Another Look at Neurosis

A REVIEW ARTICLE

BY

JIM JONES

Professor of Physiology, University of Rhodesia.

Neurosis is a disturbance of the mind in which the patient retains contact with reality (Sims, 1968), that is to say, he can still appreciate that his fears or worries are unfounded although, nevertheless, disturbing. Once contact with reality is lost, the disease progresses and enters the more serious category of psychosis. Psychiatric disturbances are becoming increasingly common in society, a change attributed to the greater "stress" of modern life. In Britain a quarter of the patients attending the general practitioner have a predominantly psychiatric complaint (Valentine, 1965), a trend that we can expect to follow as this country "develops". According to the World Heath Organisation's International Classification, the two most common neuroses should be called anxiety reaction and neurotic depression. This classification implies that there are two distinct conditions, and yet it is common experience that anxiety and depression are closely associated and that they often occur together in the same patient. The psychiatrist interprets anxiety as a failure to adapt to a threat from the outside world or a threat from incompletely repressed desires that are struggling to reach consciousness. Depression, on the other hand, is said to be the consequence of an unsatisfied desire for admiration and the attendant threat to one's self-esteem (Sims, 1968).

Although this type of explanation may satisfy a psychiatrist, I feel that a physiologist should attempt a more rational, mechanistic solution. Id and super-ego apart, the brain is nothing more than a mass of interconnected nerve cells: all mental activity, whether healthy or diseased, is essentially a pattern of nerve impulses, admittedly, involving some ten thousand million nerve cells. The recent explosion of psychotropic drugs has thrown some light on this problem; so far as one can tell, these drugs exert their various effects on the individual nerve cells. The sum total of the changes in each particular cell summate to produce an alteration in the patient's mental outlook and emotional stability.

The effects of these drugs cannot be understood without a brief consideration of nerve physiology. The nerve cell is adapted to transfer information as a very simple code consisting of brief pulses of electricity, equivalent to the "dots" in the Morse code. The only possible variation in the message is the number of "dots" transmitted per second;
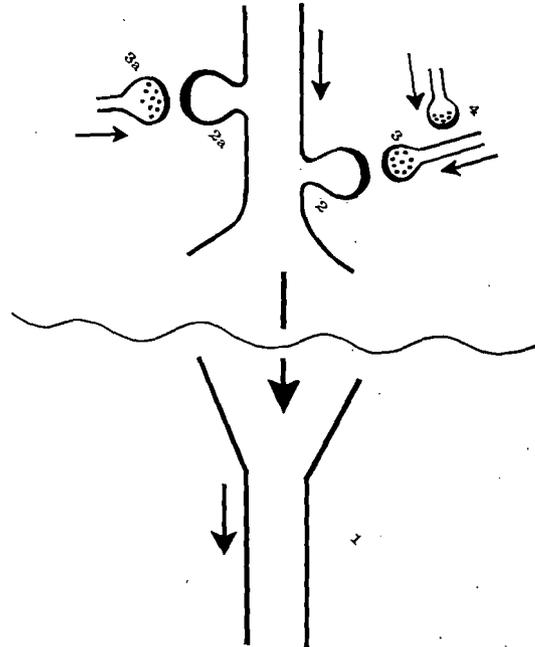

Fig. 1—Represents the structures concerned with synaptic transmission. The nerve impulses arrive at the synapse through the incoming nerve fibres and release either excitatory transmitter at excitatory endings (3) or inhibitory transmitter at inhibitory endings (3a). These transmitters either increase or decrease the activity of the post-synaptic nerve cell by their effect on the spines (2 and 2a). If the overall effect is to stimulate the post-synaptic cell, it transmits an impulse through its outgoing fibre (1). Pre-synaptic endings (4) applied to the incoming fibres can either increase or decrease the amount of transmitter that they release.

the possible recognisably different messages are limited to about ten clearly distinct frequencies.

The whole complexity depends on the enormous number of separate cells rather than on the special properties of individual cells. The nerve cells are interconnected so that each neuron is attached to another 300 neurons, and through them to the whole of the nervous system. The nerve fibre which carries the message is relatively unexciting, not much more than a telegraph wire. All the capacity for more complex functions depends on the intercellular connection called synapses. We must look more closely at the synapse if we are to understand the workings of the mind.

A rather superficial view is that each nerve fibre terminates in a collection of about 100 synaptic buttons which are applied to the surface of the next nerve cell and convey the message to it. In practice, the situation is far more complex. Many of the synaptic buttons are applied to specialised structures called spines which cover part of the surface of the post-synaptic nerve cell (Bradley,

1968). The buttons themselves come in two varieties: stimulators (which increase activity) and inhibitors (which reduce or prevent activity). There is a further complication: the buttons may be applied to nerve fibres *before* they reach the synapse, and again these "pre-synaptic" buttons can be either stimulatory or inhibitory — they can either enhance or oppose the transmission of information through the nerve fibre to the post-synaptic cell (Fig. 1). The interaction of these four fundamental processes (pre- and post-synaptic stimulation and inhibition) occurring at each of the 30,000 nerve endings impinging on each nerve cell determines the level of its activity, whether it will transmit a message at all and, if so, at which of ten possible frequencies.

A fundamental physiological discovery has been that all the changes which occur at the synapse depend on the release of chemical substances

Table I

TRANSMITTERS IN THE CENTRAL NERVOUS SYSTEM

Transmitters	Neuron	Action	Potentiating Drugs	Effect	Opposing Drugs	Effect
Acetylcholine	Cortex (20%) Reticular formation	+ +		Anxiety	Hyoscine	Sedation
	Direct Sensory path	—	Parathion	Tremor	Hyoscyamine	Less rigid
	Hypothalamus Basal ganglia Cord Cerebellum	+ + + +		Convulsions	Barbiturates Anaesthetics	Sleep Anaesthesia
Noradrenaline	Cortex	—	Amphetamine Ethanol Cocaine	Euphoria	Phenothiazine Propranolol Reserpine	Sedation
	Reticular formation	+	Dibenzazepine Phenelzine		Methyl- dihydroxy	Depression
	Cord Hypothalamus	+ + (—)	Electro- Convulsions	Elation	phenyl-ethyl- amine	Anxiolysis
Serotonin	Reticular formation	+ or —	Dibenzazepine	Euphoria	Reserpine Phenothiazine	Depression Sedation
	Hypothalamus Cord	+ —	Phenelzine Lithium	Elation	Lysergic acid di-ethyl-amide	Hallucination
Dihydroxy phenyl-ethyl- amine	Basal ganglia	—	Dihydroxy- phenyl-alanine Phenelzine	Less rigid Aggression	Haloperidol	Less tics Anxiolysis

called transmitters (Eccles, 1965); they are synthetised in the synaptic buttons by enzymes that migrate down the nerve fibre from the body of the nerve cell, where their formation was controlled by acids associated with the nucleus. The first synaptic transmitter to be recognised was acetylcholine, but very many more have now been identified, notably the amines (including noradrenaline, adrenaline, serotonin, dihydroxyphenyl-ethylamine and histamine) and the aminoacids (e.g., glycine, glutamic acid and gammaamino butyric acid) (Hebb, 1970). With the exception of the aminoacids, the putative transmitters can probably exert all four of the possible transmitter actions (i.e., pre- and post-synaptic stimulation and inhibition). The distribution and action of the transmitters are shown on Table I.

The synaptic connections and transmitters that I have described are in no way fixed or irrevocable: both can be modified in relation to past experience — indeed, this seems to be the basis of learning (Barondes, 1965). The repeated use of a particular synaptic connection leads to a change in its structure (an increase in the number of the spines and a decrease in the size of the buttons) and also a change in the chemistry of the associated cells; they synthetise more nucleic acids which are probably associated with the formation of more and different transmitters. These structural and chemical changes lead to more efficient transmission across the synapse so that the effect of repeated activity is to establish a "favoured" pathway, i.e., a semipermanent change in the nervous system. Subsequently, a lack of activity or a neglect of this path leads to its gradual reversion to its previous character; we can say that the lesson has been forgotten. An alternative, but essentially complementary view of the learning process, is that the failure to use inappropriate pathways leads to a permanent state of inhibition; learning represents the elimination of surplus and unwanted data, a theory somewhat reminiscent of the clonal selection theory for the "memory" cells of the immunological system (Young, 1970).

Although these changes can occur at every synapse in the nervous system, certain parts of the brain appear to be specialised to retain information; they are more particularly concerned with memory. The limbic complex, including the allocortex, is developmentally associated with the sensation of smell, but it has evolved into a system for regulating memory and the appropriate emotional response to any given situation. The limbic complex includes a rather involved (Papez) pathway from the hippocampus through the fornix, to the mammillary bodies to the thalamus, to the cingulate gyrus and temporal lobe; this path-

way is concerned with storing new information and with the recall or retrieval of recent memories. Before leaving the subject of memory I must at least mention the holographic theory; it maintains that memory and, indeed, brain function in general is much less localised than is generally believed. Mental activity of almost any kind involves the whole of the nervous system to a greater or lesser extent, so that a memory would not so much be accompanied by a specific change in a relatively few synapses but rather, by a generalised change, widely distributed throughout the brain. Probably both views are partly correct: localised damage in the Papez circuit can produce profound disturbances of memory, whereas widespread lesions throughout the brain can result in a more generalised loss of function.

Probably the most important aspect of current neurological research is an attempt to explain the action of drugs on the nervous system through their effects on synaptic transmission. A good example is paralysis agitans, a disease which is due to an imbalance between dihydroxy-phenylethyl-amine in the caudate nucleus and acetylcholine in the globus pallidus of the lentiform nucleus (Bradley, 1965). An interpretation of the psycho-neuroses based on transmitter function is not so well established. The two main syndromes of anxiety reaction and neurotic depression can be regarded as complementary: anxiety represents an overactivity of the reticular system, whereas depression is the reverse, a suboptimal level of reticular activity. To correct these diseases it is necessary to reduce activity in the first case and to enhance it in the second. All the main central nervous system transmitters (acetylcholine and the amines) appear to increase reticular activity (Table I), so that depression is alleviated by potentiating their effect, whereas the state of anxiety is more likely to be relieved when their action is blocked. This theory provides a rationale for the pharmacodymics of the tranquillising and antidepressant drugs. Tranquillisers (anxiolytics) can act in a variety of ways: the cholinergic postsynaptic receptor may be blocked (hyoscine); the adrenergic post-synaptic receptor may be blocked (phenothiazine, propranolol); the synthesis of adrenergic transmitter may be distorted or inhibited (methyl-dihydroxy-phenyl-ethylamine), or the store of amine transmitter may be depleted (reserpine). Conversely, depression can be mitigated by enhancing the transmitter's action by releasing adrenergic transmitters (amphetamine, ethanol), by increasing the response of the adrenergic post-synaptic receptor (cocaine), by preventing the resorption of the amine transmitter into the synaptic buttons (dibenzazepine) or by

preventing the destruction of the amine transmitter (phenelzine) (Hollister, 1970).

Unfortunately it is only too common to find that a patient presents with anxiety coupled with depression; it is hardly surprising that there is no satisfactory method for combating both complaints simultaneously, although very favourable reports on doxepin (di-methyl-di-benz-oxepin-propylamine) are now being received (O'Reilly, 1970).

In Britain the consumption of sedatives (mainly barbiturates) has remained relatively steady (over the last eight years) at 30 million prescriptions per year, whereas there has been an enormous increase in the use of tranquillisers (from five to 15 million per year over the same period). Ten per cent. of the British population relies on psychotropic drugs to overcome the stress of modern existence (Dunlop, 1970; Roth et al., 1970). I find the distinction between sedative and tranquilliser rather artificial: according to Sims (1968), a tranquilliser sedates without "lowering the level of consciousness" (i.e., reticular activity), and yet he recommends a barbiturate (the paradigm of sedatives) as being more effective than tranquillisers in relieving anxiety. On the other hand, the *Practitioner* (Dally, 1970) advocates nitrazepam as the safest hypnotic and a decided improvement on barbiturates; yet nitrazepam is a simple derivative of diazepam, a typical tranquilliser.

If depression can fairly be regarded as the consequence of an inadequate release of excitatory transmitter within the nervous system, then the obvious remedy should be to administer the transmitter itself rather than its potentiator. This simple solution can never be effective because transmitters given systemically cannot pass from the blood to the brain; they are opposed by the blood-brain barrier (capillary endothelium and astrocytes) and the blood-cerebospinal fluid barrier (choroid epithelium) which protect the brain from inadvertent exposure to fortuitous transmitter liberated in other parts of the body. These barriers appear to be deficient in the hypothalamus and allow an intravenous injection of transmitter to act on this part of the brain alone. Acetylcholine, for example, has a tranquillising effect by I.V. injection, whereas an increase in the general level of acetylcholine (as in parathion poisoning) leads to anxiety and restlessness (Sims, 1968). On the whole, drugs introduced directly into the brain have an entirely different effect than when they are injected intravenously (Feldberg, 1968).

Although I may have given the impression that each transmitter has a single predominant effect on mental activity, this is far too simple a view. With few exceptions, each transmitter can exert a variety of synaptic effects depending on which particular neuron is involved. Neither acetylcholine nor the amines are invariably excitatory; each of them can stimulate one population of nerve cells and at the same time inhibit another. Once this has been appreciated it is no longer a surprise to find that a particular transmitter can produce a bewildering variety of often antagonistic effects and that drugs which modify the release, storage or action of the transmitters are commonly unpredictable in their properties. One should not consider dibenzazepine, for example, as a drug that relieves depression by increasing the amine level of the brain, but rather that it favours the action of the transmitter amines at certain synapses which, on balance, leads to a heightening of the mood.

CONCLUSION

The fact that drugs, which are known to alter synaptic transmission in the central nervous system, have a profound effect on the mental and emotional state of a patient provides strong evidence for psychoneurotic disorders being fundamentally biochemical in nature (Coppen, 1970). It holds out the hope that when we can identify the exact nervous pathways that are concerned with each and every aspect of personality, mood and mind it will be possible to select the appropriate drug to counter a disturbance in synaptic transmission and defeat the growing spectre of mental disease.

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