INFECTION WITH SCHISTOSOMES
(*Schistosoma haematobium, Schistosoma mansoni* and *Schistosoma japonicum*)

1. Exposure Data

1.1 Structure and biology of schistosomes

1.1.1 *Taxonomy*

Schistosomes are trematode worms ('flukes') belonging to the phylum Platyhelminthes. The adult worms live in the vascular system of birds and mammals ('blood flukes'). Other pathologically important Platyhelminthes include the digenetic trematodes *Opisthorchis*, *Clonorchis*, *Paragonimus*, *Fasciolopsis* and *Fasciola* and the cestodes (tapeworms).

All the schistosomes that mature in man belong to the genus *Schistosoma* of the family Schistosomatidae, which contains 11 other genera, some of which cause cercarial dermatitis (Rollinson & Southgate, 1987). The genus *Schistosoma* contains 19 species (WHO, 1993), five of which (*Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum*) are of major pathological importance, while the others are essentially parasites of non-human mammals, although some zoonotic transmission to man does occur. An estimated 600 million people are at risk for schistosomiasis; 200 million are currently infected in 74 countries (WHO, 1993). Probably more than 95% of human infections are due to *S. mansoni* and *S. haematobium*. Several of the 'non-human' species, including *S. mattheei* and *S. bovis*, are of veterinary importance, and both domestic and feral animals are major reservoirs of infection with *S. japonicum* (but not with any of the other species) (Taylor, 1987).

This monograph is restricted to *S. haematobium*, *S. mansoni* and *S. japonicum*.

1.1.2 *Structure*

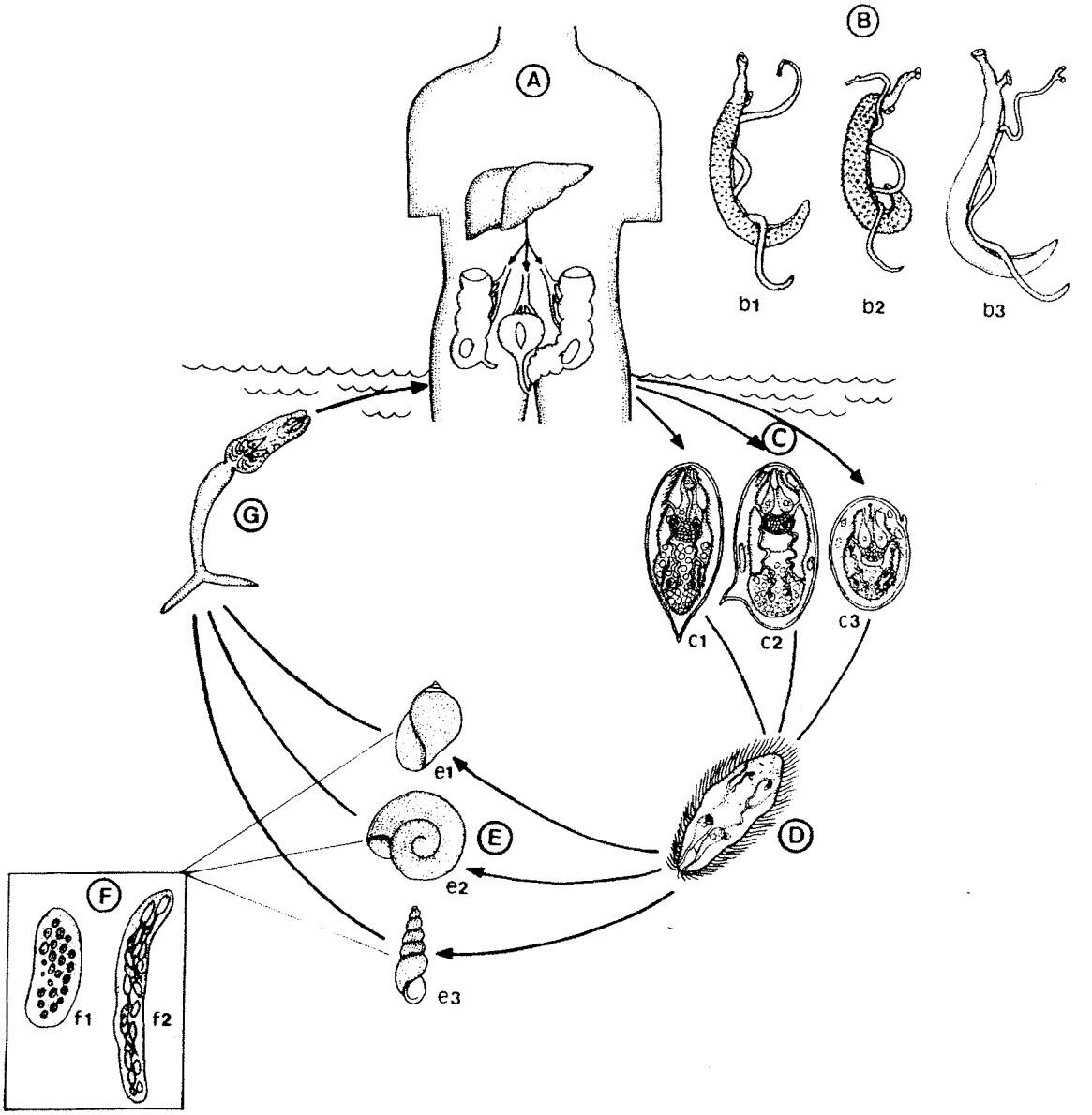
Unlike all other pathologically important trematodes, schistosomes are dioecious (rather than hermaphroditic). The adult worms are about 1 cm long, and the male has a deep ventral groove or schist (hence the term 'schistosome') in which the female worm resides permanently *in copulo*. Worms of each sex have a mouth at the anterior end, which also serves as the anus since there is only one gut opening. Around the mouth is the oral sucker, while nearby, further back, is the ventral sucker. These suckers are much better developed in male worms; they are used mainly for hanging on to the venous epithelium of the host and for locomotion of the worm pair. In order to obtain amino acids for protein synthesis, the adult worms ingest red blood cells and break down the haemoglobin with a haemoglobinase. Small molecules, including glucose, amino acids, purines and pyrimidines, are taken up via transtegumentary absorption; there is evidence that the female derives much of her nutrition

via transtegumentary absorption from the male worm. The metabolism of adult schistosomes is largely anaerobic, by glycolysis (Rumjanek, 1987).

1.1.3 *Life cycle and biology of the adult worm*

Schistosoma do not multiply in the human body. The life cycle of schistosomes is illustrated in Figure 1.

Figure 1. Life cycle of blood flukes



A: definitive host, human; B: adult blood flukes, *Schistosoma haematobium* (b1), *S. mansoni* (b2), *S. japonicum* (b3); C: embryonated egg of *S. haematobium* (c1), *S. mansoni* (c2), *S. japonicum* (c3); D: miracidium; E: intermediate host, *Bulinus* sp. (e1), *Biomphalaria* sp. (e2), *Oncomelania* sp. (e3); F: intramolluscan stages, mother sporocyst (f1), daughter sporocyst (f2); G: cercaria

Adult worms are found either in the vesical plexus of the urinary bladder (*S. haematobium*) or in the mesenteric veins (other species). Adult worms live for up to 30 years (von Lichtenberg, 1987), with a mean lifespan of 3–6 years (Anderson, 1987). They produce large numbers of eggs: 300 per day per female *S. mansoni* and *S. haematobium* and 10 times as many per female *S. japonicum*. About one-half of the eggs transit to the lumen of the urinary bladder (*S. haematobium*) or the intestine (other species), from where they leave the body in the urine or faeces, respectively. A substantial number of eggs are retained in the tissues, where they survive for a further three weeks; these are responsible for inducing most of the pathological manifestations of disease (Warren, 1978).

The eggs are large (e.g. 144 × 58 μm for *S. haematobium*) and consist of an egg shell of tanned protein containing, when laid, about 40 yolk cells and the oocyte. After about one week in the tissues, the mature egg contains the large (150 × 70 μm) ciliated miracidium larva (von Lichtenberg, 1987). It is this life-cycle stage that infects the snail host. Thus, embryonated eggs excreted from the body in urine or faeces and deposited in water hatch to liberate the free-swimming miracidium larvae. If the miracidia can locate an appropriate snail host within a few hours, they penetrate it; if not, they die, as they do not feed.

Within the tissues of the snail, the miracidium is transformed into the mother sporocyst, within which are formed several hundred daughter sporocysts. These migrate from the site of penetration to the digestive gland and reproductive tract of the snail, in which they proliferate internally to produce cercariae, the stage that infects man. This process takes about one month, and from one miracidium several million genetically identical cercariae may be produced by this asexual process during the lifetime of the infected snail.

The cercariae are shed from the snail in response to temperature and light and aggregate at the surface of the water, ready to infect the definitive human host. They swim tail first, locate the host by a combination of chance and chemotaxis and adhere to the skin by their suckers. A cercaria is approximately 0.5 mm long and consists of a head-end, bearing the oral and ventral suckers, and a tail with a pronounced fork. Cercariae respire aerobically, using glycogen as a substrate, but do not feed; therefore, if they do not penetrate the final host within a few hours they die. Cercariae penetrate intact skin rapidly, using proteolytic enzymes produced by the paired penetration glands at their anterior ends; the tail is discarded in the water. Once they are within the skin, a profound metamorphosis takes place, and the cercaria is transformed into the 'skin-stage schistosomulum'. Metamorphosis includes shedding of the cercarial glycocalyx, transformation from the single-lipid bilayer tegument of the cercaria into the double-lipid bilayer of the schistosomulum and various physiological changes, such as a change from aerobic to anaerobic respiration and the acquisition of host molecules, particularly lipids, some of which are incorporated into the tegument (Wilson, 1987).

The schistosomulum then penetrates the basement membrane of the epidermis, using proteinases secreted by the residual penetration glands of the cercaria stage. In mice, this process takes about three days, after which time the schistosomulum enters a lymphatic vessel or capillary in the dermis and is carried passively to the lungs via the right side of the heart (Wilson, 1987). The young schistosomula embolize in the capillaries—being too large to pass through the pulmonary veins—whereupon they again metamorphose, this time to the 'lung-stage schistosomulum', which, unlike the skin stage, is capable of stretching out its body to become long and thin and can cross the capillary bed of the lungs, taking three to six days

to reach the left side of the heart (Wilson, 1987). Schistosomula are then distributed all over the body via the left ventricle, in proportion to cardiac output. Those that embolize in various capillary beds migrate through these to regain the heart and recirculate until they reach the hepatic portal system, a process usually completed within three recirculations. When the hepatic portal system is reached, a third metamorphosis takes place: the elongated migratory forms return to the squat shape of the skin-stage schistosomulum. Blood feeding begins and this is followed by growth, organogenesis and sexual maturation. The mature worms pair up in the intrahepatic portal venules from about four weeks onwards and then migrate to the final sites of oviposition in the vesical plexus (*S. haematobium*) or in the mesenteric veins (all other species).

1.2 Methods for detection of infection

1.2.1 *History taking*

Information derived from simple questionnaires eliciting a history of haematuria is sufficiently accurate to identify nearly all heavily infected people (Mott *et al.*, 1985), and such questionnaires can be used for rapid identification of communities with a high prevalence of *S. haematobium* infection (Lengeler *et al.*, 1991a,b). Validation of the use of questionnaires on history of *S. mansoni* infection for identifying infected people showed a specificity of about 60% (Barreto, 1993). In community-based epidemiological studies of *S. japonicum*, although symptoms of weakness, colicky abdominal pain and diarrhoea were observed in a greater proportion of infected than uninfected individuals, these were not specific to infection (Olveda *et al.*, 1983).

1.2.2 *Clinical diagnosis*

Macroscopic and microscopic haematuria are highly sensitive, specific signs of *S. haematobium* infection in most endemic areas of Africa and the eastern Mediterranean (Savioli & Mott, 1989; Savioli *et al.*, 1990; Eltoum *et al.*, 1992; Lengeler *et al.*, 1993). Testing with chemical reagent strips to detect microscopic haematuria consistently results in the identification of 80% or more of people excreting *S. haematobium* eggs, and gross haematuria is associated with urinary egg counts greater than 50 per 10 ml of urine (Savioli *et al.*, 1990).

Schistosomiasis is a protean, multisystem disease, and the clinical signs and symptoms are often nonspecific (Abdel-Wahab & Mahmoud, 1987; von Lichtenberg, 1987; Olveda & Domingo, 1987; Prata, 1987; Wilkins & Gilles, 1987; Chen & Mott, 1989). Thus, multiple abdominal symptoms may be found in patients infected with *S. mansoni* and *S. japonicum*, of which only a history of bloody diarrhoea is significantly associated with heavy infection (Sleigh & Mott, 1986; Olveda & Domingo, 1987). Schistosome eggs and associated granulomas and fibrosis are frequently detected by liver biopsy. The degree of periportal fibrosis can now be assessed accurately by ultrasonography of the liver (*S. mansoni*, *S. japonicum*) or urinary tract (*S. haematobium*), the latter having replaced intravenous pyelography which was formerly the standard method of assessment (Hatz *et al.*, 1992a,b,c,d; Jenkins & Hatz, 1992; Wei-min *et al.*, 1992).

1.2.3 *Parasitological tests*

The best method for diagnosing infection with mature, egg-producing adult worms is to demonstrate the presence of eggs in the urine (*S. haematobium*) or faeces (other species). In routine medical practice, diagnosis is usually qualitative rather than quantitative. In both techniques, some form of concentration is used to increase sensitivity. Thus, urine samples may be centrifuged or filtered to concentrate the eggs, while eggs in faecal samples are frequently concentrated by the formol–ether technique.

For most epidemiological purposes, however, eggs are counted, although the sensitivity is limited owing to small sample size (de Vlas & Gryseels, 1992; de Vlas *et al.*, 1993). The quantitative relationship between the presence of viable adult worms and faecal or urinary egg counts has been established experimentally (Cheever, 1969) and in autopsy studies (Edington *et al.*, 1970; Smith & Christie, 1986).

For *S. haematobium* infections, filtration through standard filter paper, cellulose membranes, polycarbonate or nylon in filter holders attached to a syringe is a standard quantitative technique. The Kato technique for examination of faeces for the eggs of other *Schistosoma* involves use of a glycerine-impregnated cellophane coverslip over a measured volume of stool, ranging from 10 to 50 mg.

Light and heavy infections can be distinguished reliably by the available faecal and urinary examination techniques in all endemic areas. The limitations of their sensitivity have been well described (Savioli *et al.*, 1990; de Vlas & Gryseels, 1992; de Vlas *et al.*, 1993). A single filtration of a random 10-ml urine sample allows detection of all infected individuals with more than 50 eggs/10 ml of urine (Savioli *et al.*, 1990). Although several quantitative techniques are available for faecal egg counting, their sensitivity is dependent on the amount of stool examined, and the Kato technique has become the standard, allowing comparison of the results of epidemiological studies. A single Kato thick smear allows detection of all people with more than 100 eggs/g of faeces (Barreto *et al.*, 1990; Feldmeier & Poggensee, 1993).

In people with chronic or light infections, eggs may be difficult to demonstrate with these techniques. In such cases, rectal biopsy is sometimes used, followed by microscopic examination of compressed mucosal specimens for eggs. The sensitivity of rectal biopsy is unknown; however, it appears to be highly sensitive clinically, even if the viability of the infection cannot be determined. Sometimes eggs (or adult worms) are found by histopathological examination of lesions taken by biopsy from other anatomical sites or in cytological smears. *S. haematobium* eggs are frequently reported in diverse parts of the urogenital system, and 'ectopic' lesions of the central nervous system caused by *S. japonicum* or *S. mansoni* are seen (Chen & Mott, 1989).

1.2.4 *Immunological tests*

In the past, immediate hypersensitivy-based intradermal tests for *S. mansoni* and *S. japonicum* were widely used in epidemiological studies, but they have been rarely used since 1970 because of the lack of correlation with active infection and the availability of improved parasitological techniques. Using *S. mansoni* adult worm antigens, the sensitivity ranged from 82 to 100% and the specificity from 96 to 99% (Mott & Dixon, 1982); with

S. japonicum adult antigens, the sensitivity ranged from 77 to 99% and the specificity from 95 to 99% (Mott *et al.*, 1987). The age distribution of intradermal reactivity is not known. The specificity is not influenced by other intercurrent infections, except for certain trematode infections; the sensitivity is lower in children than in adults, and the sensitivity of the test and the intensity of the hypersensitivity reaction are greater in infections of long duration. Reactivity persists for years after a successful treatment (Kagan & Pellegrino, 1961).

Researchers have concentrated on *S. mansoni* and *S. japonicum* infections because of the ease with which the parasites can be maintained in the laboratory. Many immunodiagnostic techniques have been described and used experimentally, but so far none has been used consistently or validated in epidemiological studies (Mott & Dixon, 1982; Mott *et al.*, 1987). Difficulty in maintaining *S. haematobium* in the laboratory has limited research in immunodiagnosis of urinary schistosomes (Xue *et al.*, 1993).

Antibody detection assays are very sensitive; however, in epidemiological studies, a positive serological result may be due to either a light infection or the presence of residual antibody from a resolved infection. This is a particular disadvantage now that large-scale chemotherapy campaigns are so frequently carried out (Bergquist, 1992). Antigen detection assays may solve these problems. Several systems are being developed, the most advanced of which involve an enzyme-linked immunosorbent assay with monoclonal antibodies to detect circulating antigens of *S. mansoni* (de Jonge, 1992).

1.2.5 *Establishment of absence of infection*

The absence of infection cannot be established unequivocally. The variation in sensitivity of the diagnostic techniques is such that a combination of diagnostic tests is appropriate to establish absence of infection (Feldmeier & Poggensee, 1993). In the field, at least three successive urine filtration examinations are required to establish the absence of infection with *S. haematobium* (Savioli *et al.*, 1990). For *S. mansoni* infection, five consecutive Kato examinations are required (Barreto *et al.*, 1978). If available, antigen detection assays can be used (see section 1.2.4).

1.3 Epidemiology of infection

1.3.1 *Geographical distribution* (see Table 1 and Figures 2 and 3)

It has been estimated that over 600 million people in 74 countries are exposed to the risk of schistosomal infection, and 200 million are currently infected (WHO, 1993). Schistosomiasis may be the second most important parasitic disease in man after malaria. About 95% of cases are due to *S. mansoni* and *S. haematobium* infections and the remainder to *S. japonicum*, *S. intercalatum* and *S. mekongi*. The geographical distribution of the schistosomes roughly corresponds to the distribution of susceptible snail hosts, which are present in many tropical and subtropical regions. *S. mansoni* is the most widespread species, being prevalent in 52 countries in Africa, the eastern Mediterranean, South America and the Caribbean. *S. haematobium* and *S. mansoni* have a similar distribution in Africa and the eastern Mediterranean; *S. haematobium* does not occur in the Americas. There is a small focus of *S. haematobium* in India, but neither *S. mansoni* nor *S. haematobium* occurs in

Table 1. Geographical distribution of schistosomiasis by species

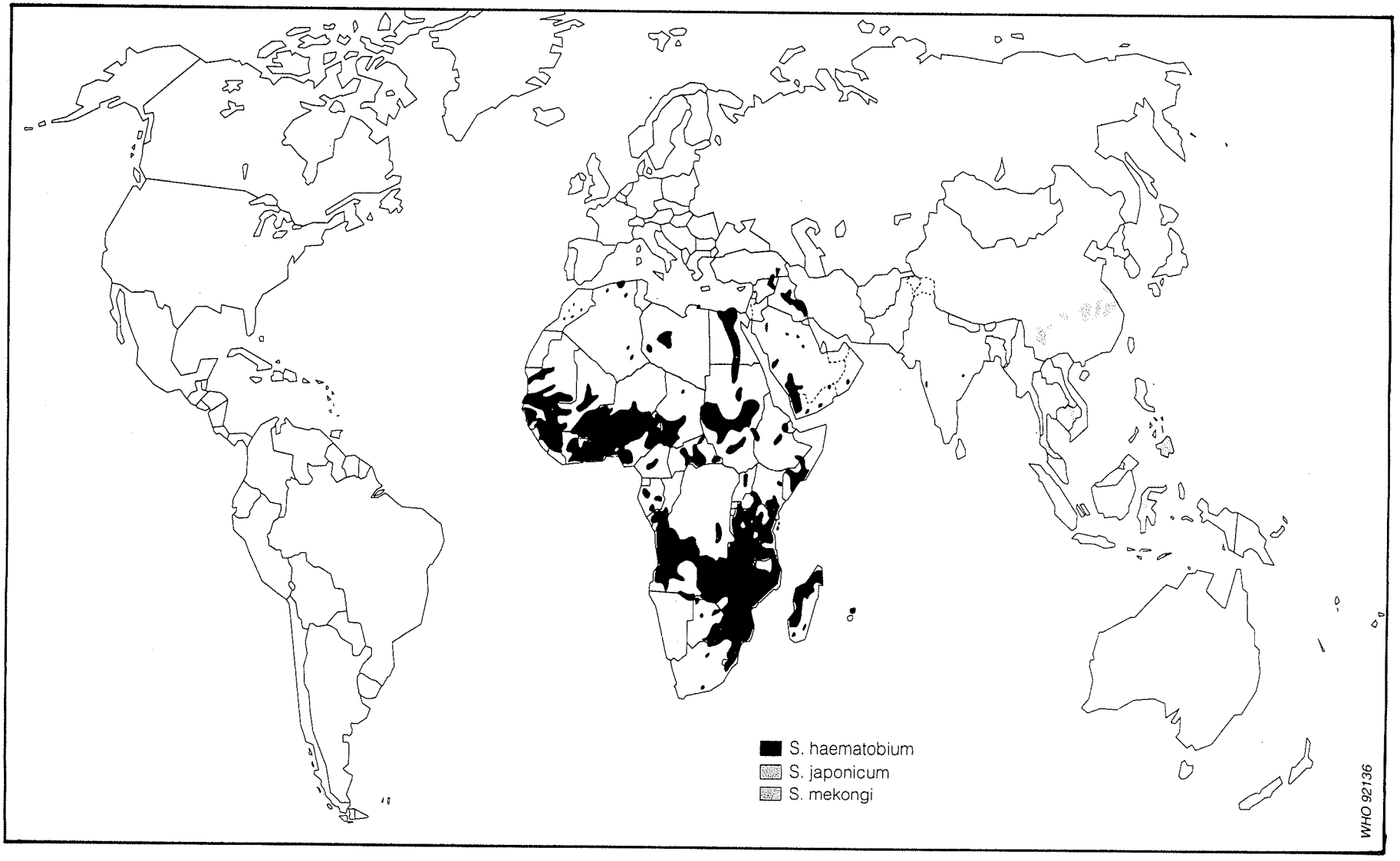
Country or area (by WHO region)	*S. haematobium*	*S. mansoni*	*S. intercalatum*
African Region			
Algeria	+		
Angola	+	+	
Benin	+	+	
Botswana	+	+	
Burkina Faso	+	+	
Burundi		+	
Cameroon	+	+	+
Central African Republic	+	+	+[a]
Chad	+	+	+[a]
Congo	+	+	+[a]
Côte d'Ivoire	+	+	
Equatorial Guinea			+
Ethiopia	+	+	
Gabon	+	+	+
Gambia	+	+	
Ghana	+	+	
Guinea	+	+	
Guinea-Bissau	+	+	
Kenya	+	+	
Liberia	+	+	
Madagascar	+	+	
Malawi	+	+	
Mali	+	+	+[a]
Mauritania	+		
Mauritius	+		
Mozambique	+	+	
Namibia	+	+	
Niger	+	+	
Nigeria	+	+	+[a]
Rwanda	+		
Sao Tome and Principe	+[a]		+
Senegal	+	+	
Sierra Leone	+	+	
South Africa	+	+	
Swaziland	+	+	
Togo	+	+	
Uganda	+	+	
United Republic of Tanzania	+	+	
Zaire	+	+	+
Zambia	+	+	
Zimbabwe	+	+	

Table 1 (contd)

Country or area (by WHO region)	*S. haematobium*	*S. mansoni*	*S. intercalatum*
Region of the Americas			
Antigua		+	
Brazil		+	
Dominican Republic		+	
Guadeloupe		+	
Martinique		+	
Puerto Rico		+	
Saint Lucia		+	
Suriname		+	
Venezuela		+	
Eastern Mediterranean Region			
Egypt	+	+	
Iran, Islamic Republic of	+		
Iraq	+		
Jordan	+		
Lebanon	+		
Libyan Arab Jamahiriya	+	+	
Morocco	+		
Oman	+	+	
Saudi Arabia	+	+	
Somalia	+	+	
Sudan	+	+	
Syrian Arab Republic	+		
Tunisia[b]	+		
Yemen	+	+	
European Region			
Turkey	+		
South-East Asia Region			
India	+		
Indonesia		*S. japonicum*	
Thailand		*S. japonicum*	
Western Pacific Region			
Cambodia		*S. mekongi*	
China		*S. japonicum*	
Japan[b]		*S. japonicum*	
Lao People's Democratic Republic		*S. mekongi*	
Malaysia		*S. malayensis*	
Philippines		*S. japonicum*	

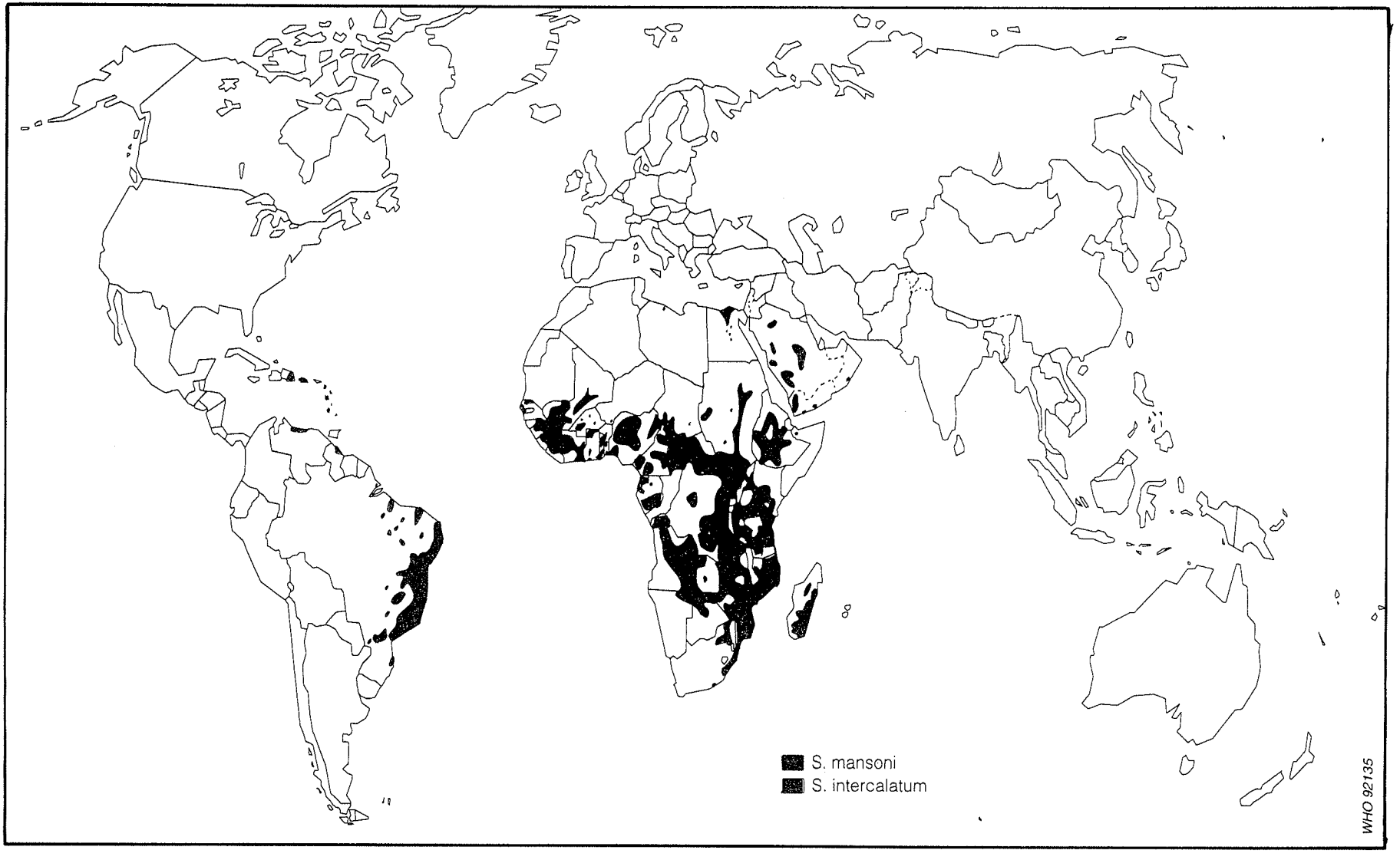
From WHO (1993)
[a]Confirmation required
[b]No recent transmission: Japan, Tunisia

Figure 2. Global distribution of schistosomiasis due to *Schistosoma haematobium*, *S. japonicum* and *S. mekongi*



From WHO (1993)

Figure 3. Global distribution of schistosomiasis due to *Schistosoma mansoni* and *S. intercalatum*



From WHO (1993)

central or east Asia; *S. japonicum* is endemic in three countries (China, the Philippines and Indonesia), while the related *S. mekongi* is restricted to the Mekong River basin in the Lao People's Democratic Republic and Cambodia. In Africa, *S. mansoni* and *S. haematobium* often coexist, and mixed infections are common. *S. intercalatum*, a much rarer species than *S. mansoni* or *S. haematobium*, is restricted to foci in 10 central and West African countries.

1.3.2 *Risk factors for infection*

Contact with contaminated freshwater is the major risk factor of infection (Jordan & Webbe, 1993). Many other environmental factors influence the distribution, prevalence, intensity of infection, morbidity and mortality of schistosomiasis (WHO, 1993). Among these are the type and size of intermediate snail host populations, human population density and behaviour in relation to freshwater bodies, and climatic and hydrological features. Infection may be constant in endemic areas owing to repeated contact with water, particularly among children.

Susceptibility to infection is influenced by genetic factors (Abel *et al.*, 1991), but genetic differences between parasites are not known to influence their infectivity. Acquisition of infection depends on the duration of exposure, proportion of the body surface exposed, degree of body movement during exposure, presence of intermediate snail hosts, cercarial concentration in the water and water temperature. These conditions are fulfilled in endemic areas, usually in open water bodies where frequent recreational contact occurs.

Since schistosomes, like most other helminths, do not multiply in man, it is a striking feature of schistosome epidemiology that, although the prevalence of infection may be very high, significant symptoms are present in only the small segment of people who are most heavily infected. The decline in prevalence and intensity of infection after the second decade of life is believed to be due mainly to the gradual acquisition of immunity, although other age-related factors, such as decreasing contact with infected water and physiological changes associated with the onset of puberty, may also be important (Hagan *et al.*, 1991; Rihet *et al.*, 1991; Dessein *et al.*, 1992; Dunne *et al.*, 1992) (see Figures 4 and 5).

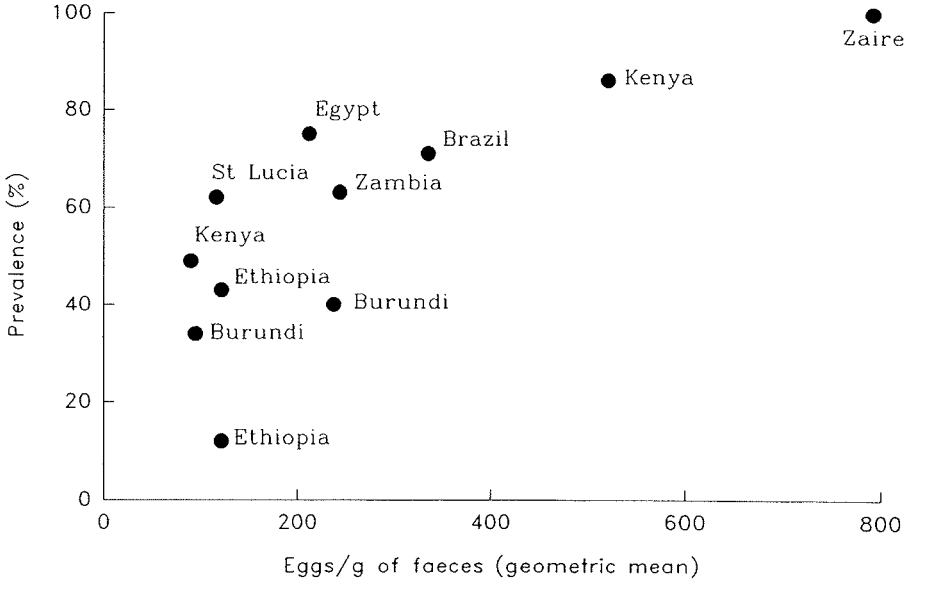
1.3.3 *Aggregation of infection*

Within any endemic area, transmission is highly focal and the prevalence and intensity of infection vary between households, communities and progressively more population agglomerations. This heterogeneity or aggregation is determined by the risk factors cited in section 1.3.2. In common with other worms, *Schistosoma* are not randomly distributed among infected persons but are aggregated in heavily infected people in a manner best described by a negative binomial distribution. The amount of tissue damage caused by the *Schistosoma* infection is roughly proportional to the numbers of worms present; it is the heavily infected segment of the population that is at greatest risk of developing disease and which contributes the most to transmission of the parasite.

1.3.4 *Prevalence and intensity of infection*

For epidemiological studies, the intensity of infection is measured by the number of eggs/10 ml of a urine sample (*S. haematobium*) or per gram of faeces (all other species).

Figure 4. Relationship between overall prevalence and intensity of infection with *Schistosoma mansoni* as determined by the Kato technique in different endemic areas in various studies



From Jordan & Webbe (1993)

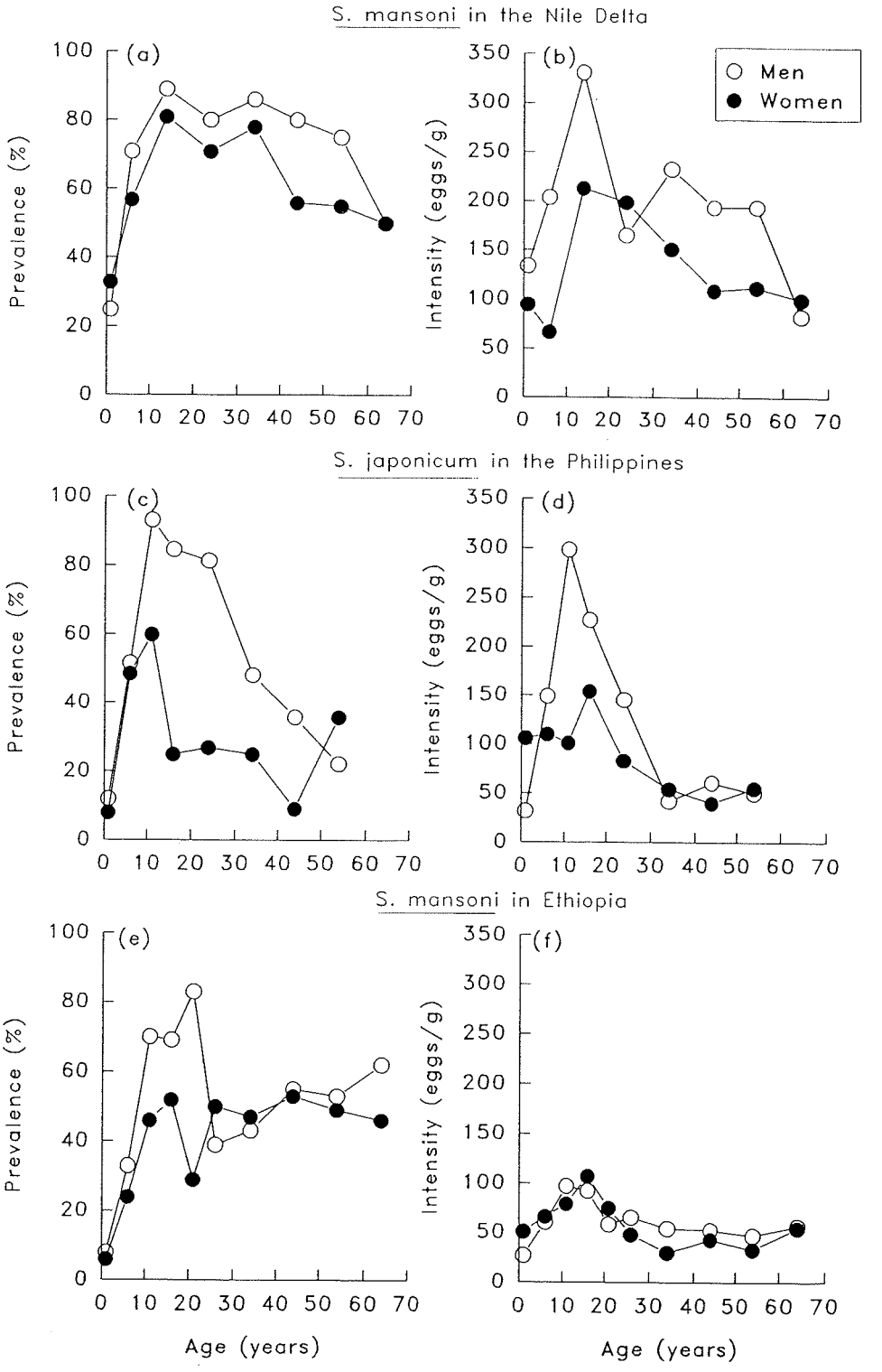
Definitions of 'heavy' infections are routinely included in most epidemiological studies (Sleigh & Mott, 1986). Throughout areas endemic for urinary schistosomiasis, most infection in people who excrete more than 50 eggs/10 ml of urine is associated with haematuria (Mott *et al.*, 1983). The definition of heavy infection due to *S. mansoni* varies from a mean of 16 eggs/g of faeces in areas of low prevalence such as Puerto Rico (Hiatt *et al.*, 1980) to 1000 eggs/g of faeces in Burundi (de Vlas & Gryseels, 1992). About 10% of infected people in areas endemic for *S. mansoni* have heavy infections. *S. japonicum* infections have been considered to be heavy when more than 400 eggs/g of faeces are found; they occur in up to 4% of some populations (Olveda & Domingo, 1987).

Analysis of 11 methodologically similar studies (Jordan & Webbe, 1993) showed that there is a general trend to a proportional relationship, i.e. the higher the prevalence, the higher the intensity (Figure 4). A similar relationship was seen for *S. haematobium* infection, but few similar population-based studies have been reported using comparable methods.

The peak prevalence of all *Schistosoma* infections occurs in the second decade of life. In general, the decrease in intensity of *S. haematobium* infection after that time is accompanied by a comparatively greater decrease in prevalence than in *S. mansoni* infection. That is, while the intensity of *S. mansoni* infection tends to decrease in the same period, the prevalence remains high, i.e. a few eggs are excreted over a long period.

Few studies have been carried out on the interaction of *S. mansoni* and *S. haematobium* infections. The data reported by Robert *et al.* (1989) suggested that the intensity of *S. haematobium* in mixed infections was greater than that in infections with *S. haematobium* alone.

Figure 5. Age–prevalence patterns based on faecal and urinary egg counts



(a) and (b) from Abdel-Wahab *et al.* (1980); (c) and (d) from Hiatt (1976); (e) and (f) from Olveda *et al.* (1983). Intensities are geometric means.

1.3.5 *Sex-related patterns of infection*

Differences in the sex distribution of infection were seen in three selected epidemiological studies (Figures 4 and 5). In general, although not universally, the prevalence and intensity of infection are higher in men than in women, owing to greater employment in agricultural work. The interpretation of any statement about sex differences must, however, take into account the focality of infection and its variable distribution (see section 1.3.3). In predominantly Islamic countries such as Egypt, the prevalence and intensity of urinary schistosomiasis tend to be lower in girls and women than in boys and men (El-Malatawy *et al.*, 1992) owing to lower rates of contact with water.

1.3.6 *Relationship of morbidity to intensity of infection*

Morbidity due to *Schistosoma* infection becomes apparent during the period of peak prevalence and intensity of infection as well as many years later. In urinary schistosomiasis due to *S. haematobium*, the intensity of infection is correlated with morbidity, especially in children. The degree of haematuria and proteinuria detectable by chemical reagent strips is correlated with the intensity of infection (Mott *et al.*, 1983; Savioli *et al.*, 1990). Changes in the urinary bladder and ureters detected radiologically (Forsyth, 1969; Pugh *et al.*, 1979; Warren *et al.*, 1979) or by ultrasound (Hatz *et al.*, 1992a), cystoscopic abnormalities of the urinary bladder (Abdel Salam & Ehsan, 1978) and pathological signs at autopsy (see section 4.1) are also correlated with intensity of infection.

Although *S. japonicum* adults lay more eggs per day (see section 1.1.3), the rates of hepatic and splenic enlargement are similar to those observed in *S. mansoni* infections when the egg counts are similar (Olveda & Domingo, 1987).

Kloetzel (1964) showed in population-based studies in Northeast Brazil that the rates of splenomegaly associated with *S. mansoni* infection are proportional to the intensity of infection, as measured by faecal egg counts, particularly in the first two decades of life.

1.3.7 *Relationship of morbidity to mortality from infection*

Annual mortality due to *S. haematobium* infection in East Africa has been estimated at 2/1000 infected adults (Forsyth, 1969). The proportional contribution of urinary bladder cancer or hydronephrosis leading to end-stage renal disease is not known.

In 1984, annual mortality due to portal hypertension caused by schistosomiasis from *S. mansoni* in Brazil was estimated at 0.5/100 000 total population; at the same time in Suriname, the figure was estimated to be 2.4/100 000 inhabitants. The control of schistosomiasis through large-scale chemotherapy in Brazil was associated with a decline in related annual mortality between 1977 and 1988 from 0.67 to 0.44 deaths per 100 000 inhabitants (WHO, 1993).

Before the introduction of praziquantel in China, severe acute schistosomiasis due to *S. japonicum* resulted in a mortality rate of 2.5–20.7%. Mortality from schistosomiasis during 1975–79 in 10 counties in the Jiaxing area, Zhejiang Province in China was reported to vary from 0.69 to 39.8/100 000 in men [median, 15.1] and from 0.45 to 44.6/100 000 in women [median, 7.7] (Liu *et al.*, 1983). Cumulative (0–64) mortality rates during 1973–75 were reported from 49 counties in various Chinese provinces. No mortality was seen among men

in 29 counties or among women in 36 counties; the rates in counties with some deaths from schistosomiasis varied from 0.03 to 37.2/1000 for men [median, 1.3/1000] and 0.07–42.1/1000 for women [median, 1.4/1000] (Chen *et al.*, 1990). In Leyte, the Philippines, annual mortality among 135 untreated patients was 1.8% (Blas *et al.*, 1986). More widespread use of antischistosomal drugs in highly endemic areas should reduce both morbidity and mortality.

1.4 Clinical disease in humans (other than cancer)

Infection with *Schistosoma* is not synonymous with clinical disease: many infections are asymptomatic. The clinical outcome of schistosomal infection is affected by many factors, including: the target organs of the different species of *Schistosoma*; the intensity and duration of infection; host HLA type and race (Salam *et al.*, 1979; Sasazuki *et al.*, 1980; Kamel *et al.*, 1984; Kojima *et al.*, 1984; Wishahi *et al.*, 1989; Ohta *et al.*, 1990; Abel *et al.*, 1991; Hafez *et al.*, 1991; Proietti *et al.*, 1992); host immunological responses (Phillips & Lammie, 1986; Boros, 1989; Weinstock, 1992); and concomitant infections, notably with hepatitis viruses (Bassily *et al.*, 1992; Uemura *et al.*, 1992; Chen *et al.*, 1993; Darwish *et al.*, 1993). Therefore the manifestations of schistosomiasis vary greatly from patient to patient and among endemic areas.

Most of the pathological manifestations of schistosomal infections are due to fibrosis consequent to immunological reactions to parasite eggs embolized in tissues (Abdel-Wahab & Mahmoud, 1987; von Lichtenberg, 1987; Prata, 1987; Wilkins & Gilles, 1987; Chen & Mott, 1989). As adult *S. haematobium* worms reside in the vesical plexus and ureteric veins, the most badly affected organs are the urinary bladder and ureters, where egg deposition is heaviest. The other schistosome species live in the mesenteric veins, depositing their eggs in the intestine and liver.

The larval forms of the schistosomes are also involved in the disease process. Repeated penetrations of the skin by cercariae (particularly of non-human species of schistosomes, which die in the epidermis) can cause a severe form of dermatitis, which is known to be a complex, immunologically mediated reaction involving both immediate and delayed hypersensitivity components (Boros, 1989).

The presence of maturing schistosome infections with *S. mansoni* or *S. japonicum* can cause an acute febrile illness called 'Katayama syndrome' or 'acute schistosomiasis'. Although the exact timing of exposure to cercariae is usually difficult to establish, in most cases the onset of this syndrome appears to coincide with the start of egg laying by adult worms, three to four weeks after exposure to cercariae (eggs do not appear in the faeces for at least one week more). Since the symptoms of acute schistosomiasis resemble those of serum sickness, the former may also be a form of type III immune complex disease (Butterworth, 1993). The cercarial glycocalyx contains carbohydrate antigens which cross-react with antigens of the egg stage, and small soluble immune complexes may be formed in the period of initial egg laying when egg antigens are present in greater amounts than low-affinity antibody. As antibody titre and affinity increase, larger insoluble immune complexes are phagocytosed and the symptoms subside. Alternatively, treatment of the worms leads to resolution by removal of the source of antigen.

Mature *S. haematobium* lay their eggs in the subepithelial tissues of the urinary bladder and ureters. Those eggs that leave the body via the urine cause petechial haemorrhages which, when sufficiently numerous, result in visible haematuria. The aggregation of large numbers of eggs and granuloma formation in the tissues of the urinary bladder and ureters can lead to filling defects in the urinary bladder and stenosis and eventual obstruction of the ureters. Eventually, inflammatory polyps may subside, leaving fibrous 'sandy patches' on the urothelium. Eggs retained in the subepithelial tissues have a life span of three weeks; they then 'mineralize', acquiring calcium and magnesium salts, and subsequently persist for many years as 'calcified' black eggs. If these are very numerous, they form a ring of radio-opaque tissue that is clearly visible on an X-ray photograph of the so-called 'calcified bladder'. The progressive accumulation of eggs and the attendant inflammatory and granulomatous host reactions usually affect urinary bladder function, and frequency of micturition and dysuria are common symptoms. Obstruction of urine flow in the ureters causes hydroureter and hydronephrosis, and failure of the ureteric sphincter can lead to ascending bacterial infection of the ureters and kidneys (pyelonephritis) (von Lichtenberg, 1987; Wilkins & Gilles, 1987).

Adult *S. haematobium* worms often migrate to the veins of pelvic organs other than the urinary bladder and ureters to produce eggs, with their attendant inflammatory and granulomatous reactions. Dead (calcified) eggs are frequently seen in the submucosa of the colon (although they are rarely excreted in the faeces), where they are of little pathological consequence. More important are the reactions to eggs in the tissues of the reproductive tract: ectopic schistosomiasis of the vagina, uterus, fallopian tubes and ovaries can result in sterilization or misdiagnosis as cancer (Berry, 1966; El-Maraghy *et al.*, 1982). Similarly, schistosomal orchitis can be mistaken for malignancy (Mikhail *et al.*, 1988). Many eggs that fail to lodge in the pelvic organs are shunted to the lungs, where they cause granulomatous reactions. Central nervous system involvement is, perhaps surprisingly, rare in *S. haematobium* infection.

Mature worms of the other species deposit their eggs in the distal mesenteric veins in the submucosa of the intestine. About one-half of these eggs transit the bowel and leave the body via the faeces, causing, as they do so, petechial haemorrhages which often give rise to visible traces of blood in the faeces. Large clusters of eggs in the mucosa can cause the formation of haemorrhagic polyps and colitis, with resulting serious blood loss and colonic dysfunction (El-Masry *et al.*, 1986; Mohamed *et al.*, 1990).

Many of the eggs fail to lodge in the submucosa and are swept upstream to the intrahepatic branches of the hepatic portal vein. Being too large (approximately 45 μm in diameter) to enter the sinusoids, they embolize and elicit granulomatous reactions. Large granulomas are formed in sensitized individuals, which are 100 times the volume of the eggs themselves. The granulomas consist of a complex, mixed population of cell types, mostly lymphocytes, monocytes, macrophages, eosinophils, epithelioid cells and fibroblasts. Collagen deposition occurs in granulomas in response to cytokines produced by granuloma lymphocytes. When the miracidium dies (after three weeks), further fibrosis ('scar tissue') may occur, although the granulomas are sometimes resorbed completely. The gradual accumulation of granulomas in liver tissue can cause hepatomegaly and portal hypertension. Fibrosis occurs not only within the periovular granulomas but also at distant sites, around large branches of the intrahepatic portal vein, probably in response to cytokine action. In

prolonged infections, significant periportal fibrosis (Symmers' fibrosis) often develops, associated with severe portal hypertension, development of gastrooesophageal varices and haematemesis. Splenomegaly is present, caused partly by congestion and partly by a reactive hyperplasia (Abdel-Wahab & Mahmoud, 1987; von Lichtenberg, 1987; Prata, 1987).

Chronic *S. mansoni* and *S. japonicum* infections are usually well tolerated by the patients for many years because the liver lesions are restricted to the portal triads and hepatocytes function normally. The development of fibrosis and collateral circulation may, however, progress insidiously, and fatal haematemesis may occur without warning. Some patients develop liver failure, perhaps caused by concomitant infection with hepatitis viruses (Chen *et al.*, 1993).

If collateral circulation is present, many eggs bypass the liver and instead embolize in the lungs (El-Rooby, 1985), where progressive accumulation, granuloma formation and fibrosis develop, leading to pulmonary arteritis and cor pulmonale (right ventricular hypertrophy). The development of collateral circulation also predisposes to an immune complex-mediated glomerulonephritis (Andrade & Van Marck, 1984).

S. mansoni and *S. japonicum*, but rarely *S. haematobium*, sometimes reach the central nervous system and cause transverse myelitis. *S. japonicum* eggs tend to localize in the brain and may be associated with epilepsy (Norfray *et al.*, 1978; El-Rooby, 1985; Scrimgeour & Gajdusek, 1985).

Particularly when infection intensity is high, schistomiasis can lead to decreased working capacity (Parker, 1992, 1993), and there is increasing evidence that *S. japonicum* (McGarvey *et al.*, 1993), *S. haematobium* (Stephenson *et al.*, 1985, 1989) and *S. mansoni* (Jordan & Randall, 1962; de Lima e Costa *et al.*, 1988; Corbett *et al.*, 1992; Stephenson, 1993) can each affect child growth and nutrional status adversely. It has also been shown (Kimura *et al.*, 1992) that *S. haematobium* infection depresses cognitive function in children.

1.5 Treatment and control

1.5.1 *Treatment*

Safe, effective chemotherapy has been available for the past 20 years against all the schistosomes that affect man (WHO, 1993). The most versatile drug is praziquantel, which is effective in a single oral dose against all species of schistosomes (and some other trematodes and cestodes). Large-scale treatment is costly (US$ 0.35 per treatment), and, in areas of infection with *S. haematobium* only, the much cheaper metrifonate may be preferred, which, however, must be given in two or three doses at two-week intervals. Metrifonate is effective only against *S. haematobium*, while the third available drug, oxamniquine, is effective only against *S. mansoni*, for which it provides safe and effective treatment. None of these drugs is significantly effective against infections by immature worms; thus, prophylactic treatment is not available. Katayama syndrome is usually treated symptomatically for hypersensitivity reactions, but praziquantel is also given to kill adult worms as they mature. In advanced or ectopic disease, surgery for anatomical consequences and complications of infection may be necessary, but, even in advanced cases, antischistosomal drug therapy usually produces great improvement.

Treatment of all forms of schistosomiasis with safe, effective antischistosomal drugs (i) results in a high rate of resolution of infection, even in endemic areas where reinfection is a risk; (ii) prevents development of disease in people with heavy infection; (iii) arrests progression of existing severe disease; and (iv) reverses some manifestations of disease, such as haematuria and proteinuria, particularly in children. Liver fibrosis caused by *S. mansoni* and *S. japonicum* infection is usually arrested by the treatment and may even be reversed (Mohamed-Ali *et al.*, 1991; Wei-min *et al.*, 1992). Similarly, in cases of *S. haematobium* infection, hydroureter and hydronephrosis are reversible by treatment (Doehring *et al.*, 1986; Hatz *et al.*, 1990; King *et al.*, 1990).

1.5.2 *Control*

Control of schistosomiasis in the community may in practice by achievable by removing the adult worms by chemotherapy, by eliminating the snail intermediate hosts by modification of their habitat or by chemical attack, by changing human behaviour through health education, by providing safe water supplies and sanitation, so that excreta containing live eggs do not reach water containing snails, and by ensuring that people avoid water contaminated with cercariae.

Effective drugs are available. Trivalent antimonials were introduced in 1918, although these toxic compounds were far from ideal for control programmes since they required repeated intravenous injections. Chemical control of snails by molluscicides became possible in the 1920s, when copper sulfate was introduced for the control of the aquatic vectors of *S. mansoni* and *S. haematobium*, and when lime was first used to attack the amphibious vectors of *S. japonicum*.

Using integrated control measures since the 1920s, the Japanese eventually eradicated schistosomiasis by the end of the 1970s (Kitani & Iuchi, 1990). Similarly, in the much more extensive endemic areas of *S. japonicum* in China, unremitting integrated control measures over a 40-year period have reduced the prevalence of schistosomiasis by 90% (Chen, 1989; Anon., 1992). Eradication has also been achieved in two other countries: *S. haematobium* has been eliminated in Tunisia, and *S. mansoni* in Monserrat (WHO, 1993). In several countries, particularly those where schisosomiasis was identified early on as a major public health problem, such as Brazil, Egypt, the Islamic Republic of Iran, the Philippines and Venezuela, significant reductions in disease prevalence have been achieved, usually by national control programmes that incorporate integrated measures. Even in cases where prevalence of infection has remained high, the prevalence of serious disease manifestations (such as Symmers' fibrosis and fibro-obstructive lesions of the urogenital tract) has often been reduced, largely by the use of population-based chemotherapeutic campaigns (WHO, 1993).

Set against this, however, is the demographic increase in younger people, who are most affected by the disease, thus increasing the size of the susceptible population. This, combined with the expansion of water resource developments and irrigation, has led to spread of the disease to new areas and to intensification of transmission in existing endemic areas. The WHO (1993) report on schistosomiasis control thus concluded that the global number of infected cases was similar to that in 1984. Furthermore, in only a very few areas has the snail vector been eradicated, so that, if control measures break down or are relaxed, the disease will rapidly sweep back and may in fact become worse than before because of loss of

immunity by the population. Currently, no antischistosomal vaccine for humans is available, although intensive efforts are being made to develop one.