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Strongyloidiasis: challenges in diagnosis and management in non-endemic Kuwait

P. R. HIRA*, F. AL-ALI†, H. M. SHWEIKI‡, N. A. ABDELLA§, M. JOHNY¶, I. FRANCIS**, J. IQBAL*, R. THOMPSON†† and F. NEVA††

**Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait*
†*Microbiology Laboratories, Farwania Hospital, P.O. Box 18373, Farwania, 81004, Kuwait*
‡*Laboratory Department, Jahra Hospital, P.O. Box 40206, Jahra, 01753, Kuwait*
§*Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait*
¶*Microbiology Laboratories, Amiri Hospital, P.O. Box 4077, Safat, 13041, Kuwait*
***Department of Pathology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat, 13110, Kuwait*
††*Laboratory of Parasitology, National Institutes of Health, Bethesda, MD 20892, U.S.A.*

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Among immunocompromised individuals, hyper-infection with *Strongyloides stercoralis* may occur and lead to fatal strongyloidiasis. To clinicians and laboratory diagnosticians in non-endemic countries such as Kuwait, this severe infection poses a particular problem. The clinical histories and signs and symptoms of four Kuwaiti cases of *S. stercoralis* hyper-infection were reviewed. Each of the four was found not only to have lived in an area where *S. stercoralis* was endemic but also to have been treated with immunosuppressive steroids (for medical problems unrelated to the nematode infection). When they presented with undiagnosed hyper-infections their clinical features were confusing. Three of the cases, all with low eosinophil counts, died but the other, who was treated with thiabendazole, survived.

In the light of these observations, healthy medical examinees who had recently moved from endemic zones were checked for asymptomatic *S. stercoralis* infection, both by stool examination and ELISA-based serology. Of 381 stool samples investigated over a 3-month period, 183 (48%) were found positive for helminths, 7% for *S. stercoralis*. Of 198 individuals from endemic zones who were screened after another medical examination, 71 (35.8%) were found positive for intestinal helminth parasites, including one (1.45%) infected with *S. stercoralis*. Although ELISA appear reliable in making a presumptive diagnosis of strongylodiasis, the results of such assays are not very specific and are best interpreted in conjunction with the patient's clinical status. The concurrent administration of anthelminthics to patients prescribed steroids who, because they live or have lived in an area where *S. stercoralis* is endemic, are at risk of infection with the nematode, should be considered.

Human infection with the nematode *Strongyloides stercoralis* is prevalent in the tropics and subtropics. The parasite is notorious as the cause of a chronic, usually asymptomatic infection that may persist in the immunocompetent host for very long periods and so be detected several decades after the host has left an endemic area (Liu and Weller, 1993). With the advent of immunosuppressive therapy and the emergence of diseases causing immunodeficiencies, the parasite has acquired renewed prominence as the cause of potentially fatal hyper-infection and dissemination in the immunocompromised. Such severe complications may go unrecognized or

Reprint requests to: P. R. Hira.
E-mail: hira@hsc.kuniv.edu.kw; fax: +965 531 8454.

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unappreciated, particularly in non-endemic areas. In one such area, Kuwait, the very large expatriate community makes up almost 70% of the population. This community includes many migrant workers who, at some time in their lives, have lived in areas where *S. stercoralis* infection is common. Before the oil industry revived the local economy, many Kuwaitis (now the elderly) visited endemic areas, for trade. In Kuwait, the prevalence of occult infection with the nematode may therefore be surprisingly high for a region in which no transmission occurs. Such asymptomatic infections would not be of great public-health concern were it not for the rising prevalence of immunodeficiency — the result of diabetes, other metabolic disorders and HIV/AIDS, which may leave patients immunocompromised, and more frequent treatment with drugs that are intentionally or accidentally immunosuppressive

In the present study, four cases of severe strongyloidiasis who presented in Kuwait are reviewed. Further, in an attempt to evaluate the prevalence of asymptomatic infection with *S. stercoralis* in Kuwait, stool samples were collected, from individuals who had recently arrived from endemic areas and from patients, and checked for the parasite. ELISA were then used to check 43 sera, from known stool-negatives and stool-positives, for anti-*Strongyloides* antibodies, to assess the usefulness of serology in the diagnosis and management of patients.

SUBJECTS AND METHODS

Hyper-infections

The clinical histories of four patients who presented in hospitals in Kuwait between 1992 and 1998 were retrospectively reviewed. Each was a suspected case of *S. stercoralis* hyper-infection associated with immunosuppression. Three of the hyper-infections appeared to be fatal but the fourth case survived.

Parasitological Surveys and Serology

Initially, over a 3-month period, stool samples were collected in the Farwania Hospital, Farwania, Kuwait, from medical examinees who had lived in endemic areas ($N = 381$). The aim was to gauge the prevalence of *S. stercoralis* infection among the examinees and so get some idea of the general magnitude of the problem (see Table). A single stool sample from each individual was examined, for *S. stercoralis* and other helminths, using direct unstained smears, formol–ether concentration, and staining with trichrome and safranin–Methylene Blue. Later, another 198 medical examinees from endemic areas and 9670 hospitalized patients (the consecutive, consenting patients who presented at the Farwania Hospital between October 1999 and August 2001) were similarly investigated (Table). The results of these investigations were compared with some corresponding older data, collected from

TABLE 1. *The results of some parasitological surveys in the Farwania Hospital, Farwania, Kuwait, each based on the microscopical examination of a single stool sample per subject*

Survey			No. of (%) of subjects:		
Subjects	Study period	Duration (months)	Examined	Positive for helminths	Positive for *Strongyloides*
Hospital patients	August 1988	1	465	57 (12.3)	1 (1.8)
Hospital patients	September 1988	1	516	27 (5.2)	1 (3.7)
Medical examinees*	February–April 2001	3	381	183 (48.0)	13 (7.1)
Hospital patients	October 1999–August 2001	23	9670	1260 (13.0)	36 (2.9)
Medical examinees*	April 2000–March 2001	12	198	71 (35.9)	1 (1.4)

*Who had lived in an area (outside of Kuwait) where *S. stercoralis* was endemic.

981 in-patients at the Farwania Hospital in the August ($N = 465$) or September ($N = 516$) of 1988 (i.e. before the Gulf War in 1991).

The ELISA and cut-off thresholds described by Neva *et al.* (1981) were used to check 43 sera, from patients who had lived in endemic area and appeared to be stool-positive for *S. stercoralis* and/or other helminths or stool-negative for all helminths, for antibodies reacting with antigen from the filariform larvae of *S. stercoralis*.

RESULTS

Hyper-infections

CASE 1

In February 1999, a Bangladeshi male aged 28 years presented at the Jahra Hospital, with severe epigastric pain and diarrhoea. Sections of duodenal biopsies demonstrated the presence of *S. stercoralis* — adult females (Fig. 1) and filariform larvae. A stool sample was found to contain enormous numbers of the nematode's rhabditiform larvae and a serum sample contained a high titre of anti-*Strongyloides* antibodies. Although the patient's leucocyte count rose from 9300 to 32,000/μl in the 3 weeks post-admission, his eosinophils always represented $< 2.5\%$ of his leucocytes. A medical history revealed that the patient had been prescribed prednisolone, to correct an ophthalmic problem (uveitis), a month before he had presented with the epigastic pain. As a part of the management of his strongyloidiasis, he was prescribed albendazole (thiabendazole was not available) but died soon after treatment with this drug. The causes of death were recorded as peritonitis and meningitis. Unfortunately, a post-mortem was not carried out, for religious reasons. The exact cause of death thus remained undetermined.

CASE 2

A 60-year-old Iraqi male, a known bronchial asthmatic, presented at the Mubarak Al-Kabeer Hospital in January 1992 with chronic obstructive airways disease (COAD), manifesting as an acute exacerbation of the asthma. He was admitted to hospital as he had concurrent cardiac problems. He was

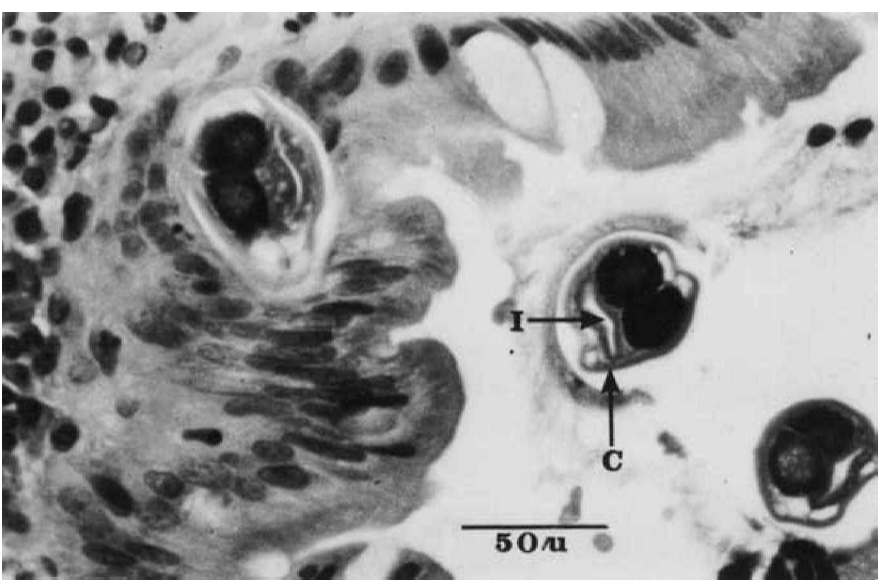

FIG. 1. A section of a duodenal biopsy from a patient with *Strongyloides stercoralis* hyper-infection (case 1). Sections of at least one adult female *S. stercoralis* in the biopsy show the delicate cuticle (C), the intestine (I), and the uterus (which appears as a double tube).

given steroids after an episode of vomiting and transient diarrhoea of 10 days' duration. There was no blood or mucus in his stool. When admitted, he had 10,700 leucocytes/μl, of which 1% were eosinophils.

An abdominal X-ray showed a dilated stomach and small intestine. Endoscopy of the upper gastro-intestinal tract revealed dilation of the second and third parts of the duodenum, with an oedematous and hyperaemic mucosa with superficial erosions. The duodenal lumen contained excessive bile. A tentative diagnosis of duodenal lymphoma was made. Duodenal biopsies, however, revealed the presence of many *S. stercoralis* adults and filariform larvae, and subsequent, serial stool samples showed the presence of many rhabditiform larvae. Although treated with thiabendazole, the patient showed a poor response and died shortly thereafter.

CASE 3

A 69-year-old Kuwaiti male was admitted to the Farwania Hospital in March 1998, with a cerebro–vascular accident (CVA) causing hemiparesis. He had no history of cough and was not hypertensive or diabetic. He had a history of generalized aches and pain and episodes of headache for 4–5 years. On admission he had 4800 leucocytes/μl (3% eosinophils). He was discharged after 4 weeks, while on aspirin, heparin, flucortolone (Ultralan®; Schering, Berlin), a growth-hormone 'booster' (NeoTroprin™) and, from a week pre-discharge, prednisolone. Two weeks later he was re-admitted, a computed tomographic scan showed evidence of a cerebral infarction, and his leucocyte count had risen to 10,300/μl but with only 1% eosinophils. He deteriorated rapidly. A week after re-admission, the patient developed a pulmonary infection and was treated with antibiotics. A chest X-ray at this time revealed bilateral patchy consolidation (Fig. 2) and a sample of sputum, collected to screen for methicillin-resistant *Staphylococcus aureus*, was found to contain the filariform larvae of *S. stercoralis* (Fig. 3). The patient died 2 days later. A serum sample collected shortly prior to death was strongly positive for anti-*Strongyloides* antibodies.

CASE 4

A Kuwaiti male aged 57 years was admitted to the Mubarak Al-Kabeer Hospital in September 1992, as a case of inflammatory bowel disease. He was initially prescribed prednisolone during his hospital stay. Following bowel surgery, he developed pneumonia. The sputum sent for bacterial cultures showed filariform helminth larvae which were later identified as those of *S. stercoralis*. He was treated with thiabendazole and eventually made a full recovery.

Parasitological Surveys and Serology

The Table shows the various groups of individuals whose stools were examined to get some idea of the threat posed by asymptomatic *S. stercoralis* infection in Kuwait. Curiously, there is some indication that the prevalence of infection with any intestinal helminth was higher after the Gulf War of 1991 than before the conflict.

In the ELISA for anti-*Strongyloides* antibodies, the seven sera from subjects who were stool-positive for *S. stercoralis* (three of whom were also stool-positive for other helminths) were all found seropositive. Although five of the 11 sera from subjects whose stools appeared helminth-free and 10 of the 25 sera from subjects who were only stool-positive for helminths other than *S. stercoralis* also appeared ELISA-positive, they gave weaker reactions than the sera from subjects who were known to be carrying *S. stercoralis* (data not shown).

DISCUSSION

Severe strongyloidiasis, with disseminated hyper-infection, has become more common over the last few decades, largely as a result

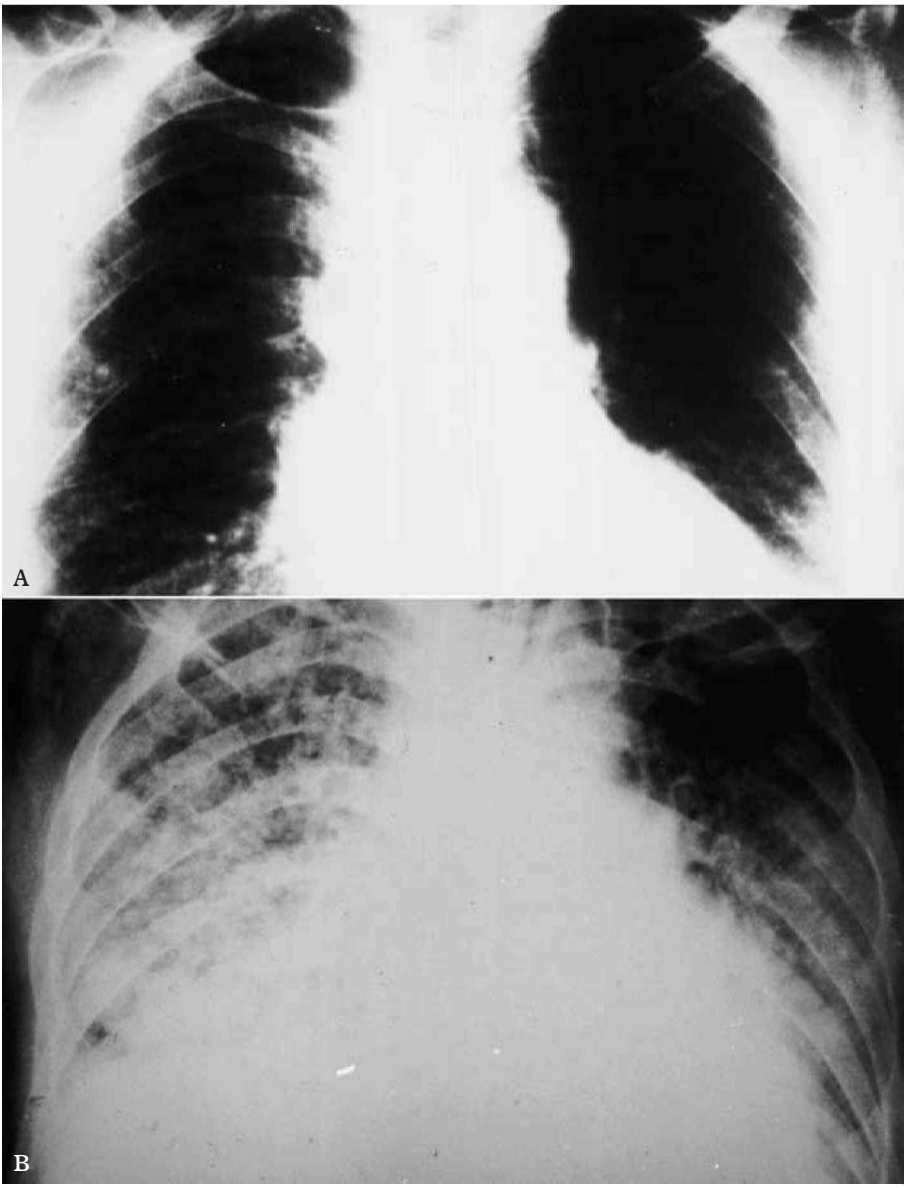

FIG. 2. The normal chest X-ray of case 3 at the time of his first admission (a) and the later, abnormal X-ray (b), showing the diffuse bilateral interstitial and alveolar opacities resulting from the *Strongyloides stercoralis* hyper-infection that had developed a week after the patient was re-admitted.

of the wide-spread use of immunosuppressive drugs. The problem is becoming better appreciated in the more affluent countries of the western hemisphere (Longworth and Weller, 1986) but the present case reports appear to be the first from a developing country in the Middle East. Although the health system of Kuwait is well developed, and in many clinical areas as good as many in Europe or the U.S.A., there seems to be a lack of awareness about the potentially fatal manifestations of *S. stercoralis* infection in the immunocompromised. This lack of awareness, perhaps exacerbated by a lack of

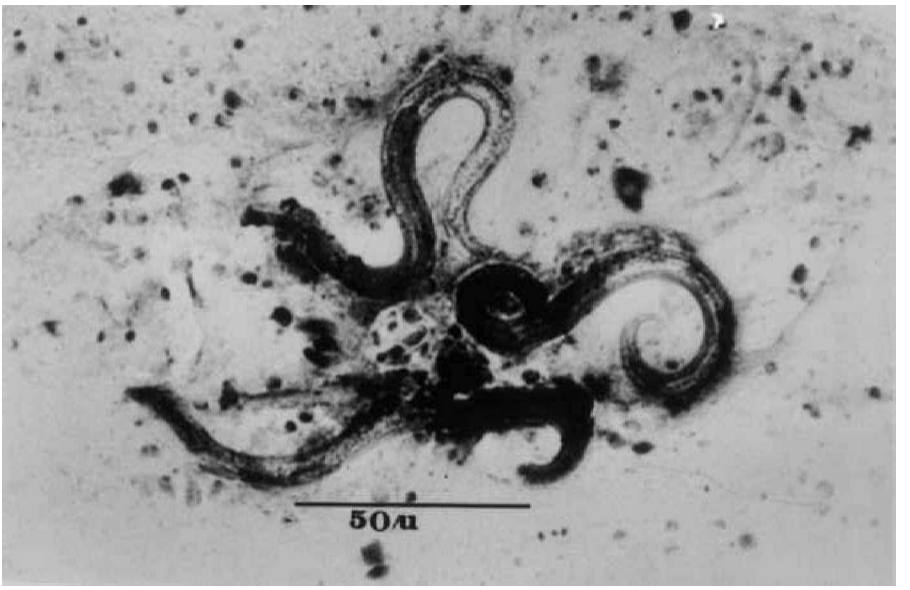

FIG. 3. Filariform larvae in the sputum of a patient (case 3) with *Strongyloides stercoralis* hyper-infection.

the expertise necessary to diagnose severe strongyloidiasis, has clearly resulted in delays in the appropriate management of this disease and perhaps in preventable deaths.

The four cases described here had several features in common. They had all been treated with steroids (either pre- or post-admission), they all had filariform nematode larvae in their tissues and/or sputum, they all had low percentages of eosinophils among their leucocytes, and they all either had *S. stercoralis* hyper-infection when admitted with complaints and medical conditions apparently unrelated to the nematode, or subsequently developed such hyper-infection. It was assumed that the administration of a steroid to each of these patients caused them to become immunosuppressed and thus precipitated the hyper-infection.

The four cases were at risk of hyper-infection for different reasons. Case 1 was an expatriate from an Asian country. Asians who emigrate to Kuwait often have low socio–economic status, usually come from a region where *S. stercoralis* is endemic, and often have language problems making it difficult for them to give adequate medical histories. Even at the best of times, an ophthalmic problem like case 1's will rarely be linked to diarrhoea. Case 2 exemplifies an expatriate coming to Kuwait, living in the country for a long time, developing bronchial asthma, and only developing a symptomatic *S. stercoralis* infection when treated with an immunosuppressive steroid (prednisolone). Though a stool sample from case 2 was sent to the laboratory, culture did not yield any enteric bacteria. It seems likely that the *S. stercoralis* in this sample were overlooked, as subsequent examinations did show the presence of the rhabditiform larvae. Case 3 was a Kuwaiti who also probably acquired his infection abroad several decades previously. When his CVA occurred he was also treated with prednisolone. When discharged, he was kept on prednisolone and it was almost certainly this that turned his occult infection with *S. stercoralis* into an overwhelming hyper-infection within about 10 days. Case 4 was an elderly Kuwaiti who had previously visited an endemic area. He presented with a medical condition that required surgery and steroids, and subsequently developed severe strongyloidiasis that was fortunately recognized before anthelminthic treatment became ineffective.

The clinical diagnosis of pulmonary strongyloidiasis, in which many filariform larvae invade and perforate the alveoli, is difficult and often delayed because of the non-specificity of the signs (diffuse, alveolar and interstitial infiltrates on a chest X-ray; Woodring *et al.*, 1994) and symptoms (cough and wheezing). The clinical picture is often indistinguishable from many other causes of pulmonary infiltrates on a chest radiograph. The signs and symptoms of bronchitis or bronchospasms caused by *S. stercoralis* may be misdiagnosed, particularly in patients (such as case 2 in the present study) who have a history of lung disease. While filariform larvae may be present in sputum or bronchial washings, they may be overlooked during casual routine microscopy by the uninitiated, who lack experience. Even diligent microscopists may overlook or ignore such larvae in sputum samples or washings, when they only expect to see them in stools. Such microscopists often have no access to the patient's full clinical records and are therefore unable to make informed decisions on unexpected diagnoses. Clinicians who request laboratory tests often give the bare minimum of information about the patient on the request forms. In at least two of the present cases (3 and 4), action could have been taken earlier had the examining clinicians appreciated and recognized the effects of the dissemination of *Strongyloides* larvae into the pulmonary tree. In each of these cases it was the staff conducting the laboratory tests who highlighted the immediate emergency.

Although patients given immunosuppressive drugs to prevent them rejecting organ transplants may also develop severe strongyloidiasis (Morgan *et al.*, 1986; DeVault *et al.*, 1990), none of the 600 transplant patients in Kuwait are known to have developed hyper-infection with *S. stercoralis*. Most transplant cases in Kuwait are now managed with a triple combination (cyclosporine A, azathiaprine and prednisolone) that, however, includes a drug (cyclosporine A) known to have anthelminthic activity (Schad, 1986).

The results of the parasitological surveys have to be treated with some caution, as there is clear selection bias in the choice of subjects (who were either medical examinees, who had lived in areas where *S. stercoralis* is endemic, or hospitalized patients) and, as only one sample/subject was checked, they probably under-estimate the true prevalences. They do demonstrate, however, that asymptomatic infections with *S. stercoralis* or other intestinal helminths are probably quite common in Kuwait. Of the 198 healthy medical examinees investigated over a 12-month period after the 1991 Gulf War, for example, more than one in three was stool-positive for helminths (Table). In the larger group of 381 medical examinees, over 48% harboured helminths and 13 (7%) had *S. stercoralis* (Table). The prevalences of infection with intestinal helminths recorded after the Gulf War were markedly higher than those recorded before this conflict. It seems possible that the large numbers of South–east Asians who emigrated to Kuwait following the liberation of the country in 1991 were more likely to be carrying intestinal helminths than those who had lived in Kuwait before the war. The sensitivity of detecting *S. stercoralis* in stools microscopically increases with the number of samples examined per subject. In general, examination of a single stool sample from each subject will reveal only about 30% of the infections, examination of three samples/subject will demonstrate approximately 50% of the infections, and almost all cases of infection will be detected by checking seven samples/subject (Pelletier, 1984; Sato *et al.*, 1995). The microscopical examination of just one stool sample per patient, which is the routine practice in Kuwait and many other countries, therefore leaves many infections with *S. stercoralis* (and other intestinal helminths) undetected. Clinicians are, however, reluctant to request the investigation of multiple stool samples per patient prior to the commencement of therapy (because it is inconvenient, time-consuming, and may often have no impact on treatment), and patients are usually

reluctant to undergo this type of prolonged screening. If patients need to be carefully checked for *S. stercoralis*, the production and examination of one faecal culture on agar per patient, which may reveal 96% of all infections with the nematode (Panosian *et al.*, 1986; Arakaki *et al.*, 1990; Salazar *et al.*, 1995), is to be preferred to the microscopical examination of stool smears.

In the present study, as in previous investigations (Neva *et al.*, 1981; Gam *et al.*, 1987; Genta, 1988; Gyorkos *et al.*, 1990), the serological detection of anti-*Strongyloides* antibodies was found to be a sensitive but apparently a not very specific method of detecting *S. stercoralis* infections. The question must be asked if such serology is useful, especially among patients who live or have lived in areas where several species of intestinal helminth are common. The ELISA employed in the present study has already been used to detect *S. stercoralis* infections (Neva *et al.*, 1981). In the present study, since only a single stool sample from each of the patients checked by ELISA was investigated, it remains possible that all of those found ELISA-positive were infected with *S. stercoralis*, even though many of them appeared stool-negative for this parasite. Repeat ELISA (barring re-infection) is claimed to be useful in indicating therapeutic effectiveness (Loutfy *et al.*, 2002), since the titre of anti-*Strongyloides* antibodies seems to fall more quickly after parasitological cure than the titres of antibodies to several other parasites (Genta, 1988).

There is yet to be a consensus on the optimal therapy for systemic strongyloidiasis. Symptomatic infections with *S. stercoralis* are usually treated with albendazole, either alone or in combination with ivermectin, or thiabendazole (DeVault *et al.*, 1990). Thiabendazole is the recommended drug but its availability is restricted, mainly because albendazole is cheaper, safer and better tolerated. Thiabendazole was only available for the treatment of two of the four cases of hyper-infection described above, one of the two being the sole survivor. It remains unclear if the three cases who died would have survived if given treatment with thiabendazole instead of albendazole, or earlier treatment with thiabendazole or albendazole. The full potential of ivermectin, another safe drug, in the treatment of strongyloidiasis — including the potentially fatal hyper-infections — remains to be explored (Marti *et al.*, 1996; Toma *et al.*, 2000; Zaha *et al.*, 2000). Muennig *et al.* (1999) recommended that all migrants at risk should be given presumptive treatment with albendazole, as this would save lives and money and be more cost-effective than screening the migrants and treating only those with positive stools. In Kuwait, to avert the fatal dissemination of *S. stercoralis* infections in migrants from endemic areas who are being treated with immunosuppressive drugs such as prednisolone, it may be appropriate to administer an anthelminthic concurrently. Stool samples should be collected and carefully screened when the patient is first prescribed an immunosuppressive drug and then weekly thereafter. In such circumstances, the examination of duodenal aspirates and multiple stool samples will probably prove cost-effective and serology may also provide a useful guide. Every patient on immunosuppressive medication who presents with chest complaints, including the acute respiratory distress syndrome (ARDS), should be considered a possible case of systemic strongyloidiasis and immediately be carefully checked for *S. stercoralis*. Secondary bacterial and fungal infections and ARDS are common in strongyloidiasis patients. Development of a lung abscess might indicate a superimposed bacterial infection but this is not a feature in patients who have not lived in an endemic area for decades. Many would claim that the routine screening of patients, who have none of the signs and symptoms of strongyloidiasis, for *S. stercoralis* infection is unwarranted. An awareness of the problems posed by this parasite is essential, however, especially for clinicians examining immigrants from developing countries.

Curiously, while eosinophilia is often considered a hallmark of strongyloidiasis (and of most other helminth-related diseases; Loutfy *et al.*, 2002), the four cases of hyper-infection reviewed above did not have eosinophilia, perhaps because they were not immunocompetent. Patients known to be harbouring *S. stercoralis* but having abnormally low counts of eosinophils should be considered medical emergencies.

A direct link between disseminated hyper-infection with *S. stercoralis* and immuno-deficiency seems unlikely (Genta, 1992). It has been suggested that prednisolone and other administered steroids affect the parasites themselves, stimulating the rapid development of the rhabditiform larvae into the infective third-stage larvae (Genta, 1992). Among the cases of hyper-infection recognized in Kuwait, it took fewer than 10 days for an asymptomatic infection with *S. stercoralis* to develop into an overwhelming one (case 3) and even subconjunctival prednisolone (case 1) or dexamethasone (West and Wilson, 1980) appears sufficient to trigger a severe dissemination of the parasite.

In conclusion, although the country is not an endemic area for *S. stercoralis*, strongyloidiasis can be an important and life-threatening disease in Kuwait. Patients who are already immunodeficient or are to be immunosuppressed by chemotherapy need to be carefully checked for *S. stercoralis*. Stool examinations and serology are both important in the further management of such patients.

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