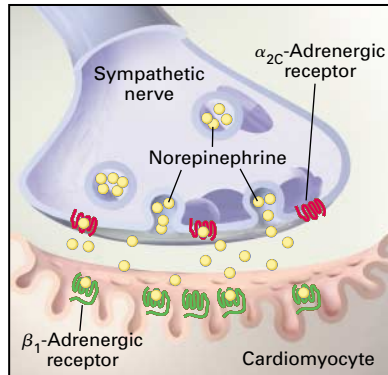




This Week in the Journal

October 10, 2002

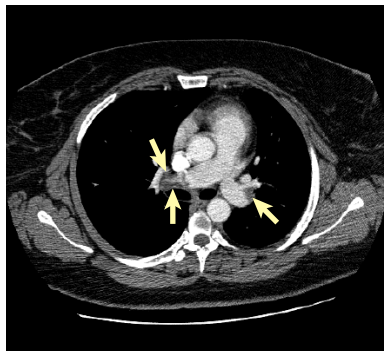


Polymorphisms of Adrenergic Receptors and Heart Failure

Sustained activation of the sympathetic nervous system contributes to the development and progression of heart failure. This study examined two polymorphisms in the β_1 - and α_{2C} -adrenergic receptors, which are associated with an increase in sympathetic activity. In black subjects, these polymorphisms, particularly when both were present, markedly increased the risk of heart failure.

There is substantial variation among persons in the development and progression of heart failure. This study identifies genetic factors that may contribute to this variation.

see page 1135 (editorial, page 1196)

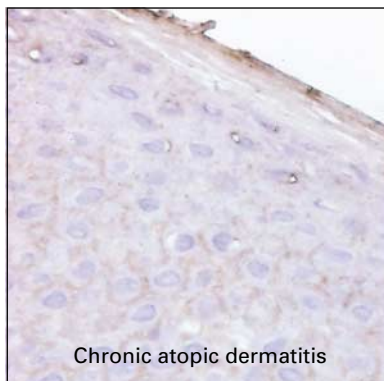


Alteplase for Submassive Pulmonary Embolism

Thrombolysis is known to be effective in the treatment of patients with massive pulmonary embolism, but its efficacy is less certain in patients with submassive pulmonary embolism. In this large, randomized trial, the combination of heparin and alteplase was found to be superior to heparin and placebo in the treatment of such patients.

The superiority of heparin plus alteplase over heparin alone was due primarily to a reduced need for secondary thrombolytic therapy. Since there was no increased risk of serious bleeding with the combination therapy, it should be considered for use in the absence of contraindications.

see page 1143 (Perspective, page 1131)

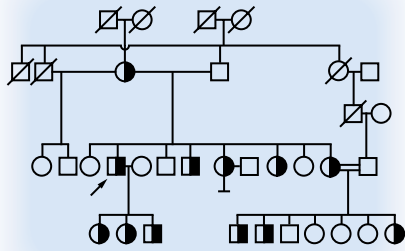


Endogenous Antimicrobial Peptides in Atopic Dermatitis

Staphylococcal infections of the skin are more common in patients with atopic dermatitis than they are in normal persons or patients with psoriasis. In this study, the investigators hypothesized that the elevated rate of skin infections in atopic dermatitis could be attributed to reduced levels of the endogenous antimicrobial peptides LL-37 and human β -defensin 2. They found that the levels of these peptides were lower in skin from patients with atopic dermatitis.

These data provide evidence that a deficiency of endogenous antimicrobial peptides in the skin may account for the increased role of infections in patients with atopic dermatitis. Proof of the concept will require the demonstration that up-regulation of these peptides leads to fewer skin infections.

see page 1151 (editorial, page 1199)



Special Article: Screening Extended Families for Genetic Hemoglobin Disorders

This article reports a feasible strategy for identifying and counseling carriers of recessively inherited diseases in developing countries. The basis of the approach is testing the extended family of a person with an index case, usually a child with the disease.

In Pakistan, where consanguineous marriage and the genes for β -thalassemia and hemoglobin S are common, more than 5000 babies with transfusion-dependent β -thalassemia are born annually. In a country with an average annual income of \$420, screening for genetic diseases by methods used in industrialized countries is impractical. This article describes a practical method for identifying carriers and suggests that it is possible to reduce the incidence of costly genetic disorders through counseling.

see page 1162 (editorial, page 1200)



Clinical Practice: Otitis Media

An otherwise healthy 17-month-old boy had a cold accompanied by two days of rhinorrhea, cough, and fever (temperature of up to 38.8°C). On day 5, he became fussy and woke up crying several times during the night. The following day he was afebrile, and a physical examination was normal except for findings of a slightly red left tympanic membrane with no middle-ear fluid and a bulging right tympanic membrane with white fluid behind it, obscuring the umbo. How should he be treated?

see page 1169

“Peptic ulcer disease is now approached as an infectious disease, in which elimination of the causative agent cures the condition.”

Medical Progress: *Helicobacter pylori* Infection

H. pylori is one of the most common bacterial infections in human beings, and its discovery 20 years ago altered the diagnosis and treatment of gastroduodenal disease. This review considers current knowledge about the epidemiology and transmission of *H. pylori*, as well as the role of this infectious agent in the pathogenesis of upper gastrointestinal tract disease. Diagnostic approaches, indications for therapy, and measures of therapeutic efficacy are reviewed.

*The 1998 U.S. guidelines recommend testing for *H. pylori* only if treatment is intended. The primary indications for testing and subsequent therapy include active peptic ulcer disease, a history of documented peptic ulcer, or gastric mucosa-associated lymphoid-tissue lymphoma.*

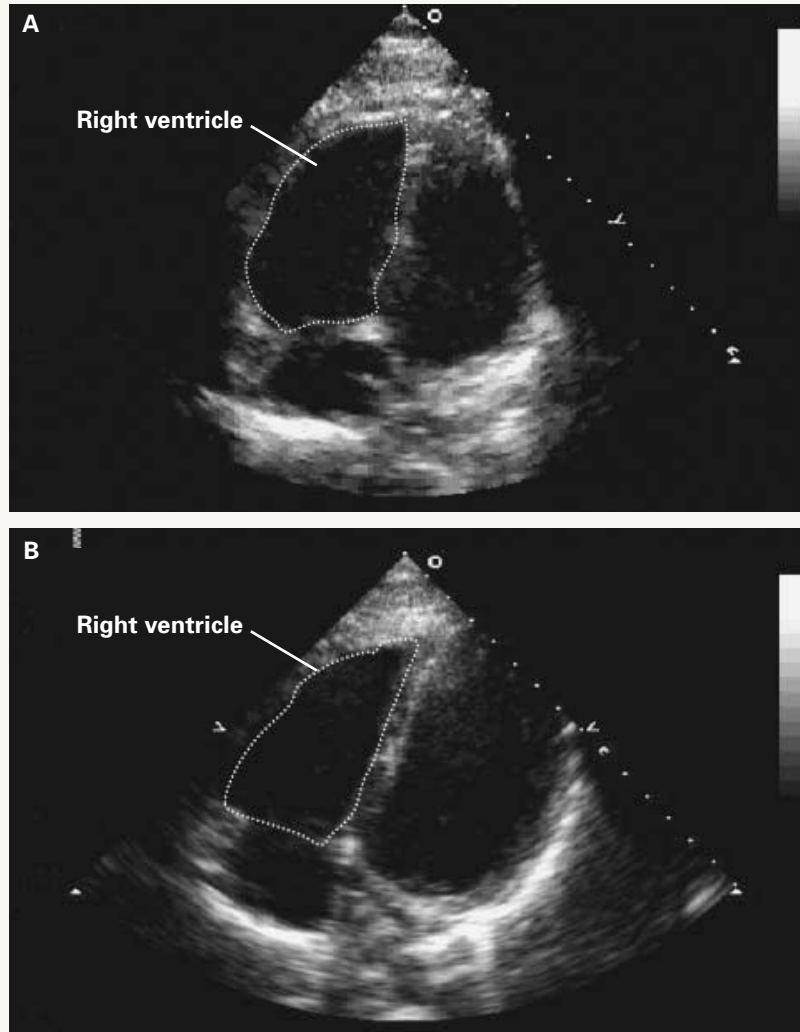
see page 1175

PERSPECTIVE

Thrombolysis for Pulmonary Embolism

The primary therapy for acute pulmonary embolism is anticoagulation with heparin and warfarin to prevent additional thromboembolism. Traditional teaching relegates the use of thrombolysis to the rare situation in which massive pulmonary embolism causes cardiogenic shock. Thrombolytic agents such as alteplase (recombinant tissue plasminogen activator) act on plasminogen by cleaving the peptide bond between arginine at position 560 and valine at position 561, thereby converting plasminogen to plasmin, which dissolves the embolus. Should we expand the indications for thrombolysis to encompass pulmonary embolism in patients with right ventricular dysfunction, even in the presence of normal systemic arterial pressure (see Figure)? This simple question lacks a straightforward answer and continues to generate intense controversy after three decades of debate.

Right-sided heart failure is the usual cause of death from pulmonary embolism, and right ventricular dysfunction is a crucially important warning of a possible adverse outcome. Physical examination may reveal distention of the neck veins, an accentuated pulmonic heart sound, or a tricuspid regurgitation murmur. The electrocardiogram may show right ventricular strain with an $S_1Q_3T_3$ pattern (prominence of the S wave in lead I and a Q wave and T-wave inversion in lead III), right bundle-branch block, or T-wave inversion in leads V_1 through V_4 . However, the most objective, uniform, and quantifiable measure is the echocardiogram, which can be used to estimate pul-



Echocardiograms before and after Thrombolysis.

A 29-year-old woman presented with progressive shortness of breath. A computed tomographic scan of the chest showed a central "saddle" pulmonary embolism. An echocardiogram (Panel A) showed an enlarged right ventricle and hypokinetic motion of the right ventricular free wall. After treatment with alteplase, the right ventricular size and wall motion returned to normal (Panel B). Echocardiograms courtesy of Scott D. Solomon, M.D., and Jose M. Rivero. (Videos of these images are available with the full text of this article at <http://www.nejm.org>.)

monary-artery systolic pressure and can show right ventricular dilatation and hypokinesia.

Proponents of expanded criteria for thrombolysis claim a potential survival benefit, fewer recurrences of pulmonary embolism (through dissolution of the clot at its source, in the pelvic veins and deep veins of

the leg), long-term prevention of pulmonary hypertension, and improved quality of life. Opponents contend that the bronchial collateral circulation provides continued pulmonary perfusion and usually makes thrombolysis unnecessary in patients with pulmonary embolism. They cite complications of throm-

bolysis, especially intracranial hemorrhage, and increased use of hospital resources such as beds in the intensive care unit and more extensive use of laboratory tests. They note that most patients who are treated with anticoagulation alone will catch up with thrombolysis-treated patients within several days. Most important, they remind us that trials of thrombolysis for pulmonary embolism have not shown decreased mortality rates or decreased rates of recurrence.

Thirty years ago, advocates of thrombolysis for pulmonary embolism administered 24-hour infusions — “prolonged baths” — of streptokinase or urokinase to dissolve large emboli. We subsequently learned that extended exposure to thrombolytic agents provokes major hemorrhage and is less effective than infusing these agents at a high concentration over a short period.

In 1990 the Food and Drug Administration (FDA) approved a contemporary thrombolysis dosing regimen: 100 mg of alteplase as a continuous peripheral intravenous infusion over a two-hour period. No subsequent regimen of thrombolysis for pulmonary embolism has received FDA approval, primarily because pharmaceutical companies are not currently focusing on the use of thrombolytic agents for this indication. The FDA label recommends thrombolysis for the treatment of “massive pulmonary embolism” but does not define “massive.” From the practitioner’s viewpoint, there is tremendous ambiguity in this recommendation. Does “massive” mean cardiogenic shock, profound hypoxemia, impending respiratory failure, or perhaps simply an anatomically large pulmonary embolism on pulmonary angiography or computed to-

mography of the chest? Imaging criteria are the most clear-cut but do not account for underlying cardiopulmonary disease, older age, or coexisting conditions that modify the physiological response to pulmonary embolism.

In this issue of the *Journal*, Konstantinides and colleagues (pages 1143–1150) report findings from the largest trial of thrombolysis for pulmonary embolism ever conducted. They recruited the most controversial group of patients, those with “submassive” pulmonary embolism, defined as right ventricular dysfunction but preserved systemic arterial pressure. They show that a combination of alteplase (100 mg given over a two-hour period) and heparin prevented the need for escalation of treatment (with open-label alteplase, catecholamine infusion, or mechanical ventilation) due to clinical deterioration more often than a combination of placebo and heparin. Clinical deterioration usually meant worsening symptoms, especially worsening respiratory failure.

Does this trial expand the indications for considering the use of thrombolysis among properly selected patients with pulmonary embolism who present with normal blood pressure and right ventricular dysfunction? Definitely. Is the controversy now resolved? Hardly. Critics will point out that in the study by Konstantinides et al. there was no significant difference in mortality between the two treatment groups. They will denounce the end point of an escalation of treatment because of clinical deterioration as “soft” and inadequately objective. Nevertheless, no one is currently planning to launch a trial of similar or larger scope. Organizing trials of thrombolysis for pulmonary embolism is challenging for several reasons: the illness is difficult to detect,

collaboration among the physicians from multiple disciplines who care for patients with pulmonary embolism is unwieldy, and public awareness of this major cardiopulmonary illness is unacceptably low.

Every reader of the current report will note the remarkable near-absence of hemorrhagic complications, including intracranial hemorrhage, among the patients assigned to receive alteplase and heparin. In contrast, in the International Cooperative Pulmonary Embolism Registry, the largest prospective registry of management of pulmonary embolism to date, 304 of 2454 patients received thrombolysis, with an intracranial-hemorrhage rate of 3.0 percent.

My advice is to use echocardiography for risk stratification by identifying patients who have either evidence on scanning of proximal pulmonary-artery thromboembolism or underlying cardiopulmonary disease, regardless of the size of the pulmonary embolism. The risk of major hemorrhage should be assessed. For patients with contraindications to thrombolysis who nevertheless require more intensive therapy than anticoagulation alone, alternative strategies, such as catheter-based or surgical embolectomy, should be considered. On the basis of the current report, we should seriously consider expanding the indications for thrombolysis and administering 100 mg of alteplase over a two-hour period in carefully selected, normotensive patients with pulmonary embolism who have moderate or severe right ventricular dysfunction.

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Editor’s note: Dr. Goldhaber is a consultant to Paion.

The New Federal Medical-Privacy Rule

On August 9, 2002, the Department of Health and Human Services released the final version of the federal medical-privacy rule (*Federal Register* 67: 53182–53273, 2002). The release ended a tortuous process dating back to September 1997, when the secretary of the Department of Health and Human Services provided Congress with recommendations for legislation to protect the privacy of medical information. Congress was unable to pass a medical-privacy statute by August 1999, the deadline specified by the Health Insurance Portability and Accountability Act of 1996. The act empowered the secretary of the Department of Health and Human Services to issue regulations protecting the privacy of certain health information if Congress failed to pass medical-privacy legislation. Creation of these rules has been delayed by controversy. Since the federal medical-privacy rule was first proposed in 1999, it has been revised several times, requiring nearly three years to finalize. Individual providers and hospitals must comply with the rule by April 14, 2003.

The Clinton administration first issued a version of the privacy rule in December 2000. The research community responded with the concern that the limits on the use of, and access to, health records that the rule imposed would unduly burden biomedical, epidemiologic, and health-sciences research. An additional concern was that the new liabilities and compliance requirements associated with disclosing patient information would discourage individual providers and hospitals from sharing data with researchers. But before anyone would have been required to comply with the December 2000 version of the privacy rule, the Bush administration pro-

posed modifications, leading to the August 2002 version (see Table).

How does the 2002 rule differ from the earlier version, and how will it affect medical research? Both versions are extraordinarily complex, mandating multiple new forms, restrictions, and procedures for the use or disclosure of “protected health information” for a number of purposes, including research. Only information that has been “de-identified” is exempt from these requirements, but the rule defines protected health information so broadly and de-identified information so narrowly that it will be difficult and legally risky for hospitals and individual providers to assume that all identifiers have been satisfactorily removed from health information.

Under the 2000 rule, protected health information could be used or disclosed for research only with a specific, time-limited, written authorization from the patient, in addition to the written informed consent that a patient ordinarily provides to participate in research. Two separate authorization forms with different mandatory disclosures were required for research involving both treatment and access to medical records. The 2002 version of the rule streamlines the authorization requirements, permitting a single form with fewer disclosures and no expiration date. The authorization form must still specify the information to be disclosed, the researchers who may receive it, and the protocol for which it may be used; using the information for secondary analyses or sharing it with other researchers will require another authorization.

For research in which the use or disclosure of information poses a “minimal risk,” the 2000 rule permitted researchers to seek a waiver of authorization from an institutional review board (IRB) or a newly created “privacy board.” The waiver provision remains in the 2002 rule, though in slightly different form. The 2000 rule contained

eight criteria for a waiver, several of which were criticized as ambiguous and contradictory. The most problematic criterion was a judgment by the IRB that the research would not adversely affect “privacy rights” (an undefined concept in the rule) and that the risk of a violation of privacy was “reasonable” in relation to the anticipated benefits. Under the 2002 rule, the IRB must determine the adequacy of a researcher’s provisions for protecting the confidentiality of data and the adequacy of the researchers’ “written assurances” that the data will not be misused. The rule still requires determination by the IRB that the information requested by the researcher is the “minimum necessary” to conduct the research. Moreover, the IRB must grant a waiver of authorization separately from the waiver of consent required by federal research regulations, a requirement that will prolong the process of reviewing and approving research involving medical records.

The 2000 rule required providers and hospitals to shoulder the administrative burden of providing patients with a detailed accounting of all research disclosures, including the health information to be disclosed, the purpose of the research, and information on how to contact the researchers. The 2002 rule lessens this burden somewhat by eliminating the accounting requirement when patients have authorized the disclosure of their information and by permitting a less specific accounting for disclosures under a waiver of authorization when the research involves records of more than 50 persons.

The strict de-identification requirements in the 2000 rule are retained in the 2002 rule and will complicate the current practice among hospitals and providers of rendering data anonymous for release to researchers without the patient’s consent. The research community has observed that to meet the rule’s legal standard, the data

Changes in Major Research Provisions of the Federal Medical-Privacy Rule.		
PROVISION	DECEMBER 2000 VERSION	AUGUST 2002 VERSION
Authorization	Separate time-limited authorization forms required for "research involving treatment" or access to existing medical records	A single authorization form is required for all research; no expiration date is required; authorization must specify nine elements, including proposed use or disclosure
Waiver	Eight criteria must be met for a researcher to obtain data without specific permission	Three simplified criteria must be met, with a focus on the adequacy of measures to protect confidentiality of data
De-identification	Data must be stripped of 18 specific identifiers; data cannot be released if it is known that the remaining information could be used, alone or in combination with other information, for identification	Researchers may be given a limited data set with fewer identifiers removed but must sign a data-use agreement governing specific use; data released must be the "minimum necessary" for research
Accounting for disclosures	The hospital or provider must give detailed accounting of all research disclosures within the past six years	The hospital or provider need not account for disclosures that a patient has authorized; for other research involving at least 50 records, "simplified" accounting may be used, with a list of active protocols; the hospital or provider must agree to help the patient contact researchers
Transition provisions	For research that does not involve treatment (records research), a new authorization or waiver is required for any information used or disclosed after the compliance date, even if the patient gave informed consent for the research before the compliance date	The hospital or provider may continue to use or disclose protected health information after the compliance date if informed consent was obtained for the research or was waived by the IRB before the compliance date

must be stripped of so much information, including most ZIP Codes, birth and discharge dates, and other unique identifiers, that the remainder may not be useful for research. In response to this concern, the 2002 rule permits providers and hospitals to use or share a "limited data set" for research. A limited data set is information stripped of fewer identifiers. It is not de-identified information and may be released only if the researcher signs a data-use agreement, which limits the parties that may receive the information, specifies how it may be used, and prohibits attempts at re-identification of the subjects. Hospitals or providers who learn that researchers have breached data-use agreements must attempt to mitigate the effects of the breach and, if unsuccessful, report the violation to the Department of Health and Human Services.

Although the new rule is improved, we think it still poses serious and ill-advised obstacles to the conduct of clinical studies and all

other research involving access to health information. We question whether, on balance, the public gains more than it loses when even research that is already regulated under the federal "common rule" (the rule that governs all research requiring IRB approval) is further encumbered by these additional regulations. The new privacy rule will be expensive: the secretary of the Department of Health and Human Services has estimated that implementation of the research-waiver provisions alone, even after modification, will cost nearly \$450 million over a 10-year period. More difficult to estimate are the rule's costs in terms of research impeded or forgone. Research institutions will probably comply with the rule by diverting resources from other endeavors. Given the burden of compliance, it seems almost certain that the pace and volume of research will diminish. Community health care providers — whether individual physicians, clinics, or hospitals —

are a vital source of data for population research, but they will be forced to reconsider whether researchers should be allowed access to their medical records. Since the rule still has rigid authorization and accounting requirements, community providers may decide to withhold data from researchers in order to avoid the expense of compliance, along with possible investigations by the Department of Health and Human Services triggered by complaints from patients or employees. The consequences for epidemiologic, health services, and other public health research could be devastating, and in the end, the public may conclude that the new medical-privacy rights have too high a price.

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