IV. NEUROHUMORS IN PSYCHOSES*

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It has long been known that a number of drugs or chemicals are capable of inducing psychic disturbances. Recent reports on central nervous system effects of certain neurohumors and chemically related agents prompted us to investigate some humoral aspects of psychoses. Hofmann discovered that LSD-25 induces psychotic phenomena in man, a finding which was described in detail by Stoll (14). Amin and his coworkers (1) found to be present in the brain an agent which is related to LSD-25, and which was identified as serotonin (5-hydroxytryptamine). Woolley and Shaw (15) suggested that a deficiency of serotonin in the brain may cause schizophrenia. Goodman and Gilman (11) reported that in some people epinephrine produced psychic effects such as fear, anxiety, tenseness and restlessness — symptoms which to us suggested a similarity to manifestations of the manic phase of manic-depressive psychosis. They also, delineating the psychic effects of amphetamine (and other epinephrine congeners), stated that in therapeutic doses these drugs cause elevation of mood, euphoria, elation, and increased motor and speech activity; and in large dosage cause dizziness, agitation, confusion, dysphoria, apprehension, delirium, fatigue, or depression. Again, we feel that these drug effects resemble manifestations of manic-depressive psychosis. In our earlier studies, we reported that serotonin has potent neurotropic properties (6). When this agent was administered to the dog brain via the internal carotid artery, transient hemiplegia developed. Small doses of serotonin were found to cause spastic paralyses, whereas large doses produced flaccid paralyses.

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BIOASSAY METHOD:

The finding that serotonin, given in different amounts, caused neurological reflex changes that were indicative of its approximate concentration, enabled us to develop a bioassay test for serotonin and other chemicals with similar neurotropic properties.

The bioassay method may be described briefly as follows: Pairs of mongrel dogs, each animal weighing approximately five kilograms, were anesthetized with sodium pentothal. Heparin was injected intravenously to prevent blood coagulation. Both dogs were placed on an operating table in such manner as to permit a cross-circulation technique; the internal jugular venous blood of the experimental dog was conducted into the common jugular vein of the recipient dog. To prevent exsanguination of the dog, the cranial end of his left femoral artery was connected through a tube with the cranial end of the right femoral artery of the recipient dog. The systemic blood pressure of both animals was recorded by connecting their left common carotid arteries with two separate manometers. The intensity of the quadriceps tendon reflex of the dog was quantitatively measured by placing an automatic reflex hammer (giving impulses in intervals of five seconds) over each tendon, and by attaching a pneumograph to the distal ends of the right and left legs. Recordings were made with a kymograph. Pain responses were elicited by touching the outer margin of the eyelid and cornea with a hair. Upon completion of the surgical procedures, the animals were kept under light sodium pentothal anesthesia throughout the experiment.

The desired level of anesthesia was maintained by administering just enough sodium pentothal intravenously to sustain optimal and regular quadriceps tendon reflexes of the right (ipsilateral) hind leg. The drug effects upon the cerebral motor centers were measured by recording the intensity of the contralateral tendon reflex. The anesthetic was administered into the left femoral veins via cannulae. Serotonin and other chemicals with similar neurotropic properties, as well as physiological saline for the control, were injected into the cannulated left internal carotid artery of the dog.

RESULTS:

In previous publications, we have reported that the dose-effects produced by serotonin constitute an irregularly descending partial depression of the central nervous system (8, 9). Epinephrine produced

similar effects, but unlike serotonin, even in small doses, it caused a transient elevation of the blood pressure (10).

To establish whether serotonin and epinephrine may play a role in psychoses, fifty-two samples of cerebrospinal fluid from nonpsychotic and psychotic individuals were bioassayed in double-blind tests. As a result of this study we reported that the cerebrospinal fluid of schizophrenics contains varying amounts of substance with neurotropic properties which cannot be distinguished from those of serotonin by our bioassay method (8, 9). Particular concentration ranges of this neurohumor were indicative of particular schizophrenic reaction types. None of this agent was found in cerebrospinal fluid samples taken from nonschizophrenic individuals.

The cerebrospinal fluid of manic-depressive psychotics of the manic type contained small amounts and the cerebrospinal fluid of patients of the depressive type relatively large amounts of an agent with neurotropic properties similar to those of epinephrine (10). In control tests neither a serotoninlike nor an epinephrinelike agent could be found in the cerebrospinal fluid of mentally normal individuals (8, 10).

It was therefore concluded that an agent having the neurotropic properties of serotonin is involved in the pathology of schizophrenia; and that an agent having the neurotropic properties of epinephrine plays a role in manic-depressive psychosis.

EXPERIMENTS WITH SEROTONIN, EPINEPHRINE, AND ITS CONGENERS:

To arrive at an understanding of the mechanism by which serotonin and epinephrine act on the brain, the two agents and their congeners, LSD-25, amphetamine, and mescaline were studied in a series of experiments.

The method was adapted from that of Brodie and Shore (2). Rabbits weighing 1.5 to 2.5 kilograms were used as experimental animals. One hundred milligrams per kilogram body weight of iproniazid – a monaminoxidase inhibitor – were injected intravenously in order to prevent the enzymatic metabolization of subsequently administered serotonin or epinephrine. No behavioral changes due to treatment with this drug could be observed. Two hours after iproniazid administration, serotonin or epinephrine was injected in increasing dosage by the same route. Chemically related drugs, such as LSD-25, ampheta-

mine, or mescaline were given intravenously in increasing doses to rabbits not pretreated with iproniazid or other drugs.

RESULTS:

The animals exhibited the following symptoms and signs (Table I): (*a*) In minute doses, the pain responses became sluggish. (*b*) In small doses, the neurological reflexes became exaggerated. (*c*) In medium doses, the pain responses became further reduced, while neurological reflexes appeared to be normal. (*d*) In high doses, pain responses were partly abolished, while the neurological reflexes were depressed. (*e*) In very high doses, pain responses were almost completely abolished and neurological reflexes were absent. The type and sequence of these reflex changes seem to indicate that the drugs cause a dose-related progressive depression of the brain, from the highest down to the lowest strata in the following order: (*a*)Highest cortical centers. (*b*) cortical inhibitory centers; (*c*) subcortical centers; (*d*) spinal cord. (*e*) Medullary centers.

This irregularly descending depression of the central nervous system is very similar to that caused by other central nervous system depressants such as ethanol and anesthetics of the aliphatic series. There are, however, important differences between the neuropharmacological properties of serotonin, epinephrine and their congeners and those of the anesthetics.

The former do not induce unconsciousness, nor do they abolish all functions of one brain stratum before affecting the next lower one. This peculiar phenomenon could be interpreted as being the result of a selective depression of serotonin- or epinephrine-sensitive synapses. In other words, it appears likely that some synapses in the brain are sensitive to serotonin only (serotonergic), some are sensitive specifically to epinephrine (adrenergic), and some are not affected by either serotonin or epinephrine. All synapses, however, seem to lose their impulse-transmitting property by the action of general anesthetics. The fact that both serotonin and epinephrine are capable of interfering with synaptic functioning has been shown by Marrazzi and his coworkers (12, 13).

Serotonin and epinephrine, as well as their congeners, affect the autonomic nervous system directly – a property which is not shared by the anesthetics of the aliphatic series in low or medium doses. Although both serotonin and epinephrine are capable of inducing an ir-

TABLE I

Drug	Dose ranges	Pain threshold (corneal reflex mechanical press)	Neurological reflex changes (righting reflex knee jerk)	Autonomic reflex changes (heart-resp. rate)	Progressing depression of brain centers
Serotonin	minute	slightly elev.	none	none	highest cortical
Mescaline	"	" "	"	"	" "
LSD-25	"	" "	"	"	" "
Epinephrine	"	" "	very slightly exaggerated	very slightly increased	" "
Amphetamine	"	" "	"	"	" "
Serotonin	small	elevated	exaggerated	none	cortical inhibitory
Mescaline	"	"	"	"	" "
LSD-25	"	"	"	"	" "
Epinephrine	"	"	"	increased	" "
Amphetamine	"	"	"	"	" "
Serotonin	medium	further elev.	seemingly normal	none	subcortical
Mescaline	"	" "	" "	"	"
LSD-25	"	" "	"	"	"
Epinephrine	"	"	" "	increased	"
Amphetamine	"	" "	" "	"	"
Serotonin	high	further elev.	depressed	none	spinal cord
Mescaline	"	" "	"	"	" "
LSD-25	"	" "	"	"	" "
Epinephrine	"	" "	"	increased	" "
Amphetamine	"	" "	"	"	" "
Serotonin	very high	further elev.	absent	depressed	medullary
Mescaline	" "	" "	"	"	"
LSD-25	" "	" "	"	"	"
Epinephrine	" "	" "	"	"	"
Amphetamine	" "	" "	"	"	"

TABLE II

Dose-Effect Responses of Iproniazid-Pretreated Rabbit to Serotonin

Effect on:	0.000,000,01 μg = 0.01 μg	0.01 as 1 μg	1 - 10,000 μg	10,000 μg and more
General behavior	sedation and prostration	excitement	sedation and prostration	sedation and prostration
Responses to touch or noise	unchanged	exaggerated	- -	- - -
Pain reflexes	-	- -	- -	- - -
Motor activity	- -	+ + +	- - -	none
Neurological reflexes	unchanged	+ + +	- - -	absent
Righting reflex	present	present	sluggish	none
"Catalepsy"	brief	none	long	long
Respiratory rate	normal	+ +	- -	- - -
Heart rate	"	+ +	- -	- - -
Eye	enophthalmos	exophthalmos	enophthalmos	enophthalmos
Pupil	miosis	normal	miosis	miosis
Palpebral fissure	ptosis	widening	ptosis	ptosis
Vision	apparently normal	apparently normal	apparently blind	apparently blind
Pilomotor response	none	present	none	none

\+ Slightly increased
\+ + increased
\+ + + markedly increased
\- slightly decreased
- - decreased
- - - markedly decreased

"Catalepsy" denotes animal remains in unnatural position (forelegs behind ears).

(Mescaline given intravenously produces analogous manifestations in the rabbit having not been pretreated.)

TABLE III

Dose-Effect Responses of Iproniazid-Pretreated Rabbit to Epinephrine

Effect on:	0.000,000,000,01 μg	0.000,01 - 10 μg	10 μg - 10,000 μg
General behavior	excitement	excitement (spells of sedation)	prostration
Responses to touch or noise	exaggerated	exaggerated	none
Pain reflexes	-	--	- - -
Motor activity	+ + + insecure	+ + (-)	- - -
Neurological reflexes	+ +	+ (-)	- - -
Righting reflex	present	present	absent
"Catalepsy"	none	none	long duration
Respiratory rate	+ + +	+ (-)	- - -
Heart rate	+ + +	+ (-)	- - -
Eye	exophthalmos	exophthalmos	normal
Pupil	dilatation	dilatation	normal
Palpebral fissure	widened	widened	normal
Vision	apparently normal	apparently normal	apparently blind
Pilomotor response	present	none	none
Tremors	present	present	none

\+ slightly increased

\+ + increased

\+ + + markedly increased

\- slightly decreased

-- decreased

- - - markedly decreased

(-) shows occasional spells opposite to the predominant response.

"Catalepsy" denotes animal remains in unnatural position (forelegs behind ears).

(Amphetamine and LSD-25 given intravenously produce analogous manifestations in the rabbit having not been pretreated.)

regularly descending, partial depression of the central nervous system, they differ markedly in the overt symptoms they produce in similar dose ranges (Tables II and III). Serotonin in increasing dosage produces several distinguishable phases of central nervous system depression, whereas epinephrine induces only two main phases of depression: The first phase consists of excitement, owing to depression of the cortical inhibitory centers; the second, in markedly decreased motor activity resulting from a depression of lower brain strata.

The striking similarity between the effects of serotonin and epinephrine on the animal brain and the central nervous system changes produced by their congeners in humans, together with our finding of a serotoninlike agent in the cerebrospinal fluid of schizophrenics and of an epinephrinelike substance in that of manic-depressive psychotics, led us to formulate the following tentative working hypotheses.

HYPOTHESES:

1. *Schizophrenia* appears to be the result of intracranial release of serotonin or a similar agent, possibly induced by a derangement of some brain chemistry or psychogenic factors (5):
   a) Impairment of rational thinking, judgment, etc., seems to be due to minute amounts of serotonin depressing highest cortical centers.
   b) Excitement and hallucinations appear to be due to small amounts of serotonin depressing cortical inhibitory centers.
   c) Catalepsy seems to be due to large amounts of serotonin partially depressing cortical, subcortical, and spinal functions.
2. *Manic-depressive psychoses* appear to be the result of intracranial release of epinephrine or a similar agent, possibly induced by a derangement of some brain chemistry or psychogenic factors (5):
   a) The manic phase seems to be due to small amounts of an epinephrinelike agent depressing certain higher cortical centers and cortical inhibitory centers.
   b) The depressive phase appears to be due to large amounts of an epinephrinelike agent depressing cortical as well as lower brain centers.

REMARKS ON POSSIBLE INTERACTION BETWEEN ATARACTICS AND NEUROHUMORS:

This concept of central serotonin and epinephrine action seems to be supported by some clinical and laboratory findings resulting from

investigations of ataractics. The modern tranquilizing agents produce no overt psychic effects in mentally normal, nonexcited individuals. Given in doses sufficient to calm excited psychotics, they do not markedly impair cerebral cortical functioning; thus they must be assumed to differ in action from general anesthetics such as barbiturates, which are known to sedate patients through central nervous system depression. Clinical observations have shown that the ataractics are different in action not only from the anesthetics, but also exhibit differences among themselves; e.g., patients receiving the tranquilizer chlorpromazine appear to be more sedated than those given reserpine.

The finding of Brodie and coworkers that reserpine causes almost complete elimination of serotonin and epinephrine (4), and our finding that chlorpromazine enhances the central nervous system depressant effect of both these neurohumors (6, 7), seem to indicate that these two ataractics cause tranquilization through their influence upon the neurohumors, but by opposite actions. This fact also seems to be supported by the findings of Brodie and others (3). The tranquilizing effect of reserpine could thus be explained by its property of eliminating the neurohumor which caused a depression of the cortical inhibitory centers. Chlorpromazine would tranquilize by enhancing the central nervous system depressant effect of either serotonin or epinephrine to such a degree that even the subcortical centers become depressed.

Finally, it remains to be emphasized that the foregoing findings do not represent a solution to one of the most perplexing problems in medicine, but serve as working hypotheses to be substantiated by further evidence.

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