LETTERS

Chronic Versus Acute Diseases

IN THEIR EDITORIAL "GLOBAL CHRONIC DISEASES" (21 Jan., p. 317), D. Yach *et al.* quote a World Bank analysis that states that more gains in life expectancy would accrue from the control of cardiovascular diseases (CVD) than from targets related to child and maternal mortality (*1*), and they question the Millennium Development Goals (MDG), which target infectious diseases and maternal/child health. We think it is unfortunate to base suggestions for global funding changes on what was essentially a regional report.

Although we share the view of the authors that obesity-related diseases and smoking are rapidly becoming pandemic, we strongly believe that infectious diseases still remain a major economic burden for low- and middle-income countries. Annually, malaria kills about 3 million, 3 million die from HIV/AIDS, and tuberculosis (TB) claims another 2 million lives. The total costs of malaria as a proportion of household income have been estimated to be between 4.9 and 18% for infected households in endemic countries, and this burden can be considerably higher for poorer households, reaching up to 32% (*2*). Economic growth has been estimated to be 1.3% lower in malaria-endemic countries (*2*).

Although the monetary value of economic losses due to TB is difficult to assess, estimates for India, where there are 2 million new cases and 500,000 deaths annually, indicate that the total cost of TB could reach as high as 40% of annual per capita household income (*3*).

It is projected that by 2010, there will be 25 to 50 million AIDS orphans, most of them in Africa and Asia. A World Bank document (*4*) reports that in the typical developing country, cost per adult death ranges from 8 to 400% of annual income per capita (average = 150% annual income/capita). The number of AIDS orphans stands at over 10 million, and destitute children may turn to violence and prostitution and drop out of school.

Effective prevention and treatment programs as envisioned under the MDG will go a long way to save lives, reduce poverty, and help economies to develop. We fear that the statements made by the authors could generate a climate of confusion, diverting allocation of resources from much-needed health interventions. We cannot afford to focus on chronic noncommunicable diseases at the expense of preventable killer infectious diseases.

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Labnya Boro and her husband Ranjan Basumatary, both suffering from malaria, lie on a hospital bed in Nowkata village in the eastern state of Assam in India.

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Response

THE NEED FOR EFFECTIVE INVESTMENT IN global health is urgent. Senok and Botta balance our call for attention to noncommunicable diseases by arguing persuasively for continued investment in infectious disease control. Such investments will have their major impact among the poorest billion people.

But we cannot wait until these problems are solved before addressing concurrent chronic disease risks like tobacco, increasingly unhealthy diets, and increasing physical inactivity, which are prevalent in much of the developing world. In low- and middle-income countries that are home to over 4 billion people, tobacco use (already causing nearly 5 million deaths a year) (*1*) and diabetes rates are soaring (*2*). Waiting would accelerate both a health and an economic tragedy.

Heart attack and stroke, thought to be quintessential western diseases of affluence, are fast becoming major threats in developing countries. They now cause four times as many deaths in mothers in most developing countries as childbirth and HIV/AIDS combined (*3*). Worldwide, HIV/AIDS causes 3 million deaths a year; stroke and heart attacks cause 17 million (11 million deaths in developing countries) (*3*).

Yet heart disease, diabetes, and cancers receive only trivial interest from international agencies committed to improving global health. Heart disease and stroke are pushing families into poverty in developing countries as breadwinners and mothers die young. These breadwinners are also the most productive members of the workforce, and their efforts determine future prosperity and investment.

Billions of dollars have been committed to the Global Fund for AIDS, Malaria and TB, and the Global Alliances for Vaccine and Immunization (GAVI) and for Improved Nutrition (GAIN). But although it is true that chronic diseases are more prevalent among countries that are above desperate poverty, virtually no funds have been raised to reduce chronic diseases or their risks. Less than 5% of the World Health Organization budget, less than 3% World Bank loans for health, and few international donors support chronic disease research, policy development, or actions.

Is the case for investment in global health either/or? We think not.

An investment approach to global health that includes diseases on the basis of need rather than whim or fashion has much to commend it.

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Domesticated Pigs in Eastern Indonesia

IN THEIR REPORT "WORLDWIDE PHYLOGEOGraphy of wild boar reveals multiple centers of pig domestication" (11 Mar., p. 1618), G. Larson *et al.* note the potential significance of island Southeast Asia in the ancestry of pig mtDNA lineages in the Old World, but they fail to address archaeological data from this region. The authors report the possible existence of an indigenous clade of *Sus scrofa* in Wallacea and suggest that the island of Halmahera (the largest in Maluku Utara) might have been important in the genesis of their Pacific clade, which spread ultimately from New Guinea to Polynesia. Unfortunately, a substantial program of archaeology in Maluku Utara has revealed that pigs were completely absent here until after 3500 years B.P., when their bones appear in Neolithic contexts, with pottery and polished stone adzes, succeeding preceramic flake industries dating back into the late Pleistocene. Before 3500 years B.P., the islands of Maluku Utara contained only marsupial mammal faunas (wallabies, bandicoots, phalangers), some of which were translocated from New Guinea or Misool Island during the Early Holocene (~10,000 years B.P.). Samples of over 5000 identified animal bones, from five cave and rock shelter sites on Halmahera, Morotai, Kayoa, and Gebe islands, render this conclusion very well founded (*1*–*3*).

If pigs were taken initially to New Guinea from Halmahera, they must also postdate 3500 years B.P. there, as archaeological evidence now suggests (*4*). Where does the Pacific clade originate? This remains uncertain, but it cannot be Halmahera and must be some other region of island Southeast Asia, either Sundaland or Sulawesi, or perhaps the Philippines or Nusa Tenggara/Timor, island chains not included in the analysis by Larson *et al.*

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Response

ALTHOUGH WE ACCEPT THE IMPORTANCE (and significance) of the archaeological evidence noted by Bellwood and White, in our Report, we do not single out Halmahera as the origin of the "Pacific clade" of pigs. Instead, we point out that the close genetic association of a pig from Halmahera with pigs from Papua New Guinea, Vanuatu, and Hawaii is analogous to the pattern found in rats (*1*) and in humans (*2*). Rather than arguing that all pigs found on Pacific islands trace their ancestry to Halmahera, we point out that Halmahera is currently the most westerly point represented by our "Pacific clade."

The current picture regarding the status of *Sus* specimens located on islands east of the Wallace line is far from clear. And although the fossil and archaeological record is important in this respect, it is by no means definitive (*3*). This uncertainty is further compounded by a lack of resolution on our phylogenetic tree, which obscures the relationships between distinct, well-supported clades, thus preventing us from drawing firm conclusions about both the geographic relatedness of the clades and the specific origin of the "Pacific Clade."

We agree with Bellwood and White that that there exist many possible points for origin of the "Pacific clade," including both areas we sampled in our Report and regions we have yet to sample.

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Mechanism of JCV Entry into Oligodendrocytes

IN THEIR REPORT "THE HUMAN POLYOMAvirus, JCV, uses serotonin receptors to infect cells" (19 Nov. 2004, p. 1380), G. F. Elphick *et al.* report the dramatic finding that human polyomavirus (JCV) infection of SVG astroglial cells in culture can be mediated in part by serotonergic receptors, in particular 5HT2aR. This finding is potentially of great clinical importance, as it suggests that serotonin receptor antagonists may be useful in the treatment of progressive multifocal leukoencephalopathy (PML), a devastating demyelinating disease resulting from JCV infection and destruction of oligodendrocytes. Highly active antiretroviral therapy (HAART) remains the only partially effective treatment option.

We caution though, that in the midst of the growing enthusiasm for testing serotonin receptor antagonists clinically for the treatment of PML, that more should be done to explore the mechanism of JCV entry into oligodendrocytes. Our concern arises from two observations: (i) The cell line used in the authors' experiments, SVG-A cells, has been previously characterized as astrocyte-derived rather than oligodendrocyte-derived (*1*, *2*), and (ii) immunohistochemical analysis of human and animal central nervous system (CNS) tissue reported in the literature, and from our personal experience of analyzing serotonin receptor expression has shown that astrocytes express 5HT2aR (*3*, *4*); there is as of yet no clear report that oligodendrocytes also express 5HT2aR.

Although JCV can infect both astrocytes and oligodendroglia in human patients, productive infection is established in oligodendrocytes, and it is these cells that are predominantly destroyed by the virus. It clearly remains possible and even likely that JCV infection of astrocytes and other 5HT2aR-expressing cells such as vascular endothelial and choroid plexus cells play an important role in the pathogenesis of PML. We

Letters to the Editor

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believe, though, that whether JC virus enters oligodendrocytes by a serotonin receptor-mediated mechanism and whether entry can be blocked by serotonin receptor antagonists require further investigation.

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Response

I AGREE WITH SANTAGATA AND KINNEY, BUT wish to point out that laboratory work with JCV is limited to cells and cell lines that permit viral infection. The only cell types permissive for JCV growth in culture are primary human fetal glial cells (predominantly astrocytes) and some cell lines such as SVG, SVG-A, and POJ that were derived from these primary cultures by transformation with either SV40 T antigen (SVG and SVG-A) or JCV T antigen (POJ). Primary cultures of oligodendrocytes isolated from adult brain are rare and difficult to obtain. A human oligodendrocyte cell line has not been established.

In our Report, we show that the 5HT2a receptor is required for infection of SVG-A cells by JCV. Expression of the 5HT2a receptor in receptor-negative HeLa cells restored their susceptibility to infection by JCV, indicating that the 5HT2a receptor is an important receptor for the virus on diverse cell types. We also agree with Santagata and Kinney that there are no clear reports demonstrating 5HT2aR expression on human oligodendroctes. Because of this, we are examining normal human brain and brain from HIV-infected patients with and without PML for the presence of 5HT2a receptors on oligodendrocytes. It is possible that 5HT2a receptor expression is low in normal brain but higher in the brains of patients infected with HIV, which might explain their increased susceptibility to PML. We suggest that 5HT2a receptor antagonists may be useful prophylactically by preventing the spread of JCV into the CNS and establishment of disease. Whether these compounds are useful in the treatment of an already established CNS infection is less clear, and more work clearly needs to be done to determine the potential efficacy of the latter approach.

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