

an impressive list of unexpected associations between genes or chromosomal regions and a broad range of diseases. There have been few, if any, similar bursts of discovery in the history of medical research. Relatively conventional statistical techniques are adequate for the analysis and interpretation of these initial studies. But as we delve further into the genome in the search for networks of interacting gene variants and interactions between

these networks and environmental factors,⁵ much more sophisticated methods of statistical analysis are likely to be required.

Dr. Hunter is a professor of epidemiology at the Harvard School of Public Health, Boston, a statistical consultant to the *Journal*, and codirector of the National Cancer Institute's Cancer Genetic Markers of Susceptibility project. Dr. Kraft is an assistant professor of epidemiology and biostatistics at the Harvard School of Public Health, Boston.

This article (10.1056/NEJMp078120) was published at www.nejm.org on July 18, 2007.

1. Christensen K, Murray JC. What genome-wide association studies can do for medicine. *N Engl J Med* 2007;356:1094-7.
2. Witte JS. Multiple prostate cancer risk variants on 8q24. *Nat Genet* 2007;39:579-80.
3. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004;96:434-42.
4. NCI-NHGRI Working Group on Replication in Association Studies, Chanock S, Maniolo T, et al. Replicating genotype-phenotype associations. *Nature* 2007;447:655-60.
5. Thomas DC, Clayton DG. Betting odds and genetic associations. *J Natl Cancer Inst* 2004;96:421-3.

Copyright © 2007 Massachusetts Medical Society.

FOCUS ON RESEARCH

Rheumatic Heart Disease in Developing Countries

Jonathan R. Carapetis, Ph.D., F.R.A.C.P.

Related article, page 470

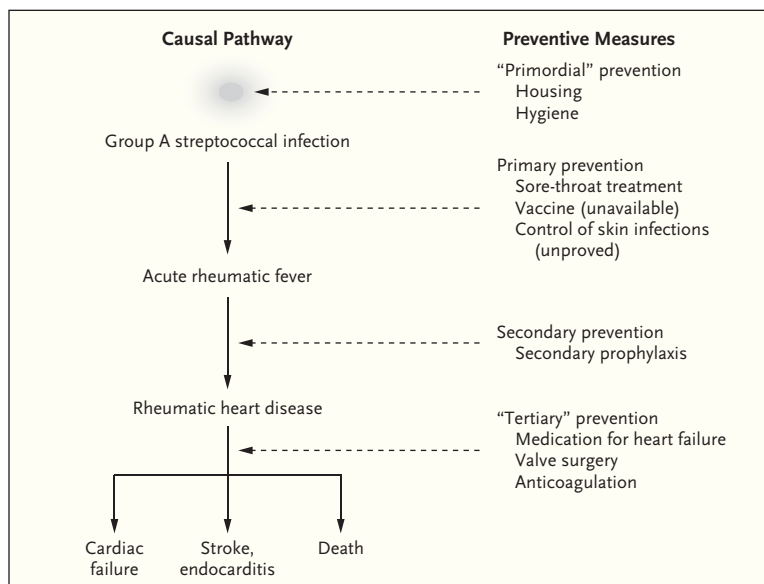
Only 30 or 40 years ago, rheumatic fever was a common topic in the *Journal*. A PubMed search for articles on rheumatic fever published between 1967 and 1976 returned 55 *New England Journal of Medicine* articles — fewer than for endocarditis (77) but more than for stroke and syphilis (24 entries each). A similar PubMed search for the decade 1997 through 2006 yielded just eight entries for rheumatic fever. This trend holds for all Medline-indexed journals: an average of 516 articles on rheumatic fever per year from 1967 through 1976, but only 172 per year from 1997 through 2006. Most observers would probably consider this decrease to be a reasonable reflection of the waning incidence of the disease. After all, in the mid-20th century, children with rheumatic fever occupied many of the beds in pediatric wards in industrialized countries — indeed, entire hospitals were dedicated to

the treatment of, and rehabilitation from, rheumatic fever. But in the latter half of the 20th century, rheumatic fever receded as an important health problem in almost all wealthy countries. Today, most physicians in these countries are unlikely ever to see a case of acute rheumatic fever, and their experience with rheumatic heart disease will be limited to heart-valve lesions in older patients who had rheumatic fever in their youth.

The reality, however, is that the decrease in publications reflects only the waning burden of disease among the less than 20% of the world's population living in high-income countries. For everyone else, rheumatic fever and rheumatic heart disease are bigger problems than ever. It was estimated recently that worldwide 15.6 million people have rheumatic heart disease and that there are 470,000 new cases of rheumatic fever and 233,000 deaths attributable to

rheumatic fever or rheumatic heart disease each year.¹ These are conservative estimates — the actual figures are likely to be substantially higher. Almost all these cases and deaths occur in developing countries.

How did rheumatic fever become rare in wealthy countries? Medical science can take some of the credit, thanks largely to the use of penicillin for primary prevention, but most of the reduction is attributable to improved living conditions, which have resulted in less overcrowding and better hygiene, with consequent reductions in transmission of group A streptococci. In other words, rheumatic fever is a disease of poverty. That it is in many ways the epitome of diseases of poverty and social injustice is exemplified by the situations in Australia and New Zealand. In these countries, which boast living standards that are among the best in the world, there are indigenous populations,



Potential Preventive Measures for Rheumatic Fever and Rheumatic Heart Disease.

"Sore-throat treatment" refers to primary prophylaxis — that is, diagnosis and treatment of group A streptococcal pharyngitis.

many of whose members live in poverty, with documented rates of rheumatic fever and rheumatic heart disease that are among the highest in the world.¹ Among aboriginal people of northern Australia, for example, acute rheumatic fever develops in 0.2 to 0.5% of school-age children each year, and more than 2% of people of all ages have rheumatic heart disease.

An unfortunate consequence of the decline in rheumatic fever in industrialized countries has been a parallel reduction in related research. Indeed, although our understanding of the pathogenesis of this mysterious disease has improved somewhat, the only advances that have substantially altered the management or prevention of rheumatic fever during the past 40 or 50 years have occurred in the medical and surgical treatment of severe rheumatic heart disease — treatment that is largely palliative and neither accessible nor affordable to

the majority of affected patients. The mainstays of the control of rheumatic fever remain treatment of group A streptococcal pharyngitis with penicillin (primary prophylaxis) and administration of penicillin G benzathine injections every 3 to 4 weeks for many years in people with a history of rheumatic fever to prevent recurrent episodes (secondary prophylaxis). Both strategies are based on findings from seminal studies in the United States published in the 1950s.^{2,3}

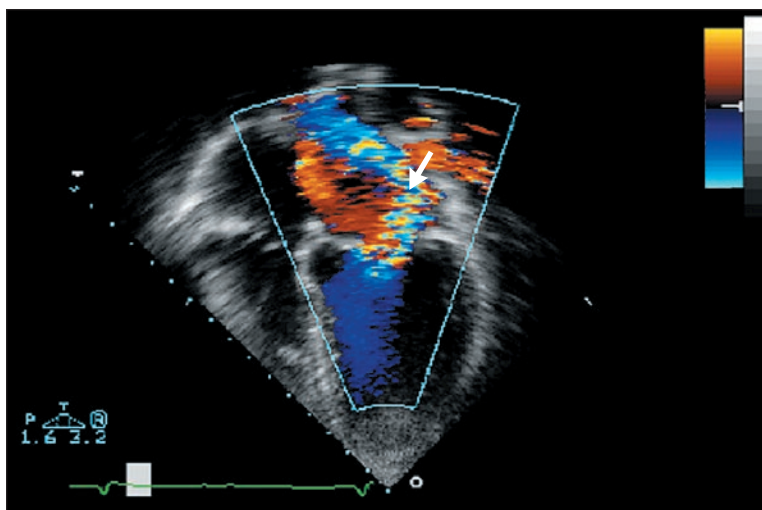
The available and potential control measures for rheumatic fever and rheumatic heart disease are summarized in the diagram. Of these, only one — secondary prophylaxis — has been proved to be cost-effective and practical even in the poorest countries. For more than 20 years, the World Health Organization has recommended secondary prophylaxis, most effectively delivered within a coordinated program using a registry of patients, as the first

priority for the control of rheumatic heart disease.⁴ Yet most developing countries still do not have effective secondary-prophylaxis programs.

How to ensure that secondary prophylaxis is delivered to those who need it is one of several critical questions related to the implementation of current knowledge about the control of rheumatic fever and rheumatic heart disease. Other relevant questions include how to identify people with mild rheumatic heart disease so that they may be offered secondary prophylaxis earlier, whether primary prophylaxis can be a practical and cost-effective public health measure in developing countries, and how to ensure that limited health care funds are spent most effectively — which may entail shifting some funding from the provision of expensive cardiac surgery for severe rheumatic heart disease to the development of robust secondary-prophylaxis programs.

Other key issues revolve around the need to develop new approaches to primary prevention, particularly a vaccine that protects against rheumatic fever. A number of vaccines are in development, and a safe and effective vaccine may well be available within one or two decades. However, experience with other relatively recent vaccines, including conjugate pneumococcal and *Haemophilus influenzae* type B vaccines, suggests that there may be many barriers to the funding, acceptance, and use of new vaccines in the places that need them most. Potential alternative strategies, including controlling streptococcal skin infections, are intriguing but of unproven benefit.⁵

How will these issues be ad-



Still Image from a Two-Dimensional Echocardiogram in a Patient with Moderate Mitral Regurgitation Due to Rheumatic Heart Disease.

An apical four-chamber view is shown, with color Doppler imaging illustrating a regurgitant-flow signal that extends along the lateral wall of the left atrium. The blue-and-yellow mosaic pattern indicates the regurgitant jet (arrow). (Courtesy of Dr. Andrew Steer, University of Melbourne.)

dressed? Although some basic research on pathogenesis and the development of early-stage vaccine candidates can take place in laboratories anywhere in the world, the clinical, epidemiologic, and public health studies require access to populations with high rates of disease. In recent years, many such studies have been conducted in Australia, New Zealand, and the Rocky Mountain region of the United States. But applied research of relevance to developing countries should take place in developing countries — a proposition that presents many obvious challenges. Even if barriers caused by poor education, the absence of a skilled workforce, limited finances, inadequate technology, and remoteness of the populations that are at the highest risk of disease can be overcome, the burden of rheumatic fever and rheumatic heart disease is often either unappreciated or

dwarfed by epidemics of human immunodeficiency virus, malaria, tuberculosis, and pneumonia.

Marijon and colleagues are to be applauded for the results of the study reported in this issue of the *Journal* (pages 470–476). The study represents a partnership among researchers in Mozambique, Cambodia, France, and Australia. It tackles an important practical issue: whether and how to conduct screening for rheumatic heart disease among school-age children in developing countries. Also, it presents a compelling argument for the use of echocardiographic screening (see image). The counterargument is that the use of such expensive technology is neither feasible nor affordable in the countries with the highest disease burden. Yet if clinical diagnosis had been relied on, approximately 90% of echocardiographically detected cases would have been missed. It is not ac-

ceptable to leave these cases undiagnosed and these children at risk for recurrence of rheumatic fever simply because echocardiographic screening is seen as an inappropriate use of modern technology in developing countries. Instead, further research is needed to define models of echocardiographic screening that are practical, affordable, and widely applicable.

Marijon et al. found that 2 to 3% of school-age children in Cambodia and Mozambique have rheumatic heart disease, almost all of it previously undiagnosed. We know that this represents the tip of the iceberg: cases in children 5 to 14 years of age are likely to represent only 15 to 20% of all cases in the population.¹ These data confirm that rheumatic fever and rheumatic heart disease are of sufficient importance to warrant the urgent attention of the international public health and research communities.

Dr. Carapetis is the director of the Menzies School of Health Research, Charles Darwin University, Casuarina, Northern Territory, Australia.

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis* 2005;5:685-94.
2. Stollerman GH, Rusoff JH, Hirschfeld I. Prophylaxis against group A streptococci in rheumatic fever: the use of single monthly injections of benzathine penicillin G. *N Engl J Med* 1955;252:787-92.
3. Denny F, Wannamaker LW, Brink WR, Rammelkamp CH Jr, Custer EA. Prevention of rheumatic fever: treatment of preceding streptococcal infection. *JAMA* 1950;143:151-3.
4. Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation. *World Health Organ Tech Rep Ser* 2004;923:1-122.
5. McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infect Dis* 2004;4:240-5.

Copyright © 2007 Massachusetts Medical Society.