Despite the setbacks successes have been achieved. Of the 18 SCID patients treated for their life-threatening condition, 17 are still alive and have had a healthy, functioning immune system for up to five years and a good quality of life. In addition to monogenic conditions, gene therapy also represents a viable treatment for multigeneric disorders, such as cancer, either as a standalone treatment or in combination with chemotherapy or radiotherapy. A huge amount of work is yet to be done, but with efficient monitoring of trials and continuous improvements of viral vectors, gene therapy may still represent an important addition to the treatment armamentarium for a range of diseases.

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Case reports

Case 1
A month after a holiday in South America, a 38 year old man was investigated at a regional centre for infectious and tropical diseases for a persistent cutaneous ulcer on his buttock and associated inguinal lymphadenopathy. Biopsies failed to establish a diagnosis, and, as the lesion was healing, the patient was discharged. Nine months later, however, the patient developed nasal congestion that persisted for six months until he developed lesions on the exterior of his nose (fig 1, left). Examination of the nasal mucosa showed a granulomatous lesion of the septum (fig 1, centre), and mucosal biopsies were obtained under topical anaesthesia. No parasites were found on microscopy or culture, but DNA of *L. viannia* parasites was detected using polymerase chain reaction, confirming a diagnosis of MCL. He was treated with intravenous sodium stibogluconate and made a full recovery (fig 1, right).

Case 2
A month after a school trip to Belize, a 17 year old woman developed persistent erythema and swelling of the nasal tip and rhinorrhoea. She was treated as an inpatient at her local hospital with intravenous antibiotics for suspected low grade bacterial cellulitis. After referral to the Hospital for Tropical Diseases, cutaneous and mucosal biopsies were negative on microscopy and culture but polymerase chain reaction was positive for *L. viannia* DNA, establishing a diagnosis of MCL. She was successfully treated with sodium stibogluconate.

Case 3
A 19 year old woman consulted her general practitioner shortly after returning from extensive travels in rural South America, complaining of persistent skin ulcers and nasal congestion. Her doctor contacted the Hospital for Tropical Diseases immediately concerned that her patient might have MCL. A differential diagnosis of Wegener’s granulomatosis was considered as the patient was known to have serum antinuclear antibodies. Clinical examination showed florid inflammation of the nasal and oropharyngeal mucosa and five cutaneous ulcers with raised margins. Diagnoses of cutaneous leishmaniasis and MCL were established by positive culture and polymerase chain reaction of mucosal and cutaneous biopsies. She was successfully treated with intravenous sodium stibogluconate.

Discussion
Muco-cutaneous leishmaniasis is reported infrequently among travellers returning from Latin America to countries where the disease is not endemic. The cases described here were all young healthy travellers who had spent time in tropical forest areas of Latin America; none had any risk factors for HIV infection. MCL is endemic in such areas between southern Mexico and the northern tip of Argentina. The trend towards “adventure travel” to Latin America may lead to MCL being more often imported to the United Kingdom. Patients with MCL may present to a wide variety of clinicians, including general practitioners, all of whom should be aware of the potential significance of a history of rural travel in Latin America. Familiarity with the manifestations of cutaneous leishmaniasis and MCL may speed diagnosis and limit disease progression.

Recognition of cutaneous leishmaniasis lesions may help to prevent development of MCL or facilitate diagnosis of established MCL. The disease can be prevented by treating *L. viannia* cutaneous leishmaniasis before mucosal involvement. Alternatively, in patients with established mucosal disease, the presence of cutaneous leishmaniasis (or a history suggestive of a previous self healing cutaneous leishmaniasis lesion) may provide a strong clue to a diagnosis of muco-cutaneous disease.

Cutaneous leishmaniasis lesions often develop on exposed parts of the body within a few weeks of exposure to infected sandfly bites. Single or multiple ulcers typically have a raised, indurated margin and a sloughy base (fig 2). There may be satellite lesions (sporotrichoid spread) and cord-like infiltration of proximal lymphatic vessels and local lymphadenopathy.

Box 1: Differential diagnosis for nasal congestion

- Rhinitis (allergy)
- Anatomical cause (septal deviation, hypertrophic turbinates)
- Hormonal disorder (puberty, pregnancy, hypothyroidism, acromegaly)
- Granulomatous disease (sarcoidosis, Wegener’s granulomatosis)
- Drug induced cause (rhinitis medicamentosa, prazosin, cocaine)
- Impaction (crusts, foreign body)
- Mass (adenoids, nasal polyps, nasopharyngeal carcinoma)
- Infection (leishmaniasis, tuberculosis, leprosy, syphilis, rhinoscleroma, coccidioidomycosis, histoplasmosis, blastomycosis)
The differential diagnosis for cutaneous leishmaniasis includes secondary infected insect bites, sporotrichosis (a fungal infection implanted into the skin by a thorn or other penetrating injury), or more rarely cutaneous tuberculosis. Appropriate drug treatment promotes rapid healing of cutaneous leishmaniasis lesions, but the great majority will heal spontaneously over several months; such healing, however, does not preclude the later development of MCL, as illustrated by case 1.

The most common symptom of MCL is persistent nasal congestion, for which the differential diagnosis is broad (box 1). Anterior nasal septal granulomas may be visible with a light source and Thudicum’s speculum, whereas posteriorly located granulomas require nasendoscopy to be seen. Progressive MCL lesions destroy upper respiratory tract mucosa over months and years. Common sites are the turbinates and nasal septum, where erosion of underlying tissue and cartilage may result in perforation. Progressive tissue destruction at the nasal mucocutaneous junction in advanced disease may cause marked disfigurement, requiring reconstructive surgery. Lesions may also affect the palate, pharynx, and larynx, causing palatal dysfunction, dysphagia, dysphonia, and aspiration. Bony structures are not involved.

Diagnostics of cutaneous leishmaniasis and MCL are established by demonstrating the presence of Leishmania parasites in infected tissues. Serology is rarely helpful except in advanced MCL. Punch biopsies should be taken from the raised, indurated edge of cutaneous leishmaniasis lesions and sent fresh for microbiological and parasitological examination and in formalin for histopathological assessment. Examination of Giemsa stained impression smears for the presence of the intra-cellular form of the parasites (amastigotes) may quickly yield a diagnosis in some patients. Amastigotes may also be seen in histopathological sections. The flagellate form of the parasite (promastigote) may be cultured from biopsies on modified Novy-McNeal-Nicolle medium incubated for up to three weeks.

Polymerase chain reaction is the most sensitive diagnostic test, however, and is also used to differentiate L. major subgenus infections, which are associated with the greatest risk of MCL. Similarly, in patients with suspected MCL, biopsies of mucosal lesions are required for diagnosis, and additional biopsies may be taken from the turbinates even if these are not overtly involved. Histopathology of mucosal biopsies shows granulomatous changes for which the differential diagnosis is broad (box 2). Compared with cutaneous leishmaniasis, Leishmania parasites are less readily visualised or cultured from MCL lesions because the vigorous host response limits the tissue parasite burden. In recent years, however, polymerase chain reaction has proved to be a sensitive tool.

MCL requires prolonged parenteral treatment with pentavalent antimonials (treatment of choice) or amphotericin preparations. Such treatment is associated with toxicity and risk of relapse. Patients require joint management from infectious or tropical diseases physicians plus otorhinolaryngologists who have clinical experience of MCL and access to the necessary specialist laboratory investigations. Expeditious and appropriate care, however, can be given only after the diagnosis has been suspected.

Interactive case report
A 35 year old woman with diabetic nephropathy who wants a baby

This case was described on 18 and 25 September (BMJ 2004;329: 674-729). Debate on the management of the patient continues on bmj.com (http://bmj.com/cgi/letters/329/7468/729). On 16 October we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from the patient and relevant experts.