

This Week in the Journal

JANUARY 2, 2003

VOL. 348 NO. 1

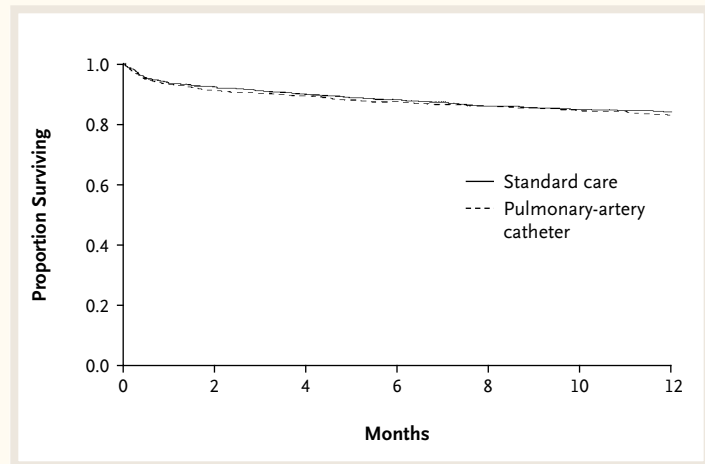
ORIGINAL ARTICLES

Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients

In this large trial, elderly, high-risk patients were randomly assigned before surgery to goal-directed therapy guided by a pulmonary-artery catheter or to standard care without the use of such a catheter. There was no significant difference between the groups in mortality in the hospital or at 6 or 12 months. Pulmonary embolism was more frequent in the catheter group.

These findings argue against the routine use of a pulmonary-artery catheter in caring for elderly, high-risk patients during and after surgery.

SEE PAGE 5; EDITORIAL, PAGE 66



Natalizumab for Multiple Sclerosis

Natalizumab is an antagonist of α_4 integrin, a very late adhesion antigen that is expressed on the surface of activated lymphocytes and monocytes. In this double-blind, placebo-controlled trial, the patients who received natalizumab had fewer new enhancing lesions on gadolinium-enhanced magnetic resonance imaging and significantly fewer relapses.

This carefully controlled trial involved patients with relapsing multiple sclerosis. The follow-up lasted six months, so longer studies are needed, but the results indicate that treatment with agents that inhibit adhesion and transendothelial migration of activated immune cells may offer clinical benefits.

SEE PAGE 15; EDITORIAL, PAGE 68

Natalizumab for Active Crohn's Disease

In this 12-week randomized, placebo-controlled study of patients with active Crohn's disease, natalizumab, an α_4 integrin-specific humanized monoclonal antibody, did not result in a significantly higher rate of clinical remission at 6 weeks (the prespecified primary outcome measure). However, analyses of secondary outcome measures suggest that natalizumab reduced disease activity and improved the quality of life.

This study suggests that α_4 integrin is important in Crohn's disease. The value of natalizumab relative to other available treatments for Crohn's disease is not yet known.

SEE PAGE 24; EDITORIAL, PAGE 68

THIS WEEK IN THE JOURNAL

ORIGINAL ARTICLE

Hallervorden–Spatz Syndrome

Hallervorden–Spatz syndrome is an autosomal recessive disorder characterized by dystonia, parkinsonism, and brain iron accumulation. The authors found that all patients with classic disease (characterized by early onset and rapid progression) and one third of patients with atypical disease (later onset and slow progression) had mutations in the gene encoding pantothenate kinase 2 (PANK2). All patients with PANK2 mutations had a characteristic abnormality on magnetic resonance imaging of the brain.

Many patients now classified clinically as having Hallervorden–Spatz syndrome can be better described as having neurodegeneration associated with PANK2 mutations.

SEE PAGE 33; PERSPECTIVE, PAGE 3

CLINICAL PRACTICE

Preventing Falls in Elderly Persons

A 79-year-old woman with a history of congestive heart failure, arthritis, depression, and difficulty sleeping presents for a follow-up visit. She takes several prescription medications, including an antidepressant, a diuretic, an angiotensin-converting-enzyme inhibitor, and a beta-blocker, as well as over-the-counter sleep and allergy medications. Her chronic conditions appear to be stable. Her daughter reports that the patient has fallen twice during the past six months. What can be done to prevent future falls?

SEE PAGE 42

GENOMIC MEDICINE

Population Screening

Newborns are now routinely screened for the presence of a number of inherited diseases. In these cases, early diagnosis allows treatment to be instituted before there are irreversible adverse consequences. However, as outlined in this installment in the Genomic Medicine series, clinical benefit can be derived from screening adults as well — not only for the genes associated with classic inherited conditions, such as cystic fibrosis and Tay–Sachs disease, but also for genes that are better considered risk factors for complex diseases, such as factor V Leiden and mutations associated with hereditary hemochromatosis.

SEE PAGE 50

CLINICAL PROBLEM-SOLVING

Easy to See but Hard to Find

A 46-year-old woman from the Philippines reports fatigue, body aches, and weight loss. On examination, she is pale and has diffuse bony tenderness. The hemoglobin level is 8.0 g per deciliter; the white-cell and platelet counts are normal. The serum creatinine level is 2.8 mg per deciliter (247.5 μ mol per liter), and the serum calcium level is 13.2 mg per deciliter (3.3 mmol per liter).

SEE PAGE 59

Hallervorden and History

Michael Shevell, M.D.C.M.

To quote Abraham Lincoln, “we cannot escape history.” Not even in the pages of a medical journal devoted to the elucidation of the scientific basis of disease can we do so. In this issue of the *Journal*, Hayflick et al. (pages 33–40) report on the genetic, clinical, and radiographic delineation of Hallervorden–Spatz syndrome. Mutations in the gene encoding pantothenate kinase 2 (PANK2), a key enzyme in the biosynthesis of coenzyme A, are correlated with phenotypic features observed in both classic and atypical cases of Hallervorden–Spatz syndrome. Their report is a prototypical example of the precision of the “scalpel” of molecular biology in pinpointing what has previously been defined by astute clinical observation. Their report also reflects the advances of the latter part of the 20th century in our understanding of the genetic basis of disease — advances that are nothing short of revolutionary in scope and that will be a lasting hallmark of this particular scientific epoch.

However, another sort of history is called forth by the current report and cannot be ignored. It is one conveyed by the life of Julius Hallervorden, after whom the syndrome is named. As is evident in his choices and actions, this history concerns the corruption of medicine’s core values within the framework of the most malevolent of 20th-century totalitarian societies, Nazi Germany.

Alarming, the roots of this corruption lie in “science.” This so-called science was racial hygiene that advocated the application of a distorted version of Darwinian principles to human populations as a whole. The primacy of genetic factors in determining even the most complex biologic or social traits was emphasized, and thus the institutional and supportive care provided to chronically ill persons was considered counterproductive to the health of the population as a whole. To the Nazis, this provided an objective basis for the reformulation of perceived political and social problems as medical problems to which biologic solutions (i.e., eradication or ex-

termination) were required. To quote Deputy Führer Rudolf Hess, “National Socialism is nothing but applied biology.” From this outlook flowed an active euthanasia program targeting disabled children and adults, the development of scientific means of killing people on a mass scale, the medicalization of the selection process within concentration camps, and horrific experimentation on human subjects. Although we now interpret the term “euthanasia” to mean “good death,” the Nazis appropriated the term and used it to describe a program that effected the involuntary transfer and killing of large numbers of ill and disabled persons.

At the outbreak of World War II, Hallervorden was the pathologist of the Brandenburg State Hospital, which included the chronic care institution at Brandenburg-Görden. This would be one of the six elimination centers established under the Aktion T-4 adult-euthanasia program. The program effected the transfer of institutionalized patients from all parts of Germany after a secret review of questionnaires based on their medical files by a central committee of physicians. After their transfer and a brief period of observation to verify the underlying diagnosis, patients were killed by gassing with carbon monoxide in disguised shower facilities. The operation was never legally mandated and was rife with deception of the affected families. A memorandum signed by Adolf Hitler, dated the opening day of the war, empowered physicians “to grant a mercy death to those judged to be incurably ill.” In operation for less than two years (during the period from 1939 to 1941), the Aktion T-4 program resulted in the deaths of 70,273 persons.

To an academically oriented pathologist such as Hallervorden, Aktion T-4 provided an opportunity for the study of rare specimens on a previously unimaginable scale. Hallervorden’s reports to the German Association for Scientific Research and the German Research Council detail his use of specimens derived from the Brandenburg-Görden kill-

ing center. Dissatisfied by the quality of medical information in the patients' dossiers for a funded project entitled "Inherited Feeble-Mindedness," Hallervorden himself selected and examined a number of living patients before personally removing their brains at the killing center. On the basis of these materials (and others he obtained through the child-euthanasia program and the Jewish Hospitals of Warsaw and Lublin in Poland), Hallervorden published 12 scientific articles (7 as sole author) in the postwar era on a variety of topics, including the effect of carbon monoxide exposure on the fetal brain.

Hallervorden's awareness of, participation in, and moral indifference to Aktion T-4 is captured vividly in quotations from his interrogation by Leo Alexander (an American neurologist and himself a Jewish refugee from central Europe) after Germany's defeat: "I heard that they were going to do that, and so I went up to them and told them, 'Look here now, boys. If you are going to kill all those people, at least take the brains out so that the material can be utilized'"; "There was wonderful material among those brains, beautiful mental defectives, malformations and early infantile disease"; "They asked me: 'How many can you examine?' And so I told them an unlimited number — the more the better"; and "I accepted the brains, of course. Where they came from and how they came to me was really none of my business."

Medicine is replete with eponyms. They create a convenient, shorthand way to communicate among health professionals. They allow us to recall our historical roots and to recognize the pioneers who have been instrumental in the clinical art of disease recognition. Mastering the argot of eponyms provides

access and initiation into the medical profession. Most important, eponyms represent a means of conveying honor and immortality to practitioners.

Sufficient documentary evidence exists to characterize Hallervorden's actions during the war as those of an accessory to mass murder. Simply stated, we as physicians are not a profession given to honoring mass murderers. The time has come to abandon the term "Hallervorden-Spatz syndrome." Our knowledge of pathogenesis, genetics, and molecular biology has advanced to a stage that permits us to do so. We can hope that our moral indignation has advanced as well. "Pantothenate kinase-associated degeneration" or "neurodegeneration with brain iron accumulation" would be accurate descriptive options.

Although we must bury the eponymous name, we must not bury the memory of the numerous victims of a medical profession that acted as an instrument of a philosophy that denied human beings their autonomy and dignity. Although the names of the victims are lost in the fog of history, we can perhaps begin to honor them by reflecting on these words from William Seidelman whenever we encounter the sorry tale of medicine in the Third Reich: "What needs to be published and studied today is not the 'scientific' data from the experiment, but a recounting of the consequences of ethical compromise where human life and dignity become secondary to personal, professional, scientific and political goals."

From the Department of Neurology and Neurosurgery and the Department of Pediatrics, McGill University, and the Division of Pediatric Neurology, Montreal Children's Hospital—McGill University Health Center — all in Montreal.