Biomedical Approaches

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Essential Papers on Depression

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Part IV

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Somewhat different criteria had to be employed to select the articles for this section. The articles that were chosen were written by recognized authorities and summarize current knowledge of some important biomedical aspects of depression. They are not classics in the sense that that term might be applied to Freud's "Mourning and Melancholia." It would have been difficult to find a biomedically oriented article written at the same time as the Freud article that had anything but historical interest today. An excerpt from the writings of Kraepelin might have been included. Yet, beyond his drawing of the still useful distinction between dementia praecox and manic-depressive psychosis, he was a product of

his age and tended to lapse into dogmatic and unscientific assertions about disease entities and elusive predispositions and constitutional defects.

The development of a biomedical perspective with a solid basis for its claims to a scientific status has depended upon both serendipitous findings about drug effects and tremendous technological advances in the fields of anatomy, neurophysiology, and biochemistry. For example, current interest in electrolyte metabolism in depression can be traced to Cade's attempts in the late forties to induce mania in animals with urea (Whybrow, Akiskal, & McKinney, 1984). He employed lithium urate because of it solubility. Although he did not find support for his hypothesis that urea acted as a toxic agent in the onset of mania, he did discover the therapeutic potency of lithium. Success in treating mania in humans led to an extensive research program, but

development of our current state of knowledge about electrolyte metabolism in affective disorders depended upon the more recent availability of isotope-dilution techniques. Similar patterns of serendipitous findings about drug effects, followed by a close collaboration between clinical and basic scientists that depended upon technological advances followed upon the discoveries of reserprine-precipitated depressions and the antidepressant effects of imipramine.

The biomedical perspective has undergone rapid changes in the past few decades, and obsolescence comes quickly to ideas. Statements made in the early sixties about the role of amines in depression would be rejected as simplistic today. As Baldessarini (this volume) points out, any hypothesis is now suspect that posits that a single amine is responsible for the full range of biological depressive phenomena.

Technological advances have meant that the evidence that can be cited is much less circumstantial than it was only two decades ago, but the enormous complexity of biomedical aspects of depression is also being appreciated. There is a consensus that some depressions have stronger biological components than others, but we are far from any "gold standard" for the identification of such depressions. Numerous biological markers have been proposed, but it is generally unclear whether they identify the same, overlapping, or quite different groups of patients (Clayton & Barret, 1983).

There is ambiguity, confusion, and controversy within the biomedical perspective, and yet there is an overwhelming sense of progress. The nature of this progress is quite different than that within psychological and social perspectives, where—although there is undeniably an accumulation of

new research data—the ascension of one theory over another is more often a conceptual rather than an empirical matter.

Winokur opens the section with a fresh discussion of the old controversy of how best to draw distinctions among types of unipolar depressions. He acknowledges that the endogenous-reactive distinction is an imprecise one, but suggests that this does not rule out that there might be a kernel of truth in it. Yet anyone who is going to argue that the distinction is valid has to contend with accumulated research findings that (1) whether a precipitating event is present has not proven to be a good discriminator, and (2) symptoms and other clinical features work somewhat better but are still far from satisfactory (Fowles & Gersh, 1979). Part of Winokur's solution to these problems is to rely on family background and laboratory tests. However,

Winokur argues also for the importance of considering whether a patient has had a "stormy" life-style or personality prior to becoming depressed—a history of marital and sexual problems and lifelong irritability. This, he argues, is a better predictor of response to treatment than is precipitating stress.

Winokur goes on to validate the use of a stormy life-style as a discriminator using family background and laboratory tests. Much of the past research on the family background of depressives has centered on the presence or absence of affective disorder among first-degree relatives. However, Winokur also attends to whether there is a family history of antisocial personality or alcoholism. Next he shows that the discrimination that he has made also predicts response to what is becoming a standard laboratory test in depression, the dexamethasone suppression test.

(See the discussion below and Baldessarini for a description of this test.) Winokur concludes that there is converging evidence for the usefulness of this distinction, but that further research is needed.

The logic of Winokur's arguments is consistent with other developments in the diagnosis and classification of depression. It is clear that symptoms do not by themselves provide an adequate basis for distinguishing among unipolar depressed patients and that new categories will need to be developed on the basis of the convergence of symptoms with family history and laboratory test results. Yet, as in Winokur's data, there is also some slippage when multiple perspectives are combined, and it is unlikely that the resulting distinctions that can be drawn will be sharp ones.

The second diagnostic question that Winokur addresses is whether there are differences between persons in the community who are diagnosed as depressed on the basis of symptoms and those who are hospitalized. Family background data discriminate well between these groups. Depressed people in the hospital are more likely to have relatives who committed suicide than do community-residing persons who are identified as depressed. He concludes that there is evidence that important differences in the two populations do exist but that they remain to be described more fully.

Winokur is clear in his assumption about the stronger biological basis for the "familial pure depressive disease" than for the "depressive spectrum disease" or "sporadic depressive disease," as well as for hospitalized versus community-residing depressed persons. However,

some cautions are in order. As noted in the Introduction, we should reject the dualism and reductionism involved in any strict dichotomizing of biological versus nonbiological depressions. We should not prematurely close discussions about either the psychosocial features of supposedly biological depressions or the biological aspects of depressions that do not have identified familial or laboratory-test correlates. The separation of a subgroup of depressed persons who have a stormy lifestyle definitely does not in any way rule out the likelihood that psychological and social factors influence the onset, clinical features, and course of the "pure" depressives who lack such a background. The findings concerning the difference between hospitalized and community-residing depressed persons raises some fascinating questions about the social processes by which the hospitalized group are identified as

different from other seriously depressed persons and face the outcome that they do. How does the community identify and extrude them?

Finally, it should be noted that the population studied by Winokur is a severely depressed hospitalized group, and one must be cautious about making overgeneralizations about less disturbed outpatient populations. Klerman (1971) has noted that the bulk of biomedically oriented research is conducted with severely disturbed hospitalized patients, even though the bulk of current clinical experience is with less disturbed, noninstitutionalized patients.

Dunner (this volume) discusses progress in the study of the genetics of depression. He notes the types of evidence that can now be mustered as evidence for a genetic component in depression: the clustering of depression in families;

differences between monozygotic and dizygotic twins; rates of depression among the offspring of depressed parents who have been adopted by foster parents without a history of depression; and the linking of depression to a specific gene. Of these types of evidence, the first three are strongest; yet, the last remains most crucial, and the findings thus far remain the weakest and most controversial.

Reviewing some recent large scale studies, Dunner concludes that the risk for affective disorders among the relatives of unipolar and bipolar depressed persons is about 15-20 percent. The lower figure comes from a New York study in which patients were drawn from an outpatient population, whereas the higher figure comes from hospitalized samples. Apparently, there is a weaker genetic component to the less severe depression found in clinic and community samples

(Leckman et al., 1984a). The lower figure of 15 percent is large enough to establish a genetic component to at least some depressions, but the higher figure is still small enough to suggest that other factors are involved.

The study of the genetics of depression remains in its infancy. Further advances are going to require better ways of subtyping affective disorders and the discovery of biological markers that are not state dependent, that is, tied to whether someone is currently disturbed. Dunner describes some of the distinctions that he and his colleagues have drawn for bipolar disorder, in terms of the severity of manic and depressive phases (e.g., whether one or both require hospitalization). It is probably true that bipolar disorder is more homogeneous and has a stronger genetic component than unipolar depression, and because of this, Dunner suggests that that is more

likely to yield advances in the near future. Some researchers are attempting to identify subtypes of unipolar depression that "breed true," such that the relatives of depressed persons who have a particular pattern of symptoms will themselves show this pattern if they become depressed. There have been some promising findings with concomitant appetite disturbance and excessive guilt (Leckman et al., 1984b), but any substantial advances are going to depend ultimately upon the identification of genetic markers that have thus far proven elusive. Rieder and Gershon (1978) have noted that such markers will need to be stable, heritable, and state independent; capable of differentiating persons with an affective disturbance from persons drawn from the general population; and among the relatives of depressed persons, capable of identifying those who develop affective disturbance from those who do not.

Baldessarini reviews a full range of developments in our understanding of biomedical aspects of severe depression: diagnosis, genetics, endocrinology, and neurophysiology. He notes how technological advances are allowing the field to move beyond its previous reliance upon studies of drug effects make inferences about the role of neurotransmitters in mood disturbance. The hypotheses that could be tested in this manner were always imprecise and oversimplified. Available drugs generally had multiple effects on diverse transmitters, and evidence of any specific effect was always indirect (Montgomery, 1985). Furthermore, as Baldessarini notes, such research was often used to make unwarranted inferences about the underlying biochemical basis for mood disturbance. By analogy, the effectiveness of aspirin in relieving a headache does not necessarily imply that an aspirin deficiency is

implicated in the causes of headaches.

Baldessarini indicates how there has long been a belief that there is some disruption of hormone secretion in severe depression and that one part of this is an excessive secretion of cortisol. The dexamethasone suppression test that he describes as particularly promising has seemed to be an excellent tool for investigating cortisone secretion, but in the past 18 months, it has become the object of considerable controversy. Baldessarini and Arana (1985) are among the many researchers producing discouraging data concerning its utility.

The ideal test for some specific disregulation in a particular type of depression has not yet been discovered, but it would have 100 percent *specificity* in not falsely identifying someone as having the mood disturbance who did not, and 100 percent *sensitivity* in identifying everyone

who did have the mood disturbance. Initial results with the dexamethasone suppression test indicated that it had a high degree of specificity (90-96 percent) and at least a moderate level of sensitivity for endogenous-melancholic depression (40-67 percent). Thus, these results suggested that the test might be quite revealing when positive, although less so when negative. Almost all positives would be endogenous melancholics, but about half of all endogenous melancholics would test negative. The test is simple, painless, and inexpensive enough to become the first generally used clinical test in psychiatry.

The test became widely accepted immediately, and when some researchers failed to obtain such striking results, the failure was first ascribed to problems in the administration of the test and the fuzziness of the existing criteria for endogenous-

melancholic depression. It is certainly true that current diagnostic criteria are problematic, and some still hold to this explanation (Carroll, 1985). However, others are reporting that 15-19 percent of normal volunteers test positive and that factors such as upper respiratory tract infections, moderate weight loss, and aging might produce false positives (Amsterdam, et al., 1982; Brown, et al., 1985). Baldessarini and Arana (1985) concluded from their results that the dexamethasone suppression test has limited power in differentiating major depressive disorders from other acute and severe illnesses. The fabled "gold standard" thus has not been found. Yet Baldessarini and Arana (1985) note the enduring significance of the dexamethasone suppression test. Work on the DST has sharpened the focus on current diagnostic problems and encouraged a further search for simple tests of

biological markers. In the article in this volume, Baldessarini has noted some of the current leads that are being pursued.

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