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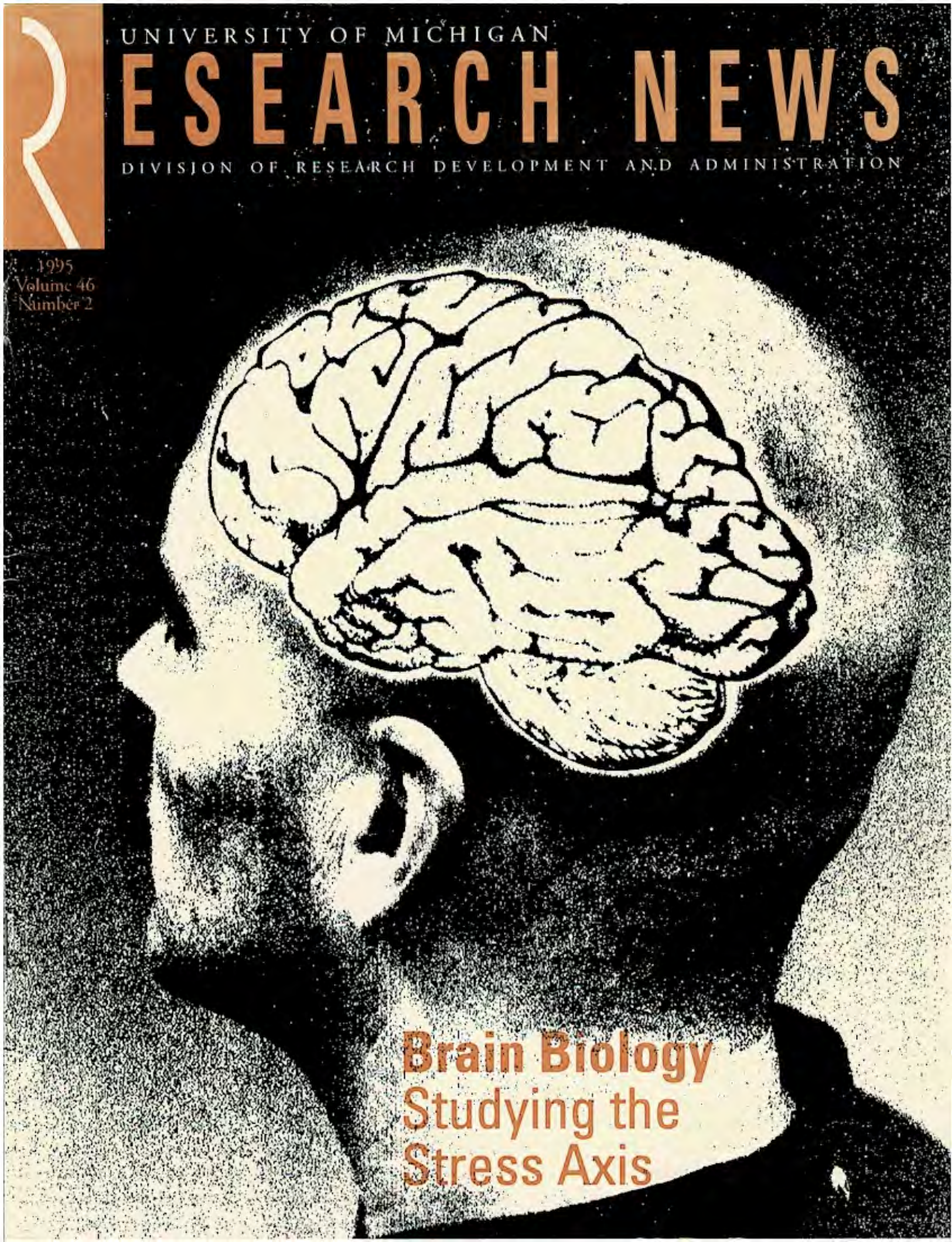

Brain Biology
Studying the Stress Axis

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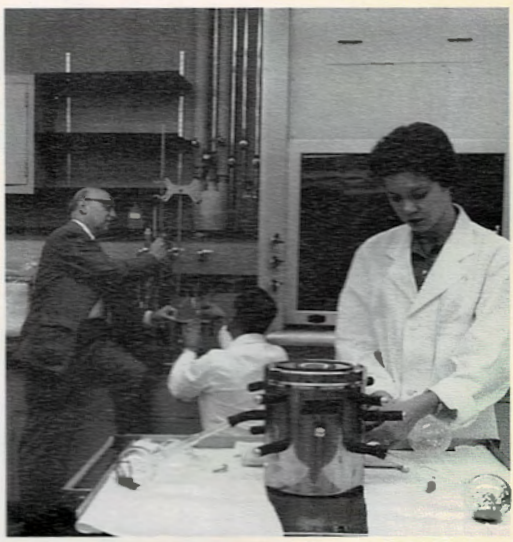
Suzanne Tainter



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IN THIS ISSUE

Listening in on the Stress Axis

The brain is clearly the most complex biological system scientists can study. There are 50 billion cells, trillions of connections among these cells, several "neurotransmitters" (small molecules that transmit messages among nerve cells), and genetic and hormonal controls for the entire system. Tackling this is more than a lifetime occupation; it's the work of many lifetimes, observes Stanley Watson, a senior neuroscientist at the University of Michigan. He suggests that science is likely to need another 200 or 300 years to completely understand how the brain functions.

"We don't really know what the brain's core operating system is. The brain is a lot more complicated than we thought 20 years ago," says Watson, Theophile Raphael Professor of Neurosciences, professor of psychiatry, and associate director and research scientist in the Mental Health Research Institute (MHRI).

Watson recalls that one of the early analogies used to describe the brain was that of a telephone switching center. In this view, the brain was the central receiver and distributor of messages from and to other parts of the body. Data came in from the senses or an organ, the brain "processed" this information, and a response or instruction was sent to appropriate sites throughout the body.

In its simplest form, the brain was responsible for point-to-point communication between it and the rest of the body's systems. Scientists needed only to identify all of the possible connections and understanding the brain's function was their prize.

"But we now know that it's probably a mistake to think of a molecule doing a single job," of matching single neurons or neurotransmitter molecules to individual tasks conducted by the brain or nervous system, says Watson. Each nerve cell is more powerful than a single telephone line or switch, able to send and receive multiple "messages" all at the same time.

"We now know that most neurons don't have just one neurotransmitter. Rather, each has many, four or five or maybe more," he says. And the messages carried by neurotransmitters are not simple on/off or yes/no choices. What seems to be happening is a "complex modulated sentence or paragraph" communicated by cascades of neurotransmitters released and absorbed by neurons.

"The secret is the complexity. It's what makes the brain the brain," says Huda Akil, Gardner C. Quarton Professor of Neurosciences, professor of psychiatry, MHRI research scientist, and director of the UM Neuroscience Program. She says the brain's messages are probably not found in individual signals, but in the patterns of complexity in a host of signals.

Akil says a closer analogy to the brain's function is a symphony. The symphony is more than any one instrument playing it's part, even if you can pay attention to it in preference to other instruments. "The timing, the coincidence of the parts, all of this is the 'message' of the symphony," she says. Likewise, the timing of waves of different signals provides the information the brain receives and responds to.

In studying the brain, scientists cannot just sit back and try to absorb the whole "symphony" played by the brain. "We really have to go back and forth, understanding the pieces *and* the whole," says Akil.

In this issue of *Research News*, Akil, Watson and their colleagues at the Mental Health Research Institute describe their efforts to understand one movement of this symphony, a part neuroscientists call the *stress axis*. This system — involving the brain, pituitary gland, adrenal glands, and several hormones — is important in helping the body adjust to physical and psychological stress. We offer an overview of UM research on the stress axis and its current focus on identifying and understanding the system's biochemical, neuronal, and genetic mechanisms, both in its "ready" mode and when responding to stress. This issue also looks at studies that view the stress axis through the lens of depression, since this disorder may be due in large part to a stress axis gone bad.

Eventually, the UM scientists would like to know much more about this important system. How does the body define a stimulus as "stressful"? Why do some people cope well with stress, or at least with some stresses? Memory of past stress and learning how to respond to stress seem to be involved, but how does the brain accomplish this? Getting to these questions will take time...perhaps lifetimes of study. □

MHRI Turns 40

The Mental Health Research Institute is a special place at the University of Michigan. This fall, the MHRI celebrates 40 years of research. In this issue, we offer a brief look at the history of the MHRI, beginning on page 12. The MHRI will mark its first four decades with a special day-long symposium on October 13 in the Rackham Amphitheater on the UM campus. Distinguished scientists from the UM and other institutions will speak on topics in basic neuroscience, the development of biological psychiatry, and the bridge between these areas of study. The symposium will conclude with talks about health policy issues and their implications for psychiatric research.

The Stress Axis at Work
How the Body Copes with Life's Challenges

The phone rings. You answer calmly with, "Hello." A voice on the line curtly says, "Please hold for the President of the United States." Hearing this, your heart begins to thump, your mouth goes dry, your mind races through all kinds of thoughts. "Why am I getting this call? did I do something? am I getting an award? are they after me? is it a wrong number?...or maybe a joke!"

Courtesy of MHRI

Neuroscientist Huda Akil says that by looking both at the biological and psychological aspects of stress researchers hope to eventually explain how the biology of stress is linked to depression, mental illness, and possibly drug addiction.

In a situation like this, almost anyone would experience an instant burst of brain and body activity. Behind your physiological responses to the unexpected phone call is an important — and complex — neurochemical system that scientists call the "stress axis." A group of University of Michigan researchers headquartered in the Mental Health Research Institute (MHRI) are exploring the stress axis, trying to understand how it operates and what happens when it fails to do its jobs properly.

This research is probing the fundamental workings of the emotional part of the brain, regions where mood and thought intersect. The UM scientists are attempting to figure out the workings of the "neurochemical circuits" involved in the stress axis and how external events influence their operation. These circuits include brain cells and their physical connections, as well as chemicals the cells release or absorb to transfer information. The eventual payoff of understanding the stress response in detail, scientists note, is the likelihood that this knowledge will open up new opportunities for treating certain mental illnesses, such as depression and schizophrenia, believed to be related to stress axis malfunction of some kind.

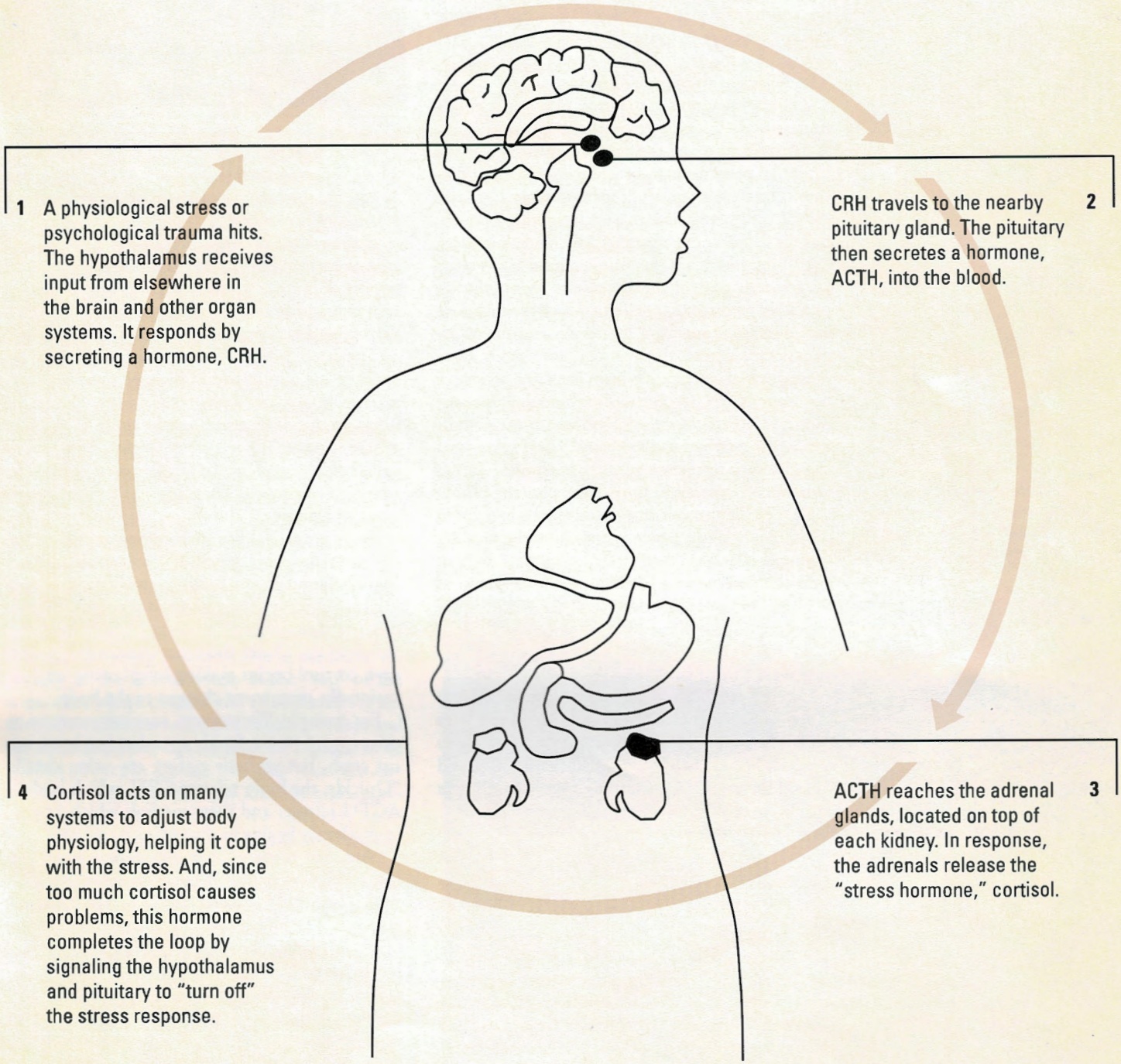
Before continuing, however, it's important to realize that the "stress" in stress axis in not limited to the kind of wear-me-down, daily aggravation of modern life that seems to afflict so many of us. "I think of stress mechanisms much more broadly than just responses to something upsetting. That is just part of what this system does," explains Huda Akil, Gardner C. Quarton Professor of Neurosciences and a senior UM investigator in the group studying the stress axis. "The stress axis really can be thought of as doing the 'matching' between the needs of the body and the conditions of the outside world it faces." The ability of humans to cope with unexpected situations, both emotionally and physiologically, is related to the function of the stress axis.

The stress system is activated when there is a "mismatch between what's there and what you expect," adds Stanley Watson, Theophile Raphael Professor of Neurosciences and a research colleague (and husband) of Akil. So when you answer the phone expecting it to be your mother calling, and it turns out to be the President, the mismatch and surprise may trigger a stress response.

A large proportion of the brain's machinery is put into action when the stress axis is activated, says Watson. "It has access to powerful levers." A stressor can prompt the stress axis to take control of the body's carbohydrate metabolism, become involved in gene regulation in many parts of the body, and cause certain body functions to go into an "idle" mode so as not to sidetrack resources from responding to the stress at hand.

Stress axis is the shorthand name scientists frequently use for this powerful system that harnesses regions of the brain, some glands, and several hormones to direct the body's response to some

Coping
Stress Axis Basics
Part One



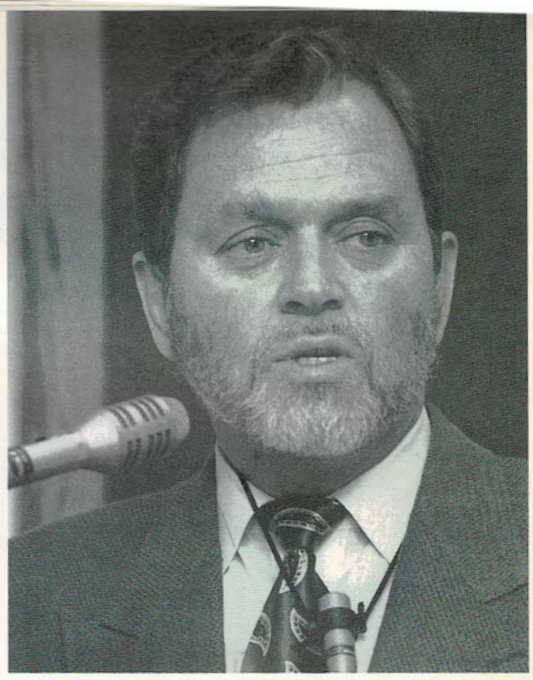
1 A physiological stress or psychological trauma hits. The hypothalamus receives input from elsewhere in the brain and other organ systems. It responds by secreting a hormone, CRH.

2 CRH travels to the nearby pituitary gland. The pituitary then secretes a hormone, ACTH, into the blood.

3 ACTH reaches the adrenal glands, located on top of each kidney. In response, the adrenals release the "stress hormone," cortisol.

4 Cortisol acts on many systems to adjust body physiology, helping it cope with the stress. And, since too much cortisol causes problems, this hormone completes the loop by signaling the hypothalamus and pituitary to "turn off" the stress response.

A large proportion of the brain's machinery is put into action when the stress axis is activated, says Stanley Watson (right). It is such a powerful system, however, that the body spends considerable resources keeping it in check.



Courtesy of MHRI

stressful event. The system's longer, descriptive (if more complicated) name is the Limbic-Hypothalamo-Pituitary-Axis (LHPA). This name identifies the main sites in the body where the stress response is generated: the limbic region and hypothalamus in the brain, and the nearby pituitary gland. The other major "players" in the axis are the adrenal glands, located above each kidney.

The stress axis can be activated in several ways, including many events other than the anxiety that we commonly associate with the modern usage of the word "stress." Exposure to extreme cold, starvation, loss of blood pressure, hemorrhage, undergoing surgery, infection, serious pain, a broken bone, strenuous exercise, and emotional trauma are among the many "stressors" that can energize the stress axis to help the body cope.

The Basics of the Stress Response

The starting point of the stress response is poorly understood. Initially, researchers presume, some "understanding" of the stressor must reach the brain, be processed, and set the stress axis in motion. The *limbic region* of the brain is the best candidate as the site where this understanding occurs, but the details of this awareness still elude scientists.

Information from the limbic region is passed to an adjacent part of the brain, the *hypothalamus*, probably by direct nerve links. The hypothalamus also receives input from the senses and major organs. Once alerted, the hypothalamus sends nerve messages to a cell group within itself and secretes a hormone, *CRH* (for corticotrophin releasing hormone). CRH enters the bloodstream for a short trip to the nearby *pituitary gland.* CRH stimulates the pituitary to release another hormone, *ACTH* (adrenocorticotrophin hormone), into the blood.

ACTH then travels through the bloodstream to the adrenal glands, where it stimulates the production and release of the "stress hormone," *cortisol.* Cortisol travels via the blood to several sites around the body — including back to the brain, promoting some functions and inhibiting others.

Cortisol's Power

One of cortisol's most important inhibitory functions is to "turn off" the stress response, says Akil. The brain and pituitary quickly respond to the presence of cortisol by shutting off CRH and ACTH secretion. "A great deal of the 'logic' of this system involves timing of activation and termination," notes Akil.

Shutting off the stress axis is important, explains Watson, because cortisol, a steroid hormone with many physiological effects, is a potent substance. The body "can't afford to have too much around. It spends considerable effort keeping cortisol under control."

Rapid responses to stress call on cortisol and two other adrenal gland hormones: *epinephrine* (sometimes called adrenalin) and *norepinephrine.* They are also given credit for the "fight or flight" responses of quickening heart rate, rising blood pressure, rapid release of stored fuel for the body, and several other functions. How cortisol aids epinephrine and norepinephrine is not fully understood. However, experiments have shown that if cortisol is absent, the activity of these other two adrenal hormones is reduced.

If the source of stress persists for a few hours, one of cortisol's major functions is to increase the supply of glucose to the brain and heart. Cortisol also makes sure that the needs of these two organs take precedence over other needs.

The stress hormone accomplishes this by promoting metabolic breakdown of proteins from muscle, bones, and a few other tissues. The amino acids produced by this breakdown go to the liver where enzymes convert them to glucose, a process called *gluconeogenesis.* Cortisol even stimulates the synthesis of the liver enzymes that convert amino acids to glucose.

Because cortisol has such powerful effects, under normal circumstances its presence signals the hypothalamus in the brain to stop production of CRH. But if the source of stress persists, the brain can override cortisol's message to shut off stress axis activity. Under these circumstances, Watson says, cortisol begins making long-lasting, and occasionally, permanent changes to the body.

For example, Watson says, suppose someone receives word that a family member has been in a car crash, but without getting any other details. "Quickly, the brain releases CRH, which leads to ACTH release, and then cortisol, which in turn immediately begins to shut off this cascade."

Now, five minutes later, this person hears that the accident was only a fender bender and all is well. This news "removes the drive" for stress axis activity. "The body begins to make adjustments to bring all of these hormones back to their normal levels," says Watson.

But, he continues, suppose the message is that this family member is seriously injured and is being taken to the hospital. This enhances the stress drive, and the body begins to make further adjustments to "ignore the cortisol feedback suppression. The longer this goes on, the more these changes become longer lasting," says Watson.

"We see big differences in people who have experienced acute stress compared to chronic stress," he says. "The [body's] machinery becomes very different." If the stress remains long enough, a person may develop major depression.

It is this kind of finding, say the UM researchers, that provides one reason to believe that depression has important connections to the stress axis, and why much research at the MHRI on this topic has involved clinical studies of people with major depression.

The Effects of Circadian Rhythm

While the stress response is meant to help the body cope with unexpected events and challenges to its normal condition, Akil points out that the "tone," or resting state, of the stress axis is not constant. "An essential feature of the stress axis is the fact that it exhibits *circadian oscillations.*"

Over the course of each 24-hour day, the amount of cortisol in the blood varies, peaking in humans in the early morning and hitting a low point in the evening. These levels are baselines, not the amounts that may be produced when exposed to some stressor.

Circadian rhythm, which is controlled mainly by food intake, traces a person's activity over each 24-hour day, says Akil. Research conducted at the MHRI has shown that basal blood levels of ACTH also follow a circadian rhythm, but shifted so that the cycle's peak and valley are reached one or two hours ahead of the cortisol cycle.

The circadian cycles of cortisol and ACTH are "associated with changes in sensitivity and responsiveness to stressful stimuli," according to Akil. When the level of cortisol is lowest — in the evening — humans are "exquisitely responsive to stress." Sensitivity is also heightened for turning off the stress response through the negative feedback provided by rising cortisol levels. Just the opposite is true in the early morning: both the initiation of stress responses and their termination is relatively sluggish.

Evidence to date points to sites in the brain, especially in the limbic system at the "top" of the stress axis, where cortisol and related steroids act to mediate the interaction of circadian rhythm and the stress response, says Akil. Much remains to be learned about the "subtle interplay" between circadian rhythm and the stress axis, she adds, especially as they are involved in the "intricate brain circuitry that controls activation and inhibition of stress responses."

Cortisol's ability to turn off the stress response is believed to involve the interaction of this hormone with the genetic machinery in the hypothalamus that is responsible for controlling the synthesis of CRH, the first "messenger" in the stress axis cascade. But this control of gene activity does not take place fast enough to account entirely for the speed with which the stress response can be regulated, notes Akil.

One possibility being explored by scientists is a sensitivity to the rate at which cortisol levels are increasing, rather than just its presence in the blood stream. How the body detects this and uses it to turn off the stress response is not yet known, says Akil. Messages delivered by neurons are thought to be involved, as opposed to the somewhat slower intervention through genetic activity.

Overall, says Akil, the stress axis uses "nested loops" of neurons and chemical messengers to provide many avenues for regulating the body's response to stress. Controls via the genetic machinery appear to "define the limits" of the stress response. Other pathways probably provide the various nuances of response. Many control mechanisms, however, remain to be discovered.

Genetic Controls of the Stress Response

Mechanisms of control on the stress response at the gene level are the targets of MHRI researcher Audrey Seasholtz. An Assistant Professor of Biological Chemistry and Assistant Research Scientist, Seasholtz is currently focusing on two areas: 1) the molecular mechanisms that control the gene responsible for CRH synthesis; and 2) the molecules that mediate the activity of CRH, its receptors, and the CRH binding protein.

One basic method the body uses to regulate the stress axis is to influence the expression of important genes. Genes exist in the nucleus of cells, and when activated, they direct the synthesis of RNA molecules. These RNA molecules move out of the nucleus where they become the template for the production of protein. For CRH, the steps are: CRH gene → CRH RNA → CRH protein.

Proteins and other small molecules can enter the nucleus of a cell and speed or slow a gene's production of RNA. Seasholtz is trying to identify such substances, known generally as "second messengers," that influence CRH gene activity.

Seasholtz says that likely candidates as second messengers include calcium ions, the stress hormone cortisol, and a small molecule called *cyclic*

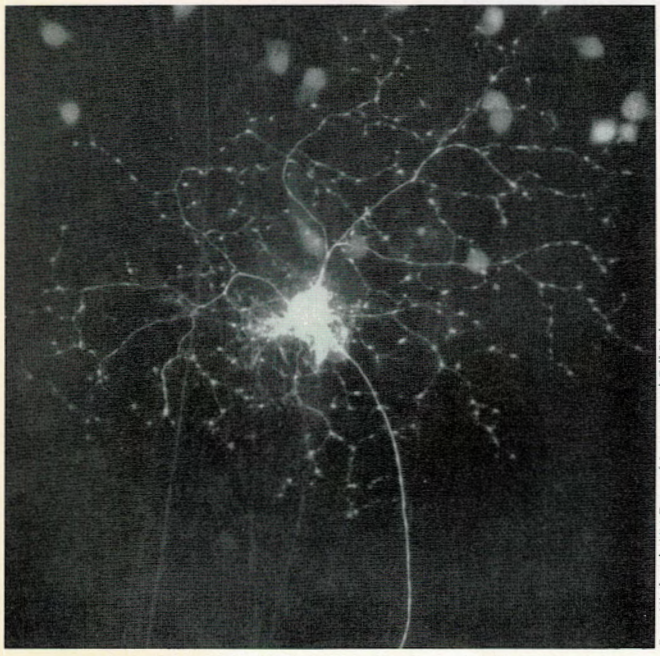
Courtesy of MHRI

Researcher Audrey Seasholtz uses cells grown in culture to find stress axis control mechanisms at the gene level.

AMP that plays a messenger role in many biological systems. In fact, she thinks that cortisol and cyclic AMP may work together to influence CRH synthesis in some cells.

She is also looking for the proteins that mediate the effects of second messengers, and localize the specific DNA sequences where these mediators exert their influence.

CRH is synthesized in many sites around the body, not just the hypothalamus in the brain, says Seasholtz. Furthermore, some mediators appear to promote CRH synthesis in some cells while the same molecules inhibit CRH synthesis in other cells. "There must be some way for the cells to control this," Seasholtz points out. Perhaps a mediator acts on or near the CRH gene according to type of cell.



Peter Hitchcock, UM Dept. of Anatomy and Cell Biology

Photomicrograph of a single nerve cell. The tip of each tendril branch connects to another nerve cell.

Seasholtz follows this basic scenario to study the regulation of CRH gene activity, or gene *expression*. She transfers CRH "gene constructs" into cells in culture in a process known as *transfection*. These foreign gene fragments contain DNA sequences that may be able to interact with mediators to activate or repress the gene that directs CRH synthesis. As she tries various combinations of DNA sequences cloned from near the CRH gene with different mediators, Seasholtz forms a picture of how CRH synthesis can be controlled at the genetic or molecular level.

"We like to perform these studies in cell lines so that we can test for direct effects on the CRH gene," Seasholtz adds. This removes any confusion over whether a mediator is directly influencing the CRH gene or sending a secondary message to the CRH neuron to direct CRH gene expression. However, Seasholtz is always cautious when interpreting her results because cultured cells may not exactly reproduce the behavior of CRH-producing cells in the body.

A little more than two years ago, Seasholtz became interested in a newly identified protein, given the name *CRH binding protein* for its strong affinity to CRH. "At first, we thought it might be a variant of the CRH receptor," she recalls. But her lab and others soon eliminated that possibility and began to wonder what this protein was doing.

Experiments are needed to determine when and where the binding protein is expressed and what regulates binding protein levels. Seasholtz would like to know what happens to binding protein levels when CRH levels increase, as when the stress response is activated. She wonders what role, if any, its plays in depression. The answers to these questions may provide clues to new levels of regulation within the stress axis, Seasholtz notes.

"The stress axis is harder to study than a lot of other motor or sensory systems," observes Stanley Watson. In part, this is due to relatively vague or generalized outward signs of its activity. In humans, researchers monitor the stress axis at work by measuring hormone levels in the blood stream. But since much of the control involves genetic direction of protein synthesis, or nerve activity, many facets of the stress response are not easily measured.

When the Stress Response Falters

This is where animal studies, the use of tissue cultures, and other biochemical and recombinant DNA techniques come into play. For instance, the UM researchers have undertaken studies of the aged rat. "It responds to stress the same as the younger animal," explains Watson, but there are clear aberrations in how some parts of the stress axis operates in old age. "We get to see the workings of axis by the contrasts" in how the stress response is mediated in young and old animals.

In addition, the MHRI scientists have undertaken clinical studies of people with major depression, another way to use dysfunction to shed light on the details of healthy function. (See the following article.) "We study depression because it probably reflects a poorly regulated stress axis," says Watson. Likewise, some studies have looked at the stress axis in shift workers, people whose daily cycle of activity changes often enough so as to disrupt the normal circadian rhythm.

"We hope that by covering this whole gamut and looking both at the biological and psychological aspects of stress, we'll eventually be able to address the questions of how the biology of stress is linked to depression, mental illness, possibly even drug addiction," says Akil.

A stumbling block facing this research is how to account for individual differences in designing experiments. "It is very hard to define stress in humans," says Akil. A needle prick, a math problem, or a driving test might all cause stress enough for some studies. But among individuals faced with any of those tests there will be a range of reactions. Over time, their responses may change. "It really brings home that it's how you perceive a stress and how you cope that is almost at the heart of the matter," she says.

This also ties into the biology of how we are motivated and how we learn, Akil adds — topics the MHRI researchers hope to address in the future. The limbic system in the brain, thought to play a role in the stress axis, also has important duties in learning and memory. The idea that some people "cope" with stress better than others, or that an individual may have more or less difficulty dealing with recurring stressful events, is in part associated with the biology of how we remember past events or face new situations. Studies of the stress axis and its links with other brain functions provide an opportunity for scientists to move toward their ultimate goal: understanding the entire operating system of the brain. □

When the Stress Axis Goes Tilt

Studying Mental Illness Provides Clues About the Normal Stress Response

Whether from living through a divorce or recovering from major surgery, the body faces serious psychological or physiological challenges from time to time. When these events occur, the "stress axis" is called on for assistance. This system involves a complex interaction of brain, neuronal, and hormonal activity used by the body to cope with stress.

Answers to questions about how this important system operates has started to emerge from the laboratories of scientists at the University of Michigan Mental Health Research Institute (MHRI) and other institutions. One approach UM researchers have adopted is to study stress axis abnormalities thought to be associated with certain mental illnesses as well as with aging.

"We learn by seeing where things go wrong as well as by studying the perfectly constructed system," explains Huda Akil, Gardner C. Quarton Professor of Neurosciences. Repairing a building, notes Akil, tells you more than just studying the completed, intact structure. Likewise, studying the stress axis gone awry reveals — through contrast — important features of the normal situation. "It lets you see how things are put together, what pieces are 'hidden behind walls'," she says.

So it is with certain studies of depression or schizophrenia — they let researchers compare the behind-the-walls views of the normal and disrupted stress axis. And the more scientists understand about the proper function of the stress axis, the more likely that new treatment ideas will emerge.

"A more thorough understanding of the neuronal systems underlying stress biology and psychology should prove essential to an understanding of the biology of depression and of several other psychiatric disorders," says Akil. Any clues to depression that stress biology can provide will be especially useful, since this mood disorder is so common and recurs in many people. It afflicts about 10 percent of the U.S. population during any one year and 17 percent of people at least once in their lifetimes.

Depression: A Window to Stress Axis Biology

Much evidence exists that depression and the stress axis are somehow linked. In about three-quarters of those who become depressed, some stressful life event — a family death, a divorce, losing a job, enduring a major physical injury — has occurred during the preceding several months. If the depression persists, these individuals begin having experiencing depression without any trigger event. One thought is that the stress axis, altered by previous episodes of depression, may supply the trigger for subsequent depression.

Elizabeth Young, Associate Professor of Psychiatry and Associate Research Scientist at the MHRI, points out that depression can be thought of as a "natural" response to stress. "Still, the majority of people who experience a stressful life event do not become depressed," she says. This suggests that some people are more vulnerable to depression than others, which might be rooted in differences in stress axis biology among individuals. It also raises the question of whether susceptibility to depression and stress axis changes seen in depressed people are tied to a "gene" that expresses itself as hormonal abnormalities seen in depressed patients.

More evidence supporting a link between the stress axis and depression is the finding that once a person becomes depressed, the disorder itself becomes a source of stress. "The depressed person might not work as well, have difficulty concentrating, might even lose a job or go through a divorce," says Young. "Impaired functioning [due to depression] is itself a stressor." Depression seems to act as a "feed forward cascade," she says, with depression causing new stressors, and the stress possibly promoting continuing depression.

Also suggestive of a depression-stress axis link is the finding that disruptions in the stress axis often spawn appetite irregularities or sleep difficulties, problems also observed in depressed individuals. "We also know that high cortisol levels in an individual may cause the symptoms of depression," says Young, suggesting a way for stress axis abnormalities to increase a person's susceptibility to depression in the future.

The term "endogenous depression" was originally used in psychiatry to identify depression with no known originating event, says Young. Now research has shown that people diagnosed with endogenous depression also exhibit the largest stress hormone abnormalities. "It appears that in these people, depression is activating the stress axis," says Young, particularly by elevating the base levels of cortisol throughout the day.

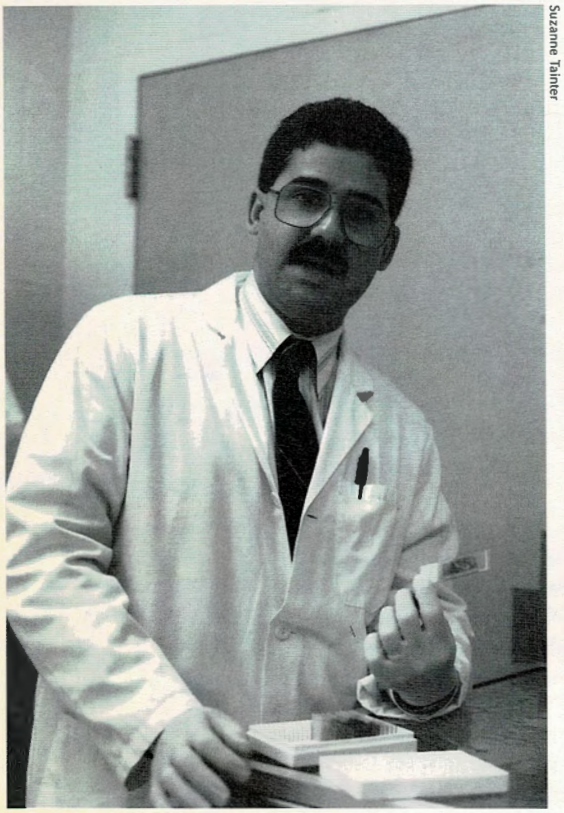
Courtesy of MHRI

Elizabeth Young conducts both clinical and animal studies to explore the links among depression, sex hormones, and the stress axis.

A conundrum of the stress axis-depression link is the uncertainty over how much an abnormal stress axis causes depression or how much major depression precedes stress axis abnormalities. Or, possibly, both are true.

These complexities have prompted UM researchers to study this system and its relationship to mental illness from many angles. "We're trying to put together information from many different systems," explains Juan Lopez, Assistant Professor of Psychiatry and MHRI Research Investigator. "The strength of our research group is that we ask questions at so many different levels." MHRI investigators build on each other's work to create a total picture from the basic molecular biology to rat studies to live patients to looking at brains of people who have died.

"It's exciting doing research here," adds Audrey Seasholtz, Assistant Professor of Biological Chemistry and MHRI Assistant Research Scientist. "There's so much opportunity to collaborate."



Suzanne Tainter

Brain tissue from suicide victims, such as on this microscope slide, may help us understand how the biology of depressed individuals may differ from other individuals, explains Juan Lopez.

Although research has shown that many severely depressed individuals exhibit a "hyperactive" stress axis, the mechanisms that establish and promote this hyperactivity still elude scientists. There have been studies conducted at the UM and elsewhere that suggest the link with depression is due to disrupted feedback signals which fail to rein in the stress response. Other work points to an out-of-sync daily hormonal cycling, or circadian rhythm, as a culprit. Additional research indicates that in depression, the original signal from the limbic system might be scrambled, starting out the stress response on the wrong foot.

Early on, some scientists proposed that high levels of the stress hormone cortisol were caused by some abnormality in the brain. This caused a defective chain of signals to be passed down through each step of the stress axis — from limbic system, to hypothalamus, to pituitary, to the adrenal gland, where too much cortisol was synthesized and secreted. But research at the MHRI shows that this step-wise model oversimplifies the operation of the stress axis. Instead, the UM scientists found that each step is sensitive to signals from nearly all other steps as well as other external signals. Elevated cortisol, they concluded, could result from any number of disturbances in the stress response.

When the stress response operates normally, an elevation of stress hormones sends messages that turn off the stress axis, a process known as *feedback suppression.* "In depressed patients, stress hormones don't seem to succeed at this," says Young. This failure even occurs in some patients who are administered additional cortisol or related hormones to artificially induce feedback suppression.

Research shows that there are least two types of feedback that the stress axis monitors. One is a high level of cortisol. The other is the rising rate of circulating cortisol (even if the amount of cortisol is low). This second type of "message" to the stress axis based on the rate that cortisol levels are changing is referred to as "fast-feedback inhibition." It handles rapid adjustments to stress axis activity.

Animal experiments have shown that elevated levels of stress hormone associated with sustained stress can cause fast-feedback to go awry. In one experiment conducted by Young, rats were stressed with a commonly used method of forcing them to paddle around a small tank of water for 30 minutes straight. Prior to the swim stress, one group of rats received daily stress hormone injections for two weeks, mimicking a chronic stress situation. When ACTH levels were monitored in rats given extra stress hormone and a control group of untreated rats, Young found an abnormal ACTH profile in the stress hormone treated animals.

Young and Akil found that exposure to chronic physiological stress upset normal pituitary function in the stress axis. When UM researchers looked at depressed patients (who generally show higher stress hormone levels), they found a stress axis that failed to respond to feedback messages under some conditions compared to non-depressed individuals. What remains to be discovered is the precise biological mechanism by which chronic stress or depression disturbs feedback inhibition.

Upsetting Daily Rhythms

Understanding brain controls over the circadian rhythm of stress hormones may also reveal something about depression biology. A number of experiments show differences in stress responsiveness between depressed and non-depressed individuals.

In one study, UM researchers administered in the evening a drug that blocked the synthesis of the stress hormone cortisol. Ordinarily, evening is when cortisol levels are at their lowest of the day. Not surprisingly, the drug used in this experiment did not cause further reductions in the stress responsiveness in healthy individuals, since the stress axis is already at its least active. In the depressed subjects, however, this drug did produce detectable hormone changes, suggesting that depression alters a person's circadian rhythm.

A current project to explore circadian rhythm in depression involves taking a blood sample from individuals every 10 minutes for an entire 24-hour period, then measuring the hormone levels in each sample. Young explains that the under normal conditions, stress hormones are not secreted continuously, but in bursts. The average levels change gradually throughout each 24-hour period, but from moment to moment, the absolute amount of hormone may differ greatly.

By sampling hormone levels so frequently — 144 times in 24 hours — the researchers hope to be

able to understand the details behind the seemingly smooth daily hormonal cycling. Young and her colleagues also want to know more precisely the times of day when hormone levels differ most in depressed and healthy individuals.

Other clues to the operation of the stress axis come from studying ways that information is initially received by the hypothalamus. One set of neurons that extend into the hypothalamus are of special interest because they probably play a role in depression. These neurons employ a neurotransmitter, *serotonin*, to carry messages.

"We know that serotonin can affect some secretions in the stress axis, and we have found that adrenal gland products [cortisol] can affect serotonin in the limbic system," says Juan Lopez, who has been involved in UM studies of serotonin. For example, administering drugs that stimulate serotonin release also produce higher levels of stress axis hormones, ACTH from the pituitary, and cortisol from the adrenal glands.

A focus at the MHRI has been on the effects of stress hormones on serotonin activity. In a series of experiments, Stanley Watson, Theophile Raphael Professor of Neurosciences, and Lopez showed that by stimulating or inhibiting the stress axis in rats, it was possible to influence the production of a particular type of serotonin receptor. In humans, this serotonin receptor is thought to be involved in the regulation of mood. Their work found that chronic stress may cause the total number of these serotonin receptors to drop to abnormally low levels in the brain's hippocampus.

Serotonin is the target of antidepressant drugs known as *specific serotonin re-uptake inhibitors (SSRI)*, such as Prozac. While this class of drugs has some direct effect on serotonin's role in depression, UM research shows that these drugs can inhibit the stress axis response to a stressor. This research fuels the idea that serotonin re-uptake inhibitors and some other drugs gain some of their antidepressant properties from causing stress hormone levels to decline, thereby allowing the level of serotonin receptors to return to normal levels.

Depression and Sex Hormones

Another possible key to understanding the stress axis-depression relationship is through the study of the influence of sex hormones on the stress response. Epidemiological research shows women are about twice as susceptible to depression as men. Elizabeth Young is conducting research aimed at answering whether female sex hormones make women more vulnerable to stress-related abnormalities, especially in depression.

Young is currently looking at how the sex hormones, estrogen and progesterone, might prevent the proper control of cortisol production. Past research suggests estrogen can effect the gene that controls synthesis of corticotrophin releasing hormone (CRH) in the hypothalamus. Other research indicates that progesterone can block production of stress hormones.

Some of Young's studies are conducted using rats. Researchers remove the ovaries or testes — the sources of sex hormones — and see how stress hormone levels are affected. Then, the researchers add back progesterone, estrogen, or testosterone in various amounts and at different points of the day to see how the stress axis responds to stress.

In general, Young finds that the stress response occurs more quickly and strongly in female rats than in male rates, as indicated by biochemical markers. For example, in females, the pituitary gland produces higher ACTH levels more quickly in response to experimentally induced stress than in males. Female rats are also "more resistant" to the feedback signals from rising stress hormone levels that are meant to moderate the stress response. And if the ovaries are removed, she adds, the stress hormone profiles in females become more like those found in male rats.

If similar sex hormone-related differences are discovered in humans, the higher prevalence of depression in women may be due in part to the greater "ease" with which the female stress axis can be disrupted.

Thomas Treuter

Animals play a key role in research to understand the workings of the brain and human mental illnesses.

Another approach UM researchers are using to determine the effect of sex hormones on the stress axis has been through studies of menopause, when sex hormone levels begin to subside. "We find there are changes to stress hormone sensitivity in postmenopausal women," says Young. She recently received grant support for a clinical study of menopausal, depressed women to see how these two conditions operate on the stress axis.

The Stress Response and Aging

"Aging disrupts almost every level of the axis," report UM scientists. Studies of the rat in old age is an approach MHRI researchers have been using to investigate the stress axis. Yet these studies show

Suzanne Tainter

James Meador-Woodruff investigates neurochemical circuits thought to be involved in schizophrenia. He locates the receptors for neurotransmitters such as dopamine and glutamate in brain tissue from animals and humans.

that the net stress response is about the same in young and old rats. It appears that aging-related changes in the stress response at one level are compensated for by changes somehow induced at neurochemical points further along the axis.

In an experiment conducted at the MHRI, UM scientists monitored stress hormone levels in young and old rats around the clock. They found that throughout the daily circadian cycle, the hormone levels of young and old rats were "completely superimposable." However, when they then subjected these same rats to stress from mild restraints, the older animals produced an abnormal response.

Akil says these results suggest that as an animal ages, the amounts of circulating stress hormone may not be as directly associated with "stress responsiveness" as in younger animals. But even this conclusion requires qualifiers, she adds. Experimental results have varied depending on the type of stressor applied and the strain and sex of the rats. "The picture that emerges suggests an uneven pattern of dysregulation of the stress axis with age."

It's conceivable that over an animal's life cycle, the stress response may be altered in steps. The UM researchers have conducted studies on old and young rats to produce data supporting this possibility. For instance, the overview they draw from their research suggests that the early disruptions involve secretion of transmitters and hormones. Later problems may stem from changes in genetic control of the synthesis of stress "messengers." The most extreme aging-related change appears to be complete loss of input into the stress axis from the hippocampus region of the brain.

Still, they point out, every change appears to be compensated for by a secondary change at the next step, leading to a new, but still fairly effective, resting condition of the stress axis. Only when placed under certain kinds of stresses do aged rats show delays in recovering from the stress compared to young animals.

Postmortem Brain Studies

Until the last few years, animal research provided the only practical way to examine the anatomy of the neurochemical circuitry that comprises the stress axis. Now, however, MHRI scientists have gained access to the brains from deceased people, some of whom suffered from mental illness, such as depression or schizophrenia.

Starting about five years ago, MHRI researchers have received brain donations with the help of the Veterans Administration (VA) hospital in Battle Creek, Michigan. Since then, additional collaborations have been established with the Bronx VA Hospital and with St. Elizabeth's Hospital, affiliated with the National Institute for Mental Health.

"The mechanics of getting brains is difficult," explains James Meador-Woodruff, an Associate Professor of Psychiatry and Associate Research Scientist who is involved in brain studies related to schizophrenia. "People don't think of donating a brain like they might a kidney or cornea," especially when the deceased suffered from serious mental illness.

The mechanics of handling human brain tissue in the laboratory is exacting, adds Meador-Woodruff. For one thing, such tissue may contain virulent viruses and so special containment and disinfection procedures and equipment must be used to insure against any viral release. Then there are the rigors of preparing thin tissue slices, treating them with mildly radioactive chemical "labels" that will point out specific neurochemical features, and then making the photographic images of the labeled slices for analysis.

It has taken eight months to prepare the 30 brains from the Bronx VA Hospital that Meador-Woodruff will examine for his schizophrenia work. "It takes a significant amount of labor," he says. Analyzing the labeled tissue is equally daunting. "We have data from 50 regions of the brain, and tens of thousands of data points from each region."

In the schizophrenia studies, Meador-Woodruff explains that he is looking at brains from three groups of people: 1) those who had schizophrenia and received drug treatment during the year prior to death; 2) those with schizophrenia who had not been treated in the year before death, and; 3) a control group of non-psychotic individuals matched for variables such as age, sex, and elapsed time from death to autopsy. This last item is important for knowing that differences in the brains from the groups are due to schizophrenia and not differences in tissue deterioration since death.

Meador-Woodruff is trying to understand the causes of schizophrenia and the consequences of the disease for the brain, primarily by trying to specify the location and function of certain neurochemical circuits thought to be involved in this disease. These studies do not specifically involve the stress axis, but the techniques he uses and some regions of the brain he focuses on are also important for the stress work at MHRI.

For some time scientists have known that the neurotransmitter dopamine was involved in schizophrenia. "All of the drugs useful in treating schizo-

phrenia also block dopamine in various ways," says Meador-Woodruff. In recent years, some progress has been made in understanding schizophrenia with the identification of at least three new dopamine receptor types, bringing the total to five or more. Some of the newly identified dopamine receptors are more localized, perhaps showing the way to the mechanisms of operation of the schizophrenia-related brain circuits.

A second neurotransmitter of particular interest to Meador-Woodruff is g*lutamate*. "A small, but growing group of researchers [including himself] believe that glutamate is involved in schizophrenia," he says. Meador-Woodruff has done some experiments in rats looking at interactions of dopamine and glutamate in the brain. His human brain studies will also look for relationships between these two neurotransmitters.

"I don't think that schizophrenia will have a single neurotransmitter or gene as its cause," he says. The apparent complexity of the disease suggests that no single drug or treatment will be found to "cure" this disease. "Successful management of the disease will probably come from understanding the neurochemical circuitry," he adds.

UM scientists are also studying postmortem brains of suicide victims, examining neurochemical circuits for markers of psychiatric illness such as depression. In work completed to date, says Juan Lopez, these studies have found evidence of increased stress axis activation in the pituitary glands of suicide victims compared to other individuals. "We're now looking at the hippocampus for related changes," focusing on serotonin receptors.

The newest member of the MHRI team studying the stress axis is Jon Zubieta, Assistant Professor of Psychiatry and MHRI Assistant Research Scientist. Zubieta's initial focus will be the use of a noninvasive imaging technology, PET (positron emission tomography), to examine the brain biochemistry of patients experiencing depression. This research will permit the UM team to monitor aspects of stress axis activity in humans that cannot be easily studied any other way.

All of the research into the biology of depression and other affective illness feeds into the creation of a larger picture of the "neurochemical circuits" involved in stress axis function. As their understanding of the normal stress response grows, UM researchers hope to uncover new approaches for treating mental illness from a stress axis that goes tilt. □

Coping
Stress Axis Basics Part 2

Hypothalamus
The "first stop" along the stress axis and site of CRH synthesis in response to stress. This region of vertebrate brain is involved in regulation of neural and hormonal functions.

CRH
Abbreviation for corticotrophin releasing hormone, a peptide synthesized and secreted by the hypothalamus in the early stages of the stress response.

Pituitary Gland
A gland located just below the brain, adjacent to the hypothalamus. When CRH reaches the pituitary, this gland synthesizes and secretes a hormone, ACTH.

ACTH
Abbreviation for adrenocorticotrophin hormone, a peptide from the pituitary that carries the "stress response" message to the adrenal glands.

Adrenal Glands
A pair of glands fount atop the kidneys. In response to ACTH, the adrenals synthesize and secrete the stress hormone, cortisol, into the blood.

Cortisol
The stress hormone in humans. This steroid-type hormone can influence the operation of many physiological systems.

Serotonin
A chemical substance, known as a neurotransmitter, used by neurons to carry a "message" to an adjacent neuron. Serotonin is a neurotransmitter implicated in depression. Its activity is probably influenced by the stress axis.

Circadian Rhythm
Pattern of body activity that occurs on an approximately 24-hour cycle.

The Mental Health Research Institute Turns Forty

An interdisciplinary institute — a pioneer in 1955 — remains a vital intellectual center for basic science research on the brain in 1995.

In 1955, the theories of Sigmund Freud held American psychiatry in thrall. Researchers were looking for ways to put a stop to the misery of schizophrenia and other mental illnesses. And against the backdrop of the recent horrors of World War II, the mental health of entire societies was of concern.

That year, Raymond Waggoner, chairman of the UM psychiatry department, convinced the State of Michigan to provide $175,000 to create the Mental Health Research Institute (MHRI) at the University of Michigan to conduct basic research on mental health. Waggoner, who kept an open mind on the causes of mental illness, believed that basic research offered the best opportunity for progress because it could lead in so many directions. He recruited an interdisciplinary group to the MHRI with the goal of "applying scientific methods to the study of human behavior, normal and abnormal."

By 1995, research at the MHRI had helped bring about a revolution in how we view mental illness. The institute was a neuroscience pioneer, using basic research to uncover the biological underpinnings of mental illness. Today, schizophrenia is no longer viewed as a disease caused by bad mothers, but as the manifestation of a "broken" brain, just as diabetes is a result of a "broken" pancreas.

"Our focus is neuroscience and biological psychiatry," says Bernard Agranoff, the MHRI's current director. "Many [mental illnesses] appear to be based on molecular defects, so we are trying to understand basic mechanisms and solve problems at that level."

Research in recent years has emphasized the genetic and molecular mechanisms of how the brain operates. Areas of research include stress regulatory mechanisms, how the brain develops, and how it falls apart through aging. Brain imaging technologies such as PET scanners allow investigators to study the human brain at work.

These fundamental biological considerations relate directly to clinical research in the UM department of psychiatry, with which the MHRI is aligned. Clinical research has emphasized mood and anxiety disorders, schizophrenia, childhood developmental disorders and autism, geriatric psychiatry, and substance abuse.

Since 1957 when the MHRI employed 40 people and had a state appropriation of $300,000, the institute has grown to its current group of 18 senior scientists, with 136 technical and administrative staff. The budget is now more than $7 million from state, federal, and private sources of support.

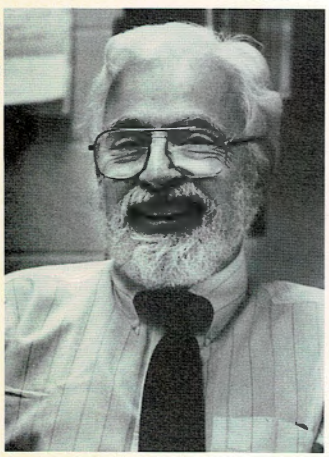
Through the years, the interdisciplinary focus of research has narrowed. James Grier Miller, the first MHRI director, envisioned it as a place to study all levels of phenomena relating to mental health—from the cell, organ, individual, and group to society. His idea was to find rules of operation common to all these levels, a systems approach to behavioral science. A leading journal in this field, called *Behavioral Science*, was founded at the institute. MHRI staff included biologists, psychiatrists, psychologists, and political scientists.

Along with Miller, other founding members of the MHRI were Anatol Rapoport, a mathematical biologist; and Ralph Gerard, an eminent neurophysiologist, credited with the discovery of the microelectrode. Both created new research directions while at the MHRI.

Rapoport's classic book, *Fights, Games, and Debates*, published in 1960, outlines a scientific method of analyzing human conflict based on a large experiment conducted at the MHRI. Research subjects participated in games that allowed them to choose among various cooperative or competitive strategies. His application of mathematical game theory to behavioral and social problems was of great interest to social scientists.

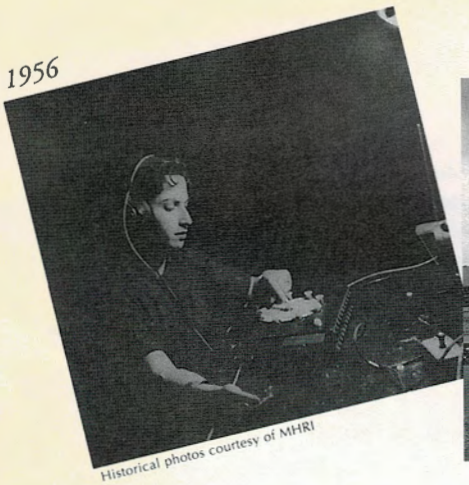
Gerard was director of the laboratories at the MHRI and coined the term "neuroscience." He led a pioneering study aimed at establishing the biological basis of schizophrenia. In cooperation with Ypsilanti State Hospital, researchers collected data on 200 schizophrenia patients, using many different biochemical, psychological, and psychiatric measures. Analysis of these data, aided by a new research tool — the computer — revealed seven groups among the patients. Psychiatry continues to try to identify biological sub-types of mental illnesses that might respond to different treatments.

Miller left the UM in 1967, and Gardner Quarton, a key member of the neuroscience study program at Massachusetts Institute of Technology and Massachusetts General Hospital, was recruited as director in 1968.



Thomas Treuter

Bernard Agranoff
MHRI Director 1983-95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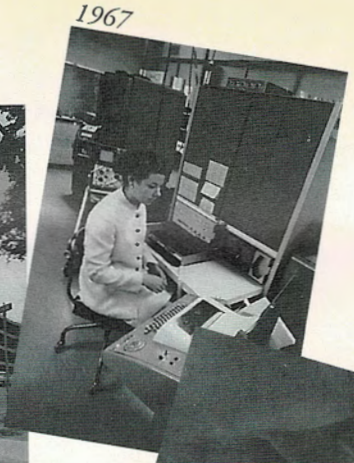
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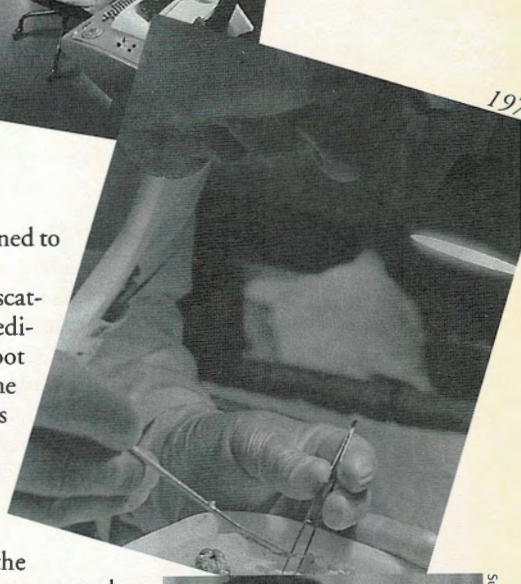
Historical photos courtesy of MHRI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Quarton continued the diverse approaches to research on mental health, and favored studies with links to clinical work in psychiatry. Over the next decade, as neuroscience made inroads in understanding the workings of the brain, the institute became increasingly involved in "wet lab" activities. In the Quarton years, the MHRI became well known for work in the neuroendocrine basis of depression.

In 1983, the directorship was turned over to the MHRI's own Bernard Agranoff, a renowned researcher on the biochemical basis of memory formation. Agranoff has continued to sharpen the institute's focus on molecular neuroscience.

The current emphasis on the molecular underpinnings of brain function has spurred MHRI collaborations among an array of scientists from traditional academic disciplines—geneticists, biochemists, anatomists, physiologists, pharmacologists, as well as clinical investigators. Psychologists at the institute continue to pursue behavioral themes with interests in logic, games, and computers.

A major goal of the MHRI since its inception has been to promote interdisciplinary research, hoping for "cross-fertilization" of ideas and approaches. In the 1950s, it was a daring experiment to house specialists in anatomy along with neurologists and physiologists, let alone psychiatrists, psychologists, and social scientists. One critic predicted it would lead to "cross-sterilization," Agranoff recounts with a wry smile. Now such cross-disciplinary collaborations at the MHRI are commonplace, albeit within the limits of neuroscience, he adds.

Agranoff says such interactions can't be forced. "When you hire people, you make sure they are comfortable with our stated goals and working in the environment offered by the Institute. Then you hope they will interact with their neighbors." The success of this strategy seems evident in the number of times MHRI scientists appear as co-authors on scientific papers.

Throughout the institute's history it has been a center for training future neuroscientists, psychiatrists, and behavioral scientists. It is the home of a multidisciplinary postdoctoral training program funded by the National Institute of Mental Health and part of the UM interdisciplinary graduate program in neuroscience. Several institute senior scientists received their training in brain research at the MHRI, and have remained or returned to run their own MHRI laboratories.

At first, institute laboratories were scattered among various facilities on the medical campus. In 1960, a 50,000-square-foot building was completed to house the MHRI. In 1970, MHRI laboratories expanded into the nearby, newly opened Neuroscience Laboratory Building, doubling the laboratory space available to MHRI investigators.

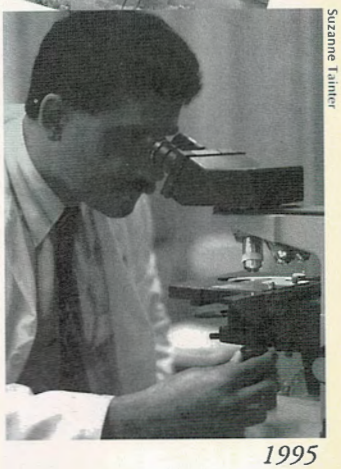
Agranoff, who is also director of the Neuroscience Laboratory Building, has nurtured MHRI relationships with other researchers in that facility. He and other MHRI investigators were instrumental in developing a PET imaging facility at the UM that made possible pioneering studies to measure neurotransmitter receptors in human subjects.

Now Agranoff is ready to step down as director. The MHRI will be led, in a novel arrangement, by co-directors Huda Akil and Stanley Watson, two of MHRI's premiere researchers (and a wife-husband team, as well.) Currently, Akil heads the UM neuroscience graduate program and Watson is the MHRI's associate director. [More on their research is found elsewhere in this issue of *Research News.*]

Before Agranoff departs the director's chair, he is overseeing a symposium to commemorate 40 years of Institute history. The program, which features work by many MHRI scientists, looks forward, rather than back. "I'm particularly optimistic about the youth of the institute's members," he says. Like organisms, institutes age, Agranoff explains. Many young researchers have been recruited to the MHRI in recent years. Some of the senior researchers are younger than the institute itself. This "young blood," he hopes, will keep the MHRI vigorous for another 40 years. "It also does wonders for our older scientists," he adds.

"We have accomplished much, but there is much more left to do," Agranoff wrote recently. "As one millennium draws to a close and another approaches, we look forward with excitement to new discoveries on how the brain works and — importantly — when it malfunctions, how to restore it."

—Suzanne Tainter


Suzanne Tainter

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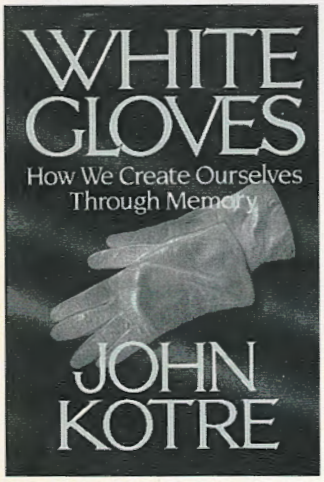
In its 40 years of existence, the Mental Health Research Institute has pioneered many research methods and approaches while sharpening its interdisciplinary focus on neuroscience and biological psychiatry.

Making Life Stories Out of Memories



"There's a hammock that fits right out there," John Kotre says. He points to his tree-edged back yard, indicating the spot where he wrote much of his recently published book. It is fitting that Kotre, a professor of psychology at the University of Michigan-Dearborn, used this personal setting to craft a book that includes many of his own life stories.

In *White Gloves: How We Create Ourselves Through Memory* (The Free Press 1995), Kotre explores the power of autobiographical memory. "Autobiographical memory is memory for the people, places, objects, events, and feelings that go into the story of your life," he says. For example, remembering how to drive a car is not an autobiographical memory. But remembering the first time you drove a car, a car crash you lived through, or car trips with your family are autobiographical memories.

One of Kotre's own autobiographical memories inspired the book's title. "There's a pair of white gloves that live in my memory," the book begins. "I can see them now, lying on top of some old clarinets in the cramped, dusty attic of my grandmother's house back in the niche where the roof meets the floor."

These are the white, leather gloves of a musician, Kotre's grandfather, who gave up his passion for music for a life of labor shoveling coal. When his grandfather died, leaving a family to support, Kotre's father went to work for the same utility company.

Kotre first heard the story of the white gloves while recording his father's life story. It did not make a great impression on him then, but years later when he listened to it at a turning point in his life, Kotre embraced the story as one that pointed to where he came from, who he was, and what he wanted to be. To Kotre, the memory of these gloves symbolizes self-sacrifice and lost dreams, and it motivates him to keep sight of his own dreams.

Fascinated by what people reveal about themselves and how they view others in these self-told tales, Kotre began collecting life stories through recorded interviews. He directed an eight-year project that resulted in a public television series called *Seasons of Life*, which presented interviews of people of all ages telling stories about their lives. The goal of the series was to "convey a lifespan perspective of development," says Kotre, to show that development takes place not just during childhood, but throughout one's life.

Interviewing people for their life stories and analyzing what they said led Kotre to his interest in memory. "After hearing about all of these life experiences — sometimes it's a whole life story, sometimes it's part of one — my thoughts turned to, 'What is this stuff that these people are telling me? What are these memories? Are they true? Did the events really happen? Was the meaning that people now see in the stories present back then?'"

Kotre studied the psychological research on autobiographical memory and then re-examined the life stories he had recorded over the years. "It was amazing to me to see how much science had missed [in trying to explain memory]. This is an old problem in psychology — to do science on human experience you have to close your eyes to some of that experience. You ask those questions that your scientific methods can answer. The other ones just fall away."

Kotre wanted to take a different tack in *White Gloves*. "I wanted to consume the science of autobiographical memory, but I also wanted to capture its spirit — what science often misses. I wanted to use concepts and examples that were close to experience rather than distant from experience."

Kotre found other researchers with concerns about how memory had traditionally been studied. Most of the time it had been in the context of short tasks such as remembering some nonsense syllables or number sequences. Another approach was the "everyday memory movement" which called for research subjects to remember in a natural context. This approach led to a fundamental change in thinking about memory.

In 1980, most psychologists thought of memory as a machine, like a computer, where everything a person ever experienced in life is stored. Every memory is there just as it went in and all someone needs to do is find the right buttons to retrieve it.

Researchers now know memory is more malleable. For example, Kotre recounts in his book research on eyewitness identification. Subjects viewed films of a car accident who were then tested on what they remembered. One question asked, "Was there broken glass?" There wasn't, but the subjects would sometimes remember broken glass just because they were asked about it, says Kotre. This research helped criminal investigators understand that it is better to let witnesses remember on

their own, rather than asking questions that may taint their memories.

The everyday memory and eyewitness research have helped to show that memory is "reconstructive," explains Kotre. Two kinds of information go into a memory. "The first is the original perception of the event; the second is information supplied after the event. With time the two become blended into a single memory that replaces what was originally present."

The point of memory, says Kotre, is not to make an exhaustive mental archive like some videotape library of a person's life, but to "edit" your experience so you can "view" that episode as part of your life story — present and future. "The neat thing about autobiographical memory is that it's doing that for you all the time. It's putting your memories in a form you can use."

Kotre describes memory as a river that changes with the terrain it flows through, the changing terrain representing the changes in life. And like a river, memory loses some of its contents and is added to periodically.

Although this changeability of memory may seem a bit unsettling, Kotre sees it as potentially positive. From the time we begin deciding who we are as individuals we are able to mold our autobiographical memories into life stories that support our identity. Autobiographical memories become the stuff of our own "personal myth."

Even memories of ourselves that are inconsistent with our idea of who we are can be used for contrast. "I am so much different from that now," these memories say. Or they can be forgotten altogether. As Kotre explains, our autobiographical memory allows us "to make use of the past or recover from it."

Kotre describes in *White Gloves* a study that located 300 people who had received psychological treatment as children. The researchers found that those whose lives were now well adjusted had little memory of their troubled childhood, but that those who were still having trouble tended to remember their early problems.

Some therapists use this malleability of memory in a process called "memory repair." The patient recalls a painful autobiographical memory and the therapist helps the patient create a new image of what they wish had taken place.

Because painful memories leave deep scars, memory repair cannot completely erase an original memory. But it can ease some of the pain associated with that memory, Kotre says. "In some ways the emotion attached to the memory may change, may be lessened. You may see new meaning in it, and that's a change, and because of that you might remember different details or remember them in different ways."

Kotre stresses he is not saying most memories are fantasies. As he writes in *White Gloves*, there are two sides to memory. The mythmaker is the side that takes our memory's records and fashions stories out of them. "It seeks to know the truth and generate conviction about the self, about who I am." But the other side of memory is "the keeper of the archives." This side works at "guarding the original records and trying to keep them pristine."

"The mind is doing both at the same time," says Kotre. For example, a memory from infancy may be based on a factual event that was told to you later in life, and the archive-keeper side of memory stores those facts. But the mythmaker side to memory puts those facts into a first-person story, reconstructing the record as if you had always remembered it yourself.

Despite knowing the benefits of a malleable memory, it is likely that most of us still want to know whether a memory is authentic. "We do want to know what really happened. So much of who we are is based on our memories and staked on them. It really has to do with the anchoring of the self," says Kotre.

Devices designed to aid our memory such as cameras, tape recorders, computers, video cameras and even writing have influenced the way people view memory. "No one talked about photographic memory before we had the camera," Kotre points out. "It's a paradox. Human beings create all of these things to help this memory of ours but then we look at the devices and say, 'Oh, that's how our memory works.'

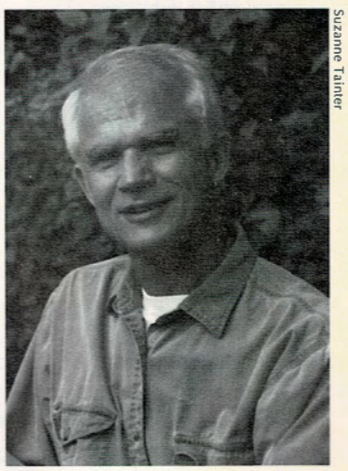
Kotre notes that human survival is dependent upon our ability to keep in touch with the reality of the past. And that there are very specific instances where we need to separate out as much of the myth as possible in order to get closest to the truth.

"There are times, take a case of abuse, where [accurate memory] matters a lot because there is something to be done about it." Likewise, some people try to deny the reality of the Holocaust. Here, too, says Kotre, "It matters greatly that we establish what really happened."

But, Kotre writes, the mythmaker that helps create our life stories is necessary for mental health. It is the part of memory that "gives the self strength as it looks to the future and interprets the past."

Kotre himself is unconcerned about whether personal stories are real or not. "My slant is, how does memory speak about you?" He leans back in his chair, crosses his arms and smiles, "I picture my old age as being filled with memories and fantasies and I won't give a rip which is which."

—Jamie Saville



Suzanne Tainter

John Kotre

NOTES

POET'S MANUSCRIPTS EXAMINED WITH NUCLEAR POWER

The manuscripts of 17th-century poet John Donne are being examined with the help of nuclear power, by University of Michigan-Dearborn researcher **Ted-Larry Pebworth.** The Michigan Memorial-Phoenix Project is employing low-energy carbon-14 isotopes to make images of the watermarks in the Donne manuscripts for Pebworth to study.

Having examined the watermarks in seventy-six manuscripts, Pebworth is tracing their origin and dates by comparing them with other watermarks of the period.

"My goal is to date the individual manuscripts more precisely than has so far been possible, and to place each manuscript more exactly within the various circles of admirers who collected and transcribed Donne's poetry during his lifetime," according to Pebworth.

The exact publishing dates are extremely important for scholars. Donne published very little of his poetry during his lifetime, and the posthumous printings of his collected poems are riddled with inaccuracies. Pebworth will use his findings to establish a scholarly edition of Donne's poetry.

By comparing the Donne manuscript watermarks with the watermarks of other period works, Pebworth will be able to place each manuscript in its proper milieu. If two manuscripts bear the exact same watermarks, it is likely they were created close to one another in time and place.

Beginning in the 13th century, European paper mills identified their products with marks impressed onto the paper with molds shaped to create designs such as shields, dragons and hunting horns.

In Donne's era, the molds had an average life of six months or less; therefore, all of the paper with identical watermarks was made in a short time.

Since the 1950s, researchers have used a process known as *beta-radiography* to photograph watermarks without damaging the paper or its text. A plastic sheet impregnated with a carbon-14 isotope is placed on one side of the watermark and x-ray film on the other. After 10 minutes of exposure, the film is removed, developed, and printed. This imaging process also allows scholars to examine sections of a watermark obscured by ink and to measure a paper's thickness.

Pebworth plans to identify, photograph, and study the watermarks of the remaining Donne-manuscripts and publish reproductions of all the watermarks, providing other scholars with an important reference to Renaissance watermarks. □

Lee Katterman

SMOKING AMONG TEENAGERS ON THE RISE

Cigarette smoking is increasing among young Americans, conclude scientists at the University of Michigan Survey Research Center. This trend in included among the findings of their 20th national survey of American high school seniors, and their fourth national survey of eighth- and tenth-graders.

For a decade the rate of smoking among high school seniors was holding constant despite accumulating evidence of smoking's lethal effects, restrictions on cigarette smoking, and smoking reductions among adults, says **Lloyd D. Johnston**, the principal investigator of the study.

Johnston and colleagues **Jerald Bachman** and **Patrick O'Malley** have directed the Monitoring the Future Study of drug use for over 20 years, under a series of research grants from the National Institute on Drug Abuse.

"We are now in a period of clear and continuing increase in cigarette smoking among teens. Twelfth-graders showed an increase in smoking which began in 1992, while the eighth- and tenth-graders have shown a steady increase since first surveyed in 1991," states Johnston. "This is extremely bad news for the health and longevity of the next generation."

The proportional increase in smoking is greatest among the eighth-graders. The daily smoking rates for 8th-, 10th- and 12th-grade students in 1994 are 9 percent, 15 percent, and 19 percent, respectively.

The increases in smoking are very broad. They are found among boys and girls and at all socioeconomic levels. The rise is seen among whites, African-Americans, and Hispanic-Americans, in all regions of the country, and in large cities as well as rural areas.

The investigators conclude that teens greatly underestimate the dangers of smoking. Only about half the eighth-graders believe smokers run a great risk of harm by smoking a pack or more daily.

Also, there has been a clear weakening of peer norms against smoking, Johnston points out. "While the majority still say they disapprove of regular smoking, that proportion has been declining steadily since the early 1990s."

The costly implications of this increase in adolescent smoking cannot be overestimated, say the investigators. "Cigarettes will kill far more of today's children than all other drugs combined, including alcohol. But because these consequences do not emerge for a few decades, we seem to be much less concerned about them. If cigarette smoking killed quickly, like drunk driving does, the country would be treating the current rates of adolescent smoking as an extreme emergency." □

VINCENT MASSEY NAMED NAS FELLOW

Biological chemistry professor **Vincent Massey** has been named a fellow of the National Academy of Sciences, one of the highest honors awarded to American scientists by their peers.

Massey conducts research on biological oxidation mechanisms. His discoveries include the existence of a group of enzymes that play a significant role in the energy metabolism of all mammalian and most bacterial cells. His research currently focuses on molecular events in oxygen activation caused by flavoproteins. This work builds on his discovery of flavins as the major source of superoxide.

Massey has been at the UM since 1963. He delivered the 1995 Russel Lecture. The annual lectureship is the highest honor the university gives to senior faculty. □

LETTERS

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We reserve the right to edit letters for length and clarity.

To the Editor:

I was glad to see that Holly Craig and Julie Washington are "Sorting Disorder from Dialect: Language Tests in Error for Some Children, say UM Researchers." [*Research News* 1995, No. 2] Their work should have immediately followed up on what was known before the Green Road children's court case. In 1979, in Martin Luther King Junior Elementary School Children v. Ann Arbor School District Board, the expert witnesses included UM professors Richard Bailey, who is still around, Daniel Fader, and Geneva Smitherman. The latter (now at Wayne State University) and others discuss it often, such as in *Tapping Potential: English and Language Arts for the Black Learner* (ed. by Charlotte Brooks, published by the National Council of Teachers of English, Urbana, IL, 1985).

UM researchers should continue this work.

Carolyn Green Hartnett
Texas City, Texas

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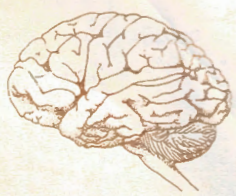

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