trophoblastic tumour. These advances have become possible because of the ability to measure tumour load with hCG, diagnose hydatidiform mole in early pregnancy by ultrasound, and the ability to determine whether or not metastases are present on CT and MRI, together with greater understanding of the pathology and molecular physiology of trophoblastic neoplasia.[6]

Schmid and colleagues focus on a rare entity of trophoblastic neoplasia, which is placental-site trophoblastic tumour. The condition was first described in 1976 and named trophoblastic pseudotumour,[7] and was thought to be benign. It was not until 1981 that Twiggs and colleagues[8] encountered a patient who had metastases, and in 1982 Eckstein and colleagues[9] reported four further cases from Charing Cross Hospital. Most reports since then have been case reports or the small number of patients that are cited in today's report.

It is now accepted that placental-site trophoblastic tumours differ from other trophoblastic neoplasms in that the tumour load is not accurately correlated with the concentration of hCG, and that the tumour might be less sensitive to chemotherapy that is effective in the other types of trophoblastic neoplasia. Placental-site trophoblastic tumours might follow any type of pregnancy event, not infrequently becoming clinically apparent even years later, and there is great variability in its malignant aggressiveness. The neoplasm arises from intermediate trophoblast, unlike choriocarcinoma, which arises from villous trophoblast. There can be difficulty with the diagnosis if access to biopsy is not easy, and there is difficulty in histological differentiation of placental-site trophoblastic tumours from the other trophoblastic neoplasms. Unlike with postmolar trophoblastic neoplasia, precise histological diagnosis is essential. Immunohistological staining for human placental lactogen and hCG is especially helpful. Raised free β-hCG concentration in serum can also point to the diagnosis when germ-cell tumours of the ovary and other cancer entities can be excluded by clinical examination and imaging.[10]

What Schmid and colleagues show more convincingly than was previously evident is that the greater the interval between the index pregnancy and appearance of overt neoplasia, the more likely the disease will be aggressive. It is gratifying to find that the investigators advocate adjuvant chemotherapy even for stage I disease.

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# NECT trial: more than a small victory over sleeping sickness

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The natural history of central nervous system infection by *Trypanosoma brucei gambiense* consists of a distinctive neurological syndrome (sleeping sickness) proceeding to inevitable death. For more than 50 years intravenous melarsoprol has been the most common therapeutic approach, but this arsenical compound can cause a reactive encephalopathy with high risk of mortality and shows falling efficacy in certain areas.[1] Eflornithine is an efficacious alternative with fewer side-effects,[2-4] but the need for its 6-hourly administration via slow infusion, over 14 days, has limited uptake in resource-poor settings. Oral nifurtimox shows too low an efficacy for routine use as monotherapy[5] but has been tested recently in combination with eflornithine,

Charles Woodrow

**Mobile active case-finding team in Negage, Angola**

yielding encouraging data on efficacy and side-effect profile.[6–8]

In *The Lancet* today, Gerardo Priotto and colleagues[9] present an open-label randomised trial comparing standard eflornithine (400 mg/kg per day in 6-hourly infusions for 14 days) with nifurtimox-eflornithine combination therapy (NECT: oral nifurtimox 15 mg/kg per day for 10 days, eflornithine 400 mg/kg per day in 12-hourly infusions for 7 days) in adults with stage II African trypanosomiasis. Both the trial methodology and results are noteworthy. The study design was non-inferiority, a pragmatic decision in view of the predicted cure rate of more than 90%.[10] Non-inferiority trials demand robust diagnosis, treatment, and follow-up (notoriously difficult in this context), because weak methodology tends to dilute differences in efficacy which increases the chance of a type I error (false conclusion of non-inferiority[11]). In this regard, the study performed optimally with a completed follow-up rate of 93%, a truly remarkable figure in view of the logistical challenge of doing lumbar punctures over an 18-month period in nearly 300 patients living in remote communities.

As it turned out, in the planned primary outcome analyses of efficacy, NECT seemed superior to eflornithine alone (cure rates of around 97% *vs* 92%). Even the worst-case sensitivity analysis, in which losses to follow-up were regarded as failures, confirmed non-inferiority. Adverse events were generally fewer in the NECT group. These findings suggest that NECT has typical advantages of a combination therapy: equivalent or improved efficacy and reduced side-effects. Furthermore the reduced frequency, duration of course, and total quantity of eflornithine infusion in NECT favour its use in resource-poor settings, in view of the savings in transport and equipment costs as well as staff time. On theoretical grounds, the combination should inhibit the development of resistance to the individual component drugs, as seen for various other infections.

WHO has already endorsed the study's findings by entering NECT into its Essential Medicines List. It should be pointed out that there has not been a direct comparison of NECT with melarsoprol, or nifurtimox–melarsoprol, a combination favoured by some practitioners that proved efficacious in another large trial.[5] However, we believe that there is now a strong evidence base to support promotion of NECT within national treatment strategies.

Despite the optimism generated by today's trial, innumerable challenges remain, including the urgent need to develop improved treatments for the earlier haemolymphatic phase (stage I) of African trypanosomiasis. Despite best efforts, there are still no reports of successfully completed phase III randomised trials in stage I, in which treatment (pentamidine administered by 7–10 daily intramuscular injections) has also remained unchanged for half a century. In our experience it is paradoxically more difficult to recruit and follow up patients with milder clinical manifestations than those in stage II disease, and these studies will require particularly intense support from sponsors and collaboration from all partners. There is also room to refine diagnosis as well as develop coherent strategies for control and surveillance.

Today's study with NECT shows the way forward, setting a high bar in terms of trial methodology that other studies should aim to replicate. The success of this study depended on collaboration between a wide variety of agencies, including the Drugs for Neglected Disease Initiative and Médecins Sans Frontières (the trial's sponsors), several academic centres, and the national trypanosomiasis programmes of the Republic of the Congo and the Democratic Republic of the Congo. Fundamentally, this project builds on the efforts of countless individuals in sleeping sickness teams across Africa who work in indescribably difficult conditions year after year with a positive and indomitable spirit.[12] This potent combination

has produced a study that in every respect rivals those in diseases for which research receives vastly superior funds.

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CW has received a *Lancet* International Fellowship. JO is principal investigator in the TDR-funded 3-day pentamidine study, Uganda (ISRCTN55042030).

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# G8 Summit 2009: what approach will Italy take to health?

In the past decade, the G8 played an important part in the establishment or support of global health initiatives that are at risk today of becoming part of the problem rather than the solution for granting health coverage to disadvantaged populations. The fragmentation of financing for global health and increased transaction costs contrast with the need for efficient and effective health systems, and underline the need for a review of quick-fix and selective approaches. In view of the present economic crisis, a heightened commitment from wealthy countries to sustain global health will be needed. As chair of the G8 Summit 2009, Italy will have a unique opportunity to renew its commitment to global health and orient action towards a more effective approach.

Italy's Official Development Assistance continues to suffer from structural weaknesses, characterised by an absence of clear political direction, weak management, and inadequate and unstable funding.[1] The health sector has been no exception. Nevertheless, two aspects deserve to be noted. First, as the result of contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria, launched at the Genoa G8 Summit in 2001, the donations of Italian Official Development Assistance for Health tripled between 2001 and 2007[2] (Italy is the fourth largest contributor to the Global Fund along with Japan, after France, the USA, and the UK).[3] Italy also engaged in new financing mechanisms, including the International Financial Facility for Immunisation and the Advance Market Commitment for vaccines initiatives, by pledging substantial funds. Arguably, this shift towards vertical initiatives has not been accompanied by attempts to address concerns about potential consequences for global health governance and the negative system-wide effects at a country level. The shift also contrasts with the longstanding guiding principles of the Italian Development Cooperation in the health sector—characterised by a comprehensive rather than a selective approach to health—and also with the domestic experience of the Italian National Health Service that provides universal and comprehensive care.

Second, Italy's contribution to global health already goes beyond traditional Official Development Assistance. The Italian National Health Service and the decentralised public institutions (regions and municipalities) are increasingly engaged in development cooperation. Civil society is very active (in Italy, 1433 not-for-profit organisations are associated with international cooperation and solidarity activities,