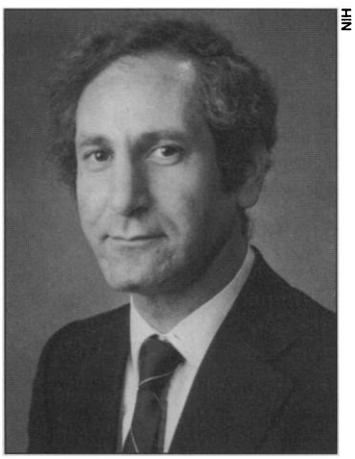
Depression: The News Isn't Depressing

Researchers are closing in on a "final common pathway" for all types of depression—which might lead to better treatments than are now available

New Haven—HERE'S A DEEPLY DEPRESSING statistic: In any given year severe depression affects more than 15 million people in the United States alone. That's about 6% of the population. Worse, depression is almost always a factor in the more than 30,000 suicides that occur in the United States each year, which makes the syndrome one of the most widespread of all life-threatening disorders. No surprise, then, that more effective treatment of depression is a high priority for improved public health. Indeed, the National Institute of Mental Health (NIMH) has been spending close to $2 million annually over the past several years on its DART (Depression Awareness, Research, and Treatment) campaign.

Since the 1960s, the development of a series of antidepressant drugs has been gradually transforming treatment of the disorder. No single innovation has had as much effect, however, as the introduction of Prozac, which—primarily because it is relatively free of side effects—in the past few years has been helping unprecedented numbers of the nation's depressives. But the news isn't all good. According to researchers at a recent Yale Medical School conference on the neurobiology of affective disorders,* antidepressant drugs still leave a lot to be desired: They can take as long as 6 weeks to kick in, they don't work for everyone (about 30% of sufferers fail to respond), and their side effects can be unpredictable. And improving the success rate of drug treatment, it turns out, will require not just tinkering with drug chemistry but a better understanding of the basic biology of the disorder—which many scientists say is far from clear. Adds Yale psychiatrist Pedro Delgado: "Before we can really understand the illness and what the medications are doing, we have to understand a great deal more about the regulation of mood states and stress responses in normal people."



NIH

Learning the blues. *Robert Post believes depression can cause long-term changes in the brain.*

But after 2 days of sessions at the conference, it can also be said that all is not bleak. Substantial progress is being made in decoding the biological underpinnings of the disorder. In fact, conference attendees heard that researchers are homing in on an intriguing notion: that all forms of depression ultimately operate through a shared chemical pathway, the identification of which could lead to the development of more effective and faster-acting drugs.

Despite the biological mysteries of depression, all researchers in the field agree on one thing: that it is a heterogeneous disorder. Depression can be triggered by stressful life events, can occur with many medical or mental disorders, or can raise its ugly head for no apparent reason. But clinically speak-

*The third annual Bristol-Myers Squibb Symposium on Neuroscience Research.

Imprinting Depression on the Brain

Is depression a"learned" disease? Research relating depression to stress is linked to some provocative findings emerging from the lab of psychiatrist Robert Post at the National Institute of Mental Health. Episodes of depression and manic depression, says Post, may be "leaving an imprint that paves the way for future episodes."

Post uses a model called the "kindling response." Kindling refers to the fact that if you give a rat repeated electrical stimulation in a tiny area of the amygdala, this will lower its threshhold for seizures. It takes time to trigger an initial seizure, but then seizures become more readily induced—to the point where they occur spontaneously.

Post first applied the kindling model to epilepsy, but he believes it applies also to mania in bipolar illness—where a link is supported by the fact that antiseizure medications can sometimes block mania. He also thinks the model applies by analogy to depression. It seems that once a patient has a severe episode, the threshold for a subsequent one is lowered—so that depression that initially seems reactive can eventually come out of the blue. There is poignant evidence from manic depressives that permanent changes are involved: Post says that patients who go off their lithium and eventually suffer another episode will, in some instances, no longer respond when put back on the drug.

Post believes these changes will ultimately be explained at the level where genes modulating manic or depressive behavior are turned on. "Usually we have thought about stress at the level of neurotransmitters and receptors," where effects tend to be "acute and transient," he says. But in rat studies, the researchers found that an "acute stressor" can turn on genes for substances that initiate long-term cell alterations. They did this by mapping the role of the proto-oncogene *c-fos*, which transcribes a protein that appears to be a marker for long-term brain changes. With repeated stimulation, effects first appearing on one side of the hippocampus spread throughout the brain.

Post says the findings from his lab carry an important message for clinicians: that preventive drug therapy should be used more in cases of recurrent affective illness. Research has shown that the relapse rate for patients who continue medication is half that for those on placebo therapy. Says Post: "Early prophylaxis may be doing a double service" by not only preventing recurrence but "preventing sensitization." ■ C.H.

ing, regardless of cause, depression is depression. While traditional categories, such as "endogenous" and "reactive," or "primary" and "secondary," are still used to describe depression, researchers are finding that they carry little or no relevance for treatment. Nor is family history much of a guide. In short, descriptive diagnoses don't appear to be holding up as signals of biochemical differences.

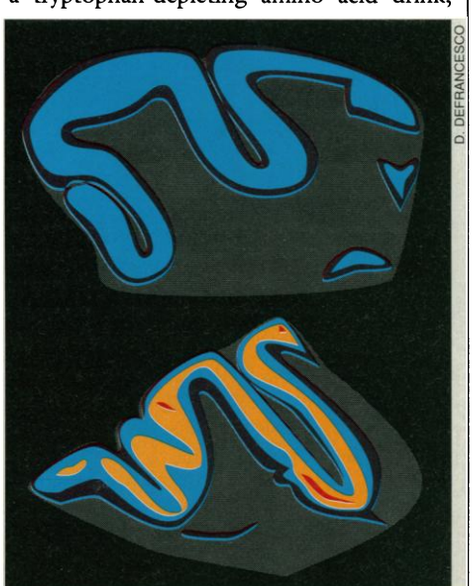
In fact, says Delgado: "The only clear subtype biochemically" may be people who don't benefit from any therapy, and that difference can be inferred only from their nonresponse. Like fever or high blood pressure, says Delgado, chronic depression "is probably a combination of many different disorders that just look similar." And particularly when it occurs out of the blue, he adds, depression could be an indication of defects "anywhere along the [biochemical] cascade" through which signals are transmitted and received in the brain.

So it has been the pharmaceutical research community's triumph over this bewildering heterogeneity of the disorder—developing antidepressants that are effective in some 70% of cases—that keeps hopes alive. Intriguingly, these drugs don't all act in the same way. Most types of antidepressant medication act on one or both of two major neurotransmitter systems: the serotonergic system (which uses serotonin as a transmitter) and the noradrenergic system (which uses norepinephrine). The drugs block re-uptake of these neurotransmitters by the cells that send them, making larger quantities available to stimulate post-synaptic receptors—ultimately leading to the regulation of a variety of functions such as mood, arousal, appetite, and sleep.

Two of the main classes of antidepressants now in use (the tricyclic antidepressants and the monoamine oxidase inhibitors) act on both neurotransmitter systems. The newer drugs, notably fluoxetine (Prozac), the only one now in widespread use, act exclusively on serotonin. The fact that drugs operating on different brain systems achieve the same effect raises the question of whether there is a final shared biochemical pathway to depression. Yale psychiatrist George Heninger, the conference chairman, told *Science* that anemia offers a good analogy: Anemia may be caused by many things, such as iron deficiency or defective red blood cells. But all these disparate causes ultimately produce the same critical effect: insufficient hemoglobin. Similarly, says Heninger, there may be "a [final] pathway where both the primary and secondary abnormalities interact to produce the symptom of depression."

One leading candidate for the final common pathway in depression is a deficiency of serotonin (also known as 5HT). Psychiatrist John Mann, director of the Laboratories of Neuropharmacology at Western Psychiatric Institute and Clinic in Pittsburgh, Pennsylvania, reported to the conference that he has recently confirmed earlier findings that people who commit suicide are likely to have low levels of a serotonin metabolite, 5HIAA, in their cerebrospinal fluid. He also found a significant change in the numbers of 5HT receptors in a particular area of the prefrontal cortex—consistent with decreased transmission. Animal research has affirmed the serotonin connection by demonstrating that its neurotransmission is affected similarly by several antidepressant drugs, shock treatment, and diets low in L-tryptophan, a 5HT precursor.

But other work presented at the conference casts doubt on the notion that 5HT is really the ultimate route to depression. Delgado related that clinical experiments conducted in his lab—"the only ones directly probing monoamine involvement"—suggest that something other than serotonin is the common path. Delgado controlled levels of 5HT in the brains of depressed patients by manipulating their intake of tryptophan. "We hypothesized that if serotonin is the final common pathway, all antidepressants would stop working if we diminished 5HT in the brain," says Delgado. Indeed, when patients on 5HT-enhancing drugs were given a low tryptophan diet (such as corn, gelatin, cream cheese, and salad), followed the next day by a tryptophan-depleting amino acid drink, they rapidly got depressed again. But when the same regimen was tried on patients taking desipramine, a tricyclic that primarily affects norepinephrine, the patients did not relapse, suggesting that "there may be at least two ways in which antidepressants work."



Dead end. *The brain of a suicide* (bottom) *shows a striking increase in binding sites for serotonin in the prefrontal cortex as compared to the brain of a control. Red indicates highest receptor density; density decreases through yellow, blue, and purple.*

ILLUSTRATION BASED ON IMAGES BY VICTORIA ARANGO AND JOHN MANN OF THE UNIVERSITY OF PITTSBURGH LABORATORIES OF NEUROPHARMACOLOGY.

Says Delgado: "We believed very strongly when we started out that serotonin was" the key chemical regulating depression. But the team has now concluded that "the real cause lies elsewhere in the brain." That underlying cause, says neuropharmacologist Ronald Duman of Yale, is "the silver bullet everyone is looking for"—the one that might lead to development of more effective and fast-acting drugs. And, getting around the serotonin-norepinephrine opposition, many researchers now believe such a mechanism is likely to be found at a more basic level than synaptic transmission. Therefore, says neuroscientist Bruce S. McEwen of Rockefeller University, they are "refocusing from the level of neurotransmitters and second messengers to the level of genes and long-term structural and chemical changes" in the brain.

One factor that could play a role in such long-term changes is stress. Both animals and people who experience chronic stress respond by secreting glucocorticosteroids, known as the "stress hormones." The excess secretion of one of these hormones, cortisol, says psychiatrist Robert Post of NIMH, is "the most robust biological concomitant of depression"—showing in up to 50% of cases, especially severe ones.

This has led to the theory that depression in many instances is caused by a maladaptive response to stress, with concomitant disruption of many mechanisms, including serotonin and norepinephrine transmission. According to neuropsychopharmacologist Fridolin Sulser of Vanderbilt University, "the pharmacological evidence is very strong that the three systems"—noradrenergic, serotonergic, and endocrine (which produce the stress hormones)—"work together to modify the transcription of target genes." In fact, cortisol is an essential factor in the successful adaptation to stress, says McEwen. One function is counter-regulation—that is, keeping the reaction of serotonergic and noradrenergic systems within normal bounds.

Too much stress, however, can overwhelm adaptive mechanisms, leading to dangerously high levels of cortisol. McEwen reported, for example, that repeated stress (such as physical restraint) in rats leads to atrophy of neurons in the hippocampus. It has been proposed that hippocampal damage may lead to faulty shutoff of the cortisol response to stress. Indeed, research by Huda Akil and colleagues at the University of Michigan has demonstrated faulty cortisol feedback in severely

depressed patients. McEwen says one role of antidepressant treatments may be to interrupt this negative sequence of events and restore normality of steroid levels and the adapative response to them.

Delgado believes both human and animal research is converging to suggest that scientists "are on the right track"—the track that leads to the final common pathway. Electroconvulsive therapy (ECT) supplies another important road sign. Because it works rapidly and is 90% effective (according to Heninger), some researchers see it as the "gold standard" for treatment of depression. ECT seems to have the same effects on brain chemistry as do antidepressants—and investigators suspect it may work by actually altering gene transcription. Duman, for example, has found that a course of ECT will alter the responsivity of the proto-oncogene *c-fos* in rats.

Many clinicians are still wary of the procedure, which developed a scary reputation from early indiscriminate use, and side effects—namely memory loss—are a problem in some cases. Thus, what scientists would ideally like to find, says Heninger, is "a drug as effective as ECT." Sulser, for one, is optimistic. "We will probably come up with drugs that can bypass all these [transmitter and receptor] systems," he says. "If we can target the final common pathway we could ideally come up with a drug that directly affects gene expression"—presumably "the fast-acting antidepressant we are all looking for."

Sulser predicts, however, that in the foreseeable future, we are unlikely to see any new drugs that create a splash comparable to that generated by Prozac. Rather, we can expect continuing refinements of existing drugs, as well as possible improvements in therapy by combining those now in use. Yale researchers, for example, have tentative evidence showing that combining fluoxetine with desipramine produces faster results than either drug acting alone.

And in spite of all the hopes raised by the current work, not everyone believes that even the identification of a common pathway will lead to a silver bullet to slay all the dragons of depression. Post notes that different neurochemical systems—such as the dopamine system—may be involved in cases where patients don't respond to the usual drugs. Peptides—which may be involved in the positive effect sleep deprivation can have on depression—also need looking into. Thus, in Post's opinion, finding a faster-acting antidepressant "is not the key thing—the key thing is matching the patient with the right type of medication." But the recent inquiries into a final common pathway suggest that in the long run there will be better medications to match with patients. ■ CONSTANCE HOLDEN

The Case of the Unlikely Molecular Twins

How molecules differing in nothing but a single bond's length almost became chemical orthodoxy

IN 1971, A TRIO OF CHEMISTS LED BY JOSEPH Chatt at the University of Sussex in England synthesized a pair of chemical twins too odd to remain anonymous. The chemists were convinced that the so-called transition-metal complexes they made had exactly the same chemical formula. But one of their chemical specimens formed sapphire-blue crystals, and the other bright green ones. That much is not so unusual in chemistry. Presumably the molecular doubles were isomers: forms of a compound in which the same atoms—molybdenum, oxygen, chlorine, phosphorus, carbon, and hydrogen, in this case—are linked into different molecular geometries. But if these compounds were isomers, they were isomers unlike any that chemists had encountered before.

X-ray structural analyses of the blue and green crystals showed that both compounds' atoms were in virtually the same relative positions. The only difference the chemists could discern in the data was one they had never come across in their training: The molybdenum-oxygen bond was strikingly longer in the green compound than in the blue one.

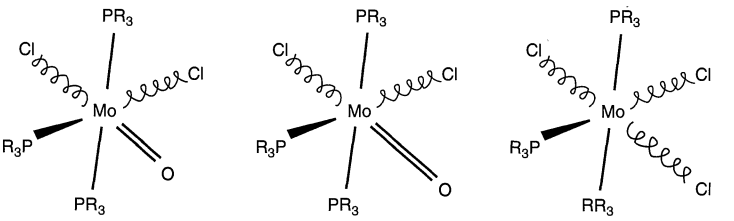
"I thought it was very peculiar," recalls Chatt, retired now for 12 years. "But it seemed to provide an explanation for the x-ray evidence." Chatt and his colleagues Ken Muir and Ljubica Manojlovic-Muir (a husband and wife team now at the University of Glasgow) called the unlikely twins "distortional isomers" and published their results in several British chemistry journals in 1971. The startling implication of the findings: Chemical isomers with strikingly different properties can differ structurally by nothing more than the length of a single bond.

Thus began a saga that took as many twists and turns as a Nabokov novel before reaching a denouement just this past year. By 1985, distortional isomers seemed on the fast track to becoming chemical orthodoxy. But a spate of papers in the past few months have attacked both the experimental evidence for distortional isomers and an influential theoretical account of how they could exist. Many (but not all) of the chemists who thought the evidence for distortional isomers was approaching textbook solidity are now acknowledging that they were thrown off by impurities—about the last thing they expected in well-formed crystals like Chatt's original twins.

The notion of distortional isomers was slow to take hold, perhaps because it is so counterintuitive. Chemists sometimes think of bonds as springs, with a characteristic length. Distortional isomers presented a very different picture, remarks Gerard Parkin, a chemist at Columbia University and one of the most influential researchers in the field. "It's like having a spring attached to the ceiling, which had always bounced up to your face when you released it from the floor, but this time it bounced above your head," Parkin says.

Rather than accept that unsettling possibility, most chemists quietly discounted the Sussex researchers' results, says Nobel Prize–winning chemist Roald Hoffmann of Cornell University. "Nobody was interested in trying to reproduce their results, probably because people thought they got something wrong about the compounds' structures," Hoffmann recalls. Besides, he adds, it usually takes more than one lab reporting one anomalous result to get theorists seriously thinking about explanations.

The requisite second anomaly arrived in 1985 when Karl Wieghardt and colleagues at the Ruhr University in Bochum, Germany, reported in the journal *Angewandte Chemie* that they had found another pair of distortional isomers: blue and green crystals from



Unlikely twins and an impostor. *The proposed bond-stretch isomers for the molybdenum complex, shown with the impostor* (right), *in which chlorine substitutes for the oxygen.*

SOURCE: PARKIN ILLUSTRATION: D. DEFRANCESCO