Biochemical Markers Identify Mental States

The concentration of norepinephrine metabolites in urine and blood can be used to select appropriate therapy for depressions

"I think that we in psychiatry have crossed the threshold into the era that I like to call psychiatric chemistry," says Joseph J. Schildkraut of Harvard Medical School and the Massachusetts Mental Health Center. "We are at a point in psychiatry today that is analogous to where our internist colleagues were in the 1950's, in that clinical laboratory medicine is starting to make an impact on the practice of psychiatry. We are probably at the very earliest stages of this, however. I suspect that 10 years from now, we will probably view what we were doing here in the early 1980's as being as crude and primitive as what the endocrinologist was doing in his laboratory in the 1950's."

What "we are doing" consists of measuring the concentration of certain chemicals in urine, blood, and cerebrospinal fluid and of using this information to assist in the diagnosis of mental disease, to select the proper medication for therapy, and to monitor therapy. The field is quite new and rather primitive, as Schildkraut suggests, and only a few psychiatrists make use of the tests. Nonetheless, the laboratory directed by Schildkraut last year performed nearly 3000 tests, and the number of clinicians who use its services continues to grow. A large part of the current credibility of the field can be attributed to Schildkraut and to James W. Maas of the Yale University School of Medicine, who are among its founding fathers and intense, albeit friendly, competitors.

That credibility was lacking when Schildkraut entered psychiatry in the early 1960's. "It was not unusual then for psychiatrists to feel a sense of failure if they had to resort to the use of psychoactive drugs in the treatment of patients," he recalls. "And the whole notion that one could measure anything in urine that would give any information about the biochemistry of the central nervous system seemed quite farfetched."

Schildkraut's own clinical experience, however, had convinced him of the efficacy of psychoactive drugs and of the importance of brain biochemistry in understanding mental illness. He then moved from Harvard to the National Institute of Mental Health (NIMH), where Irwin J. Kopin and Julius Axelrod were doing pioneering work on the metabolism of catecholamines in the brain. "I found myself in the unique position of having one leg in each of these two worlds, the clinical psychiatric world and the neuropharmacologic world, and with the awareness that there was little cross-communication between them." Taking advantage of his experience in both worlds, Schildkraut in 1965 published a seminal paper called "the catecholamine hypothesis of affective disorders." In the often bewildering jargon of psychiatry, affective disorders are those characterized by marked changes in mood or behavior, particularly depressions and manias. Within a month after Schildkraut's paper appeared, William E. Bunney, Jr., and John M. Davis of NIMH published a virtually identical hypothesis.

Schildkraut proposed that "some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain." The obverse side of depression, mania, might thus be associated with an excess of catecholamines, he continued. The paper emphasized that the hypothesis was, "at best, a reductionistic simplification of a very complex biological state." Nonetheless, the two papers—and particularly the suggestion that depressions represented a heterogeneous group of illnesses that might be differentiated biochemically—"set the agenda" for research during the next decade.

Maas and others had observed that norepinephrine and the related compound normetanephrine cannot themselves cross the blood-brain barrier. In the late 1960's, however, Norman Kirshner and his colleagues at the Duke University School of Medicine found that norepinephrine's major metabolite in the brain of the rat is 3-methoxy-4-hydroxyphenylglycol (MHPG), which can. Maas shortly obtained the same results in dogs, and Kopin, Schildkraut, and Saul Schanberg of NIMH observed it in rats, primates, and, eventually, in humans. There is still substantial controversy over how much MHPG is produced in the brain and how much in peripheral nerves, but these findings opened the possibility that measurement of MHPG concentrations might provide a biochemical index of norepinephrine metabolism in the brain.

Maas, then at the Illinois State Psychiatric Institute in Chicago, was the first to exploit this possibility. He examined "a heterogeneous group of depressed patients" and observed that the average concentration of MHPG in their urines was below normal. The very heterogeneity of the group, however, made it difficult to draw any firm conclusions about the efficacy of the approach. Schildkraut followed a different tack.

Harvard University

Joseph J. Schildkraut

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"One of the first things we looked at in our research," he says, "was whether one could see changes in urinary MHPG in certain patients with affective disorders coincident with changes in clinical state," as predicted by the catecholamine hypothesis. He and his colleagues focused on patients with so-called bipolar disorders, in which patients experience episodes of both depression and mania, since these were "intuitively"

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the most likely candidates. "Indeed, one did find that when patients were depressed, they had lower urinary MHPG excretion than when well, and when patients were manic, they had higher urinary MHPG excretion than when well."

It should be noted that the MHPG concentrations measured represent the total amount excreted during a 24-hour period. This is necessary because Frederick K. Goodwin and his colleagues at NIMH observed that the rate of MHPG excretion varies during the day. Diet and exercise should also be somewhat controlled since Goodwin has observed that the excretion rate is sensitive to both.

Schildkraut conducted a corollary study a few years later, after he had returned to Harvard, with a group of patients hospitalized for amphetamine abuse. He and his colleagues observed that MHPG excretion was substantially elevated when the patients were "high" and well below normal when the amphetamine users "crashed" after the drugs were withdrawn. MHPG levels remained low for 24 to 48 hours, then slowly returned to normal as the patients' moods also returned to normal. Geraldine Cassens in Schildkraut's laboratory has observed a similar sequence of events in rats, and this observation has become the basis for an animal model of one type of depressive disorder.

Schildkraut, Maas, and others next turned to unipolar depressions, which are the most common form of mental illness and are not accompanied by a manic phase. The psychological symptoms of bipolar depressions are quite different from those of certain types of unipolar depressions. The former are characterized by an impaired capacity for work and pleasure, lack of energy, and a slowing of thought processes, while the latter are marked by dysphoria, irritability, anger, and hypochondria. The situation in unipolar depressions, unfortunately, was not so clear-cut.

Initial studies showed that patients with unipolar depressions were a heterogeneous group, with some having low concentrations of MHPG in urine, some having high concentrations, and some intermediate. Maas, and later Schildkraut and Alan F. Schatzberg of Harvard, soon found that most of the patients with low MHPG respond well to the tricyclic antidepressant imipramine and its analog desipramine, which have been shown to enhance norepinephrine's physiological effects; Schildkraut and Schatzberg have found that these patients also respond to maprotiline, which acts in the same manner. Maas and Jan Fawcett of the Illinois institute also found that patients with low MPHG show a favorable short-term response to dextroamphetamine.

James W. Mass

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Many of the patients with high concentrations of MHPG, in contrast, respond favorably to the drug amitriptyline, Schildkraut found. Patients with intermediate concentrations did not generally respond to any drug. These observations are important, Maas says, because it often takes several weeks before the clinical effects of a drug become apparent; a measurement of MHPG in urine might thus provide the physician with guidelines for initiating therapy. Subsequently, two other groups have confirmed Schildkraut's observation about the correlation of high urinary MHPG and amitriptyline response, but three other groups have been unable to do so.

For several years, Schildkraut's research laboratory provided urine MHPG analyses for psychiatrists to use in clinical practice, but the number of requests soon became overwhelming. In 1976, he and Paul J. Orsulak of Harvard, in cooperation with the Department of Pathology at New England Deaconess Hospital, established the Psychiatric Chemistry Laboratory, a "model nonprofit clinical laboratory facility for the integration and translation of biochemical research into clinical psychiatric practice." Last year, the laboratory performed nearly 3000 analyses and also provided consultation and educational services to acquaint physicians with the use of the tests. Another large facility that provides similar services is the National Psychopharmacological Laboratory in Knoxville, established by Harry Dekirmenjian.

Other, smaller laboratories are also beginning to offer the tests, but some investigators, such as William Z. Potter of NIMH, worry whether quality-control standards can be maintained at small commercial facilities. Some psychiatrists have also been reluctant to use the services because they have been uncertain about the predictive efficacy of the tests.

That efficacy is expected to receive confirmation from a 5-year study—the Collaborative Program on the Psychobiology of Depression—conducted at six institutions under the sponsorship of NIMH. Some preliminary findings of this study were reported by Maas this summer at meetings in Göteborg, Sweden, and New York City, and a more complete report by Stephen H. Koslow of NIMH will soon appear in *Psychological Medicine*.

The study showed, Maas says, that patients who responded unequivocably to imipramine had low urinary MHPG. It also showed that low concentrations of other substances in urine and cerebrospinal fluid, such as the serotinin metabolite 5-hydroxyindoleacetic acid, likewise predict a favorable response to the drugs. Meanwhile, Potter and his colleagues will soon publish a report showing that low concentrations of normetanephrine, vanillylmandelic acid, and norepinephrine itself in urine are closely correlated with low concentrations of MHPG, and thus might also be predictive of a favorable response to imipramine, despite the fact that most of these are believed to be produced in the peripheral nervous system.

The predictive value of high concentrations of urinary MHPG remains problematic. Schildkraut believes that it is useful, but others disagree. There is little agreement on normal values of urinary MHPG, says Potter, so that interpretation of anything but low values may be "premature." The collaborative study has not yet produced enough results, Maas says, to support either viewpoint. Schildkraut speculates that there may be at least two subgroups within the pool of patients with high MHPG: those with high norepinephrine output due to alterations in noradrenergic receptor sensitivity, and those with high output due to increased acetylcholinergic activity. The former might be responsive to certain drugs, and the latter to others.

Several other chemicals are also potential markers for mental illness. Earlier this year, a team headed by Donald S. Robinson of the Marshall University School of Medicine reported that the concentration in blood of another metabolite of norepinephrine, 3,4-dihydroxy-

phenylglycol (DHPG), may be a measure of the effectiveness of therapy. They treated 48 depressed patients with either amitriptyline or phenelzine, an inhibitor of the enzyme monoamine oxidase (MAO). Each drug produced improvement in approximately the same percentage of patients. In each case where the patient improved, the concentration of DHPG in the blood decreased significantly, often before a change in mood became apparent. The group is now working to determine the concentration of DHPG in healthy individuals, and to see whether the effect is associated with any specific subgroup of depression.

Monoamine oxidase may itself be a good marker in schizophrenia, a psychotic disorder characterized by loss of contact with one's environment and disintegration of personality. In 1972, Dennis L. Murphy and Richard J. Wyatt of NIMH reported that blood platelets from some patients with schizophrenic disorders had low activities of MAO. Subsequent investigations in many laboratories have revealed a wide range of MAO activities in schizophrenia.

It now appears, says Schildkraut, that different ranges of MAO activity may be characteristic of particular subgroups of patients. Recent findings from his laboratory indicate that MAO activity is normal in platelets from schizophrenics who do not have auditory hallucinations, but below normal in those who do; these hallucinations are often accompanied by paranoia. High MAO activity was observed in patients with schizophrenia-related depressions characterized by chronic asocial, eccentric, or bizarre behavior, as well as in markedly introverted patients—those characterized as severely socially withdrawn and isolated.

Still another indicator of mental state is a defect in the transport of sodium and lithium ions across the membranes of red blood cells. Davis, Ghanshyam N. Pandey, and their colleagues at the Illinois State Psychiatric Institute, and Daniel C. Tosteson, now at Harvard Medical School, have found that this defect can be quantitively measured by incubating blood samples with lithium and then measuring the ratio of the concentration of lithium in erythrocytes to that in plasma. They found that about 30 percent of patients with bipolar illness have this defect, making the lithium ratio higher.

Manic disease has been considered to have a genetic component, and it may be related to this defect. When Davis and Elizabeth Dorus of the Illinois institute studied close relatives of manic depressive patients who have this defect, they found that those relatives who had had affective disorders also had an above-normal lithium ratio; relatives who had no history of mental illness, in contrast, had normal lithium ratios.

The Blue Devils

In 1835, British artist George Cruikshank—who himself suffered from manic-depressive illness—gave this view of depression. [Courtesy of the Countway Library Rare Books Department]

Davis and David L. Garver, who is now at the University of Cincinnati College of Medicine, also observed that some psychotic patients, who have generally been diagnosed as schizophrenic, have above-normal lithium ratios. Unlike most schizophrenics, this subgroup responds favorably to lithium therapy. Garver and his colleagues at Cincinnati have followed up on this observation, and he estimates that 25 to 40 percent of schizophrenic-like psychotics may have this lithium-responsive type of illness. He suggests that it is a variant of manic-depressive disorders since such patients have family members with a high incidence of affective disorders and few schizophrenic disorders. Such lithium-responsive psychotics also respond favorably to treatment with physostigmine, as do manic patients. Garver and Robert Hitzemann have recently found that the lithium defect is associated with an abnormality of membrane phospholipid composition, specifically a low concentration of phosphatidylcholine.

Most of these potential tests will undoubtedly remain adjuncts to conventional diagnostic procedures. "The analogy that I like to draw," says Schildkraut, "is to think of depressions as one thinks of pneumonias. Both are clinical diagnoses. One diagnoses pneumonia on the basis of history, physical examination, and the chest x-ray. Similarly, one diagnoses depression on the basis of clinical history and clinical examination. Having made the clinical diagnosis of pneumonia, the internist then orders sputum cultures to determine what antibiotics the patient's illness might be most responsive to.

"Similarly, I think we are at the point where, having made a clinical diagnosis of depression, one can turn to the clinical laboratory to gain some information on what drug the patient might be most likely to respond to. I am not suggesting that any of the biochemical tests we have today will ensure that you pick the clinically effective drug on the first trial, but using the tests will certainly increase the probability of doing so. And given the time it takes for clinical response, even a small increase in the percentage of patients who receive an effective drug on the first trial will improve clinical care significantly."—THOMAS H. MAUGH II

Additional Reading

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