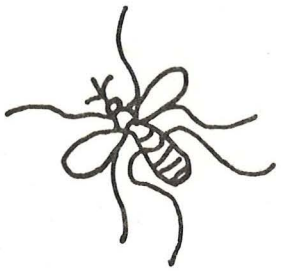
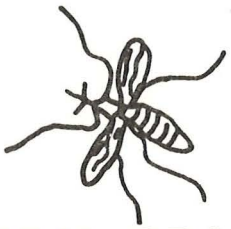
Inf. Disease

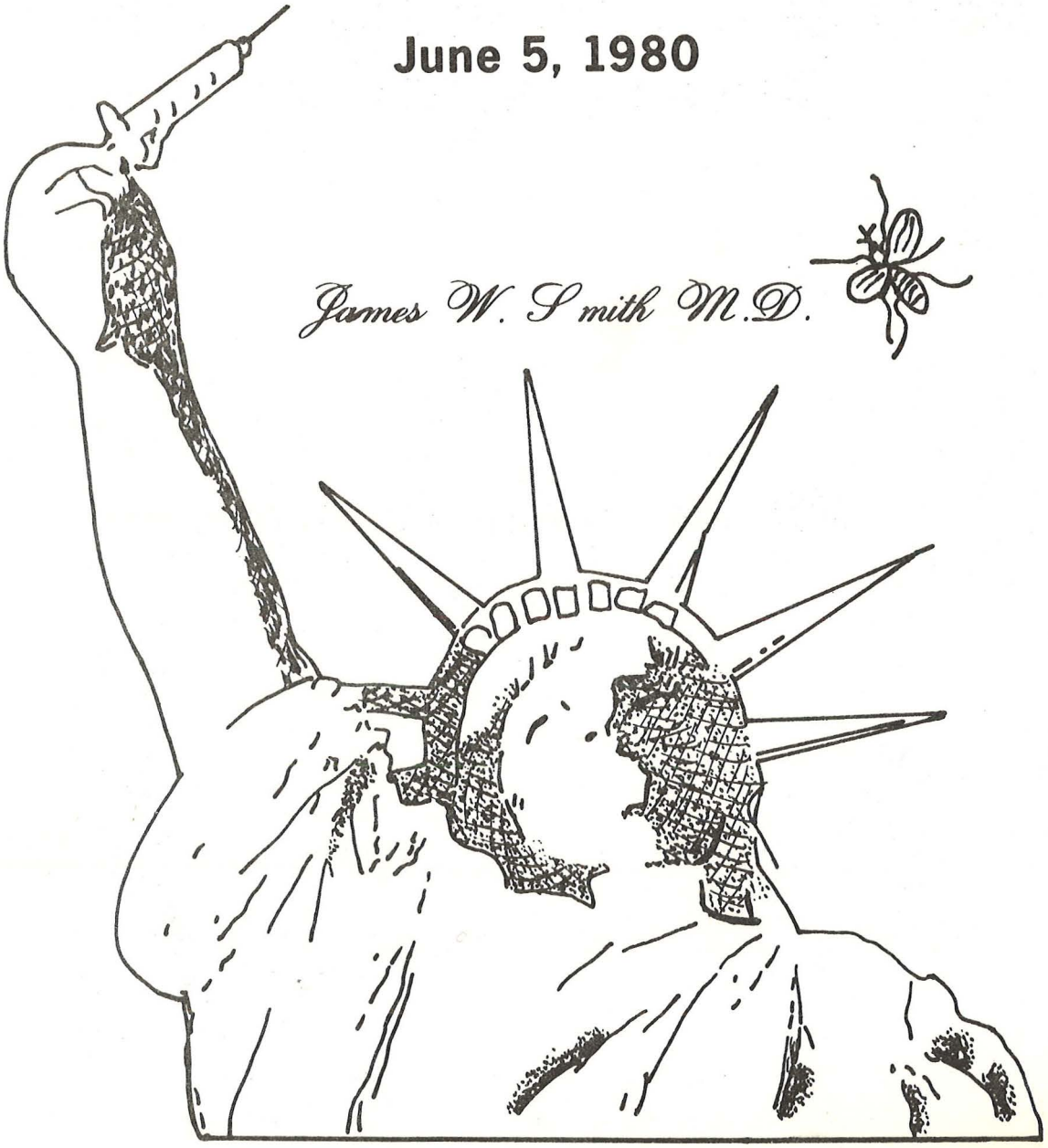
INFECTIONS IN REFUGEES FROM SOUTHEAST ASIA





MEDICAL GRAND ROUNDS

June 5, 1980



James W. Smith M.D.

"Here let them lie, till famine and the ague eat them up."
Macbeth V, 5, 4, Shakespeare

Military and political conflicts in the 20th century, as in centuries past, have led to the uprooting of many from their homeland. The United States continues an open door policy toward political refugees, as typified recently by the reception of Cuban refugees in great numbers. However, no refugee problem in the U.S. today compares in scope with the social and medical problems of the refugees from Southeast Asia. The flood of refugees, particularly from Democratic Kampuchea, "Cambodia," has had a ripple effect among medical care institutions in the United States. Since infection ranked after malnutrition as a leading health problem among these refugees, common and unusual infections which may trouble these refugees are presented. Preliminary studies indicate no unusual health problems among the Cuban refugees (1). The Cuban refugees will have very low rates of tuberculosis (said to be the lowest in Western Hemisphere), and of malaria, whereas these two diseases have been commonplace among the Kampuchean refugees (2). Furthermore, health care for Kampucheans in the U.S. is hampered by multiple dialects with a requirement frequently for an interpreter. Initial screening of all refugees arriving in the U.S. includes:
1) Physical examination for skin lesions consistent with leprosy or syphilis and all genital infections.
2) Chest x-ray for all 15 year and older with medical work-up and sputum examination for any suspicious abnormalities.
3) A rapid serological test for syphilis with treatment for all positive reactions.
4) Psychiatric evaluation to detect severe personality disorders.

I. Fever in Refugees of Southeast Asia.

The infectious causes of fever in refugees can be divided by categories as to incubation period of time following departure from point of origin (3). Some entities such as dengue, plague and some forms of gastroenteritis as cholera, paratyphoid fever or shigellosis need only be considered a short time after departure (Table 1). Other infections such as malaria, scrub typhus and typhoid

TABLE 1

INCUBATION PERIOD OF INFECTIONS IN SOUTHEAST ASIAN REFUGEES

Short (less than 10 days)	Dengue Plague Gastroenteritis
Intermediate (up to four weeks)	Malaria Scrub typhus Typhoid fever
Prolonged (greater than four weeks)	Malaria (vivax) Tuberculosis Hepatitis Amebiasis Melioidosis Filariasis

fever, may be seen within a month of return from the endemic area. However, other infections which were acquired in Southeast Asia may not appear clinically until a remote period after departure. Major clinical problems which might be recognized late would be vivax malaria, tuberculosis and hepatitis. Less common infections that may be delayed in clinical appearance include amebiasis, as amebic liver abscess, melioidosis (which can recur up to seven years after leaving endemic area), and filariasis.

An infection will be the likely cause of fever in a refugee from Southeast Asia. Although figures are not available for refugees, data is available for the frequency of etiological agents in other groups (Table 2). In military

TABLE 2

REPORTED CASES OF FEVER IN SOUTHERN ASIA

Acute fever in military personnel (4)

	%
Malaria	70
Scrub typhus	7
Dengue	5
Leptospirosis	2
Enteric fever	1
Melioidosis	0.1
FUO	12

Natives - Indonesia (6)

	%
Salmonella	43
Bacteremia	25
Gastroenteritis	18
Encephalitis	13
Malaria	2
Unknown	42

FUO in military personnel (5)

	%
Leptospirosis	20
Scrub typhus	12
Jap B. encephalitis	7
Other encephalitis	3
Infectious mononucleosis	5
Various viral infections	2
Dengue	0.6
Undiagnosed	45

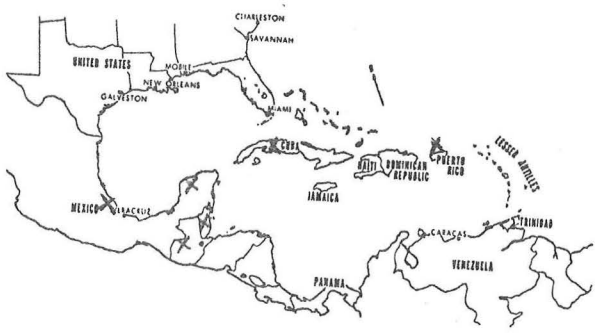
personnel in Vietnam malaria was the ranking cause of fever in persons requiring hospitalization and who did not have an upper respiratory tract illness (4). Many other causes accounted for small numbers, but after initial tests, up to 12% had no explanation for fever after four days (FUO). In a separate study of FUO in military personnel, an infection was eventually established in 55%, with leptospirosis and scrub typhus being the leading two causes (5). No specific feature provided a clue to any one of these etiologic agents. A large proportion (up to 30%) had central nervous manifestations with cerebrospinal fluid pleocytosis. Serologic tests were required for definitive diagnosis. Note that malaria was missing from this group, having been excluded by serial peripheral smears within the first 24 hours. In contrast, significant febrile events requiring hospitalization in natives of Southern Asia (Indonesia in this study), Salmonella infections were the ranking cause, followed by arthropod-borne encephalitis (old term!), but malaria was infrequent. Unlike the U.S. where noninfectious causes account for the majority of persons with

FUO, the workup in refugees will not frequently require tests for other causes such as collagen vascular disease, malignancies and obscure causes of prolonged fever (7, 8). It also is not likely that factitious fever will be the cause in this population as has been noted, particularly among persons with health care backgrounds (9). The review of potential medical problems in military personnel is also appropriate in refugees (10).

A. Dengue and viruses causing hemorrhagic fever syndromes.

Texas physicians do need to recognize the clinical characteristics of dengue, not only because of the small possibility that refugees may present with it soon after leaving Southeast Asia or Cuba but also because of the threat of spread from Mexico to Texas. A wide area of Texas from the Rio Grande valley along the Gulf Coast from Texas and Florida has the susceptible population and an ample population of the mosquito vector, *Aedes aegypti* (11). Epidemics of dengue devastated the area through the 30's (11). The dengue virus, a mosquito-borne flavi virus has moved from the Mexican state of Chiapas, near Guatemala, to Tampico in the state of Veracruz in less than a year (Figure 1). Attack

FIGURE 1.



The Caribbean-Gulf-Atlantic Region of Recurring Dengue Epidemics.
The recent path of dengue spread has been clockwise through the Caribbean Islands and along the adjacent coast of South America.

rates of 20-80% are not unusual in epidemics of classical dengue fever. After an incubation period of 5-8 days, infected persons will have a febrile illness lasting 5-7 days with headache, retroorbital pain, backache and constitutional symptoms. Approximately 40% will have the classical dengue fever with the dramatic onset of fever and racking myalgia, thus the term "backbreak" fever. A macular or maculopapular rash may appear on the 2nd to 4th day of illness on the face or trunk and spread to the extremities. If petechiae along with a positive tourniquet test occurs, then the hemorrhagic fever syndrome is likely, which occurred with epidemic disease in Southeast Asia (12). Hemorrhagic complications did occur in Texas outbreaks previously (11). The mechanism for hemorrhagic fever with dengue continues to be hotly debated over whether it is due to an immunopathologic mechanism elicited by a second heterotypic dengue virus in a person previously exposed to dengue, or that a unique strain of dengue, independent of serotype, produces the hemorrhagic fever syndrome. If a person with a viral syndrome suggestive of dengue has petechiae, obtain a platelet count and if below 50,000/mm^3, the person should be hospitalized and observed closely until the count rises above 100,000/mm^3. Fluid management is critical early.

It is important to suspect and recognize dengue since even asymptomatic individuals can play a role in transmission of the disease. Mosquitoes can become infected from asymptomatic persons who may have viremia as well as from symptomatic individuals. So, rigorous mosquito control measures should be instituted if an outbreak occurs. (The presence of respiratory and gastrointestinal symptoms is against the diagnosis of dengue). Persons presenting with typical clinical dengue syndrome should have acute and convalescent sera submitted to the State Health Department for dengue serology. Other causes of hemorrhagic fever which are possible in persons returning from various countries are listed in Table 3 (13). Chikungunya and Ross River virus can present with arthritis and rash, although Ross River agent rarely if ever causes hemorrhagic fever. Dengue must be considered in the differential

TABLE 3.

VIRUSES WHICH CAN PRESENT AS HEMORRHAGIC FEVER SYNDROME

Type	Site of Origin
Dengue	Southeast Asia, Puerto Rico, Southern Mexico and Central America
Chikungunya	Southeast Asia, India, Southern Afric
Hemorrhagic fever with renal syndrome	Korea, Japan, Siberia
Ross River virus	Samoa, Fiji, Australia
Rift Valley fever	East, South Africa, Sudan, Egypt
Yellow fever	South America, Africa
Argentina, Bolivian hemorrhagic fever	Argentina, Bolivia
Lassa fever	Sierra Leone
Marburg fever (Ebola)	South Africa, Zaire, Sudan

diagnosis of central nervous syndromes in refugees (Table 4). Japanese B encephalitis is endemic in Southeast Asia and could present in the early days after a refugee leaves. If polymorphonuclear leucocytes are present which are eosinophils, consider gnathostomiasis or angiostrongyliasis. The parasites are endemic in Southeast Asia, and infection occurs after ingestion of uncooked fish or raw mollusks (14). High on the differential diagnosis of a refugee with CNS signs should be TB meningitis (the one case at PMH in fact presented with fever and abdominal pain), so a lumbar puncture is indicated in any febrile refugee.

TABLE 4

CAUSATIVE ORGANISMS OF CENTRAL NERVOUS SYSTEM INFECTIONS
IN REFUGEES FROM SOUTHEAST ASIA

Cerebral symptoms without pleocytosis
- Falciparum malaria
- Septicemia (Salmonella, other Enterobacteriaceae)
- Dengue*, chikungunya*

Polymorphonuclear leucocytes (not eosinophil)
- Bacterial meningitis
- Early viral meningo-encephalitis

PMNs (eosinophils)
- Gnathostomiasis
- Angiostrongyliasis
- Coccidioidomycosis

Mononuclear pleocytosis with normal CSF glucose
- Early (very) tuberculous meningitis
- Japanese B encephalitis
- Leptospirosis
- Miscellaneous viral syndromes
- R/O fungal meningitis

Mononuclear pleocytosis with low CSF glucose
- Tuberculous meningitis
- R/O fungal meningitis

* Pleocytosis not reported in clinical descriptions

B. Plague

Plague is endemic in Vietnam, particularly in the central highlands. Imported cases in the United States are infrequent (Fig. 2), with the one imported case being seen at the Dallas VAMC, who was admitted to the surgery service for repair of a suspected inguinal hernia and who acquired plague while participating as a "scorer" in a rat-stomping contest in Vietnam (15). Plague is also endemic in the southwestern United States so it is possible in persons returning from New Mexico (16). Patients with bubonic plague present with fever, chills with tender adenopathy (either inguinal or axillary, but rarely cervical). [The word bubonic more properly refers to inguinal involvement. (L from Gr.: boubon-groin)]. Septicemia is not common in the United States, but was frequent in tribesman in the central highlands of Vietnam who had temperatures exceeding 40°C, tachycardia exceeding 130 per minute, hypotension or central nervous system manifestations, including delirium, agitation or disorientation (17). Plague can be diagnosed by demonstrating bipolar-staining bacilli in exudate from the skin lesion or lymph node aspirate with polychromatic (Wayson's) stains. Care should be taken to aspirate the bubo or other node away from the point of greatest prominence, since aspiration at this point may lead to fistula formation. In New Mexico, physicians rely upon immunofluorescent stains which are rapid and specific for organisms found in aspiration of nodes or sputum (if pneumonia). Persons with plague should be hospitalized with strict isolation and watched carefully for development of pneumonia

FIGURE 2

Reported human plague cases, by state, United States, 1950-1977.

or meningitis. Streptomycin 1 g bid is treatment of choice, although tetracycline and gentamicin have also been used successfully. Chloramphenicol, 3-4 g/day would be the treatment of choice for plague meningitis. If hospital personnel or family members have contact with a confirmed case of pulmonary plague, chemoprophylaxis with tetracycline 1 g qd for seven days is recommended. Some also recommend chemoprophylaxis for household contacts of flea-borne plague cases.

Plague must be differentiated from a number of other agents which cause tender inguinal adenopathy or bubo (Table 5).

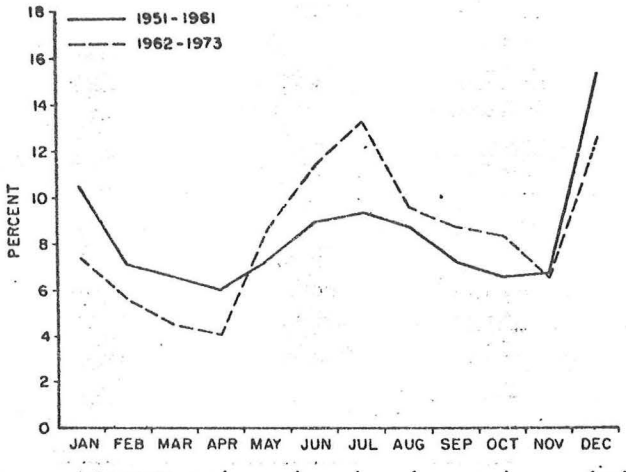
Tularemia is seen in summer (tick-borne) and early winter (rabbit hunting) Fig. 3), especially in the quad-state area of East Texas, Oklahoma, Arkansas and Louisiana (Fig. 4), although we have seen cases who live south and west of the metroplex. Most present with ulceroglandular form with an ulcer at site of bite and enlarged tender nodes (inguinal adenopathy with tick-borne and axillary usually with rabbit-associated).They may be septic or have low-grade fever , may have generalized symptoms and a significant proportion have pharyngitis (18). Serum agglutination titers exceeding 1:160 with lower titers for brucella (cross-reactions can occur) with positive epidemiological history would be an indication for therapy with streptomycin 1 g qd bid for 7-10 days, (reducing to 500 mg bid if response by 3rd day). We would not normally recommend attempting to grow *Francisella tularensis* which not only requires special media, but also is a biologic hazard in the laboratory. If a refugee presents with a bubo more than ten days after arrival, especially if a groove sign is present (groove of the inguinal ligament between enlarged femoral and inguinal nodes) consider lymphogranuloma venereum (LGV). They may give a history of a penile ulcer but rarely will the primary lesion be present when adenopathy is prominent (19). Patients with LGV may have systemic involvement including hepatitis and arthritis but are rarely toxic as with plague or tularemia. Inguinal nodes may also be seen in homosexual males or females with rectal disease following anal intercourse (20). Although some laboratories are able to culture the organism from lymph node aspirates, the complement fixation test (for psitticosis-LGV) is generally preferred with a titer $\geq$ 1:32, or a

TABLE 5

DIFFERENTIAL DIAGNOSIS OF INGUINAL ADENOPATHY (BUBO)

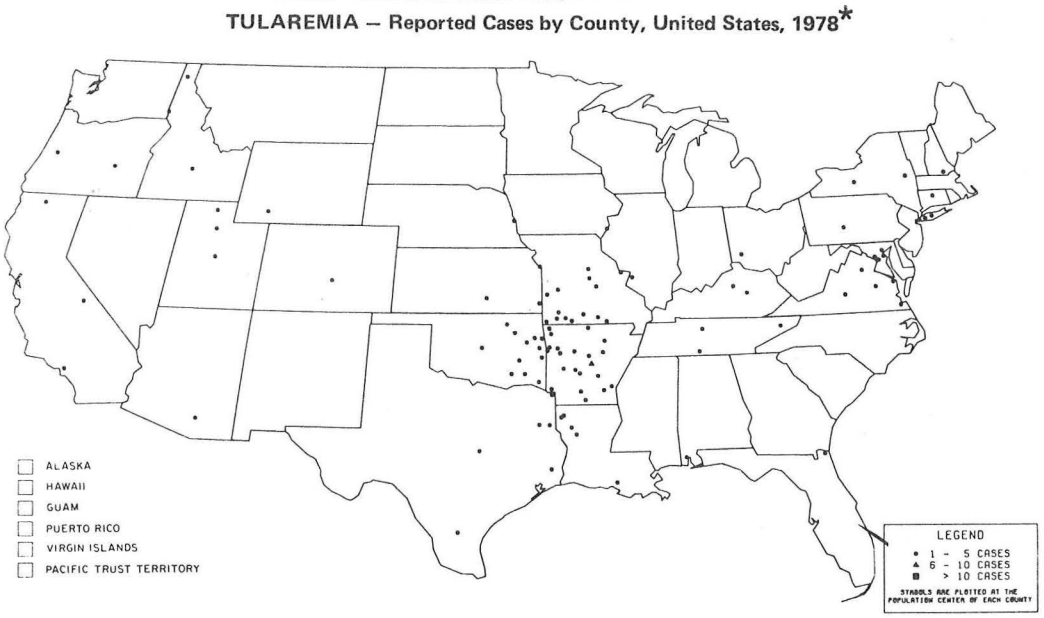
Disease	Epidemiology	Clinical Clues	Dx	Rx
Plague	Exposure, NM, Ca. Southeast Asia Prairie dog,coyote	Tender nodes, systemic disease. High temp., purulent node	IF of node aspirate	Streptomycin 1 g qd, bid for 7 days
Tularemia	East Texas, Ark., La. Rabbit hunting, muskrat.	Ulcer at tick bite site, systemic signs. Purulent node.	Bacterial agglutination $\geq$ 1:160	Strep 1 g bid, 7-10 d.
LGV	?Sexual contact	"Groove" sign, Microscopic abscess	CF $\geq$ 1:32 or 4-fold rise	Tetracycline 2 g qd, 21 d. Retreat if relapse
Cat scratch fever	Cat scratch history	History, microscopic abscess on biopsy	Skin test (Dr. Nelson).	Supportive. Observe for CNS changes
Pyogenic skin infection (Group A streptococcus or *Staphylococcus aureus*	Infection over perineal area or penis (homosexual contact)	Skin involvement plus tender node	Aspirate of node or skin	Penicillin or anti-staphylococcal drug
Syphilis	Sexual contact	Non-tender, unilateral node and penile ulcer	Dark field of ulcer + STS	Pen G 2.4 mu or tetracycline 2 g qd x 15 d.
Chancroid *(H. ducreyi)*	Sexual contact, West Coast, esp.	Painful unilateral node and penile ulcer (occasionally multiple).	Gram-stain of exudate. Special media	Sulfonamide 4 g qd for 10 d or (?) tetracycline or erythromycin 2 g qd, 2 wk.
Hodgkin's lymphoma	?tonsillectomy	Fails to respond to antibiotics, adenopathy, generalized	Biopsy	Call the hematologist?

FIGURE 3.



Percentage of annual number of reported cases of tularemia that occurred during each month, United States, 1951–1973. [Reprinted from Boyce JM: *J Infect Dis* 131:197, 1975. By permission of the University of Chicago Press. © 1975 by the University of Chicago.]

FIGURE 4



* MMWR Annual Summary, 1978

fourfold rise in titer, diagnostic. If it is not possible to determine the etiology of inguinal adenopathy with clues provided in table 5, and the patient does not have systemic signs of plague or tularemia, then tetracycline 2 gms per day for 10-14 days is indicated pending further laboratory test. If serological studies indicate LGV, a longer course of therapy is indicated with retreatment for relapse, particularly with anal disease since untreated anal LGV evolves into rectal stricture (20).

C. Fever with gastroenteritis

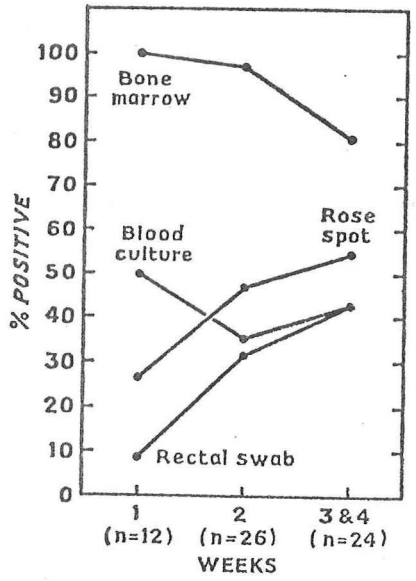
Gastroenteritis has been a major contributing factor to morbidity and case fatality in refugee camps in Thailand and Southern Asia where malnutrition and crowding contributes to susceptibility and spread of organisms (2). Shigella as a cause of bacillary dysentery was reported in the 1975 airlift along with nontyphoid salmonella (21). In the workup of patients with fever and abdominal complaints, the initial test would be a Wright's stain of the stool (or methylene blue). Published reports indicate a high predictive value (> 80%) for bacterial gastroenteritis due to either nontyphoid salmonella or shigella if polymorphonuclear leukocytes are seen in smears of stool (22). The stool should be cultured on usual media and in an enrichment media to increase the yield (23). If the refugee has leucocytes with fever, antibiotics are indicated. Although ampicillin or amoxicillin is appropriate for salmonella, trimethoprim/sulfamethoxazole (Tmp/Smx) 2 tablets bid is the preferred treatment for shigellosis since up to 20% of shigella strains are resistant to ampicillin. Trimethoprim/sulfamethoxazole is acceptable therapy for salmonella infections although not approved for this use, nor is a parenteral form yet available for very sick individuals. *Campylobacter fetus* ssp *jejuni* is now recognized as a causative agent of gastroenteritis, presenting frequently with a proctitis with blood and leukocytes in the stool (24). It has not been established as a causative agent in refugees from Southeast Asia as in refugees from renal conferences in Colorado. Isolation is difficult, requiring a media with vancomycin, Tmp and polymyxin incubated at 42°C (24). If clinical features indicate and if vibrio are seen on gram stain or phase contrast view of stool, treatment with erythromycin 2 g/day is efficacious - Tmp/Smx and amoxicillin have no value. If the patient is over five, has a mild enteritis, and salmonella are recovered from the stool but not the blood, treatment is not recommended. The course of the infection is not significantly altered and previous studies have indicated the carrier state may be prolonged (23). Nontyphoid salmonella does not spread from person-to-person, so this method of spread is a minimal public health risk in the U.S.

Typhoid Fever Today

It may not be proper to include typhoid fever in a discussion of gastroenteritis with fever since persons more commonly present with a systemic febrile illness but without gastroenteritis (6). Diarrhea and abdominal pain were seen in approximately one-half of migrant workers with typhoid in Florida (25). Bone marrow and blood cultures are more likely to be positive in the first week of infection (Fig. 5), but stool cultures are infrequently positive before 3rd week of illness (26). Chloamphenicol 50 mg/Kg/day is the treatment of choice for *S. typhora* sensitive to this agent, but resistant organisms have been detected in Vietnam (27, 28). Either ampicillin or Tmp/Smx can be used for

C-R strains (27). Chronic enteric carriers of *S. typhi* can be treated successfully albeit expensively with amoxicillin 2 g three times a day (29). Neither quarantine nor mass immunization is necessary for sporadic cases or epidemics of *S. typhi* but adequate chlorination of water supply and handwashing, if carriers prepare meals (30).

FIGURE 5

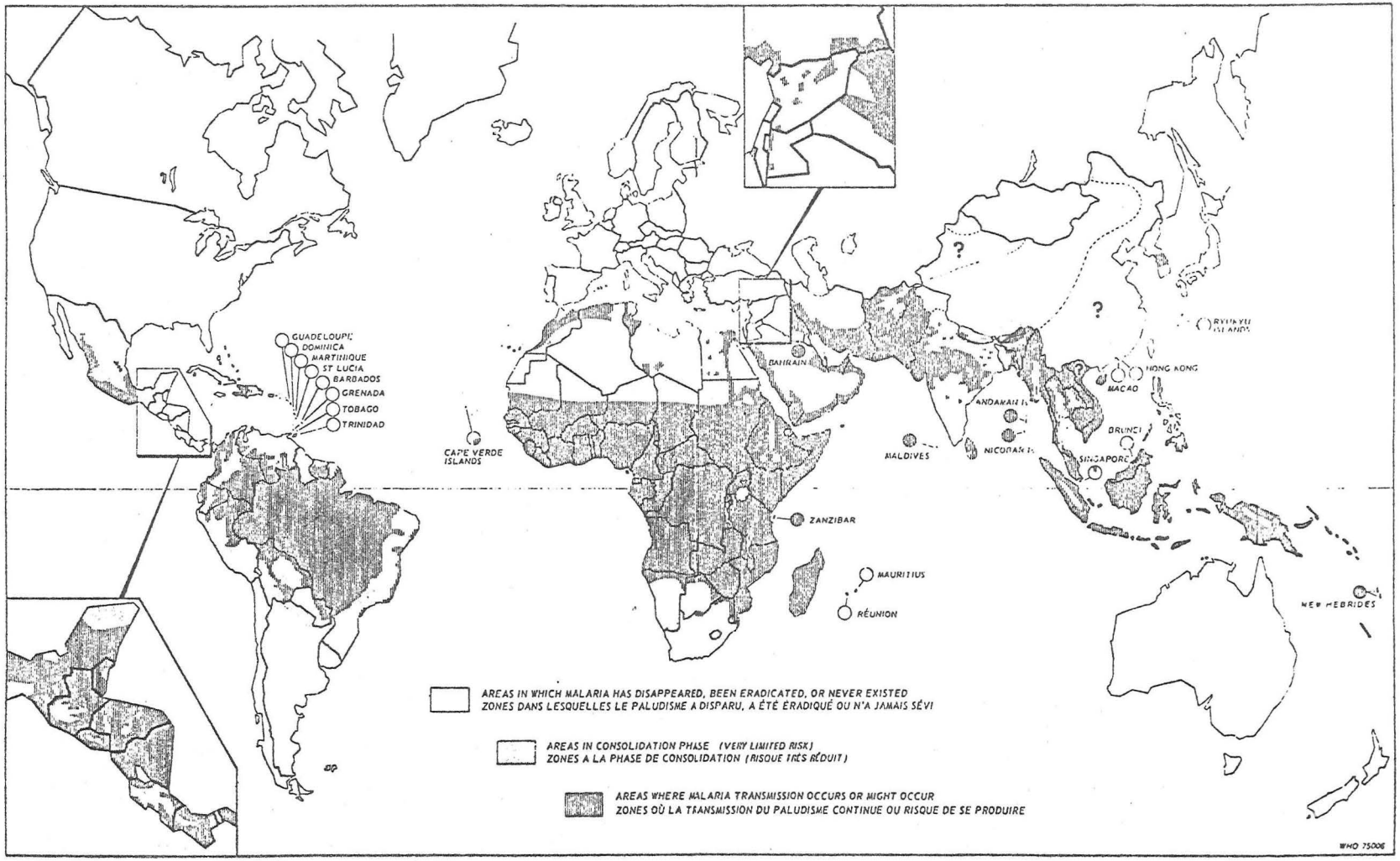


Relation between duration of clinical disease before culture and per-cent positivity of cultures for S. typhi at each site.

D. Malaria

Prime consideration must be given to malaria in any person presenting with fever after leaving an endemic area for malaria (Fig. 6). In Southeast Asia, both *Plasmodium falciparum* and *P. vivax* are present so refugees could present with falciparum malaria within the first month or with vivax malaria up to two years after the person leaves the endemic area. Infection with *Plasmodium malariae* or *ovale* are distinctly uncommon in Southeast Asia. The rates of falciparum malaria as determined by thick smears of Kampuchean refugees in Thailand has varied from one to 40% (31, 32). Consequently, in some camps in Thailand, mass treatment for chloroquine-resistant falciparum malaria (Table 6) was carried out with a fixed combination of pyrimethamine and sulfadoxine (Fansidar or Falcidar). Cuban refugees are not likely to have malaria since it is not endemic in Cuba, but malaria is endemic in Haiti (1).

FIGURE 6



Epidemiological assessment of the status of malaria, December 1973. (Courtesy of the World Health Organization, Wkly. Epidem. Rec. No. 6, Feb. 1975.)

TABLE 6

SITES WHERE CHLOROQUINE-RESISTANT *P. falciparum* EXISTS (33)

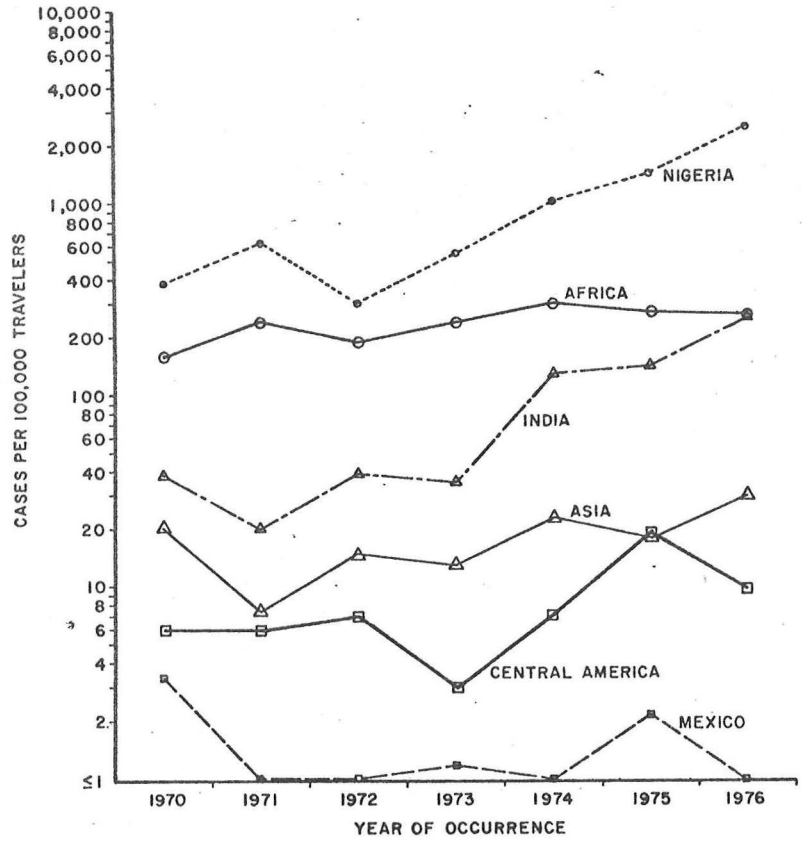
Southeast Asia
Democratic Kampuchea (Cambodia)
Laos
Thailand
Viet Nam
Malaysia
Indonesia
Philippines
Papua New Guinea
India (Assam)
Bangladesh
Burma

Central and South America
Panama (East of Canal Zone)
Columbia
French Guiana
Guyana
Surinam
Venezuela
Brazil
Equador

Malaria Acquired During Travel Abroad

Over 9,400 cases of malaria were acquired from travel abroad in the U.S. between 1970-1976 (33). Malarial attack rates were highest for travelers to Africa (13x Asian and 27x greater than travelers to Central America). Rates were highest for travelers to Nigeria and India (Fig. 7). Rates were very low in Mexico, but

FIGURE 7



Occurrence of malaria during 1970-1976 among American civilians who had traveled abroad, by place of acquisition.

malaria can be acquired if camping out in Southern Mexico (South of the Yucatan Peninsula) (Fig. 6). In all fatal cases of falciparum malaria, a delay of greater than four days occurred before the diagnosis was made, usually before the patient saw a physician. So, groups and persons traveling to endemic areas must be warned to take chemoprophylaxis and to seek medical attention immediately upon return.

Intriguing studies recently have explained why a large majority of U.S. blacks are resistant to vivax malaria (but still at risk for *P. falciparum* infection). Human erythrocytes which are Duffy-blood-group-Negative (Fy Fy) are resistant to infection with *P. vivax* (34). This homozygous characteristic is carried by 70% of U.S. blacks and by 100% of West Africans (35). This protective factor does not carry the heavy "genetic load" that exists for sickle cell anemia in its relative protection against *P. falciparum* infection since no adverse feature has been shown for Fy Fy erythrocytes (35).

Most patients present with fever, headache, and nonspecific symptoms and signs (Table 7). Classic malaria with the paroxysm of fever and chills at a regular interval was seen in only a few patients (36-37). The typical tertian pattern

TABLE 7

FEATURES OF MALARIA (36)

Clinical	%	Laboratory	%
Fever and chills	100	Positive initial smear	80
"Classic"	(30)	Thrombocytopenia	67
Headache	96	Elevated Br., SGOT	40
Splenomegaly	52	Anemia	33
Myalgia	46	Proteinuria	33
Diarrhea	42	Elevated Cr.	16
Central nervous system*	25	Leukopenia	12
Icterus*	20		

* *P. falciparum*

with vivax malaria may take several days to develop and persons with falciparum malaria may present with daily fever and prominent organ system involvement as gastrointestinal (nausea, vomiting and liver function abnormalities), central nervous system findings (disturbances of consciousness, or motor seizures without localizing stages) or renal involvement (proteinuria, pyuria and renal failure) (36). Thrombocytopenia is frequently seen although disseminated intravascular coagulopathy occurs in a rare patient with overwhelming infection with *P. falciparum*.

Rapid recognition of malaria by examination of blood smears is critical at an early period of infection. This is particularly true for falciparum malaria since rapid clinical deterioration, coma and death can ensue if parasitemia persists (for even four days). If erythrocytes have parasites with multiple small ring forms, no schizonts and characteristic gametocytes: suspect *P. falciparum*. If the parasite is peripheral in enlarged erythrocytes with trophozoites consistent with vivax malaria, then one can safely make this diagnosis. *Plasmodium malariae*, rarely seen in the United States, will have typical

erythrocyte parasites at various stages. If initial smears show no parasites in a febrile person, examine peripheral smears every six hours over a 24 hour period and then daily for two days since parasites maybe present in low numbers initially. Thick smears require a qualified trained person, so reliance on diagnosis in febrile persons is with blood smears with Wright-Giemsa stain. Occasionally, a diagnosis in transfusion-associated malaria can only be made in recipient and donor by serological studies (available at the CDC).

Serological tests for malaria will be of little benefit in SE Asian refugees since recent testing at CDC Parasite Serology Division showed that 50% of refugees had a positive test ($\geq$ 1:64) but only 5% had parasites on smears of peripheral blood. So, serology won't be as useful in refugees especially to determine if malaria is the cause of splenomegaly. It is useful in U.S. citizens who will have been in the endemic area for a brief period and thus significant titers mean recent infection. Diagnostic titer for *P. falciparum* is slightly higher ($\geq$ 1:256) than for *P. vivax* and *malariae* ($\geq$1:64) due to non-specific factors that affect the tests. Congenital malaria must also be considered in infant who presents with fever, jaundice and/or anemia with hepatosplenomegaly born of a refugee mother (38).

Introduced Malaria

The introduction of malaria into the U.S. is a constant threat but only a rare occurrence. The reported outbreaks have been in the Southeastern U.S. or in California where vector and conditions are favorable for introduction of the parasite (39, 40). Fortunately, the cases remain sporadic and only rarely will transmission occur from a person with malaria who likely infected mosquitoes while waiting on Sunday at a stoplight near Fort Benning, Georgia (39). An intensive malaria surveillance-control program is underway in the Sutter-Yuba area of California where imported and introduced malaria has been noted in farmers who migrated in the 70's from Punjab, state of India where malaria is endemic (41). Because the rice paddies provided a breeding ground for *Anopheles freeborni*, an efficient vector for vivax malaria, an active mosquito control program is underway which includes adequate drainage of standing water, stocking of fish in rice paddies to eat lavae and selective use of insecticides within ½ mile radius of household after a case has been reported (42). Mosquito fish have been used successfully in a number of countries including China (43). Recently, it has been established that flatworms are also responsible for control of mosquito larvae in rice fields (44). Treatment with chloroquine and primaquine has been administered to persons with positive smears or a significant immunofluorescent antibody titer (22% of Punjabis screened were positive in 1975). Punjabi newspapers and the local Sikh Temple have been used for dissemination of information on malarial control. As a result of these intensive efforts, all cases of malaria since 1975 in Sutter-Yuba have been imported!

Specific therapy should be instituted when the species has been identified (Table 8). Any of three regimens is effective in 95% of cases and can be used for chloroquine-resistant falciparum malaria in refugees from Southeast Asia (45, 46). If renal failure develops, IV administration of 600 mg/24 hours of quinine is indicated pending blood levels (47). Hemolytic anemia follows the administration of trimethoprim/sulfamethoxazole in Asian males with G6PD-deficiency (45). Therefore, patients should be screened for G6PD before therapy.

TABLE 8

THERAPY OF LABORATORY-CONFIRMED MALARIA IN REFUGEES

P. falciparum:	Use one of the following: a) Quinine sulfate 650 mg tid x 3d plus pyrimethamine, 25 mg bid, x 3d plus sulfadiazine 500 mg qid x 5d (given concurrently). b) Quinine sulfate 650 mg tid x 3d plus trimethoprim, 160 mg, sulfamethoxazole, 800 mg (double strength) 2 tablets bid, x 5 days*. c) Quinine sulfate 650 mg tid x 3d plus tetracycline* 250 mg qid x 10 days.
P. vivax	Chloroquine, 600 mg (2 tablets) initial dose followed by 300 mg at 6, 24 and 48 hours. If not G6PD-deficient, administer after afebrile: Primaquine, 15 mg qd for 14 d or 45 mg once weekly for eight weeks.
Chemoprophylaxis	If strains of *P. falciparum* sensitive to chloroquine, 300 mg once weekly and continued for six weeks after last exposure. Primaquine, 15 mg qd for 14 days on return if visit heavily infected area. If strains of *P. falciparum* resistant to chloroquine: Pyrimethamine 50 mg and sulfadoxine 1000 mg, (Fansidar) every other week during and for six weeks after return.

* Not approved use by FDA.

Smears should be followed after therapy since no parasites should be visible at 4-5 days of therapy. Recurrences will be seen by 30 days, for which retreatment with same drug is indicated. All strains of *P. vivax* are sensitive to chloroquine which should abolish symptoms within 24-48 hours. Since 25% will sustain a relapse within two years, daily primaquine is administered for 14 days to achieve a radical cure. Primaquine is not necessary for transfusion-related malaria, since there is no exo-erythrocytic phase . If the person is G6PD-deficient (12% of Asian males) then the once weekly regimen is preferred since this course is said to produce fewer clinical problems (45). The hematocrit should be followed and therapy discontinued if a significant drop occurs. Chloroquine is considered safe for use during pregnancy, but neither pyrimethamine, Fansidar or primaquine should be utilized because of possible teratogenic effects.

Chemoprophylaxis is recommended if a person travels to an endemic area for malaria. If the travel is to Southeast Asia, the recommended regimen is a combination of pyrimethamine and sulfadoxine, a long-acting sulfonamide (Fansidar), taken once every two weeks and continued for six weeks after returning from a malaria area (48). This produces a suppressive cure for most chloroquine-sensitive and resistant falciparum infections and is an effective suppressant for pyrimethamine-sensitive *P. vivax*. If a person journeys to an area (as Africa) where strains of falciparum malaria are sensitive to chloroquine, then chloroquine 300 mgs weekly while in endemic area and for six weeks after last

exposure is adequate. Most authorities recommend additional therapy with primaquine, either daily for 14 days or weekly for 8 weeks only when the traveler is heavily exposed to mosquitoes in an endemic area and G6PD-deficiency has been excluded by laboratory tests. Side effects are extremely uncommon with these drugs, although it is recommended that the person initiate therapy weekly for two weeks before departing to be certain that no idiosyncratic reactions occurs. Primaquine may produce gastrointestinal symptoms in some patients. The course of pyrimethamine for malaria is so short that the anti-folic acid side effects rarely appear. Use of Fansidar for six months is safe (48).

E. Scrub typhus

Scrub typhus should be considered in any refugees from Southeast Asia with fever, myalgias, headaches and other systemic symptoms with generalized adeno-pathy within three weeks of return from endemic area. The characteristic eschar found most often on the extremities begins as a small vesicle that progresses to a dark ulcer but is seen in only one-half of the patients (49). A generalized maculopapular rash best seen on nonexposed skin areas was present in one-third. A positive or rising proteus OXK antibody ($\geq$ 1:160) which is the most readily available test, will only be positive in one-half. The specific antibody test, either the indirect fluorescent or complement fixation, utilizing specific antigen for *Rickettsia tsutsugamushi*, will be diagnostic, but a significant titer may require two weeks or more. Clinical suspicion with epidemiologic support will be required in the great majority of cases. Treatment with tetracycline 2 g per day for at least seven days is curative, although recent studies indicate that single dose treatment with doxycycline 200 mg is also curative with no relapses (50).

F. Tuberculosis

Tuberculosis is the most serious potential public health problem of refugees from Southeast Asia (45, 51). Preliminary data indicate that 1% of refugees arriving during 1979 had active tuberculosis and 2% had inactive disease. The prevalence of a positive tuberculin skin test (PPD) varies from 30% in 5 and under to 100% over 40; 41% of refugees less than 18 years of age have a positive skin test. The Dallas TB Control Unit has seen 103 cases of tuberculosis in Southeast Asian immigrants since 1975 and the Tarrant County Unit has seen 60 cases. In Louisiana, rates of TB were calculated to be 7 fold more in refugees than in U.S. citizens. At present, all refugees older than two years of age are screened in the camps with chest x-rays and they are excluded from entry into the United States if tuberculosis is diagnosed. They must remain in Asia, under treatment until the disease is considered no longer active or judged to be noncontagious (two sputum smears negative for organisms). Local and state health departments in the U.S. are notified by phone and letter upon placement that the person is Class A and needs continuation of treatment. The follow-up in Dallas and Texas has been excellent due to assistance of refugee assistance groups. Rates of INH resistance of up to 10% have been detected in initial studies although this rate is even lower than the 18% rate in Harlingin, Tx (52). The recommendation has been made that those with active tuberculosis be placed on isoniazid, rifampin and ethambutol pending drug susceptibility testing (45). Organisms are infrequently ($<$1%) resistant to rifampin and ethambutol (52). Children, who are too young to be assessed for alterations of visual acuity, are to receive isoniazid, rifampin and strepto-mycin at a dose of 20 mg/Kg up to a maximum of 1 gm daily.

Therapy with isoniazid, rifampin and ethambutol is to be continued for twelve months after sputum specimens are negative. The likelihood of adverse reactions

severe enough to mandate discontinuation of the drugs will be low (< 5%), although many may have elevated SGOT levels (53). The tuberculin test should be interpreted without regard to BCG in Southeast Asian refugees since it was administered sporadically. INH alone is recommended if the patient under 35 years of age has a positive PPD and negative chest x-ray (45). If the person with a positive PPD has been exposed to an isoniazid-resistant tuberculosis case, one of the three options could be selected: 1) treat with isoniazid, 2) treat with rifampin alone or 3) use no drugs for preventive therapy (45). Efficacy of other drugs than isoniazid (as rifampin) for prevention of active disease among infected (PPD-positive) persons has not been evaluated. Close followup with frequent medical x-ray for up to two years whatever therapy is given is indicated. Tuberculosis was rarely found in refugees (1).

G. Hepatitis

Up to 13% of refugees from Southeast Asia are carriers of hepatitis B. Although the great majority are asymptomatic, symptomatic infection with jaundice could occur. Fever may be present during the prodrome of hepatitis (along with urticaria and arthritis), but fever is virtually never seen after jaundice is clinically detectable with hepatitis A or B (54, 55). Hence, other entities must be considered in refugees with fever and active hepatocellular disease (Table 7). Leptospirosis was commplace in Southeast Asia (5, 6),may be suspected

TABLE 9

INFECTIOUS CAUSES OF FEVER WITH HEPATITIS IN REFUGEES

Non-viral	Clue
Leptospirosis	Hepatitis with CNS or renal disease
Lymphogranuloma venereum (LGV)	Sexual contact history, bubo
Brucellosis	Bacterial agglutination
Gram-negative (sepsis)	Positive blood culture.
Acute cholecystitis, with or without *S. typhi*	Abdominal exam.
Viral	
Mumps	Parotitis, pancreatitis
Infectious mononucleosis	Painful throat, adenopathy, atypical lymphocytes
Cytomegalovirus	Adenopathy, splenomegaly
Parasitic	
Amebic liver abscess	Defect on liver scan, pleural involvement
Malaria (falciparum)	Blood smears

if persons have cerebrospinal fluid pleocytosis with liver function abnormalities. but serological studies will be ultimately required for a diagnosis. Serological studies on acute and convalescent serum can support the diagnosis of LGV, brucellosis, and viral entities, although two weeks may be required for tests to become positive. Clinical findings in each of these situations are not specific. Blood and stool cultures are necessary to rule out bacterial sepsis, following pyelonephritis or cholecystitis, or that rare possibility of sepsis with oriental cholangiohepatitis (a case has been seen at PMH). *S. typhi* can be present in infected gall bladder (another occurrence at PMH in a Laotian), so culture of purged stool should be done to evaluate carrier state. Tetracycline 2 gms per day p.o. for 14 to 21 days is treatment of choice for LGV and brucellosis with the addition of streptomycin 1 g per day for seven days for a patient with brucellosis (19, 56). Tetracycline administration should be monitored closely especially since > 1g parenterally can produce hepatotoxicity, especially in persons with renal or hepatic disease.

If the patient presents with right upper quadrant pain and tenderness, liver function abnormalities and pleural or pulmonic involvement such as an elevated right diaphragm in a male, then amebic liver abscess should be considered (57). A history of previous diarrhea and stool for ova will be meaningless in refugees from Southeast Asia. A single localized defect on liver scan is highly suggestive. The indirect hemagglutination test for ameba performed at CDC will be positive ($\geq$1:256) in > 95% of cases (58). The specificity of the commonly available test (the latex agglutination test) is so low (less than 10% at the DVAMC), that only a negative test is helpful since it rules out amebiasis. A person should be treated if clinical and laboratory studies (single large defect on liver scan) support the diagnosis of amebiasis with a positive test. Occasional failures with metronidazole 750 mg tid for ten days have been reported but retreatment with the same drug is indicated for clinical recrudescences (the alternative drug, emetine hydrochloride, has significant toxicity and is no longer available). Indications for aspiration or drainage of liver abscesses remains controversial, although some recommend it for hepatic defects which exceed 10 cms on liver scan or failure to respond to 5 days of drug therapy (58). Clinical responses with drug therapy alone have been seen even in cases who rupture the abscess above the diaphragm. The presence of an abscess in the left lobe of the liver requires immediate surgical drainage since rupture into the peritoneum or pericardial area is a life-threatening medical emergency.

The principle risk for hepatitis B will be medical and dental personnel (since dental caries is commonplace) who are exposed to blood products from refugees who are carriers of hepatitis B. The following procedures are recommended for individuals who are at risk of exposure to known carriers of hepatitis B (59).

1) Use disposable gloves which should be changed whenever a tear or puncture occurs. Although gloves do not prevent all puncture wounds, they do protect lesions on the hand and a sharp object may snag a glove instead of tearing the skin.
2) A surgical mask and eyeglasses should be worn by a dentist during any procedure where there is a possibility of blood falling on ocular or mucus membranes.
3. If a puncture wound does occur while working on a known carrier, hepatitis B immune globulin should be used as soon as possible, preferably within 48 hours at a dose of .05 mls per kilogram and repeated at 25-30 days. If the carrier status for the refugee is unknown and a puncture wound occurs, then laboratory results of the refugee's

hepatitis B carrier status should be determined within the next 48 hours. If it is possible to determine the antibody status of the person receiving the hepatitis B immune globulin and antibody is present, then the repeat dose of HBIG is unnecessary. Pre-exposure prophylaxis is not recommended.

4. Approved procedures for sterilization and disinfection of instruments in environmental surfaces should be rigorously carried out. Thorough cleaning of environmental surfaces should be done with detergents effective against hepatitis B, such as 0.5% solutions of sodium hypochlorite for 30 minutes or 2% aqueous glutaraldehyde for ten hours.

High rates of hepatitis B in young Vietnamese orphans (27%) and among American children of adopted families suggests that spread could occur within family groups (60). No recommendations are made for prevention of intrafamily spread of hepatitis B.

H. Melioidosis

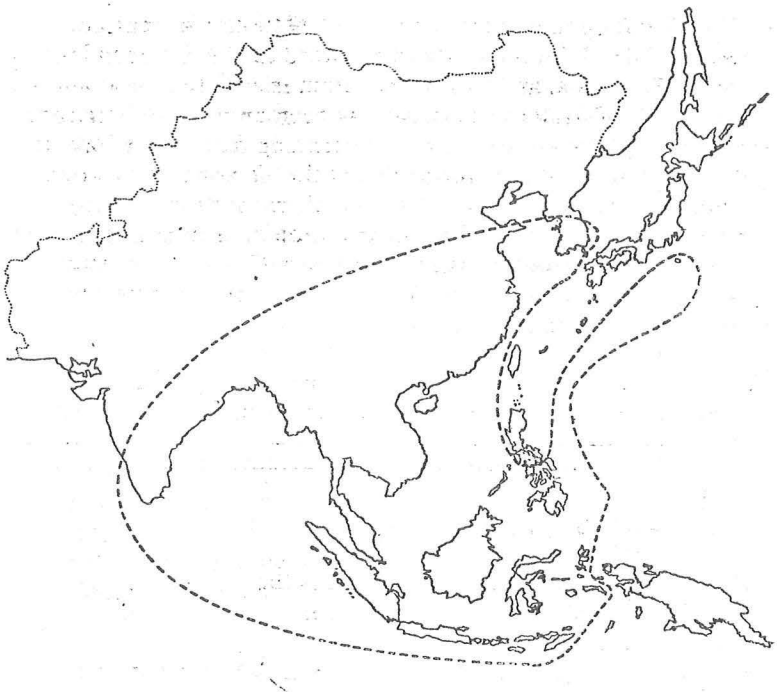
Melioidosis may recur seven years after departure from the endemic area of Southeast Asia (61, 62). Patients may present with either an acute pulmonary infection, an acute septicemic infection (as the case at DVAMC who had melioidosis following influenza A infection) and with chronic suppurative infections, as osteomyelitis. Acute pulmonary infection, the most common form, usually begins with the abrupt onset of fever, productive cough, and weight loss (63). Chest x-rays generally show upper lobe infiltrates with consolidation. Infiltrates may persist, even cavitate or may resemble granulomatous disease in a subacute or chronic case. Pleural effusions are uncommon. The laboratory may be alerted to the possibilities of this organism if bipolar staining bacilli are seen on a smear. Sputum cultures are generally positive for *Pseudomonas pseudomallei* although the culture may need to be held 3-4 days before the typical organisms grow. Blood cultures are positive in cases with septicemia. Serum can be submitted to the state laboratory or CDC. Therapy with tetracycline alone, or trimethoprim/sulfamethoxazole alone or in combination with tetracycline or doxycycline for 1-3 months is usually curative for pulmonary infections (63). Cases with septicemia or osteomyelitis probably should be treated for a minimum of one year with trimethoprim/sulfamethoxazole (62).

I. Filariasis

The causative agents for filariasis, *Wuchereria bancrofti* and *Brugia malayi*, are distributed throughout Southeast Asia (Fig. 8). Infection requires an extraordinarily large number of mosquito bites (16,000) for one case of microfilaremia (64). Infections are infrequent in Southeast Asia. Consideration should be given to filariasis in refugees presenting up to a year later with fever, backache, headache who also have acute lymphangitis or lymphadenitis (64). Epididymitis or orchitis may also be seen and may be confused with bacterial etiologies. Acute episodes may subside and recur, leading to chronic lymphadenitis, elephantitis, hydrocoele, or chyluria. Recurrent attacks of adenitis rarely occur years later, although microfilariae aren't found in blood after two years. Definitive diagnosis of filariasis is accomplished by demonstrating the microfilariae in a blood sample obtained between midnight and 2 am. Serological tests are of some value but do not distinguish among the various forms of filariasis. If filariasis is documented, diethylcarbamazine citrate at a dose of 3 mg/Kg three times daily for three weeks after initial trial with 50 mg, is indicated. This drug reduces the number of microfilariæ in the blood and will prevent further episodes of lymphangitis. Although the drug is relatively nontoxic, fever and generalized symptoms are frequent with therapy due to the

FIGURE 8

WUCHERERIA AND *BRUGIA*



Geographic distribution of endemic foci of *Brugia malayi.*

number of microfilariae killed. Specific therapy is of no value for chronic stages but supportive management of the affected extremities and analgesics for exacerbations are indicated.

Approach to Refugee with Fever

Obtain two blood cultures (anaerobic and aerobic)

Examine blood smears stained with Wright-Giemsa for erythrocytic parasites. If none seen, repeat every six hours for 24 hours and at 48 hours. Do thick smears if parasitologist available. Submit thin and thick smears to state laboratory.

If diarrhea - Wright's stain or methylene blue of stool aspirate. Wet mount of stool or rectal aspirate for ova. Culture stool on agar plates for stool pathogens, including enrichment broth for gram-negative broth. If leucocytes, blood and vibrio on smear, request culture for campylobacter.

Biopsy and culture any skin lesion. Examine blood vessels for intracellular organisms (rickettsia). Aspirate node for smear and special fluorescent antibody studies for plague.

Obtain serum for febrile agglutinins: Salmonella, Brucella, tularemia,

proteus OXK, (significant if Salmonella ≥ 1000 and Brucella, tularemia and Proteus OXK≥ 160), acute serum for viral battery, leptospira, amoeba titer (if positive, submit to CDC).

Lumbar puncture for cytologic, clinical and microbiologic studies.

If liver function abnormality or right lower lung abnormalities, do liver-spleen scan.

If pulmonary infiltrate, ask microbiology lab to hold sputum for four days to examine for *Pseudomonas pseudomallei* and do acid fast smears and cultures.

II. Other Infections

A. Gastrointestinal infections without fever

TABLE 8

CLUES TO CAUSES OF ACUTE GASTROENTERITIS (WITHOUT FEVER) IN REFUGEES

Entity	Clinical or Epidemiologic	Median Incubation Period (75)	Laboratory
Vibrio cholera	Profuse diarrhea within 5 days of departure	1-5 days	Growth on TCBS*
Vibrio parahemolyticus	Explosive water diarrhea History of shellfish ingestion	1 day	Growth on TCBS
Clostridium perfringens	Ingestion of meat or gravy kept warm long period	8-16 hours	Anaerobic culture of "culprit"
Staphylococcal enterotoxin	Projectile vomiting and diarrhea. Ingestion of egg products, pastries, salads	2-7 hours	Culture of "culprit"
Toxigenic *E. coli*	Traveler's diarrhea	1+ day	Special serology
Rotavirus	Family outbreaks of Winter-vomiting disease	2 days	Immuno-electron microscope of stool
Scromboid poisoning	Flushing, urticaria, pruritis, tuna, mackerel, skip jack, mahi-mahi	< 2 hours	Histamine level in fish
Ciguatera fish poisoning	Numbness, paresthesias (lip, tongue). Ingest barracuda, amberjack, red snapper	2-7 hours	Toxin in fish
Cadmium poisoning	Cook on refrigerator tray	< 2 hours	
Solanine poisoning	Eating green sprouting potatoes	2-7 hours	

* TCBS = thiosulfate-citrate-bile salts

Cholera with *Vibrio cholerae* 01 had been documented in seven Laotian refugees in the United States but would be expected within five days of departure since the incubation period for cholera is 1-5 days (65). Profuse, watery diarrhea with subsequent volume contraction and hypotension should alert the physician to cholera. Incubations of stool on special media (TCBS) will be required for isolation of *Vibrio cholera, parahemolyticus*, and noncholera vibrio organisms (66-68). The organism can be seen as motile vibrios in phase microscopic preparation of stool. Typing of isolates is essential to prove the organism is *V. cholerae* 01, the epidemic strain. There is little chance of a cholera epidemic occurring in the United States since the organism is killed easily by chlorine and sunlight. Either contaminated water supplies or ice was responsible for outbreak in SE Asia (65). Aggressive fluid replacement with intravenous fluid, such as Ringer's lactate solution or oral solutions (Nacl 3g, $NaHCO_3$ 2.5 g, Kcl 1.5 g and glucose 20 g or sucrose 40 g per L of H_2O in a quantity equal to the stool losses is indicated. Tetracycline will shorten the duration of the disease (69).

Texas physicians are more likely to see cholera in Texans who acquire the infection from sources along the Gulf Coast. *V. cholerae* from a resident of Port Lavaca, Tx with a previously unexplained case of cholera was shown to be the same phage type as *V.cholerae* 01 strains isolated from cases in an outbreak in Louisiana in 1978 (66). All eleven infected persons in the latter outbreak had recently eaten cooked crabs (?) obtained from five widely separated sites along the marshy coastland of Southwestern Louisiana. *V. cholerae* 01 with a unique phage type was isolated from this area. In experimental studies on crabs, adequate heat-killing of *V. cholerae* 01 required at least 10-14 minutes of boiling and steaming for 30 minutes (the Louisiana State Health Department recommends boiling crabs for 15 minutes and steaming them under pressure). These findings indicate an endemic focus along the Gulf Coast (90). Cholera must be considered in persons presenting with profuse diarrhea and consequent dehydration, especially if they have a history of ingestion of seafood while visiting the Gulf Coast. Persons who use antacids or who have had a gastrectomy or have achlorhydria are at greater risk of developing cholera, as they are for a diverse number of bacterial and parasitic enteric infections (71). Recently, an explanation for the infectivity of acid-sensitive cholera was provided by experiments that showed *V. cholerae* attached to chitin particles protected the organism from gastric acid. This enables *V. cholerae* to traverse the stomach and produce infection (72). The seasonal occurrence in the endemic area in the Delta of Bengal may relate to the attachment to copepod blooms of plankton, which occurs in late summertime as peak season for disease (70).

Other vibrios can produce diarrheal disease in the U.S. Noncholera vibrio infections with organisms that do not agglutinate 01 serum have increased since 1972 (68). Those with acute diarrhea had a history of shellfish ingestion or foreign travel. Exposure to salt water was seen in patients with systemic infection. *Vibrio parahemolyticus*, a halophilic (salt-requiring) vibrio, can produce a syndrome with equally explosive form of watery diarrhea in persons who ingest improperly prepared shellfish, as reported by P. Mackowiak in an an outbreak in Louisiana and from a "love boat" in the Caribbean (67, 73, 74). *V. parahemolyticus* also can produce a gastroenteritis with fever, resembling salmonella or shigella infections (75).

Clostridium perfringens is a frequent cause of outbreaks of gastroenteritis in the United States (75). The vehicle is usually a meat or poultry product with sauces and gravies, which is cooked one day, allowed to cool, then recooked and kept warm for long periods of time (never eat chicken fried steak with gravy after 2 pm in a Texas cafe!). *C. perfringens* will survive the initial cooking and can be recovered by anaerobic culture (thioglycolate media) from the contaminated food. (No laboratory will culture stool anaerobes!). Staphylococcal food poisoning is characterized by projectile vomiting with diarrhea following the ingestion of contaminated food products. Enterotoxigenic *Staphylococcus aureus* are most often transferred from a food preparer to this food which is then kept at a warm temperature providing good conditions for growth of organism. The incriminated food (such as high protein foods as ham, or pastries or salads made from egg or milk products) will grow *S. aureus* and presence of enterotoxin can be tested by serologic methods. Again proper food preparation methods will prevent the infection. Toxigenic *E. coli* may produce travelers' diarrhea in the refugee although studies indicate that it is a less frequent problem in travelers to the United States than *visa versa* (76) (in spite of the warning by the ex-welterweight champion from Mexico who prefers beer to our water). It has been postulated to account for a majority of diarrhea in children in Brazil, so it could occur in children from SE Asia (77). Toxigenic *E. coli* diarrhea is a diagnosis of exclusion since there is presently no readily available test to distinguish toxigenic strains (although serological tests on serum may be available in the near future) (78). Dallas is an endemic area for rotavirus infection in the wintertime, so refugees could acquire this organism here (79). The organism, which is seen on electron microscope preps of stool, produces family outbreaks of winter vomiting disease but endemic disease in tropical settings year-round.

A number of chemical toxins can produce gastroenteritis with intriguing clinical features (80, 81). They should be suspected when the onset is less than an hour after the meal. A person who presents with gastroenteritis along with flushing, headache and either an erythrematous or urticarial rash with pruritis and the history of having ingested tuna, mackerel or skipjack (or mahi-mahi in Hawaii) 30 minutes before, then scromboid poisoning is a possibility. These toxigenic effects are due to elevated levels of histamine produced by microorganisms which grow on the outer portions of the fish when improperly refrigerated (81). If the person (such as a medical resident at a Club Med outing), presents with numbness and paresthesias, particularly of the lip and tongue, resembling Chinese restaurant syndrome, and gives a history of having ingested barracuda, amberjack or red snapper a few hours earlier, then consider ciguatera poisoning. The toxin is found in the flesh and viscera of large bottom-dwelling shore fish and can be measured in the fish. Additional questions of importance in a patient presenting with gastroenteritis for whom no incriminating food history is given include: did the person use a refrigerator tray to barbeque meat, thus leading to cadmium poisoning, or ingest an acidic beverage from a metallic container; did the person ingest the green sprouts of potatoes or did the person just eat in a Chinese restaurant (81).

Nonspecific therapy of diarrhea with oral electrolyte solutions containing glucose (fruit juice) and change in diet, particularly avoiding citrus fruits and milk products, is major thrust of therapy. Lactase deficiency is commonplace among Southeast Asians (82). Whether bismuth subsalicylate is effective for other conditions than toxigenic *E. coli* is not known (78).

B. Parasitic infections of the gastrointestinal tract (Table 9)

Parasitic infections of the gastrointestinal tract will be quite high in refugees from Southeast Asia but will be of little public health significance. Recent surveys have found one or more parasite in the majority of cases (65%) (45). Hookworm infection was higher in Cambodians (64%), but Ascaris infection was higher in Vietnamese (42%) (GS Bowen, CDC). It is not likely that these infections will pose a medical problem for most of the refugees, since most are asymptomatic and transmission is interrupted by adequate sewage disposal. *E. histolytic* infection rates have been similar to base line rates in the U.S., although rates of Giardia (18%) were four times greater than U.S. prevalence so this could pose a health hazard. Visualization of *E. histolytic* in persons with recurrent bouts of diarrhea can be made on diarrheic stools but sometimes requires proctoscopy to see ova on smears of colonic aspirates (58). Treatment of choice for symptomatic infections is metronidazole. Asymptomatic carriers probably should be treated if there is the possibility of spread under crowded living conditions;but treatment with diiodohydroxyquinoline otherwise is controversial. Giardia infections may present as explosive, foul-smelling diarrhea which persists for more than seven days in most (83). A majority of cases will have the ova visualized in the stool with the yield greatest if three separate stools are collected. (Barium, antibiotics and antidiarrheal preparations interfere with visualization). Occasionally, duodenal aspirate or the Entero-test will be necessary to establish the diagnosis (83). Giardia has been the major contributing factor in extremely malnourished infants with malabsorption (J. Nelson). Most regard quinacrine as the drug of choice (83, 84). My personal choice is metronidazole since it has a lower frequency of significant immediate side effects than quinacrine. Since metronidazole is not approved by FDA for this use you should obtain informed consent. Furazolidine, at a dose of 1.25 mg/Kg qid for seven days, is the drug of choice for children and is well tolerated. Prevention of Giardia when you plan to backpack > two days in Colorado Rockies is only achieved with boiling H_2O for ten minutes or with iodine tablets:(Globaline),but not with chlorine: (Halozone).

Therapy for helminthic infections is indicated even if persons are asymptomatic (85). Therapy is quite effective with available drugs which are relatively free of side effects and work principally by affecting parasite attachment and motility (85, 86). Hookworm infections will likely only be a problem in the malnourished or those who are anemic for other reasons. It along with other helminthics should be considered in an asymptomatic refugee with peripheral eosinophilia. It responds to either pyrantel pamoate or mebendazole. Strongyloides infections are usually asymptomatic but, can on occasion, produce significant symptoms of malabsorption (87). Disseminated infection can develop in infected immunosuppressed patients who receive corticosteroids. Examine stools for strongyloides if a refugee is to receive corticosteroids, and treat with thiabendazole if detected. Patients with the other worm infections usually bring the worm to the doctor's office. Round worm infestation responds to one-dose therapy with pyrantel pamoate or three days of mebendazole (88). Treatment of whipworm infection with mebendazole is relatively effective and is indicated for malnourished children with heavy infestation (88). Tapeworm infections with *Taenia saginata*, fish and small tapeworm (*H. nana*) can be successfully treated with niclosamide (obtained from Parasitic Diseases Division of the CDC). Some specifically recommend not treating *Taenia solium* because of the fear of releasing eggs which can result in cysticercosis, a theoretical but unproven risk. Trematodes (flukes) are commonplace in rural inhabitants in Southeast Asia, but most are usually asymptomatic and rarely require therapy. If you suspect trematodes, let the laboratory know since procedures are different

TABLE 9

MAJOR INTESTINAL PARASITES

SYMPTOM	ORGANISM	HOW RX	DOSE	COMPLICATIONS	EFFECTIVENESS(%)
Diarrhea (dysentery)	*Entamoeba histolytica*	Metronidazole (Flagyl)	750 mg tid, 10 d	N & V, D. ETOH-reactions	95
Diarrhea (malabsorption)	*Giardia lamblia*	Metronidazole (informed consent)	(same)	(same)	95
		or Quinacrine	100 mg tid, 7 d	N,V, dizziness	90
	Strongyloides stercoralis	Thiabendazole (Mintezol)	100 mg bid, 2 d	N & V, weakness Odor to urine	90
Malaise, anemia	Hookworm	Pyrantel Pamoate (antiminth) or	11 mg/Kg,1X	N,V, (mild in 20%)	95
		Mebendazole (vermox)	100 mg bid, 3 d	diarrhea	90
Pruritis ani (pinworm)	*Enterobius vermicularis*	Pyrantel Pamoate or	10 mg/Kg - 1X	above	95
		Mebendazole	100 mg bid, 3 d	diarrhea	95
Pass worm					
Whip	*Trichuris trichuria*	Mebendazole	100 mg tid, 3 d	diarrhea	75
Round	*Ascaris lumbricoides*	Pyrantel Pamoate	10 mg/Kg - 1X	above	95
Tape	*Taenia saginata* also *D. latum* and *H. nana*	*Niclosamide	1 gm x 2	N & V, D	90
No symptoms (stool for O&P)	*E.histolytica*	Diiodohydroxyguin	650 mg tid, 21 d.	N. Abd. cramps	80
	Clonorchis sinensis (liver fluke)	Probably none	-	-	-
	Fasciolopsis luski (large fluke)	?hexylresorcinol	30 mg/Kg	?	?
	Heterophyes heterophyes (minute fluke)	hexylresorcinol	30 mg/Kg	?	?
	Schistosoma japonicum (blood fluke)	Niridazole* or	25 mg/Kg/d for 10 d	Vomiting, headache	?
		antimony potassium tartrate, 0.5% solution	total dose 360 ml	nausea, vomiting EKG changes	?

* Obtain from CDC, Parasitic Diseases Division, Atlanta, Georgia, 30033. (404) 329-3670

than for helminths (89). Although symptoms may occur in persons with Clonorchis infection, hepatic enlargement and abdominal pain is more likely due to other causes such as cholecystitis. Therapy with hexylresorcinol is indicated for fasciolopsiasis and Heterophyes infection. Rates of *Schistosoma japonicum* will be low in refugees and a definitive diagnosis can be made by seeing eggs in stool or with rectal biopsy (90). Treatment of Schistosoma infections does decrease significantly the egg burden in stool and recently it was demonstrated that treatment of *S. mansoni* led to a decrease in hepatomegaly as well (91). However, treatment of *S. japonicum* which is endemic in focal areas of Southeast Asia, only decreases the worm burden slightly. Niridazole has fewer side effects than therapy with the antimony compounds, whose clinical efficacy is questionable anyway.

C. Other important infections

1. Sexually transmitted diseases

Refugees are checked for obvious genital infections and with serologic tests for syphilis. The prevalence of sexually transmitted diseases is very low (45). Initial therapy for *Neisseria gonorrhoeae* would still consist of either procaine penicillin G 4.8 million units with probenecid 1 g, ampicillin 3.5 g po or amoxicillin 3.0 g with probenecid or tetracycline 2 gms a day for five days. In all cases, a test of cure with followup culture 3-5 days after initiation of therapy is mandatory since treatment failure, either due to the drug regimen (higher with ampicillin) or due to penicillinase-producing *N. gonorrhoeae* (PPNG), would be recognized at this time. Rates of PPNG are high in the Far East, particularly in Singapore and the Philippines (30%) (92). Since two of the seven reported cases in Dallas County (16%) of PPNG had contact with persons from the Far East, any person with gonorrhea requires careful followup. The Dallas cases were related to an outbreak of 25 cases with PPNG in Shreveport. If the person has *N. gonorrhoeae* at followup visit, then the organism should be tested for B-lactamase and if positive, they then should receive a single injection of spectinomycin hydrochloride 2 gms IM. All contacts should be treated also with spectinomycin. Alternative therapy for pelvic inflammatory disease and disseminated gonococcal infections with PPNG (fortunately unlikely) would be cefoxitin, 2 g q 6 hours for 5-7 days, although this drug is not approved for use in gonorrhea (K. Holmes). It was highly effective at a dose of 2g with 1 g of probenecid for urethritis with PPNG (93). Penicillin remains the treatment of choice for syphilis in refugees. Lymphogranuloma venereum is commonplace in Southeast Asia and is sensitive to tetracycline. Relapses are frequent with this infection. *Hemophilus ducreyi*, the causative agent for chancroid, may be resistant to tetracycline so initial therapy in proven cases would be sulfisoxazole 1 g qid for for 10-14 days (94). Granuloma inguinale responds to two-three weeks of therapy with tetracycline (95).

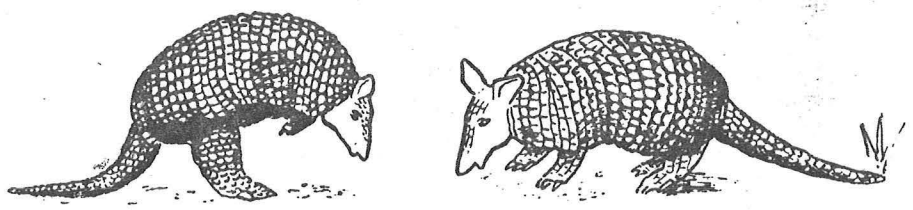
2. Diphtheria

Diphtheria has been noted in refugees in Thailand and a rare person upon entry in the United States has had *Corynebacterium diphtheriae* recovered (96). However, contacts of infected individuals have not had positive cultures and there has been no evidence of spread within the United States. Immunization rates for diphtheria, tetanus, measles and mumps will be low in the refugees since immunizations are not routinely given. Because of the appearance of diphtheria in refugees, extensive attempts are being made to immunize all refugees in the U.S. Records can be checked for immunization schedules. If clinical evidence suggests diphtheria in a person who has not been adequately immunized recently,

then treatment for diphtheria should be instituted. The antitoxin is available from CDC (call 404-329-3687*; but shipped from Houston). Immunization with diphtheria toxoid alone would be indicated for contacts of cases if they had documented previous immunization since antibody levels are demonstrated within a few days after booster immunization. Since the levels of circulating diphtheria antitoxin are low even in U.S. citizens, booster immunizations with T/d (tetanus with diphtheria) every ten years or as management of tetanus-prone wounds are indicated (97). *After hours or weekend: 329-3644.

3. Leprosy

Leprosy has been extremely rare in Southeast Asian refugees (45). All refugees are screened for leprosy and quarantined if skin lesions (macular or papular anesthetic lesions) are noted and acid-fast smears of slit skin are positive (98). Treatment with dapsone is instituted and response achieved before they are permitted into the U.S. Due to the long incubation period, active cases may not be recognized until after entry in the U.S. as in a Vietnamese child a number of years ago. There should be little concern about the infection being introduced into the U.S. from Southeast Asia. Most cases in the U.S. represent persons who migrate to the U.S., although in Texas the infection can be acquired in a county endemic for leprosy (usually a Spanish-settled county). Also, there is an East Texas focus which resulted from migration of persons from the endemic area of French Louisiana (99). Another potential contributor to leprosy is the 9-banded armadillo which does acquire natural infection and in one instance



may have contributed to a human case (100). Persons on treatment are referred to Carville, LA for education, but can remain in home on treatment. Treatment with dapsone is effective if given early. Dapsone-resistant strains have been reported for which either rifampin or clofazimine, is indicated.

4. Skin infections

Pustular skin infections are frequent in children from Southeast Asia. The causative organism, *Staphylococcus aureus* is sensitive to penicillinase-resistant antistaphylococcal drugs, as methicillin or cloxacillin, but were frequently resistant to erythromycin and clindamycin (21). Hence, alternative therapy in penicillin-allergic patients should not include the latter two drugs. Scabies infestations have also been frequently detected and may spread to family members quickly (if more than one family member itches, suspect scabies) (101). Treatment of all afflicted and close contacts is indicated by application to entire body below the chin of 1% Lindane (Kwell) or 10% crotamiton.

D. Miscellany

The Cuban refugees have not been shown to have any significant problems with infections, particularly they have not had malaria, syphilis, diarrhea and have very low rates of tuberculosis (1). BCG was used routinely in Cuba and consequently a PPD cannot be used in their evaluation. Reliance must be made on chest x-rays, sputum smears and cultures as well as clinical evaluation. They have not had dehydration or diarrhea leading to pneumonia and other infections responsible for high case fatality rates in Kampuchean refugees (2). In fact, asthma was the most frequent complication requiring hospitalization (1). If they remain in a refugee camp, they may develop epidemic keratoconjunctivitis such as was seen at a Florida refugee camp for Vietnamese in 1975 (102 - investigated by our own Ron Zwieghaft). Obviously adequate chlorination of water supply is essential in the camps to prevent outbreaks of diarrhea or typhoid (30). We need to fear only the possibility of dengue since Cuba did have an outbreak in 1978, although ultimately we are likely to see epidemics of this entity anyway (11).

One major factor inhibiting the health care of Southeast Asian refugees is the language barrier. Multiple dialects are spoken and frequently one Kampuchean or Laotian cannot communicate with another or serve as an interpreter. The problem is particularly severe for the Hmong from Laos who have no common language or name with other Laotians (103). (Their names are single syllable whereas other Laotians are multi-syllable). Also, in conversation we must remember their given name is the last name. Hence, Vang May, a Hmong with TB meningitis, May is name and Vang is her family name. (Documents with SS# frequently reverse this). Although they may appear noncommunicative, they have been very quick to learn in school (GBS).

Resource groups which are assisting in resettlement can be invaluable in providing interpretors and medical assistance. Check the service to which the person is assigned. In particular, the International Rescue Committee (521-6460) has helped in providing Laotian and Vietnamese interpreters and Chinese for ethnic Chinese Cambodians. However, only call them after hours if an extreme emergency. The groups have contributed to an extraordinarily good follow-up in treatment of TB cases and in doing skin tests on all their assigned refugees. Our own citizens could use their assistance! For interpretation of all Southeast Asian dialects call toll free 1-800-424-0212.

Credits:

To Dr. Don Molony for an excellent review of problem in conference.
To Dr. Don Allegra, Louisiana Health Dept., for information on refugees.
To Mrs. Pauline Shirley for patience and hardwork in preparing protocol.
To VAMC Medical Media for superb assistance.

QUESTIONS:

1. A Laotian has a severe case of poison ivy for which corticosteroids are indicated. You should first check _____ for _____.

2. *True or False.* A person develops vivax malaria following a transfusion of blood from a refugee. After treatment with chloroquine, a 14 day course of primaquine is indicated.

3. Which of the following pose a risk for introduction into the U.S.
   A. Malaria
   B. Dengue
   C. Hookworm
   D. PPNG

4. Refugee presents with fever and bloody diarrhea. Stool smear shows leukocytes. Symptoms persist on Trimethoprim/Sulfamethoxazole. Stool culture negative for pathogens. You should obtain _____ and change therapy to _____.

5. A refugee in U.S. for a month develops inguinal and femoral nodes with prominent inguinal ligament. STS is negative. He has no fever nor penile lesion. Appropriate therapy is _____.

6. *True or False.* Cuban refugee has right upper lobe infiltrate. Part of workup should include PPD.

7. A refugee visits friends in Beaumont. While there, she eats crabs boiled at home. One day later, she develops explosive watery diarrhea. Workup of stool should include _____. Management includes principally _____.

8. A Cuban refugee has severe flu-like illness with severe headache four days after getting off cousin's boat. LP is negative. Diagnostic test should include _____. He insists on going home. Have him _____.

9. *True or False.* Initial therapy for gonorrhea in a Kampuchean would be 4.8 mu APPG with probenicid 1 g.

10. *True or False.* A Kampuchean on treatment for Class A tuberculosis with INH, rifampin, and ethambutol. She has been doing well with no clinical symptoms. SGOT on visit was 105 (N=45). You should discontinue INH and rifampin.

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