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BRISTOL · JOHN WRIGHT

MENTAL DISEASE

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SCREENING TESTS

Thomas (1979) has provided a useful review of screening tests applied to admissions during one year to Withington Hospital, Manchester: 73 per cent of new admissions were given some form of screening test; 202 were given serological tests for syphilis. None of the six abnormal results was considered aetiologically relevant to the psychiatric disorder or in need of treatment. This finding is similar to that of Banks (1968). Thyroid function tests were given to 145 patients and the 21 abnormal results led to treatment of 2 patients for hypothyroidism, and of 1 patient for hyperthyroidism. This is in line with the findings of McLarty et al. (1978), who found a rate of 0·7 per cent for hyperthyroidism and of 0·5 per cent for hypothyroidism in psychiatric in-patients. In the latter survey the hyperthyroid cases were clinically obvious whereas many of the hypothyroid cases were not—possible examples of 'myxoedematous madness' (Asher, 1949).

In the Manchester study 99 investigations of vitamin B_{12} and folate gave 20 abnormal results, none of which was considered aetiologically relevant. This absence of 'megaloblastic madness' confirms the experience of Rose (1976) and of Phaure and Maltby (1976).

Two-hundred-and-fifty-one skull X-rays gave 10 abnormal results of which only 1 received further investigation, revealing a small pituitary tumour thought to be unrelated to the psychiatric disorder. Here the Manchester results confirm the study of Delaney (1976), who questioned the value of routine skull X-rays in psychiatry. No doubt many patients are now undergoing routine computerized axial tomography and one hopes that a well-planned study of this investigation is being carried out somewhere.

Further investigations in Manchester included 326 chest X-rays, 417 haemoglobin investigations, 329 erythrocyte sedimentation rates, 332 electrolytes and urea, 397 liver function tests and 397 biochemical profiles. These investigations revealed a certain amount of coincidental disease and also some effects of the altered fluid and food intake which occur in psychiatric disease, and also possibly some effects of psychotropic drugs on liver function.

It is perhaps disappointing that in none of the 622 admissions at Withington did a screening test discover some exciting physical disease which could account for the psychiatric state. At one time there was a vogue for the role of calcium in the aetiology of psychiatric illness because of the psychiatric abnormalities noted in patients with primary hyperparathyroidism and related disorders. However, a study by de Torrente and Scherrer (1973) of 500 psychiatric patients did not reveal any case of hyperparathyroidism. Nevertheless, however disappointing the results of screening, the case for thorough investigation becomes very cogent when cases of obvious physical causation of psychiatric disease are missed and eventually identified. This commonly occurs in the case of cerebral tumours (Hunter et al., 1968) and in acute intermittent porphyria which was dubbed

la petite simulatrice by Waldenström because of its tendency to mimic other conditions (Carney, 1972).

One's own experiences of missed or nearly missed diagnoses remain vividly in the memory. I can remember a 30-year-old policeman who importunately demanded drugs for abdominal pain after partial gastrectomy for duodenal ulcer. His behaviour was thought to be hysterical, particularly when a laparotomy revealed no cause for it. When he refused to get out of bed because of weakness the surgical team finally lost patience and transferred him to the psychiatric unit where the diagnosis of acute intermittent porphyria was made by the nurse who did his routine urine testing. He made quite a good recovery from his quadriplegia after several months in a ventilator. I well remember a case of Wilson's disease who had many years of psychiatric treatment and was finally transferred to a long-stay residential ward. Fortunately for him he fell and cracked a rib and X-ray showed certain abnormalities of the skeleton which then received further investigation. The patient was written up as a case of amino-aciduria and the diagnosis of Wilson's disease was made by the Editor of the journal to which the report was submitted.

One physical cause of psychiatric symptoms which is often missed is alcoholism and regular use of other drugs; and one should remember that while Mist. Pot. Brom. is still available at chemists there will be the odd case of bromism (Carney, 1971).

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PROGESTERONE AND PREMENSTRUAL SYNDROME

For a long time it has been thought that premenstrual tension and depression may be related to a deficiency of progesterone during the latter half of the menstrual cycle. Individual case reports and uncontrolled trials have given very encouraging reports of the use of various progestogens and progesterone itself in the treatment of the premenstrual syndrome. In order to test these ideas Sampson (1979) carried out a randomized controlled crossover trial in which placebo was compared to progesterone given either as suppositories or as pessaries. Thirty-two women completed two

menstrual cycles on placebo and progesterone 200 mg b.d., given usually on the 12 premenstrual days, and 24 of them completed a further 2 cycles in which the active preparation was given in a dosage of 400 mg b.d. The results were measured by daily ratings and by the retrospective view of the patients over the previous cycle; there was no significant difference between progesterone and placebo and if anything the patients seemed to do somewhat better on placebo. It is interesting that 60 per cent of patients reported being helped during the first treatment cycle whether they were on progesterone or placebo and this is similar to the success rate reported in uncontrolled trials.

The negative result in this trial is most disappointing. Premenstrual depression has long been considered a 'model illness' for the investigation of depression as a whole. The progesterone deficiency hypothesis was a good one and it is disappointing that a rigorous study has not supported it. It still seems likely that one or more of the endocrine changes during the menstrual cycle is responsible for the mood change and hopefully research will go on into this convenient little syndrome.

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TRIAL OF COMBINED ANTIDEPRESSANTS

In the introduction to their report of a randomized controlled trial of trimipramine, monoamine oxidase inhibitors and combined treatment in depressed out-patients Young and his colleagues (1979) point out that the Federal Drug Administration in the USA, the Committee of Review of Medicines in the UK, and the Drug Manufacturers themselves all warn against combined treatment with tricyclic antidepressants and MAOIs because of the possibility of severe and even fatal reactions. In spite of these warnings large numbers of patients have been treated with various combinations of antidepressants without mortality or unusual side-effects and the particular usefulness of combined treatment for patients with resistant depression has been claimed.

None of the 135 patients who entered the 6-week trial suffered from serious adverse effects. The 34 patients allocated to trimipramine plus placebo did significantly better than those allocated to phenelzine plus placebo, isocarboxazid plus placebo, or either of these two MAOIs in combination with trimipramine. The trimipramine was given in a single dose at night and the mean dosage was about 100 mg. It is interesting that patients on trimipramine required less sedation with nitrazepam than did those on other regimes. This study does not confirm the efficacy of combined antidepressant treatment, at least in the mild-to-moderate severity of depression seen in out-patients. Combined treatment is usually used on an in-patient basis for very severe cases of depression, often as an alternative to ECT; possibly the negative result of this trial will give ethical justification for a trial of combined treatments in the more severe depressions.

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BIOLOGICAL FUNCTION OF DEPRESSION

A challenge to sociobiology

The last decade has seen the development of sociobiology (Wilson, 1975) as a discrete discipline out of its origins in comparative ethology and population genetics. The next decade promises more developments in our thinking about the evolutionary aspects of social behaviour, and this would seem an appropriate moment to summarize some views which have been expressed sporadically over the past 50 years concerning the social function of those kinds of behaviour which are defined clinically as depressive reaction and depressive illness. Statements about the biological function of a piece of behaviour—or even of a structure—have an equivocal scientific status in that they are not readily refutable. Popper places them in a category of 'useful myths' from which testable hypotheses may be derived. These myths should be discussed critically because they determine the directions we take in our research, and even our predilections for different forms of treatment.

What is under discussion is the depressive episode, a phase of behaviour lasting some weeks or months which is outwardly largely negative in its characteristics. There is an overall reduction in behaviour, particularly those aspects which involve initiative. New social contacts are avoided, particularly those which involve sexual or competitive activity. The subjective experience of depression is unpleasant and is often likened to mental pain; it has components of shame, guilt, inferiority, failure, unworthiness, giving up, hopelessness, helplessness, anxiety, being a loser or flop and feeling unwanted, unloved and unlovable. There is a reduction of perceptive powers characterized by inattention and loss of interest in the environment, a reduction of executive powers characterized by lassitude and 'finding everything an effort', and a reduction of those cognitive processes that mediate between perception and action which can be described as doubt and difficulty in making decisions. There are vegetative components of tearfulness, insomnia, anorexia and reduction in libido. There is an odd snowball effect in which the effects of the depression seem to make the depression worse, and so on, so that it is often difficult to tell whether a person is depressed because he lost his wife or his job or whether he lost his job or his wife because he became depressed. There is no zest for life but an inclination towards death. The depressed person is inefficient and uncompetitive; he lacks the appearance of someone whose ancestors have triumphed over countless generations in a ruthless struggle for survival. In fact, if the depressive episode has indeed evolved by a process of natural selection, we are faced with the paradox that, judging by the prevalence of depressive episodes in our population, enormous evolutionary success has been achieved by a trait which makes its possessor almost a caricature of the individual doomed to evolutionary failure—not only doomed to failure but actively seizing failure even to the ultimate acts of suicide and infanticide. A process apparently geared to the evolution of successful adaptation has

yielded a behavioural entity which approaches the epitome of maladaptive failure. Here indeed is a challenge for sociobiology.

Relief of mental pain

The conceptual field is difficult, and it may be helpful to make some preliminary classification of the theories which have been put forward to account for the evolution of depression. Some theories postulate an advantage for the depressive behaviour itself, others for the behaviour which ends a depressive episode. The latter theories emphasize the importance of mental pain, so that depression may be adaptive in the way that pain is when one's hand is in the fire: it encourages one to take the hand out. Thus Lewis (1934) postulated that the function of depression is to achieve the avoidance of noxious stimuli. More specifically, Gallanter (1978) suggested that depression occurs during solitude and is relieved by affiliation with a cohesive social group, such affiliation being adaptive. The disadvantage of this type of theory is that it does not account for any of the other features of depression apart from the mental pain; it certainly is not consistent with the social withdrawal which is characteristic of depression; and it is the converse of the theory postulated by Rodger (1961) that depression subserves the exclusion of old and incapable members from a social group.

GOALS AND INCENTIVES

Some writers postulate that depression serves to lower unrealistic aspirations and leads to the re-appraisal of unattainable goals. According to Hill (1968), when the credibility gap between ego-ideal and actual ego becomes too large there is a catastrophic lowering of self-esteem and the individual then functions on a more realistic and therefore presumably more adaptive level. From a more psychological point of view Davies (1970) pointed out that the cardinal characteristic of depression is a reduction in responsiveness to a wide range of stimuli due to habituation or extinction after prolonged absence of reinforcement. Thus it cuts short ways of responding which have proved ineffective. Costello (1976) criticizes these theories on the grounds that they are not compatible with the loss of interest in *all* goals and incentives which is characteristic of depression—if one way of responding is ineffective it should be adaptive to try another—but, as he points out, 'when the depression is protracted we have to relieve it so that the patient can try something new, which is what the depression is supposed to enable him to do in the first place.'

Klinger (1975) also sees depression as related to disengagement from incentives, not causing the disengagement as Davies postulates but caused *by* the disengagement. This is alleged to be adaptive because the mental pain of depression punishes the act of disengagement from a task—normally such a rewarding experience that without the punishment of depression we would soon learn to disengage from all our tasks.

This view of depression as an aversive stimulus to disengagement is somewhat paradoxical, in that the depression is punishing disengagement which is seen as adaptive. Moreover, the depression prevents the individual from engaging in other incentives. Klinger deals with this by suggesting that the depression is really maladaptive for the individual, but adaptive for the species as a whole because it weeds out individuals who are unable to achieve their goals. This latter aspect of Klinger's theory approaches that of Sloman (1976), which is discussed below.

Costello (1976) puts forward a complex theory related to incentives. He emphasizes *loss of interest in everything* as a cardinal feature of depression, the function of which is to maintain a conservative balance between an individual's varied incentives. If I follow him correctly, he suggests that depression follows the loss of one incentive by a mechanism which impairs the reinforcing properties of all his other incentives, the function being to prevent any one incentive getting out of hand; for example (I think) it would prevent one over-eating if one lost one's sex partner. It is difficult to see how Costello's theory accounts for the loss of interest in *everything* which he very rightly points out as a major difficulty in theories relating to reduction of goals and disengagement from incentives. If one contemplates our hunter–gatherer ancestors, it would not make much sense if they lost interest in gathering because hunting was going badly. To take the argument into the psychologists' own field, does a rat in a maze lose interest in turning left because it is punished for turning right?

Klerman (1974) discusses the goal-regulation theories in the context of his own studies of life events at Yale: 'My current view is that the depressive episode may be initiated as a response to helplessness and fallen self-esteem, and thus may serve as the signal for the individual that there has been a discrepancy within the self system between ideal expectations and practical reality. There is now increasing evidence, however, that the depressive episode per se, while initiated as an attempt at adaptation, in response to environmental change, must be regarded as an index of failure and as having maladaptive consequences.'

So far I have dealt with theories in which depression acts as an aversive signal, a punishment or a facilitator of cognitive readjustment. They concern intrapsychic mechanisms and do not require an episode of depressive behaviour that is extended in time. Let us now turn to theories in which the depressive behaviour is seen as adaptive in its own right, extended for short periods (communication of distress), medium periods (hibernation) and long periods (removal from the gene pool).

COMMUNICATION OF DISTRESS

Klerman (1974) is one of the few adult psychiatrists who has made a deliberate examination of various theories of depressive function. His conclusion is a negative one as far as depression in adults is concerned, although 'the evidence points to the role of the depressive affect in infants of all mammal species, but particularly in infants of primates and humans, as an important signal of distress and helplessness that mobilises the responses of the mother and others. Thus, the depressive affect furthers the growth and adaptation of the infant, aids in the regulation of the mother-infant and peer group relations, and facilitates the infant's social, cognitive, and motor development. But what of adult depressive states? Are they similarly adaptive?'

The problem with adult depressions is that they do not mobilize the support of others, particularly, according to Klerman, if they last for more than a couple of months: 'When the depressive episode persists, however, negative social reactions occur. Most patients withdraw and their sullen, self-depreciating, and complaining interpersonal style no longer draws

others to them for nurture, reassurance and support. Rather, increasing irritation and withdrawal alternate with guilt and pity. The net result is maladaptive—withdrawal and detachment.'

On the whole I would agree with Klerman that depression subserves a communication function in infants, and that the development of an animal model of depression in the separated infant-monkey is to be welcomed for neurophysiological investigation. The communication function in adults is lacking or even negative: it is difficult to see the present prevalence of the depressive syndrome as having evolved because our ancestors rallied to the brief exhibition of ladies' tears. Klerman concludes that adult depression is maladaptive regression to a childish pattern of behaviour. This might be considered a null hypothesis for adult depression. It denies a role to adult depression, but it does provide an idea of how adult depression might have appeared in the first place for selection to act on—an example, like our own nakedness, of paedomorphism.

HIBERNATION

Not uncommonly depressed patients describe their state as one of 'hibernation'. They feel withdrawn and 'out of action'. After recovery they see their depressive episode as one of 'biding their time' or 'being kept on ice'. Lange (1928) was the first to draw the parallel between depression and animal hibernation and it was later elaborated by Harper (1975).

The conservation/withdrawal theory of Schmale (1973) fits into this category. Schmale's theory emphasizes the conservation of energy (either psychic or calorific) and Klerman (1974) rightly criticizes Schmale on the grounds that depressed patients do not conserve energy at all—they tend to be over-aroused during the day and they sleep poorly at night; so that depression fits poorly into the role of a recuperative episode after a period of exertion. Depressed patients do eat less on the whole, but it is far fetched to view depression as concerned mainly with regulation of the food supply. If we neglect the conservation aspect of Schmale's hypothesis and concentrate on the withdrawal aspect, we can include it under the general hibernation rubric.

There is no problem about the function of hibernation in animals. It permits them to get through a cold season of reduced food supply in which, without hibernation, they would need extra calories to maintain body temperature. Likewise in other species aestivation allows the individual to survive a hot period of reduced water supply in which he would otherwise require extra water for cooling. But, however much we English might like to think that mood is related to the weather, depression is only minimally related to climatic variation and in fact one of the striking things about human depressions is that they are out of phase—while the sum of depressions remains constant the individuals who comprise it change.

There is really no problem here. Depression affects mainly social relationships, and it seems reasonable to postulate that the function of depression is to see us through a period of bad *social* weather. Thus in primates (and probably dogs and birds) a basic vertebrate capacity for exhibiting phases of withdrawal has evolved along a path towards depression as a reaction to adverse social factors whereas in rodents and some other orders it has evolved along a path towards torpidity (hibernation and aestivation) as a reaction to adverse climatic factors. The exciting

implication of this hypothesis is that the underlying mechanism may be the same — we should encourage hibernation research in the hope that it may shed light on the underlying mechanism of depression.

The hibernation concept may also be useful in treatment. One of the depressing things about depression is that it seems endless — the patient sees no light at the end of the tunnel. Hibernation is known to be a temporary thing, and I have used this to get over to patients the idea that they are only 'out of action' for a limited period—'If Winter comes, can Spring be far behind?' is sometimes acceptable as a comforting refrain.

The hibernation parallel is compatible with theories which see the function of depression as being concerned with the restraint of self-assertion. If social factors are adverse they may or may not be susceptible to change — one coping strategy is self-assertion with increased involvement in the social scene (elevation of mood) and the other is self-abnegation with social withdrawal (depression of mood). We should not be surprised if patients switch from one 'strategy' to another in their attempts to cope with life's difficulties.

REMOVAL FROM GENE POOL

Depression may serve the function of removing individuals from the breeding population. In this case the advantage would accrue to the individual's group or to the species as a whole; by definition the individual himself would be less genetically 'successful'. Thus Klinger (1975) states that people who become depressed because they do not achieve their incentives or goals are likely to be incompetent and thus there is a eugenic advantage in eliminating them. Seligman (1974), in the discussion following Klerman's paper, agrees that depression is maladaptive for the species; 'Thus, those individuals who are "dumb" enough or unfortunate enough to encounter losses and traumas that they cannot deal with are removed from the gene pool'. Jonas and Jonas (1974) site 'self-elimination' as one of the functions of neurotic depression.

The most elegant exposition of this theory is provided by Sloman (1976). He sees neurotic reactions of depression and anxiety as mechanisms for amplifying minor degrees of failure. He uses Indian hunters as an example and his argument runs (with some freedom of interpretation) thus. Let there be two hunters who, by their very co-existence, are competing — both genetically and socially. Let one hunter be very slightly superior in the genetic endowment which subserves hunting. Without depression there is a slight advantage in favour of the superior hunter and his increased catch may result in his leaving more offspring, but with such slight differences the evolution of hunting ability will take a very long time. However, with depression as a reaction to being worsted in social competition, the matter is greatly speeded up. The two hunters return from the chase, the more successful hunter jeers at his rival who feels shamed and humiliated and becomes depressed. On the next hunting expedition the depressed hunter fails to attend to appropriate stimuli, cannot decide where to go, and finds the whole trip a great effort. In his depressed state he is a less efficient hunter and will return with even less catch, receive more jeers and become even more depressed—he is now in a vicious circle or 'positive feedback situation'. He may commit suicide, his family may die of starvation, in any

case he loses his libido, he becomes unattractive to women and he makes an altruistic exit from the gene pool.

Sloman's hypothesis accounts for the very rapid evolution of whatever acts as the criterion of success in social competition. In peacocks it was the tail, in stags the antlers, in monkeys the threat signals, in human beings it was probably intelligence. At the start of the rapid growth of the human brain some two million years ago it seems likely that size, strength and ferocious aspect gave way to intelligence as the criterion of success in the competitions of our ancestors, and the depressions of the brothers and cousins of our ancestors ensured that the very slight superiority of our ancestors gave them the opportunity to leave their genes to us.

There are a number of rather attractive features about Sloman's hypothesis. First, it is compatible with the features of depression as we know it. Secondly, it explains a number of features which appeared incomprehensible (such as the inefficiency of the depressed person). Thirdly, it accounts for the positive feedback nature of depression. Fourthly, it resolves the paradox outlined at the beginning of this section: the depressed person is the epitome of competitive and reproductive failure because his evolutionary role is just that—he is ideally adapted to his role of maladaptation. Fifthly, although it may not do much for the status of the depressed patient, it does a lot for the status of depression itself. According to this theory depression is not some mere error of the clockwork, it is an adaptive behaviour which is of central importance to the evolutionary process itself, and has played a major role in the evolution of intelligence and thus of our own ability to contemplate the phenomenon of depression (or anything else, for that matter). Sixthly, since the maintenance of the genetic basis of altruistic behaviour in the gene pool requires the operation of fairly intense kin selection or selection between competing family groups, the hypothesis forces us to reconsider the unpopular idea of competition between groups during evolution. Finally, it directs our attention to social competition as the generator of depression, and this has implications not only for research, prophylaxis and treatment, but for wider aspects of educational and social policy.

Sloman's theory is compatible with other theories which relate depression to social competition (at a somewhat lower conceptual level) which I dealt with when I last reviewed this field (Price, 1972). Animals show a wide range of behaviours in response to social failure (some change colour, some even change sex) which are much more promising for study than human depressions (Eleftheriou and Scott, 1971), quite apart from the difficulty in doing brain research on human patients. Although, like social behaviour in insects, depression may have evolved more than once, there is a reasonable chance that reactions to social failure in other vertebrates may be homologous to human depression and subserved by the same mechanisms.

There have been no major advances in the treatment of depression for 25 years. We need to take some new directions in research, and it may be that these evolutionary myths will prove to be useful and set us on the right road. At worst, it is good exercise to think in different ways about the phenomena that confront us.

See also Medical Annual, 1975, pp. 1–13.

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