Durrington and colleagues have used this old wisdom, and in this issue of the *BMJ* (p 1497) show that it is indeed possible to use this approach to find new patients.[7] By testing all first degree relatives of 200 patients with familial hypercholesterolaemia they found another 121 patients. In the general population at least 60 000 tests would have been needed to identify this many people with the condition. With the aid of a nurse specialist, simple cholesterol testing, and the use of small pedigrees Durrington and colleagues convincingly show that adopting an active approach to case finding works for familial hypercholesterolaemia.

Other investigators, including our group in the Netherlands, have come to similar conclusions, with two modest differences in approach. Firstly, testing in the Netherlands was not restricted to first degree relatives but included everyone in the extended family. This obviously reduces the proportion of people identified as having the disorder. On average, over a four year period one index patient led us to 20 additional family members, and eight new patients were identified (unpublished data). The second and most profound difference, however, lies in the use of DNA diagnostics. If the most sensitive test is used—namely age specific and sex specific centiles for total and low density lipoprotein cholesterol—16.6% of cases would have been missed and 12.5% would have been diagnosed as having familial hypercholesterolaemia when they actually had polygenic hypercholesterolaemia. Hence, active screening for a disorder requires a diagnosis that is rock solid, and that can only be provided by using DNA testing to actually find the genetic mutation causing the disorder.

Durrington et al correctly point out that the screening criteria developed by Wilson and Jungner easily apply to familial hypercholesterolaemia,[8] but it is unlikely that DNA testing for the disorder has harmful psychological consequences.[9–11]

We know how to organise the screening, and we have the capacity for testing, be it for cholesterol concentrations or DNA mutations. We also have safe and effective treatment that can save lives and money. Our ministries of health should not hesitate but should support screening and treatment programmes; a few specialised nurses working in close collaboration with lipid clinics could work miracles.

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1 Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia.. *BMJ* 1991;303:893-6.
2 Lansberg PJ, Tuzgöl S, van de Ree MA, Defesche JC, Kastelein JJP. Prevalentie van Familiaire Hypercholesterolemie onder volwassenen in vier huisartsenpraktijken hoger dan werd aangenomen [Prevalence of familial hypercholesterolemia in four general practices higher than supposed]. *Ned Tijdschr Geneeskd* 2000;144:1437-40.
3 Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 1999;142:105-12.
4 Mol MJTM, Erkelens DW, Gevers Leuven JA, Schouten JA, Stalenhoef AFH. Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia. *Lancet* 1986;ii:936-9.
5 Neil HAW, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ* 2000;321:148-9.
6 Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 7th ed. New York: McGraw-Hill, 1995:1981-2030.
7 Bhatnagar D, Morgan J, Siddiq S, Mackness MI, Miller JP, Durrington PN. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. *BMJ* 2000;321:1497-500.
8 Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: World Health Organization, 1968. (Public health paper No. 34)
9 Andersen LK, Jensen HK, Juul S, Faergeman O. Patient attitudes to detection of heterozygous familial hypercholesterolaemia. *Arch Intern Med* 1997;157:553-60.
10 Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's concerns. *Acta Paediatr* 1996;85:1307-13.
11 Tonstad S, Novik TS, Vandvik IH. Psychosocial function during treatment for familial hypercholesterolemia. *Pediatrics* 1996;98:249-55.

Emerging arboviral encephalitis

Newsworthy in the West but much more common in the East

The recent outbreaks of West Nile encephalitis in New York and Israel are drawing the western world's attention to the potential threat of arthropod-borne virus (arbovirus) encephalitis.[1] But in many parts of Asia, infection with West Nile virus's sister, Japanese encephalitis virus, is a daily reality.

Epidemics of encephalitis were described in Japan from the 1870s onwards, and Japanese encephalitis virus was first isolated from a fatal case in the 1930s.[2] West Nile virus was isolated from the blood of a febrile woman in Uganda a few years later in 1937.[3] Both viruses are small enveloped RNA viruses, members of the genus *Flavivirus* (family Flaviviridae), named after the prototype yellow fever virus (*flavus* is the Latin for yellow). The flaviviruses are relatively new viruses, derived from a common ancestor 10-20 000 years ago, that are rapidly evolving to fill new ecological niches.[4] Both West Nile and Japanese encephalitis virus are transmitted in an enzootic cycle between small birds by *Culex* mosquitoes, though for Japanese encephalitis pigs are important amplifying hosts. Humans become infected by *Culex* mosquitoes coincidentally, but are not part of the natural cycle.

Although known to be widely distributed across much of Africa, southern Europe, and the Middle East, West Nile virus was, until recently, considered to be relatively benign.[3] It causes a non-specific febrile illness, or a characteristic fever-arthralgia-rash syndrome, which occurred in large epidemics in Israel in the 1950s and South Africa in the 1970s. Direct invasion of the central nervous system to cause encephalitis was thought to be a rarity. In contrast, Japanese encephalitis virus has always been recognised as a killer. Over the past 50 years it has spread relentlessly across Southeast Asia, India, southern China, and the Pacific—reaching Australia in 1998.[5]

Culex mosquitoes are unavoidable in rural Asia, and almost everyone is exposed to the virus. Only about 1 in 300 infections results in disease, and there is a wide range of presentations from a simple febrile illness to a severe meningoencephalitis, as well as a newly recognised polio-like acute flaccid paralysis.[6] There are

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estimated to be 50 000 cases of Japanese encephalitis annually, with 15 000 deaths. The actual numbers may become clearer with the application of new simple rapid diagnostic tests.[7] In addition to the high mortality, about half the survivors have severe neuropsychiatric sequelae, with their associated socioeconomic burden.

The epidemiology of West Nile virus has also changed in recent years. Increasing numbers of cases of encephalitis are being seen in all areas where the virus occurs, and during a large outbreak in Romania in 1996, 393 patients with neurological disease had laboratory evidence of West Nile virus infection.[8] Then, in 1999, West Nile virus reached America for the first time. A quick-witted physician had noticed a cluster of cases of encephalitis in the Bronx, New York. Initial serological tests pointed to St Louis encephalitis virus (the American sister of the neurotropic flaviviruses, which caused encephalitis epidemics in America in the 1930s, but is not normally found this far north). However, sick birds at the Bronx zoo and crows dropping from the sky suggested something else,[9] since the local virus would not normally cause disease in its natural hosts. West Nile virus was isolated subsequently from both avian and human cases.[10] By the time mosquito spraying and the arrival of winter had reduced the population of *Culex* mosquitoes 62 people had developed encephalitis and seven had died.

These recent findings in Asia and the West raise important issues about the spread, control, and pathogenesis of arboviral encephalitis. Many theories have been proposed on how West Nile virus reached New York, including illegally imported exotic birds, airplane-borne mosquitoes, European refugees, and even biological terrorism, but infected birds migrating from Israel now seems the most likely.[11] However it arrived, surveillance has shown that the virus is now well established in the region. Japanese encephalitis virus is also thought to be spread by birds, but mosquitoes blown between Pacific islands may contribute too.[5]

Although we can do little to limit the spread of enzootic flaviviruses, we can minimise the number of human cases. Surveillance of mosquitoes, sentinel birds, and dead birds for West Nile virus in America warned of this summer's impending outbreak. Consequently the number of human cases was minimised by advising people to avoid mosquito bites and by implementing measures to reduce the mosquito population, such as removing breeding sites and spraying. Unfortunately such measures are impracticable in Asia, where the rice fields in which *Culex* mosquitoes breed are a mainstay of the economy. There are no vaccines against West Nile virus yet. An expensive formalin-inactivated and newer live attenuated vaccine against Japanese encephalitis are available, but not for the majority of the 2.8 billion people living in affected regions.[12 13] For them, the factors determining who, of all those infected with Japanese encephalitis virus, develops neurological disease may be critically important. The relative contributions of the human immune response and viral strain differences are currently being investigated.

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1 Siegel-Itzkovich J. Twelve die of West Nile virus in Israel. *BMJ* 2000;321:724.
2 Solomon T, Dung NM, Kneen R, Gainsborough M, Vaughn DW, Khanh VT. Japanese encephalitis. *J Neurol Neurosurg Psychiatry* 2000;68:405-15.
3 Hubalek Z, Halouzka J. West Nile fever—a reemerging mosquito-borne viral disease in Europe. *Emerging Infect Dis* 1999;5:643-50.
4 Gould EA, Zanotto PM, Holmes EC. The genetic evolution of flaviviruses. In: Saluzzo JF, Dodet B, eds. *Factors in the emergence of arbovirus diseases*. Paris: Elsevier, 1997:51-63.
5 Hanna JN, Ritchie SA, Phillips DA, Lee JM, Hills SL, van der Hurk AF, et al. Japanese encephalitis in north Queensland, Australia, 1988. *Med J Australia* 1999;7:533-6.
6 Solomon T, Kneen R, Dung NM, Khanh VC, Thuy TTN, Ha DQ, et al. Poliomyelitis-like illness due to Japanese encephalitis virus. *Lancet* 1998;351:1094-7.
7 Solomon T, Thao LTT, Dung NM, Kneen R, Hung NT, Nisalak A, et al. Rapid diagnosis of Japanese encephalitis by using an IgM dot enzyme immunoassay. *J Clin Microbiol* 1998;36:2030-4.
8 Tsai TF, Popovici F, Carnescu C, Campbell GL, Nedlelcu NI. West Nile encephalitis epidemic in Southeastern Romania. *Lancet* 1998;352: 767-71.
9 Anonymous. Outbeak of West Nile-like viral encephalitis: New York, 1999. *Morb Mortal Wkly Rep* 1999;48:845-9.
10 Briese T, Jia X-Y, Huang C, Grady LJ, Lipkin WI. Indentification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet* 1999;354:1261-2.
11 Rappole JH, Derrickson SR, Hubalek Z. Migratory birds and spread of West Nile virus in the Western Hemisphere. *Emerging Infect Dis* 2000;6:319-28.
12 Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, et al. Protection against Japanese encephalitis by inactivated vaccines. *N Engl J Med* 1988;319:608-14.
13 Hennessy S, Zhengle L, Tsai TF, Strom BL, Chao-Min W, Hui-Lian L, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case control study. *Lancet* 1996;347:1583-6.

Research misconduct: Britain's failure to act

Act or risk losing public confidence in research

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More than a year ago the good and the great of British medicine assembled in Edinburgh and agreed that the time had come to act decisively on research misconduct.[1–3] Unfortunately, nothing visible has happened. Yet the so far largely submerged problem of research misconduct is surfacing like a decomposing corpse.[4] If the leaders in medicine do not act they risk losing public confidence in medical research.

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Fraud in research has a long and dishonourable history, but the problem came firmly onto the agenda in Britain in the early 1980s.[5] One consequence was a report from the Royal College of Physicians of London in 1991.[6] Unfortunately the report was shelved. The excuses are familiar: fraud doesn't really matter because science is self correcting; patients have not been harmed; it's very rare; existing local systems can handle the problem; we need to act on all of scientific