CORRESPONDENCE

Success rate for surgery of conjoined twins

Sir—Improvement in survival rate for surgery of conjoined twins is due to advances in diagnostic techniques, especially computed tomography and magnetic resonance imaging, meticulous anaesthetic management with careful monitoring of fluid replacement intraoperatively, improved surgical techniques with special emphasis on restricting blood loss, such as the use of ultrasonic separation of fused livers, achieving body-wall closure, and, most importantly, the value of previous experience, and postoperative intensive care with accurate attention to potentially labile cardiovascular status.

There are four opportunities for intervention in the management of conjoined twins. Prenatally, the diagnosis of conjoined twins can be made as early as 12 weeks gestational age, with accurate anatomical detail achievable at 20 weeks. Elective termination would be considered in the event of complex cardiac (thoracopagus) or neural (craniopagus) fusion. Alternatively, elective caesarean section delivery should be planned at 38 weeks' gestation. At birth, separation may be declined because of cardiac or neural fusion or when the extent of deformity after separation would be so extensive as to be unacceptable to the parents. Emergency separation is undertaken when one twin is already dead or dying and threatens the survival of the other, or if a baby has a correctable associated congenital abnormality present which, if untreated, would be fatal, such as intestinal obstruction, midgut volvulus, or ruptured exomphalos. In all other cases, elective separation is planned at around age 3 months. Full investigations can be carried out before surgery to define accurately the anatomy of the union[1] and to apply methods such as tissue expansion to achieve primary closure.[2] From 1985 to 2000, 17 sets of conjoined twins were managed by a single surgical team. Their treatment and outcome is shown in the table. Since five of the 14 infants involved in emergency separation were already dead (two) or unsalvageable (three), the true survival rate for this group should be 44%.

Treatment	Number (infants)	Outcome	Survival (%)
Non-operative	5 (10)	All died	0
Emergency separation	7 (14)	4 alive	28
Planned separation	5 (10)	8 alive	80

Great Ormond Street Hospital, London, UK, 1985–2000.

Results of treatment of conjoined twins

The importance of previous experience in dealing with conjoined twins cannot be overemphasised. The operative approach is unusual, the anatomical configuration can be highly complex, and during the operative procedure anatomical variants might alter the planned course of action.[3] A wide range of specialties need to be involved in the procedure such as cardiologists and cardiac surgeons in thoracopagus, urologists in ischiopagus and pygopagus,[4] and orthopaedic and plastic surgeons. Nephrological expertise might be required for dialysis in the event of postoperative renal failure.

Success in the management of conjoined twins requires an experienced team functioning in the tertiary referral centre with the full range of medical and surgical specialties.

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1 Kingston C, McHugh K, Kumar Devan J, Spitz L, Kiely EM. The role of radiology in the assessment of conjoined twins. *Radiographics* (in press).
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4 Wilcox DT, Quinn SM, Spitz L, Kiely EM, Ransley PG. Urological problems in conjoined twins. *Br J Urol* 1998; **81:** 905–10.

HIV-1 viral load and scrub typhus

Sir—We do not agree with the way George Watt and colleagues (Aug 5, p475)[1] interpret the results of the viral-load measurements in patients dually infected with HIV-1 and scrub-typhus. We are not convinced that they show a decrease in HIV-1 copy numbers during acute scrub-typhus infection because of HIV-1 suppressive factors. We believe the results show an initial rise in viral load after scrub-typhus infection that is lowered during treatment, as has been seen in malaria patients.[2]

In the absence of viral load values before the onset of scrub typhus, we have taken the viral load on day 28 (after treatment) as the probable value before the disease developed. Viral load during acute scrub-typhus infection would, therefore, have increased by 193% by day 3 of the infection.

What remains is to explain why viral loads in scrub-typhus patients were lower than those in non-typhus patients. We believe that the small number of patients enrolled in the study, the way they were selected and the way viral load was measured makes impossible the interpretation of the differences in viral loads between scrub-typhus and non-typhus patients. Watt and colleages clearly describe the selection procedure for the ten scrub-typhus patients, but not for the five controls. Moreover, why only five non-typhus patients were selected is unclear, since at the two study sites in Thailand there are probably many more non-typhus than scrub-typhus patients.

The commercial viral load tests used and for which patients should be specified. Ideally, all viral-load measurements should have been done in scrub-typhus and non-typhus patients with the same tests. We are unsure whether the Amplicor HIV-1 monitor test 1.0 or 1.5 has been used. The 1.0 version is not sensitive enough to measure viral loads of subtype A HIV-1.[3] Nine of the ten HIV-1-infected scrub-typhus patients were infected with subtype E, but such strains are always recombinant A/E strains.[4] The ultrasensitive protocol of the 1.5 version is sensitive for the detection of low viral loads, but cannot differentiate viral loads of more than 50 000 copies/mL.

The in-vitro data on suppression of HIV-1 replication by serum from one scrub-typhus patient and on inhibition of syncytium-induction by sera from infected mice provide only weak evidence that cross-reacting antibodies might display some HIV-1 neutralising activity. Only one human serum was tested and we have no information on whether this neutralisation persisted beyond day 4. Sera from HIV-1-negative people can temporarily display some neutralising activity at high concentrations.[5]

We believe, therefore, that Watt and colleagues' statement "The characterisation of HIV-1 suppressive factors produced during scrub-typhus may lead to novel strategies against AIDS" should be thought of as somewhat speculative.

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1 Watt G, Kantipong P, de Souza M, et al. HIV-1 suppression during acute scrub-typhus infection. *Lancet* 2000; **356:** 475–79.
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3 Coste J, Montes B, Reynes J, et al. Comparative evaluation of three assays for the quantitation of human immunodeficiency virus type 1 RNA in plasma. *J Med Virol* 1996; **50:** 293–302.
4 Subbarao S, Limpakarnjanarat K, Mastro TD, et al. HIV type 1 in Thailand, 1994–1995: persistence of two subtypes with low genetic diversity. *AIDS Res Hum Retrovir* 1998; **14:** 319–27.
5 Nyambi PN, Nkengasong J, Lewi P, et al. Multivariate analysis of human immunodeficiency virus type 1 neutralization data. *J Virol* 1996; **70:** 6235–43.

Sir—George Watt and colleagues[1] suggest that HIV-1 replication is suppressed during acute scrub-typhus infection. The hypothesis is intriguing, but we have several concerns about the data.

The median viral load 3 days after admission is significantly lower in the ten HIV-1-infected patients with scrub typhus than in the five HIV-1-infected patients with other infections (193 *vs* 376% of day 28 values, p=0·03). That 76% (31 of 41) of original HIV-1-infected patients with scrub typhus were excluded from the final viral load analysis is worrying. How the five control patients were selected and why four with malaria co-infection were selected is unclear.

We have shown that HIV-RNA viral load transiently increases during *Plasmodium falciparum* parasitaemia, on the basis of a sequential observation of viral load of HIV-1 infected adults during the rainy season in West Africa.[2] We have also seen a significantly higher rate of mother-to-child transmission of HIV-1 during the malaria season and suggest that malaria co-infection might have increased mothers' infectivity.[3] Moreover, Hoffman and colleagues have described a seven-fold increase in plasma RNA viral load during *P falciparum* malaria.[4]

We have interpreted Watt and colleagues' data as additional evidence that malaria infection increases viral load of HIV-1 rather than scrub typhus suppresses it.

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1 Watt G, Kantipong P, de Souza M, et al. HIV-1 suppression during acute scrub-typhus infection. *Lancet* 2000; **356:** 475–79.
2 Ariyoshi K, Schim van der Loeff M, Berry N, Jaffar S, Whittle H. Plasma HIV viral load in relation to season and to *Plasmodium falciparum* parasitaemia. *AIDS* 1999; **13:** 1145–46.
3 O'Donovan D, Ariyoshi K, Milligan P, Sarge-Njie R, Whittle H. A community-based study of mother-to-child transmission of HIV-1 and HIV-2 in The Gambia. *AIDS* 2000; **14:** 441–48.
4 Hoffman IF, Jere LS, Taylor CE, et al. The effect of *P falciparum* malaria on HIV-1 blood plasma concentration. *AIDS* 1999; **13:** 487–94.

Authors' reply

Sir—Our data do support observations that malaria up-regulates HIV-1 viral load.[1,2] However, our claim that HIV-1 is suppressed by scrub typhus is not based on comparisons with malaria. There was at least a three-fold drop in RNA copy numbers in four typhus-infected patients, and copy numbers fell to lower than the assay threshold in two. As R Colebunders and colleagues and Koya Ariyoshi and Hilton Whittle point out, and we report, day 3 viral loads in the typhus group were higher than day 28 values, which could reflect baseline values. However, the clinical courses were heterogeneous, and the observation of interest is that a subset of patients had a fall in HIV-1 RNA. The sample was small, but, irrespective of size, the same phenomenon has not been seen with malaria.[1]

Individuals with advanced AIDS presenting to hospital with fever will probably have multiple opportunistic infections. Our challenge was to identify for study AIDS patients with a single co-infection of interest, given limited diagnostic capability. About three-quarters of enrolled patients had suspected additional co-infections and we excluded them before we measured viral load. We selected scrub typhus, malaria, and leptospirosis because they cause acute illness and can be diagnosed rapidly on site. All AIDS patients with these co-infections were considered for the study. Most of the study volunteers were recruited at Chiangrai Hospital, where scrub typhus is more common than malaria and leptospirosis is relatively rare.

We used Roche's amplicor version 1.5, according to the standard protocol, to measure RNA copy number in the first four patients—two with malaria and two with scrub typhus. This version of the assay quantifies subtype E accurately and has an upper limit of detection of 750 000 copies/mL. We assessed viral loads for the remaining study volunteers by Chiron bDNA, which is clade insensitive. The concentration of serum used for neutralisation was 1:20, which is optimum for detection of HIV-1 specific neutralisation.[3] We tested several scrub typhus sera in the peripheral blood mononuclear cell assay, and most were inhibitory (data not shown). The serum chosen for further investigation was unique because it was more inhibitory that the HIV-1 seropositive control.

Our primary focus was the viral load results, and we agree with Colebunders and colleagues that the in-vitro data do not provide iron-clad proof of a strong suppressive effect. We hoped that the in-vitro data would provoke useful suggestions for further investigation, such as those of Masayuki Ikeda and Shohji Yoshida. We are currently investigating lymphocyte activation and agree that interferon-gamma could be playing a part in vivo. Heat-labile cytokines probably don't mediate in-vitro HIV-1 suppressive activity, since all samples

were heat inactivated before use.[4]

Finally, although we share the caution expressed by Colebunders and colleagues, we do feel that our findings merit further investigation.

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1 Hoffman IF, Jere CS, Taylor TE, et al. The effect of Plasmodium falciparum malaria on HIV-1 RNA blood concentration. *AIDS* 1999; **13:** 487–94.

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Nerve function in leprosy

Sir—Richard Croft and colleagues (May 6, p 1603)[1] reported on nerve-function impairment among leprosy patients in Bangladesh, where we are based.

We agree that a prediction rule for nerve-function impairment would be useful and that some cases can be prevented through timely and appropriate use of steroids. Without the label of a rule, and perhaps without recording evidence, many leprosy centres and leprologists have been using steroids to prevent nerve-function impairment and nerve damage for more than two decades, by use of the criteria of enlarged nerve, neuritis, and signs of nerve impairment as a guideline.

In Croft and colleagues' table 1, 230 (9·2%) of 2510 enrolled patients have ulnar or post-tibial nerve enlargement—two of the truncal nerves most commonly involved in leprosy. This finding is acceptable. However, a further 1754 (69·9%) have other truncal nerves enlarged that are less commonly involved. We find this number extremely high and have serious reservations about its validity.

Among the 96 pure neural cases (more appropriately defined as cases with clinical evidence of enlarged peripheral nerves without the presence of skin lesions suggestive of leprosy), the 2-year risk of nerve-function impairment is only 12%. We would have expected a higher risk in this group.

We visited nine districts in Bangladesh allocated to non-governmental organisations, including the four Danish-Bangladesh Leprosy Mission districts, where the study patients live. We were dismayed and concerned that leprosy field workers routinely mark one or more truncal nerves as enlarged. On verification, we believe that some of these nerves were not enlarged or, at best, the enlargement was doubtful. In one non-governmental organisation district, we verified 246 patients' cards and found that 92% of these patients had one or more truncal nerve marked as enlarged (ie, only 8% of the 246 patients had no nerve enlargement).

We also noted that the nerve-function impairment recorded by field workers is influenced by subjectivity on the part of the patients and the workers and, at times, we believe there was a kind of suggestiveness in favour of impairment!

Given our observations on the recommendations made by Croft and colleagues most patients in Bangladesh would be categorised as being at intermediate or high risk of nerve-function impairment and would be subjected to active surveillance, periodic assessment, and steroid treatment. If our observations are correct the patient and the programme would incur a lot of unnecessary and unproductive efforts and expenses.

Leprosy programmes have, first and foremost, to try to reach a quality standard by which we can achieve early detection of all definite cases, before nerve enlargement or loss of function occurs.

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1 Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Smith WCS. A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet* 2000; **355:** 1603–06.

Authors' reply

Sir—The prediction rule is intended to be a simple tool by which leprosy workers can predict the risk of a leprosy patient developing nerve-function impairment after starting chemotherapy. This rule would enable workers to be extra vigilant of high-risk patients and to relax follow-up of low-risk patients. We aimed to find straight-forward predictive variables that could be easily measured by leprosy workers at all levels and be reliably applied. This approach is not, however, the same as prevention.

We concluded that two criteria were of high predictive value for risk of nerve-function impairment: the assignment of leprosy patients into a multibacillary group, and any nerve-function loss at registration. The assessments of multibacillary or paucibacillary and sensory and motor nerve function are procedures well within the scope of leprosy workers, right down to grassroots level. The reliability of such testing beween observers is adequate.[1]

The ambiguity of the finding of nerve trunk enlargement in one or more nerves is peripheral to the main issue, since we did not use it as a predictive variable in the final model. However, detection of nerve trunk enlargement in one or more nerves was highly predictive of nerve-function impairment (hazard ratio 23 [95% CI 5·7–32]), and its detection was, therefore, meaningful.

Finally, only a few patients were at intermediate and high risk (553 [21%] of 2664). Given the high proportion of paucibacillary cases detected nationally in Bangladesh, we would not expect many patients to be at intermediate or high risk. It is unhelpful to suggest that monitoring would be a wasted exercise. Nerve-function impairment does occur during and after chemotherapy in a proportion of leprosy patients and deserves to be detected and treated. The prediction rule gives a simple way of assessing patients' risk groups. Application of this rule is expected to result in available resources being focused in an efficient way.

Pieter Feenstra[2] has noted the importance of including the diagnosis and management of nerve-function impairment in leprosy elimination campaigns and draws attention to the value of including this prediction rule.[2] We trust the validity of our study, and hope it will be taken up by national programmes.

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2 Feenstra P. Strengths and weaknesses of leprosy elimination campaigns. *Lancet* 2000; **355:** 2089.