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Facing up to re-emergence of urban yellow fever

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Urban yellow fever is transmitted from person to person by *Aedes aegypti*, a highly domesticated mosquito. By contrast, jungle yellow fever is a zoonosis, transmitted from monkeys to human beings by mosquitoes that breed in tree-holes (*Haemagogus* spp) in the rainforest ecosystem of South America. The jungle form is only partly controlled by vaccination of rural residents and provides a source of infection to population centres infested with *Ae aegypti*. Urban yellow fever was eliminated in the first half of this century, with the eradication of *Ae aegypti* from most of South America. Unfortunately, reinfestation, which began in the 1970s, is now virtually complete, and vector control is substantially more difficult than before. The threat of urban yellow fever is greatest in towns such as Santa Cruz, Bolivia, near the forest, but improved transport links increase the likelihood of spread by viraemic people to non-endemic areas.

In today's *Lancet*, van der Stuyft and colleagues report the first instance of urban transmission of yellow fever in the Americas in 44 years. The importance of the report lies not in the size of the outbreak—which affected only a few urban residents of Santa Cruz—but in the demonstration of susceptibility to outbreaks on a more striking scale. Residents of densely populated cities and much visited areas in coastal South America have never been vaccinated. An outbreak there would facilitate dissemination, which could be widespread since the entire planet is accessible by air within the incubation period of yellow fever. As van der Stuyft and colleagues point out, the best defence is to create an effective immune barrier, which includes visitors to and residents (rural and urban) of the endemic zone. In Santa Cruz, vaccine coverage rates were only 35–40%, whereas the herd immunity required to prevent person-to-person transmission of infection may be 90%.¹

Yellow fever carries a case-fatality rate of about 20%. Five of the six presumed urban cases in Santa Cruz died, which suggests that non-fatal cases were missed. Surveillance identified 51 patients who met the case definition, and 16 (31%) had IgM antibodies, which indicates recent infection, but most resided in areas at the periphery of the city, where jungle yellow fever could not be excluded. The paucity of cases emphasises the difficulty of virus spillover into the urban cycle. In Santa Cruz, barriers included vaccine immunity (which, admittedly, was low) and the low density of *Ae aegypti* (present in about 33% of households). Perhaps a more important point is that human beings are not very

efficient hosts for yellow-fever virus. In human beings, peak viral loads of yellow-fever virus are about 100-fold lower than those of dengue viruses, which infect *Ae aegypti* efficiently. Thus, outbreaks of urban yellow fever evolve slowly. Soper, who first differentiated the transmission cycles, noted that “. . . urban . . . yellow fever is a highly exotic form maintained with more difficulty than is the jungle type”.² Although urban yellow fever is a significant threat, the constrained dynamics of transmission, early recognition of the striking clinical presentation, and efforts to control the infection should limit the impact of the disease.

Van der Stuyft and colleagues note the difficulty in interpreting seroepidemiological data. 6% of Santa Cruz residents had IgM antibodies, but most of these people had been recently vaccinated. The complement-fixation test distinguishes recent natural infection from vaccine immunity, but this “old-fashioned” test is now rarely applied. There is a pressing need for improved methods to differentiate natural from artificial infections and for simple, rapid diagnostic tests derived from membrane-based immunoassays and PCR. Laboratory-based surveillance, together with the prevention and control strategies outlined by van der Stuyft and colleagues, are the critical defensive measures against the future threat of urban epidemics.

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What is “hypertension”?

The starting point for all clinical decisions on a patient with hypertension—on the severity of the disorder, the prognosis, and the treatment—is the value obtained by measurement of a haemodynamic variable, the blood pressure. The recommendations produced jointly by the WHO and the International Society of Hypertension,¹ although generally welcome, are flawed because the stated level for blood-pressure normality is based on inadequate evidence, and there is ambivalence about how blood pressure should be measured.

The burden of hypertension implied by the WHO/ISH guidelines will have serious clinical and health-economic implications, especially in the developing world, a point that has been made in an open protest on the internet (signed by more than 800 family doctors, specialists, pharmacists, and scientists from nearly 60 countries) to the Director-General of WHO (<http://www.uib.no/isf/letter>; accessed May 4, 1999).

The guidelines refer to the importance for outcome of even small differences in blood pressure—eg, that a 5 mm Hg reduction in usual diastolic blood pressure results in a 35–40% lower risk of stroke. Because small differences are so important and “because blood pressure is characterised by large spontaneous variations”, not only must measurement be accurate but also it must be repeated on separate occasions.¹ The guidelines acknowledge that the best way of achieving this is by ambulatory blood-pressure monitoring (ABPM) but then go on to argue that ABPM should not be a substitute for office measurement; instead it should be used when there

Percentage of normotensive individuals who would be classed as hypertensive by WHO/ISH guidelines

| | Number | Mean OBP (mm Hg) | Mean daytime ABPM (mm Hg) | % hypertensive (WHO/ISH) |
|---|--------|------------------|---------------------------|--------------------------|
| All ages | | | | |
| International database ^{5,6} | 4765 | 119/74 | 122/75 | 45 |
| Allied Irish Bank study ⁷ | 807 | 117/74 | 122/77 | 46 |
| Belgian population study ⁸ | 770 | 120/74 | 123/76 | 41 |
| Study by Kawasaki (see ref 5) | 548 | 123/72 | 123/74 | 44 |
| Ohasama study ⁹ | 1090 | 122/71 | 124/74 | 44 |
| Elderly | | | | |
| International database ^{5,6} (65–79 years) | 577 | 125/72 | 124/74 | 54 |
| Belgian population study ⁸ (65–79 years) | 83 | 125/74 | 124/74 | 48 |
| Study by Kawasaki (see ref 5) (70–89 years) | 183 | 124/70 | 124/75 | 62 |
| Study by Kuwajima (see ref 5) (70–89 years) | 43 | 123/62 | 125/70 | 63 |
| Ohasama study ⁹ (65–93 years) | 307 | 125/70 | 129/75 | 60 |

OBP=office (conventional) blood pressure; ABPM=ambulatory blood-pressure measurement. Normotension was defined as conventionally measured blood pressure not exceeding 140 mm Hg systolic and 90 mm Hg diastolic.

is “unusual variability of the blood pressure over the same or different visits”. How can “unusual variability” be identified if “large spontaneous variations” are inevitable?

The guidelines define hypertension as a blood pressure equal to or greater than 140/90 mm Hg but then state that “the goal of antihypertensive treatment should be to restore blood pressure to levels defined as ‘normal’ (less than 130/85 mm Hg) or ‘optimal’ (less than 120/80 mm Hg)”. If the problem of standardising the circumstances of office measurement were to be overcome by the recording of ABPM, then, according to the guidelines, at least 10/5 mm Hg must be deducted from the daytime blood pressure, which would set “normal daytime blood pressure” as less than 120/80 mm Hg and “optimal daytime blood pressure” as below 110/75 mm Hg.¹

This is a level of normality about which the two of us have already expressed serious concern.² Large population studies of ABPM have shown such remarkable consistency in 24 h blood pressure that there is consensus on normality for daytime and night-time blood pressures.^{3–12} For example, taking the 95th percentile as the upper limit of the distribution of daytime blood pressure in various studies in different countries^{5–12} gave variations of less than 7 mm Hg and 6 mm Hg for systolic and diastolic blood pressures, respectively, and the average for all studies was 138/87 mm Hg.⁸ Independent reviews by the American Society of Hypertension¹³ and our group^{3,4,8} produced the same recommendation—namely, that daytime blood pressures above 140/90 mm Hg are probably abnormal and that blood pressures below 135/85 mm Hg are probably normal. The US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure also takes blood pressures below 135/85 mm Hg to be normal for the awake state.¹⁴

There is thus a remarkable discrepancy between the 1999 WHO/ISH recommendation of a daytime average upper limit of normal of 120/80 mm Hg,¹ and a body of US and European opinion that daytime blood pressures greater than 140/90 mm Hg are probably abnormal, whereas those below 135/85 mm Hg are probably normal (blood pressure in the grey zone must be considered in the overall context of individual cardiovascular risk).² To estimate the effect of application of the WHO/ISH

recommendation to the population as a whole, we have investigated the prevalence of daytime ABPM values higher than 124/80 mm Hg among people classified as normotensive on conventional sphygmomanometry in population groups for whom data were available to us for all ages (7980) or for the elderly (1193) (panel).² For all ages the prevalence of WHO/ISH “hypertension” would average about 45%; when this threshold is applied to elderly people, 57% would be classified as hypertensive. Caution should be exercised in accepting the WHO/ISH recommendation on normality. Until the final results of longitudinal outcome studies are available, it would be prudent to repeat measurements of blood pressure, with home or ambulatory techniques, and to adhere to the following criteria of normality:

- daytime, <135/85 mm Hg probably normal, ≥140/90 mm Hg probably abnormal;
- night-time <120/70 mm Hg probably normal and ≥125/75 mm Hg probably abnormal; and
- 24 h <130/80 mm Hg probably normal and ≥135/85 mm Hg probably abnormal.

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Controlled clinical evaluation of diacetyl morphine for treatment of intractable opiate dependence

The initiation in 1995 of a large-scale study in Switzerland on diacetyl morphine (heroin) for chronic and treatment-refractory opiate dependence, represents both continuity and innovation in the longstanding efforts to provide humane medical care for addiction—a goal first articulated in the UK by Rolleston in 1926. Two recent conferences in Berne and Geneva presented promising initial results of these projects, sponsored by the Swiss Federal Office of Public Health, in which injectable heroin (commonly in conjunction with oral methadone) was prescribed to people with chronic and treatment-resistant opiate-dependence. The projects were conducted at several different sites throughout Switzerland. Although sizeable (over 1000 were enrolled altogether), the study was methodologically constrained because of its “before/after” design. This design, which can be subject to threats to internal validity, is nevertheless commonly used in early clinical and public-health research to develop the basis for considering the merits of an intervention. And at some sites (eg, Geneva) there was random allocation of treatment, with similar positive results.

The outcomes of the Swiss studies showed substantial declines both in drug use outside the programme and in criminal activity, as well as improved social reintegration. Although some people might have predicted that continually escalating doses would be needed to ward off tolerance, the Swiss scientists reported stabilisation at doses of around 500 mg—even though the protocol allowed doses of up to 1 g per day. More intriguing was the finding that, although patients were enrolled on the basis of previous failure of methadone treatment, retention was high (over 75% at 18 months) and, of the minority who dropped out, nearly half re-enrolled on methadone voluntarily. These remarkable claims and the absence of any catastrophic or chaotic consequences merit closer scrutiny through peer-reviewed publication, and through additional studies that incorporate more advanced design features.

But even the preliminary Swiss results persuaded Dutch public-health officials to initiate their own randomised study of heroin prescription (for 750

participants) in August, 1998, and plans are being formulated for conducting randomised controlled trials in Germany and Spain later this year. Another heroin trial, first proposed in Australia in 1992, has recently gained substantial support from that nation’s medical and public-health community, despite political hostility at the Federal government level. And after a meeting in New York City last summer at which the results from Switzerland and other countries (including the UK’s long-standing programme), a working group of clinical specialists, research scientists, and bioethicists formed the North American Opiate Medication Initiative (NAOMI). This group is now reviewing the data on alternative opiate-assisted therapies for individuals with chronic opiate dependence and is designing scientific protocols suitable for the USA and Canada.

Ironically, these heroin studies were born of the limitations of another once controversial pharmacotherapy—methadone maintenance. All the current heroin trials focus on patients who have failed methadone treatment (and drug-free treatment) several times as the target population. Further, it is significant that the Swiss heroin trials started in a country with one of the world’s most comprehensive and well-supported array of addiction-treatment services: more than 30% of heroin users in Switzerland are in methadone programmes. But Switzerland also has one of the world’s worst HIV epidemics among this group. In this context, heroin prescription represents the triumph of scientific evidence and a pragmatic public-health approach in setting drug-control policies.

But why is heroin prescription even being considered at this time? Most simply, because drug dependence is very complicated in its causes and clinical range, so multiple treatment approaches are needed. And although methadone and drug-free treatment programmes are important, they each have limited acceptance and efficacy. Other medication-assisted therapies, including levo- α -acetylmethadol (LAAM, a longer-acting methadone) and buprenorphine (a shorter-acting opiate agonist/antagonist) are becoming available to expand the treatment options. However, there is clearly room for a significant role for heroin prescribing. The size of the population that this approach would best serve is not trivial, but neither is it overwhelming. However, the development of even conventional therapies takes time, and the process of rigorously evaluating the therapeutic uses of heroin needs to be initiated sooner rather than later.

Further, the Swiss have developed such a large and detailed database that some of the once theoretical issues have now become practical data that may serve as the basis for the continuation and elaboration of research on the use of heroin. Before the Swiss studies, data about the pharmacology and pharmacokinetics of heroin in human beings had been very limited. The expansion of heroin trials can provide useful information for the entire range of clinical management of opiate dependency, and may prove crucial for the development of other forms of medication-assisted treatments.

Still, the broader political context of heroin prescription cannot be ignored. This is contested terrain for international drug policy and, inevitably, heroin prescription challenges the status quo. First, acceptance of a legitimate role for prescription of heroin in addiction treatment represents a reassertion of the authority of the