
ings 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 an-
nounced 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-stimu-
late 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-stimula-
> tions 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 him-
> self. 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 sec-
ondary to muscular contractions in the region of the geni-
tals. Thus, Sem-Jacobsen and Torkildsen (1960) observed:

> In secluded patients it is difficult to
> evaluate whether the change in mood is a re-
> sult of central stimulation or a central
> effect of peripheral reactions to the stim-
> ulus. 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 pa-
tients continued to "self-stimulate" for long periods even
after the current had been turned off. Bishop et al's pa-
tient was a catatonic schizophrenic with marked persevera-
tive 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 "re-
ward system" and "punishment system" in man before we can
understand their significance. But even if we were to as-
sume with Stein and Wise that there did indeed exist a un-
ified 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 col-
lected 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 'proprioceptive 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 Diction-
ary (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 popular-
ity in psychiatry and when it is mentioned, as in Meehl
(1962) it tends to be related to Rado and his theory con-
cerning schizophrenia. It is odd, too, that the term an-
hedonia is generally not applied to depressive states al-
though 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 dis-
>   balance; without this adequate tempering in-
>   fluence the emergency emotions tend to grow
>   excessive in motivational strength and integra-
>   tive 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 stimula-
tion or high decerebration involve noradrenergic pathways.
Hence, impairment of noradrenergic nerve terminals should
interfere with fear and rage, reducing the emergency emo-
tions 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 wel-
fare emotions the expected clinical picture resulting from
impairment of noradrenergic pathways should show a striking
loss of motivation. Since there is also evidence that feed-
ing 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 satisfac-
> tion 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 satisfac-
> tion; 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 him-
> self 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 nondepressed 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 nondepressed 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 individ-
ual. 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 com-
bined with homicide, in which the patient may destroy him-
self and one or more members of his immediate family; e.g.,
a husband may not only kill himself, but his wife and chil-
dren 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 de-
pression 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 particu-
larly 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 denerva-
tion supersensitivity provides a most interesting possibil-
ity for explaining the cyclical nature of some affective
disorders, e.g., manic-depressive states.

Clearly, we still have not achieved a reasonable hypo-
thesis for the neurochemical basis of schizophrenia. The
dopamine hypothesis for the etiology of schizophrenia elab-
orated 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 estab-
lished.

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 ex-
pansion of research in the neurosciences we are acquiring
sufficiently detailed information concerning brain function
to develop increasingly sophisticated and meaningful theor-
ies concerning the etiology of some major psychiatric dis-
orders. 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
theory 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 psycho-
> analytic 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 ref-
erence which is very difficult to relate to modern neuro-
physiology 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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NEURONAL MODELS OF TRANSMITTER BALANCE

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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 complex-
ity 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 transmit-
ters 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.
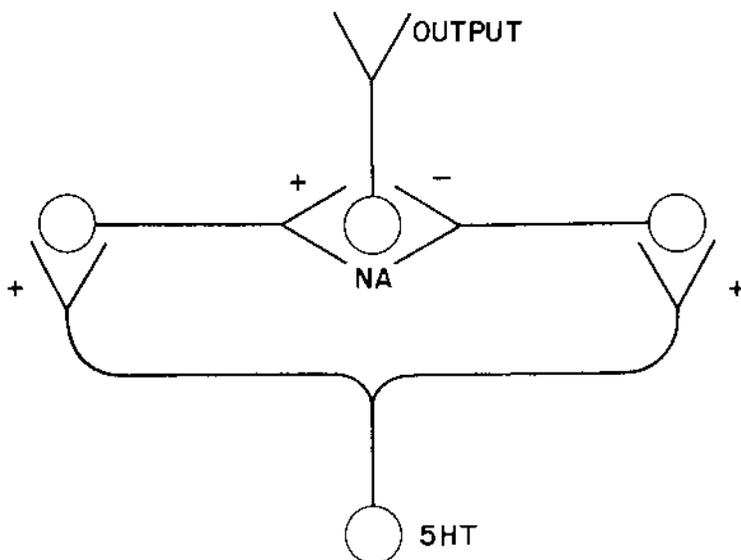
If we assume that the noradrenergic input is excitatory
but insufficient by itself to fire the output neuron, its
efficacy will depend on the fluctuations in membrane poten-
tial. If the other excitatory and inhibitory inputs to
this neuron shown in the figure both fire at a high rate,

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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 af-
fect; serotonin depletion permits mood swings but noradren-
aline 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:
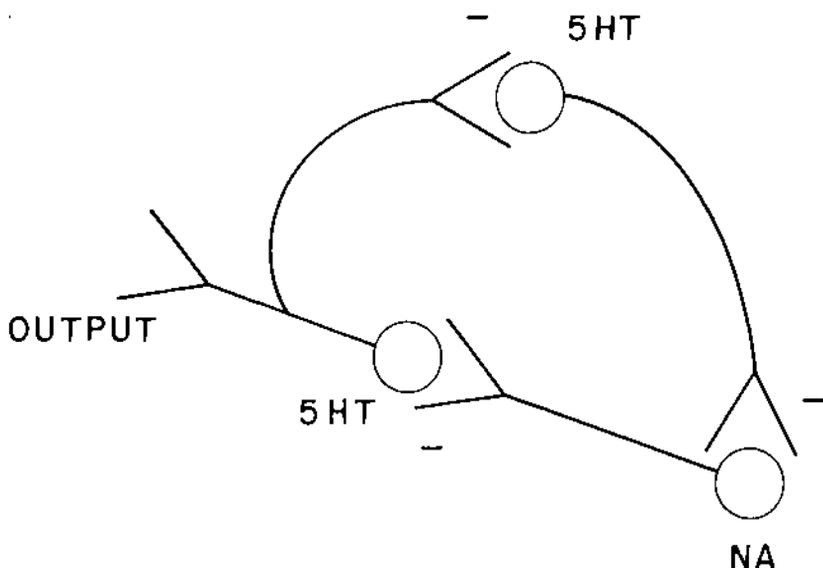
The overall action of the feedback control pathway is in-
hibitory, because $(-1)^3$ is negative. Serotonin would serve
to stabilize the noradrenergic system against fluctuations
but it might not directly influence the level of effector
activity. A serotonin blocker, for example, would disin-
hibit the 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 po-
tentiate 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, how-
ever, 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. Phenothia-
zines excite the dopamine-receptive neuron by blocking in-
hibitory synaptic input, and therefore indirectly inhibit
the cholinergic interneuron. The interneuron was not fir-
ing before the inhibition, so it is certainly not firing
now; therefore, anticholinergics have nothing to block.
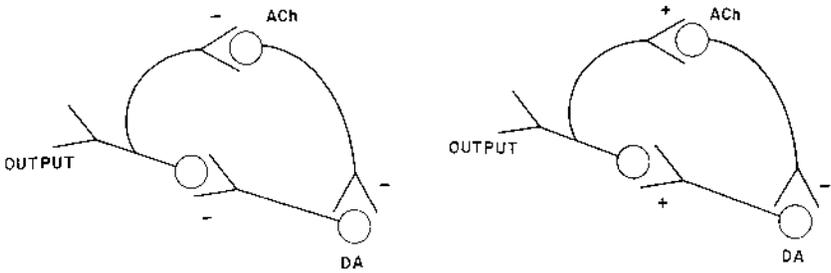
Peripheral receptors could be blocked with N-methylatropine,
although central muscarinic receptors would be affected
nonselectively. It has recently been reported that atro-
pine, locally injected into the substantia nigra, increases
neostriatal dopamine turnover, in contrast with its effects
when administered 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 fin-
ally 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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