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Original Articles

THE USE OF ANTI-DEPRESSIVE DRUGS

By

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THE diagram, which has no relation to brain structure, represents the way in which, in terms of function, mood is regulated by a mechanism which is disordered in cases of pathological elation and depression. It illustrates the points in the regulation mechanism at which physical treatment with different agents can be applied. This theoretical model reconciles the following observations:

1. E.C.T. produces little immediate effect at first in severe cases, but the depression *gradually* lifts and may proceed to elation if E.C.T. is not discontinued. Until the normal mood level is reached there is a slow relapse after each treatment. If treatments are spaced out too far, only temporary improvement occurs.
2. The indirect anti-depressive drugs (including the amino-oxidase inhibitors) such as Tofranil, Nardil, Cavodil and Niamid produce their effects after a period of time and then only if the dose is higher than a threshold level peculiar to each individual. The amino-oxidase-serotonin theory is not referred to here, as it is not established in detail.
3. Amphetamines and sympatheticomimetic (direct anti-depressive) drugs give symptomatic relief *at once*, but only in the less severe depressives. The relief occurs only while the drug is circulating in adequate concentration.
4. Lithium salts have a highly specific but purely symptomatic action on pathological elation. Once the concentration of lithium falls below threshold, elation reappears. Lithium salts do not produce characteristic depression in normal subjects.

* Among the papers left by Professor Kennedy at his sudden and untimely death, was one which bore evidence of more drafting and re-drafting than any other. He had spoken of his belief that the theoretical model he was attempting to construct might prove to be his most important contribution to psychiatry. Unhappily this was not to be. What he did leave, however, is being published here as a fragmentary contribution by Alexander Kennedy to our understanding of the treatment of depression.

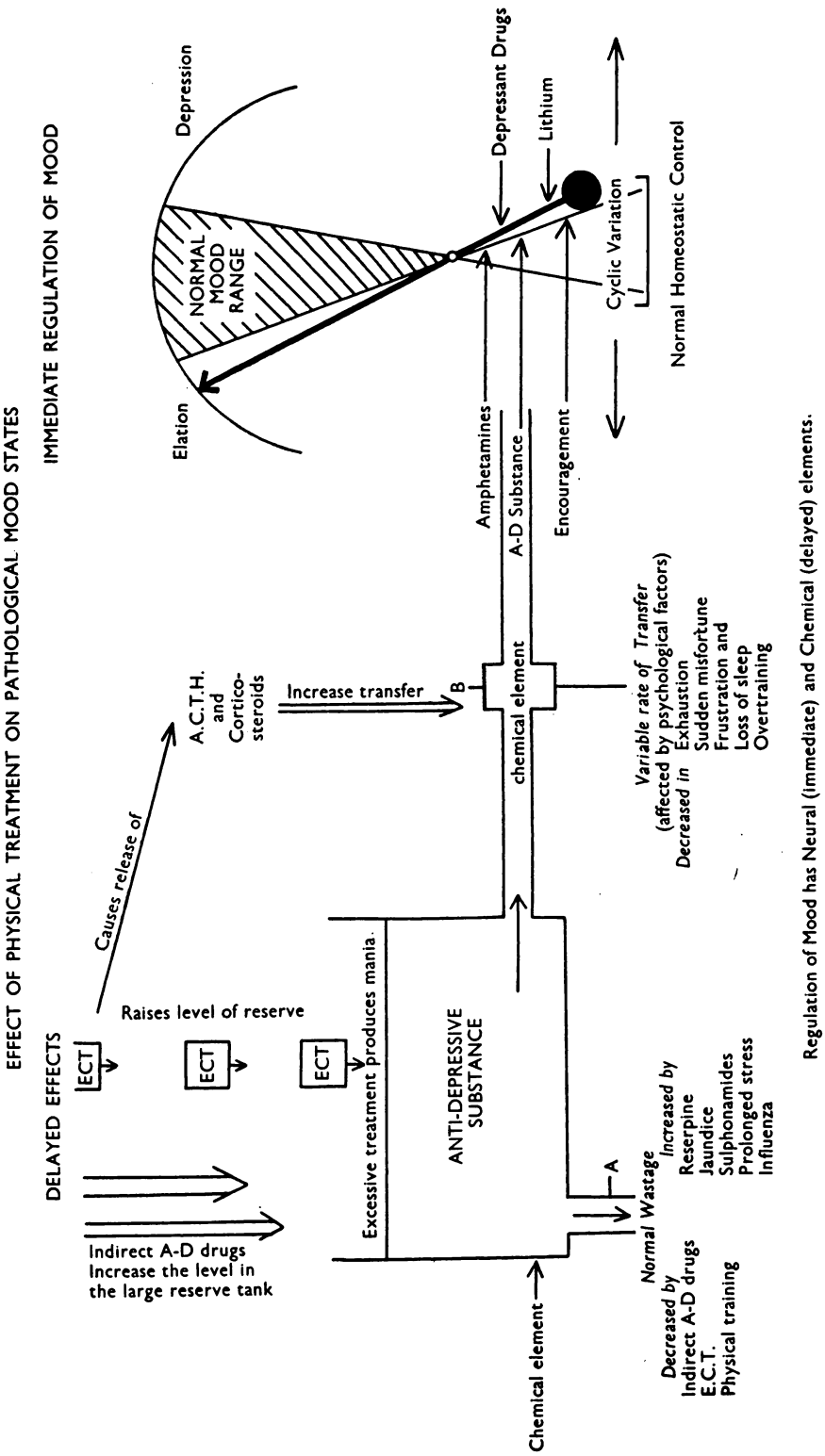
Denis Leigh

5. The depression brought on by reserpine comes on rapidly in predisposed subjects, but only after the drug has been given for weeks or months. There is no immediate depressing action. Once depression is established, it does not clear up at once if reserpine is stopped.
6. Depressives may get complete relief temporarily if they have to act in a crisis. A.C.T.H. and corticosteroids produce euphoria in some normal people. They are adjuvant to E.C.T. in depressives. They do not produce remission in severe depressives.

Theoretical Basis of the Diagram

In this theoretical visual statement, the following assumptions are made:

1. That the regulation of the prevailing mood-state within normal limits is controlled by a homeostatic mechanism which has or has had a survival value. Variations in mood are normal within certain limits and may show diurnal, menstrual and seasonal fluctuations. Pathological elation and depression may or may not show a comparable periodicity.
2. When pathological elation and depression occur, the normal operation of mood control is evidenced only by the periodic variations usually seen. There is evidence that some part of this mechanism is located in the central regions and that the thalamus and mamillary bodies are involved in it.
3. The hypothalamic-pituitary mechanism which is responsive to environmental changes and controls the bodily state by both autonomic and endocrine pathways is concerned with mood change within healthy limits. Neither steroids nor sympatheticomimetic drugs, however, can relieve pathological depression or elation.
4. A substance exists (A-D), the lack of which causes depression (or a balance between substances is disturbed). Reserpine, sulphonamides, antimony salts and jaundice lower the level of this substance until none is available for maintaining the normal mood. When this state is reached, direct anti-depressives such as amphetamine cease to be effective, but indirect anti-depressives will work in time.
5. E.C.T. and the amino-oxidase inhibitors must either increase the production of anti-depressive substance or slow its normal rate of wastage.
6. The rate at which A-D substance is available to the rest of the nervous system is influenced over short periods by adrenaline and noradrenaline, and over longer periods by corticosteroids. Once the mood-state has got well beyond the normal range limits, these substances have little effect.
7. Attacks of depression and elation are almost always self-limiting in time. Physical treatment cannot affect the constitutional tendency, but can cause each attack to remit earlier than it would do spontaneously.
8. The sudden onset of many attacks of severe depression suggests that there is some sort of *threshold effect*. The results of using anti-depressive drugs which produce no improvement for several days before remission occurs also suggest that a threshold level of some substance is necessary before recovery takes place. The effect of drugs such as reserpine which destroy A-D gives the same impression.
9. Once, as the result of treatment, the mood-state reaches the normal range, *the normal homeostatic mechanism can usually take over again.* The speed at which this occurs varies. In the manic-depressive cyclical constitution,



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normal regulation of mood may not be restored after the first attack, the patient having violent mood-swings for a period of years.

10. Pathological depression and elation occur in predisposed persons, and an inheritable *constitutional tendency* undoubtedly exists. This appears to take three distinct forms:

    (*a*) The manic-depressive constitution, liable to both depression and elation, lacking an effective mechanism for mood regulation and easily swinging beyond the median range in either direction.

    (*b*) Recurrent depressives, in whom the regulatory mechanism is normal between attacks. Some of these, however, are chronic depressives whose depression varies in depth but who rarely achieve a normal mood.

    (*c*) Cyclothymes, who are subject to swings of mood over a wider range than normal but who do not often develop elation or depression of psychotic intensity. These respond strongly to amphetamines and sometimes to corticosteroids.

11. *Psychological factors* are able to precipitate depressive illness in the predisposed, and within the median range to influence the mood-regulating mechanism. This mechanism is greatly influenced by the sensory intake, and although it is altered by metabolic and chemical changes its main purpose is to adapt the individual to his surroundings as he perceives them. This provides the reactive element in depression which operates in the median range of mood. It is not concerned in producing the extremes of elation and depression where the physical regulatory mechanism has broken down.

Guiding Principles Based on the Above for the Empirical Treatment of Depression

1. Mild depression can be helped symptomatically by drugs of the amphetamine group. Since most attacks of depression are self-limiting, amphetamines with barbiturates at night will, if the attack is short, give symptomatic relief for short periods until spontaneous recovery occurs. They should be used therefore when it is probable that the attack will end soon. Amphetamines produce tolerance, so that courses should not exceed three weeks.

2. Mild depression is much influenced by outside circumstances, so that help with pressing difficulties may cause improvement. Reactive and endogenous depression are, however, to be regarded as the same condition with different precipitating causes. Physical health influences mood, so that occupation and physical training can be expected to help to get normal regulation re-established.

3. Chronic and severe depression may sometimes reach a point at which it is not amenable to E.C.T. That it is not effective at one time does not mean that it will not work at another.

4. The indirect A-D drugs can be used successfully by reference to the explanatory diagram. This does not mean that the diagram portrays what is going on in the nervous system. It presents a caretaker hypothesis which can be used until more is known. It is in accord with the empirical facts of treatment.

5. Once the initial dose has caused normal mood to be regained (i.e. the reserve tank is now full of A-D substance), a maintenance dose must be found which will just keep it full. If this is not adequate it will produce no effect at all because it does not bring the reserve up to threshold level.

6. Side-effects of A-D drugs are immediate, while the therapeutic effect is much delayed. This is a state of affairs which the patient finds difficult to appreciate. *It is virtually impossible for a patient to regulate his own dosage in the early stages of treatment.* He becomes confused between the direct effects and those which come on later. This is especially so in those drugs (e.g. Cavodil) in which there is an immediate as well as a remote effect in mood.

7. It is quite impossible to regulate dosage if amphetamines are given at the same time. They are therefore contra-indicated for this reason alone. If both drugs are used, a proportion of patients develop severe headache.

8. Dosages of the A-D drugs are even more difficult to establish when complications, such as torsion-dystonia, cataplexy and paralytic ileus occur during the initial high-dosage period of treatment. They are, however, rare at the maintenance level of dosage.

9. There appears as yet to be no reason why, if necessary, these drugs should not be given at maintenance level for long periods. Unless the patient has had previous attacks or the family history shows a definite pattern of attack, it is quite impossible to tell how long the attack would have lasted if left untreated. Reduction of the dose with a view to continuing the drug can therefore only be by trial and error. Rapid reduction may precipitate severe depression.

10. Each drug has its own side-effects, complications and syndrome of over-dosage. It will sometimes be impossible to avoid over-dosage in the early stages. If signs of this appear, the drug must not be stopped altogether but reduced gradually if severe relapse is to be avoided. The effect of a change of dose will not be experienced at once, as is evident from the diagram.