

1982-08

Research in Progress: August 1982 v. 3, no. 2

<https://hdl.handle.net/2144/17901>

"Downloaded from OpenBU. Boston University's institutional repository."



Research in Progress

Volume 3 Number 2
August 1982

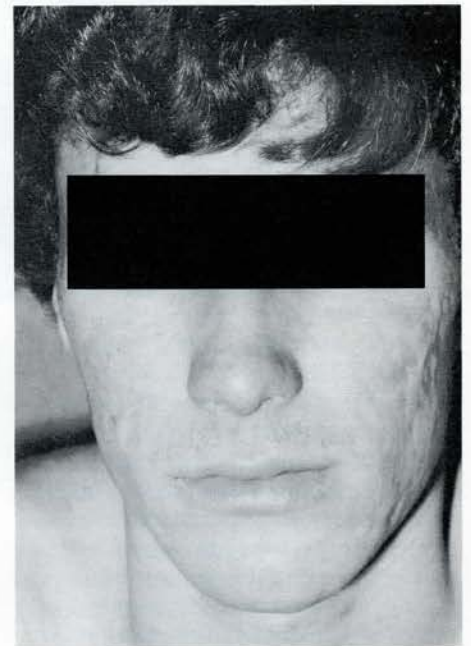
Although stroke is the third leading cause of death in the United States, relatively little is known about the disease. Philip A. Wolf, M.D., heads a BUSM research team that is exploring the causes of stroke and the best methods for treatment. See story on page 3.

Major breakthrough occurs in acne treatment with drug development

A major breakthrough in the management of severe, treatment-resistant acne, based in part on research at Boston University Medical Center, has been approved by the federal Food and Drug Administration.

Acne is a common skin disease affecting more than 15 million adolescents in the United States between the ages of 12 and 17, in addition to adults in their 20s, 30s, and even 40s. Severe cases only number about 350,000, but represent an important subset of patients because of morbidity and resistance of their disease to treatment.

Since 1979, Peter E. Pochi, M.D., a BUSM professor of dermatology, and his team of researchers in the Evans Memorial Department of Clinical Research at University Hospital in Boston, a principal teaching hospital of BUSM, have been studying the efficacy and safety of an orally administered vitamin A derivative, isotretinoin (13-cis-retinoic acid) in cases of severe, treatment-resistant acne. The drug had been tested first at the National Cancer Institute and showed dramatically beneficial results in a small group of patients. Although the exact mechanism of the action of this compound has not been determined yet, Pochi said *continued on page 2*



These before and after pictures illustrate the dramatic improvement brought about by the use of isotretinoin (13-cis-retinoic acid) in the treatment of severe acne. (Department of Dermatology photos)

Physician aims to improve diagnosis of MS: 'crippler of young adults'

By the time 25-year-old Kate sought the advice of her family physician, the numbness in her left leg was persistent and her vision frequently was blurred. At times, she stumbled for no apparent reason and seemed to tire easily. For weeks, she had told herself that these vague symptoms, some of which would come and go, simply meant that she was overworked or "under the weather."

The final diagnosis of Kate's symptoms was multiple sclerosis, a

major disorder of the central nervous system that now affects an estimated 250,000 persons in the United States, according to Charles M. Poser, M.D., a professor of neurology at Boston University School of Medicine and a nationally-recognized authority in the field of MS.

Often referred to as the "crippler of young adults," multiple sclerosis usually strikes those in the 20-to-40 age bracket, affecting women more *continued on page 5*

Acne breakthrough... continued from page 1

ical trials, funded by Hoffmann-La Roche, Inc., the drug's developer, have shown that the drug is highly effective, even in severe cases resistant to most other treatments. The drug will be on the market in September.

Of the 65 patients Pochi has treated, not a single case of facial acne failed to clear up completely in patients administered adequate doses for an appropriate length of time. Cases of back and chest acne usually responded well, although not always as completely as facial acne. Side effects were limited primarily to the skin and the mucous membranes, he said.

Acne consists of both inflammatory and non-inflammatory lesions. The non-inflammatory lesions—blackheads and whiteheads—are caused by retention of dead skin cells and hardened oils lodged deeply in the follicles (pores) of the skin in such acne-susceptible areas of the skin as the face, neck, chest and back. The inflammatory component is comprised of papules (red pimples), pustules (pus-pimples) and large inflammatory nodules ("cysts"). When these large inflammatory lesions are numerous, the term cystic or conglobate acne is used. This type of acne tends to be resistant to treatment and to lead to the formation of scars, Pochi said.

Initially, it was believed that isotretinoin was effective in acne by reducing the formation of sebum, the oil gland secretion. Pochi's former associate investigators, John S. Strauss, M.D., and Donald T. Downing, Ph.D., who now are at the University of Iowa College of Medicine, conducted at University Hospital the first tests measuring the composition of sebum in patients already being treated with the drug. In these tests it was discovered that patients on the drug had very low levels of

sebum oils. "It was an indirect measure, but we were convinced that was what the drug was doing. Subsequently, we were able to do oil measurements directly on patients with severe acne before and after treatment. The drug decreased oil secretion by nearly 90 percent," Pochi said.

Shortly afterwards, the researchers conducted a head-on test in which isotretinoin was compared with etretinate, another oral vitamin A-derivative drug that had been tested in Europe for the treatment of psoriasis, to see which one worked better in severe acne cases.

"It was no contest," Pochi said. "It was very interesting because the drugs were so similar—the same type of compound. They both belonged to a group of substances called retinoids, which are vitamin A derivatives. But one worked and one didn't. That's characteristic of retinoids. They can affect a variety of diseases differently. The other drug didn't even reduce oil secretion. It was a double-blind study, but it was not difficult to tell after several weeks who was on which drug." In a continuation of this study, Pochi said, those given etretinate were afforded the opportunity to be treated with isotretinoin, and most did very well.

Isotretinoin has a very high response rate despite the severity of the disease, Pochi said, citing a dose-response study now nearing completion on the efficacy and the incidence and severity of the drug's side effects. The BUMC research team undertook the study in collaboration with departments of dermatology at State University of New York, Downstate Medical Center, Brooklyn, and University of Iowa College of Medicine, Iowa City.

Since last summer, 150 patients with severe acne have been treated at the three institutions with three different dosages of isotretinoin for 16 to 20 weeks. In this blind study, yet to be analyzed, only the patient

and the technician administering the drug, not the physicians, knew which patient was receiving what dosage. If after 16 weeks there was not a 75 percent decrease in the number of nodulocystic lesions, the patient would continue treatment for four more weeks. Patients then were followed for two months after the drug was stopped.

"What we noticed as had others previously, and what is still unexplained, is that patients continue to improve after the drug is stopped. You don't get your ultimate benefit until approximately two months after the drug is stopped," Pochi said.

Although this implies that the drug stays in the body, that apparently is not the case. The drug is actually eliminated fairly rapidly. "Fifty percent of the drug is eliminated from the body after 10 to 20 hours," he explained.

Several other questions remain to be answered about the drug. "What's puzzling is that the oil glands recover after the drug is stopped, yet the disease, if it has responded well, rarely comes back," Pochi said. When there are recurrences, they are relatively minor. The drug shuts off the oil glands immediately. Oil secretion goes down abruptly, then comes back very slowly. But it always comes back. However, when it does, the patient's disease usually is still quiescent.

There were two patients who did not respond to treatment at all despite very marked inhibition of sebaceous gland secretion. "The results in these two patients suggest that the reduction of sebum, induced by isotretinoin administration, may not represent the only way the drug acts in alleviating the severity of acne," Pochi said.

Another factor in the disease besides oil secretion is acne bacteria, known as *Propionibacterium acnes*. Everyone has these bacteria, which reside deeply in acne-susceptible follicles. People who have acne get in trouble because

their pore walls develop abnormally and are prone to break down. The bacteria produce many enzymes and acids so when the walls break, inflammation is the result. Recent research has shown that with use of isotretinoin, these bacteria decrease markedly. "Yet the drug is not antibacterial *per se*," Pochi said. The bacteria probably decrease because one of the functions of sebum is to provide food for the bacteria. It is not yet known whether the bacteria recover, as does sebum, when the drug is stopped.

Now in the final stages of his clinical investigation on isotretinoin, Pochi has turned his attention to possible endocrine abnormalities in adult women with persistent acne.

Acne in women over age 20 can be a sign of an overactive ovary or adrenal gland, but in these cases, it almost always occurs along with excessive facial hair and menstrual irregularities.

"Most women with acne do not have other symptoms and hormonally seem to be normal," Pochi said. "Yet, in many cases, the acne persists and frequently resists treatment."

To examine this problem, Pochi is conducting a three-year National Institutes of Health-supported study in collaboration with Christopher Longcope, M.D., a professor of obstetrics/gynecology and medicine at University of Massachusetts Medical School.

—Shirley B. Moskow

Suggested Further Readings

1. Peck, G.L. et al: Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. *N Engl J Med.* 300: 329-333, 1979.
2. Pochi, P.E. and Strauss, J.S.: Sebaceous gland inhibition from combined glucocorticoid-estrogen treatment. *Arch Dermatol.* 112: 1108-1109, 1976.
3. Farrell, L.N. et al: The treatment of severe cystic acne with 13-cis-retinoic acid. Evaluation of sebum production and the clinical response in a multiple dose trial. *J Am Acad Dermatol.* 3: 602-611, 1980.

School of Medicine research team seeks to unravel mysteries of stroke

Behind the popular perception of stroke as a disease that hits suddenly, and often leaves victims paralyzed or unable to speak, lie some little-known facts about the illness:

- While stroke is a member of the family of diseases that includes heart attacks, some factors that significantly increase the risk of heart attacks—notably smoking and high cholesterol—seem to have little connection with stroke.
- The kind of problem that brings on a stroke has a lot to do with how serious and long-lasting its effects will be. Strokes that result from hemorrhage, for example, are far more likely to lead to death, or permanent disability, than those resulting from blood clots or a narrowing of the arteries, which make up about 80 percent of the total number of strokes.
- Although stroke can in fact paralyze victims, or seriously affect them in other ways, it may occasionally produce little or no permanent damage.

Even though stroke is the nation's third leading cause of death, with 500,000 victims yearly, stroke is still, relatively speaking, a mystery. Despite the emergence of new findings over recent decades, much less is known about stroke than about other major diseases.

Currently involved in a multifaceted effort to shed added light on the causes of stroke and the best methods for treating it is a Boston University School of Medicine team headed by Philip A. Wolf, M.D., a professor of neurology and an associate research professor of medicine.

Part of the group's effort is centered on BUSM's renowned Framingham Heart Study, in which health patterns of more than 5,000 men and women have been tracked

for more than 30 years.

The Study, named for the community of Framingham, Mass., where all its subjects lived at the time the project began, is best known for its contributions to the understanding of heart disease. It also has helped advance understanding of stroke. Thus, noted Wolf, more than a decade ago an examination of stroke incidence in the Framingham group confirmed a strong link between hypertension and stroke. More recently, BUSM researchers used the Framingham group to show that doctors frequently fail to report accurately on whether stroke was a cause of death.

Now, Wolf and his associates have embarked on a new examination of stroke patterns in the Framingham group, with support from the National Institute for Neurological and Communicative Disorders and Stroke. Working with Wolf in this and other stroke studies are Lee Corwin, M.D., a staff neurologist at University Hospital in Boston, a principal teaching hospital of BUSM, Margaret Kelly-Hayes, R.N., M.S., an assistant clinical professor of neurology, Eloise Licata-Gehr, R.N., M.S., a stroke research nurse, and Paula J. Murray, data manager.

One of the major issues being examined, said Wolf, is the role of noises, known technically as carotid bruits, which sometimes can be identified as coming from arteries leading to the brain, as a potential warning sign for stroke.

"These bruits may be testimony to the existence of atherosclerosis, or a narrowing of the arteries," said the neurologist. "On the other hand, there's a lot of controversy about the extent of the risk facing people with bruits, and about whether you ought to do extensive tests on them, which are potentially dangerous, or to operate."



Neurologist Philip A. Wolf, M.D., examines a patient in his University Hospital office. (Photo by Bradford F. Herzog)

If it is found that certain people with bruits are at no greater risk of stroke, then hazardous tests and surgery would not be justified, Wolf said. Digital subtraction angiography (DSA), a new technique that permits visualization of the carotid and cerebral arteries without the risks of arteriography, also can be used.

A second area of investigation is the link between stroke and diabetes. Many studies have shown that individuals with diabetes are more subject to stroke than their non-diabetic counterparts, Wolf noted. Yet, the question remains whether this is simply because diabetes and stroke are both linked to the same risk factors—especially hypertension—or because diabetes has an impact on the system that itself increases the risk of stroke.

"The brain makes use of glucose, and diabetes obviously interferes

with glucose metabolism," Wolf said. "What we may be seeing, therefore, is diabetes acting to make the brain more vulnerable to cerebrovascular attacks."

A third subject under scrutiny is the question of why stroke, on the average, tends to occur so much later in life than heart attacks. While stroke is rare among those under 60, heart attacks frequently strike people, especially men, in their 40s and 50s.

"We really have very little idea what accounts for the age difference," Wolf said. "It could have something to do with the way hypertension seems to act in producing atherosclerosis—driving the buildup of plaque in the arteries out further and further from the heart, so that eventually it affects the arteries leading to the brain."

Insight into this question could

provide information about the conditions that lead to stroke, said the neurologist. This, in turn—like findings on the role of bruits, diabetes and other potential precursors of stroke—could lead to improved strategies for preventing the disease.

In addition to seeking knowledge that will be useful in prevention, the BUSM group also is hoping to aid in improving treatment strategies. Both in the Framingham project and in the Full Phase Stroke Data Bank project at University Hospital, they are looking for answers to such questions as:

- What kinds of home-care are required for people who have been seriously disabled by stroke?
- How can the medical community's identification of different *kinds* of stroke be improved and standardized?
- And—an issue that is especially critical at a time of growing constraints on health-care spending—can better predictions be made, based on the type of stroke and the brain area affected, about the need for therapy and its chances for success?

"Since resources are limited," Wolf said, "it would be tremendously valuable to be able to predict which patients are going to do very well, which ones are unlikely to respond to even the most intensive treatment, and which ones can, through therapy, be brought to a level of independence that would enable them to live fairly normal lives."

—Richard P. Anthony

Suggested Further Readings

1. Wolf, P.A. et al: Asymptomatic carotid bruit and risk of stroke: The Framingham Study. *JAMA* 245: 1442-1445, 1981.
2. Wolf, P.A. and Kannel, W.B.: Controllable Risk Factors for Stroke: Preventive Implications of Trends in Stroke Mortality. *Diagnosis and Management of Stroke and TIAs*. J.S. Meyer, ed. Addison-Wesley, 1981.
3. Kannel, W.B. and Wolf, P.A.: *Epidemiology of Cerebrovascular Diseases*. Cerebral Vascular Diseases. R.W. Russell, ed. Churchill Livingstone, 1982.

Multiple sclerosis...
continued from page 1

frequently than men. A progressive, unpredictable disease with no known cause or cure, MS is more prevalent in colder climates. But one of the biggest problems with MS is the diagnosis.

"There is no single diagnostic laboratory test specific to MS," Poser stated. "The diagnosis is based on clinical information the physician gleans from the patient's history and from a neurological examination, using criteria developed 15 or 20 years ago—before such procedures as evoked response studies or CAT-scans were introduced," he continued. (Evoked response studies use such external stimuli as visual patterns or clicking sounds to measure the brain's electrical response.)

To further complicate the problem of diagnosing multiple sclerosis, an average of 3.3 years may pass after a patient has the first symptom before he or she is diagnosed, Poser explained. "That's because the symptoms often are disregarded by the patient or misinterpreted by the doctor."

As evidence of the lack of standardization in diagnosing multiple sclerosis, Poser in 1965 conducted a test that demonstrated a remarkable absence of correlation among diagnostic criteria. He collected detailed clinical histories of 25 patients who had died and whose autopsies confirmed previous MS diagnoses. Poser sent these reports to 106 neurologists around the world who classified each case as probable, possible or unlikely MS, using any criteria they wished.

The results were astounding: 40 percent of the cases were rated "unlikely." In other words, if Kate, mentioned earlier in this article, consulted those same 106 neurologists, complained of the same symptoms and provided the same clinical his-



Charles M. Poser, M.D., conducts a diagnostic test for multiple sclerosis. (Photo by Bradford F. Herzog)

tory, 42 of the 106 would tell her that it was unlikely she was suffering from MS.

"We have been making diagnoses based on tests of variable reliability," Poser said. "These criteria must be standardized because they are being increasingly depended upon by a growing number of neurologists. In addition," he continued, "it is vital to have a single, agreed-upon set of criteria to conduct valid epidemiological studies of the disease or to engage in clinical trials of drug regimens for the treatment of MS."

To help standardize the process of diagnosing MS, Poser has developed a numerical system that is based upon the scoring of historical, examination and ancillary clinical diagnostic procedures. Poser believes that the utilization of this simple numerical scale will help standardize the three traditional classifications of MS: possible, probable and definite. (If the cases Poser used in 1965 were evaluated using the scoring system, the accuracy of diagnosis would be increased to between 80 and 85 percent rated "definite," he noted.)

"The application of the scoring

system still requires the initial suspicion of MS on the part of the physician for it to be utilized as a diagnostic tool," Poser emphasized.

For each parameter included in Poser's criteria, such as age of onset and first symptoms experienced, a numerical value is assigned. That number corresponds to the percentage of that item's occurrence among 111 autopsy-proven former MS patients from the United States, England and Norway. The scoring system is cumulative: Once a symptom has occurred, its value remains even though it is not present at the time of examination.

Appropriate scoring values also are awarded when such procedures as evoked response studies and psychological testing provide evidence of central nervous system lesions, or areas where there is loss of tissue or function.

To update clinical diagnostic criteria for MS, a two-day workshop was convened this spring in Washington, D.C. One major purpose of the meeting, of which Poser was program chairman, was to review in detail newly-developed diagnostic techniques for MS. These

Research in Progress

Boston University School of Medicine
Office of Informational Services
720 Harrison Ave., Suite 600
Boston, MA 02118

Nonprofit Org.
U.S. Postage
PAID
Boston, Mass.
Permit No. 56031

include neurophysiological tests such as evoked response studies, neuropsychological tests, neuro-radiological procedures (CAT-scans and nuclear magnetic resonance scans), as well as immunological and urological tests.

The 25 physicians attending the conference, which was sponsored by the Paralyzed Veterans of America, were among the leading authorities on MS from the United States, Canada and Great Britain. The participants, including Daniel Sax, M.D., a professor of neurology at BUSM, assessed whether a series of diagnostic scenarios could be designed that would lead to a diagnosis of MS, or remove it from consideration, in a rapid, efficient and economical fashion.

Workshop participants also established standards for the performance of laboratory tests and the interpretation of test results. "If a neurologist wants to use evoked response tests in the diagnosis of MS, then it should be done according to a certain method," Poser said. "That way, the results can be clearly judged as normal or abnormal. The physician's subjectivity can no longer bias this determination."

In addition, Poser said, a new system for the diagnostic classification of MS is being developed that will permit the use of these laboratory procedures, but only if they conform to the standardized methods decided upon at the workshop. The numerical scoring system, he added, can be used in conjunction with or as an alternative to the diagnostic classifi-

cation of MS. The diagnostic criteria and other recommendations resulting from the workshop are scheduled to be published next April by Thieme-Stratton in New York.

The final diagnosis for multiple sclerosis is based upon evidence of two or more separate lesions of the central nervous system. Just as electrical wires are insulated, nerve fibers of the central nervous system are insulated with a fatty covering known as myelin. If the myelin sheath is destroyed, conduction of sensory or motor nerve impulses to the brain are impaired or may be completely blocked. When the brain no longer receives information from the environment or when it cannot direct the muscles and other organs to perform various functions quickly and smoothly, symptoms of neurological dysfunction appear, and the patient complains of being unable to function normally.

In MS patients, lesions are generally located in five specific areas of the central nervous system: the spinal cord, brainstem, cerebellum, optic nerve and the cerebral hemispheres. The clinical symptoms of the disease may vary greatly, depending on the site of the lesion. For example, spinal cord lesions can produce numbness, lessened or

absent sensitivity to pain, and lack of position sense (the awareness of the relationship of one's body parts to space), while lesions in the brainstem can cause double vision, involuntary movements of the eyeball or slurred speech. Many lesions, in particular those affecting the cerebral hemispheres, produce no recognizable symptoms.

Once a diagnosis of MS has been established, patients like Kate can begin a treatment plan. Although no single therapy is universally prescribed, such medications as corticosteroids and muscle relaxants often are used and may help the patient manage his or her condition. Other substances such as Interferon are being studied for their use in treating MS.

In addition to the Paralyzed Veterans of America, Poser's work is funded by the National Multiple Sclerosis Society and the Kroc Foundation.

—Susan B. Rabin

Suggested Further Readings

1. Poser, C.: A numerical scoring system for the classification of multiple sclerosis. *Acta Neurol Scand.* 60: 100-111, 1979.
2. Poser, C.: Multiple sclerosis: A critical update. *Med Clin N Amer.* 63: 729-743, 1979.

Research in Progress is published by Boston University School of Medicine, 80 East Concord St., Boston, MA 02118, to communicate the excitement of current research at the School of Medicine and the School's concern for improved health care in contemporary society.

Research in Progress is produced by Boston University Medical Center's Office of Informational Services, Owen J. McNamara, director. Editor: Marjorie H. Dwyer; Assistant Editor: Susan B. Rabin; Designer: Nannette Gonzalez. Donald R. Giller is Director of Marketing and Public Affairs. Inquiries may be directed to the Office of Informational Services at 617/247-5606.