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*

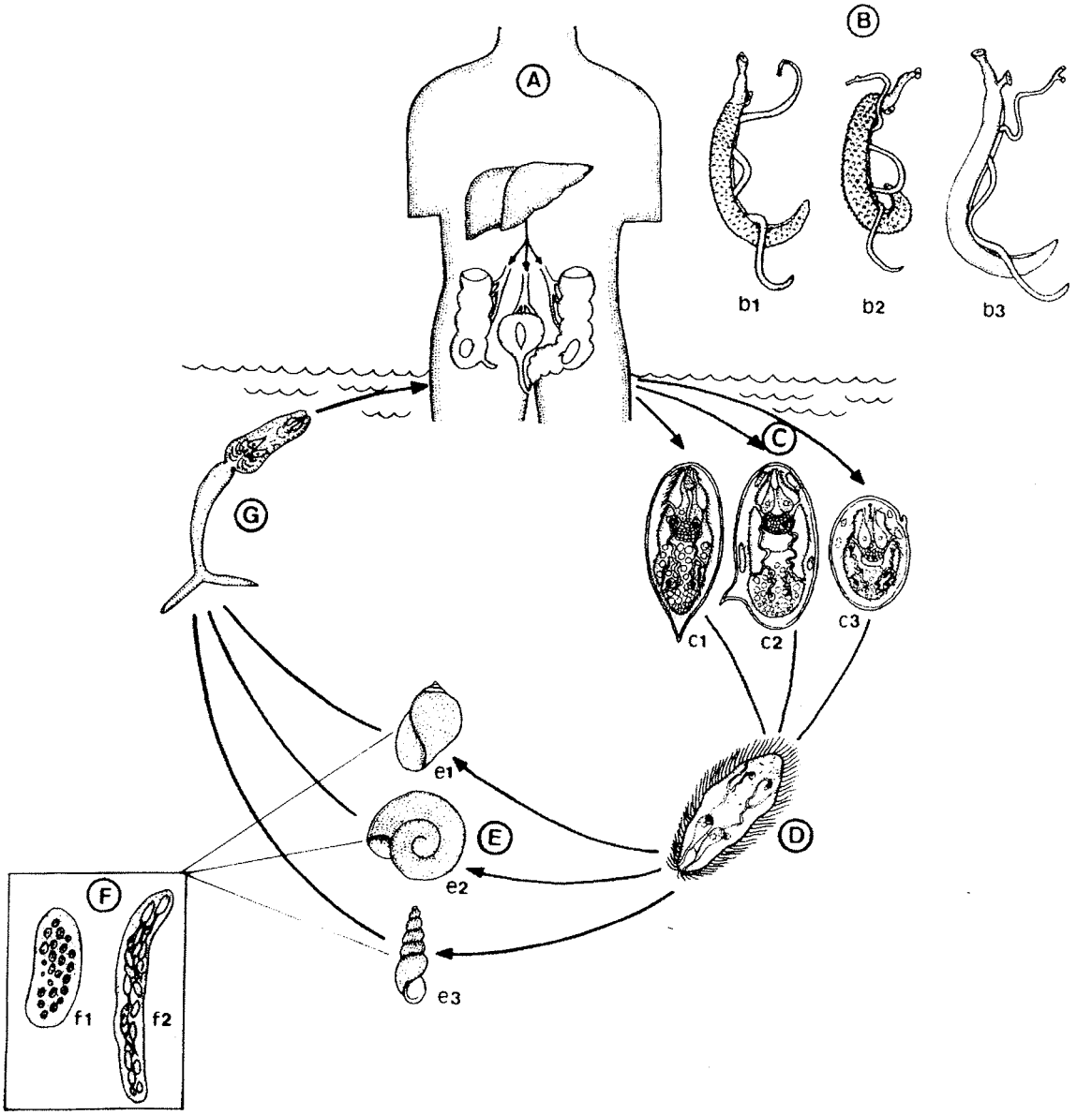
Unlike all other pathologically important trematodes, schistosomes are dioecious (rather than hermaphroditic). The adult worms are about 1 cm long, and the male has a deep ventral groove or schist (hence the term 'schistosome') in which the female worm resides permanently *in copulo*. Worms of each sex 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

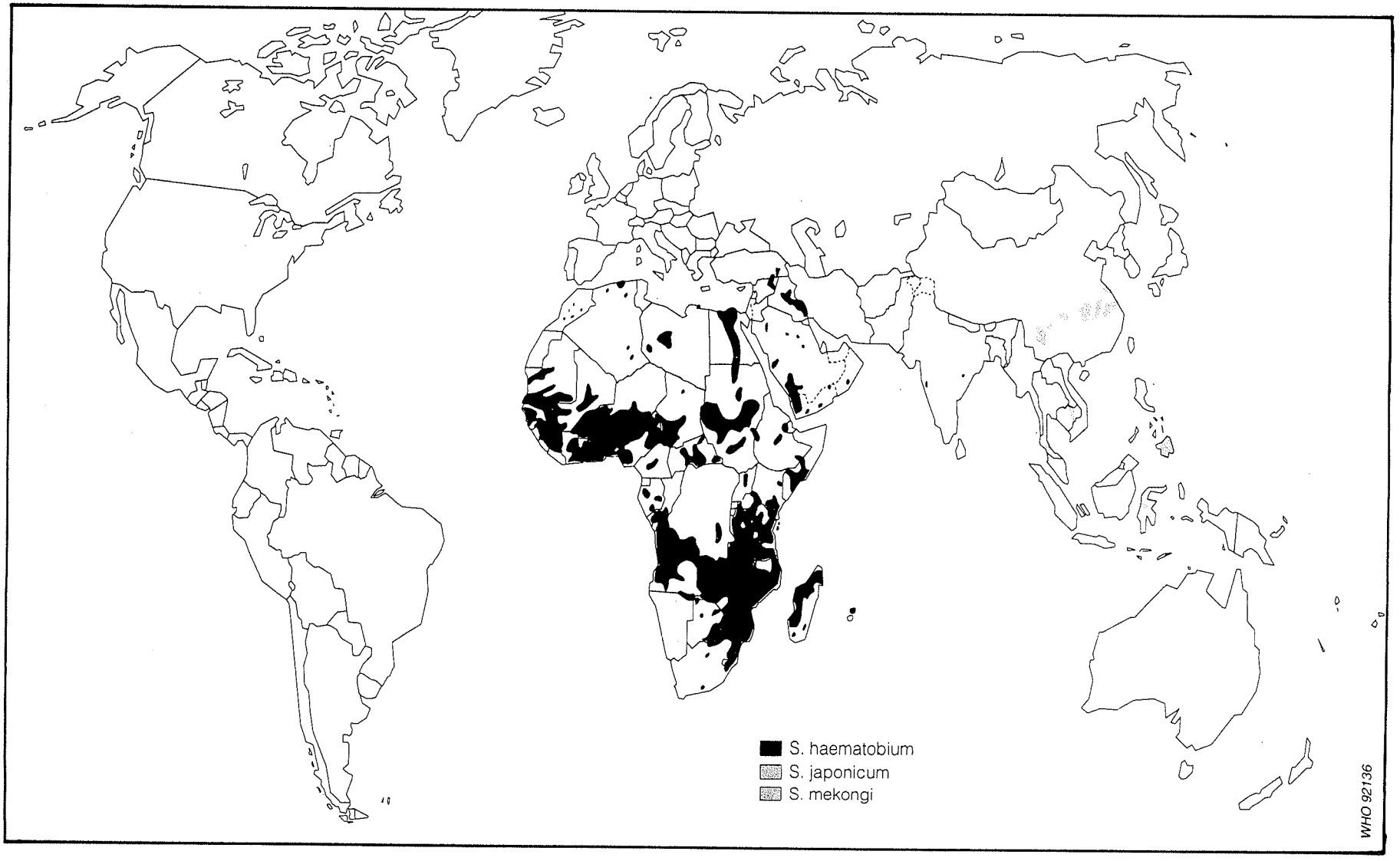
Country or area (by WHO region)	*S. haematobium*	*S. mansoni*	*S. intercalatum*
African Region			
Algeria	+		
Angola	+	+	
Benin	+	+	
Botswana	+	+	
Burkina Faso	+	+	
Burundi		+	
Cameroon	+	+	+
Central African Republic	+	+	+[a]
Chad	+	+	+[a]
Congo	+	+	+[a]
Côte d'Ivoire	+	+	
Equatorial Guinea			+
Ethiopia	+	+	
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*	

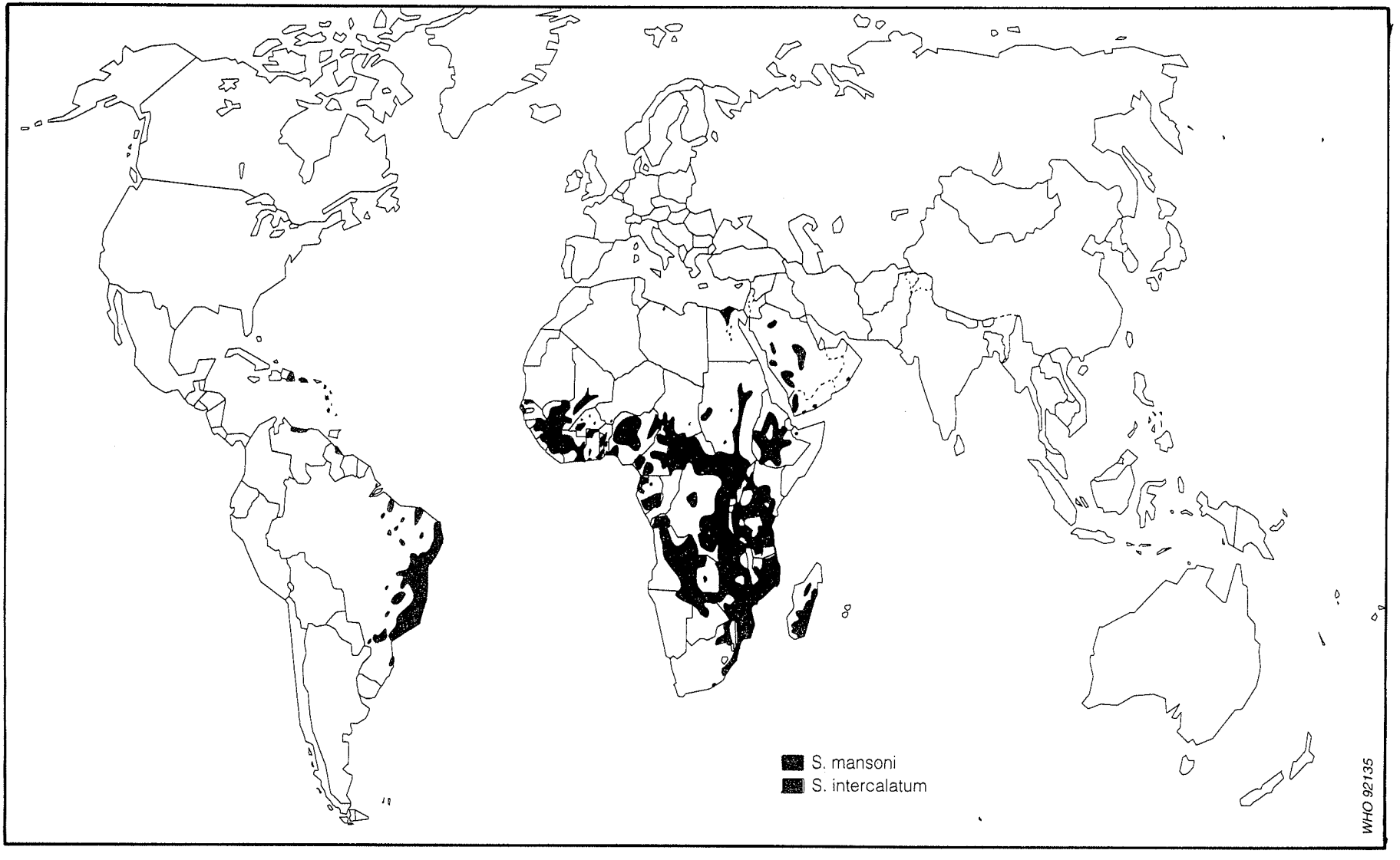
From WHO (1993)
[a]Confirmation required
[b]No recent transmission: Japan, Tunisia

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).

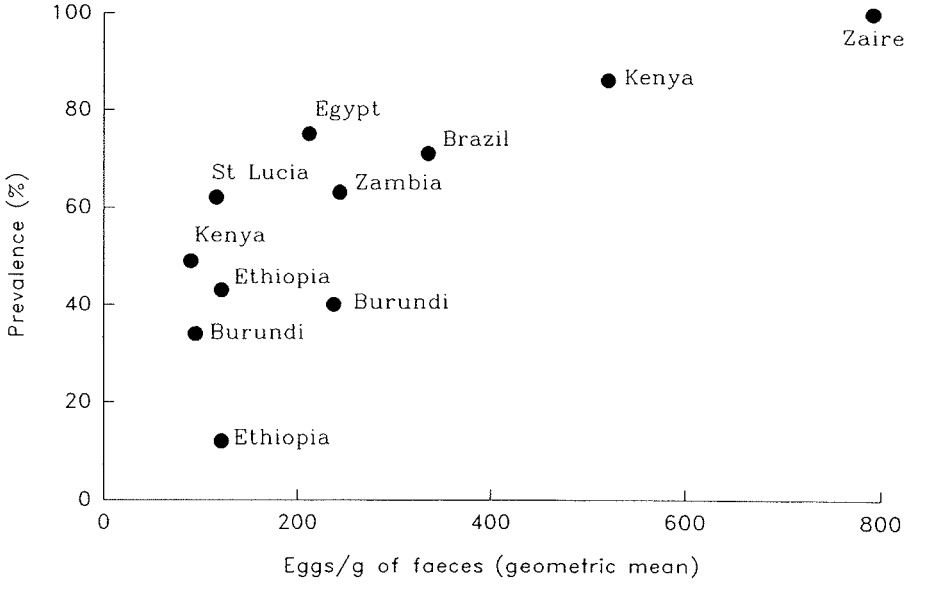
1.3.3 *Aggregation of infection*

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)

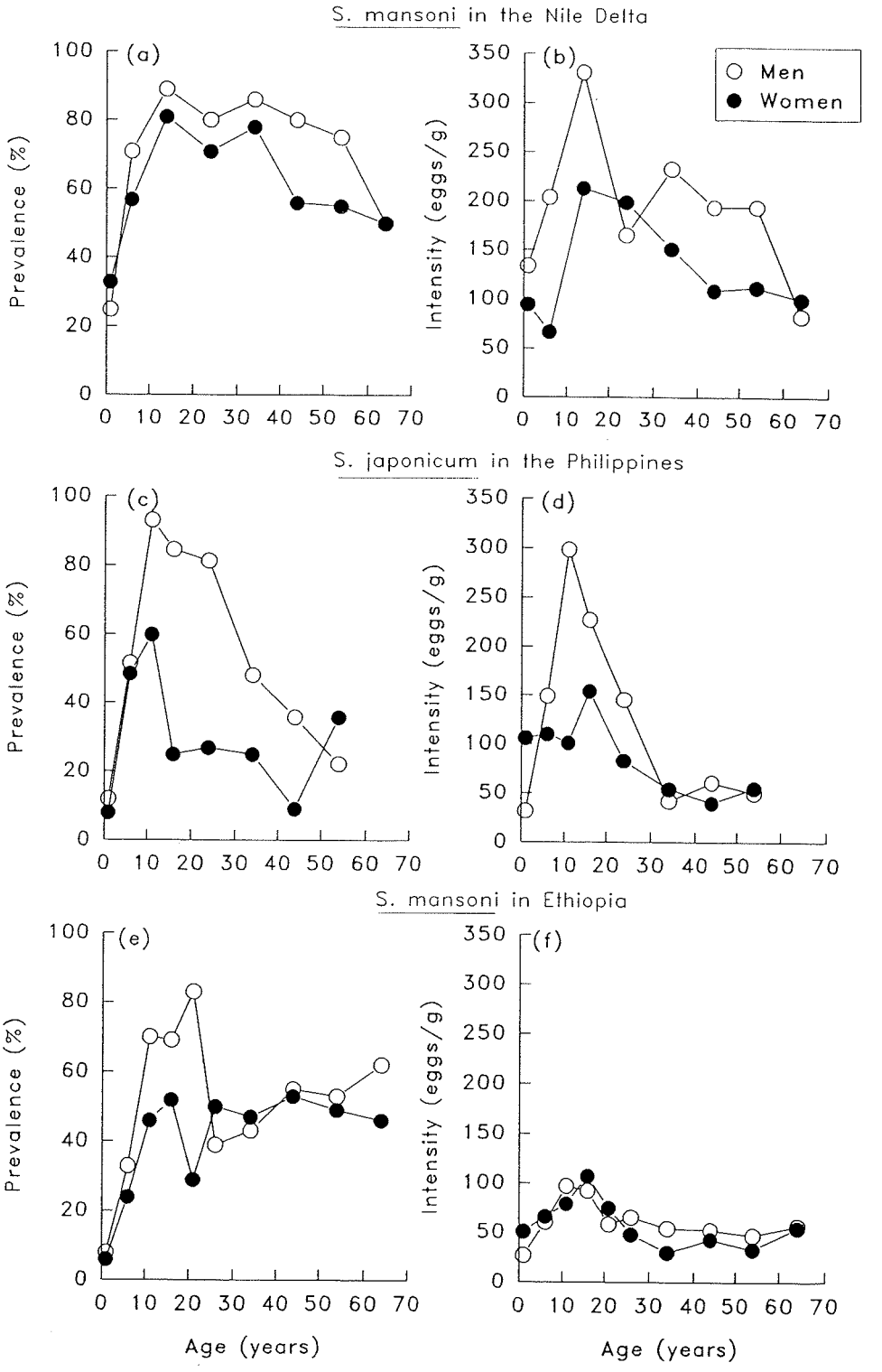
Definitions of 'heavy' infections are routinely included in most epidemiological studies (Sleigh & Mott, 1986). Throughout areas endemic for urinary schistosomiasis, most infection in people who excrete more than 50 eggs/10 ml of urine is associated with haematuria (Mott *et al.*, 1983). The definition 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.

2. Studies of Cancer in Humans

Concern about a causal relationship between infection with schistosomes and cancer is based on observations of patients who have been exposed to *S. haematobium*, *S. japonicum* and *S. mansoni*.

2.1 Descriptive studies

2.1.1 *Schistosoma haematobium*

The proportion of all cancers represented by urinary bladder cancer varies greatly within Africa and the Middle East, and the ratio of male to female frequency of occurrence is nearly as variable (Parkin, 1986). In Egypt, the proportion of bladder cancers among all cancers in men is twice that in Zambia, four times that in Zimbabwe and 10 times that in Algeria. Very few formal assessments of the correlation between bladder cancer incidence and the prevalence of *S. haematobium* have been done, but there are many informal descriptions of geographical correspondence between the areas affected by the two diseases.

Most of the early clinical descriptions of urinary bladder cancer in connection with evidence of schistosomiasis come from the Nile Delta, where there are few unexposed populations and no population-based incidence data (see section 2.2.1); however, in countries with less universal exposure, observations have been made on the geographical relationship between exposure to *S. haematobium* and bladder cancer occurrence. The common geographical pattern of occurrence of *S. haematobium* and bladder cancer has been noted by investigators in almost all endemic African countries (Table 2).

In addition to the link between the risk of a subpopulation for a haematobium schistosomiasis and the risk of the same population for urinary bladder cancer, a slightly more direct link has been noted; the proportion of bladder cancers that are squamous histologically in the population of a country is related to the proportion of cancerous bladder specimens from that population which contain evidence of past schistosomal infection in the form of eggs or egg remnants (Lucas, 1982a). This has been noted even within countries; in Iraq, for example, 36.1% of bladder cancer cases from the north are squamous-cell tumours and 4.9% have evidence of *S. haematobium*, whereas in the south, where *S. haematobium* is more prevalent, 54.8% are of the squamous variety and 32.2% have evidence of *S. haematobium*; those from the central part of the country show intermediary rates of 48.5% and 20.7%, respectively (Al-Fouadi & Parkin, 1984).

The two diseases have other characteristics in common. In a description of the pattern of urinary bladder cancer by occupation in the Nile Delta, 99% of the bladder cancers occurring in high-risk male agricultural workers (*fellahin*) were found to be associated with histological evidence of *S. haematobium* infection, whereas only 52% of the cases occurring in men with lower-risk occupations showed such evidence (Makhyoun *et al.*, 1971).

Table 2. Descriptive studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Outcome index	Exposure index	Geographical correlations	Secular or occupational correlations	Correlated sex ratios or age distributions
Talib (1970)[a]	Iraq, referral hospital	Proportional frequencies	Common knowledge	More patients from south and centre, where *S. haematobium* is endemic	–	–
Anjarwalla (1971)	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Patients from coastal area, where schistomiasis is common	–	–
Makhyoun *et al.* (1971)[a]	Egypt, Nile Delta University hospital	Proportional frequencies	Common knowledge	–	Cases in male *fellahin*: 99% histologically *S. haematobium* egg-positive Cases in men in other occupations: 52% positive	Exceptionally higher sex ratio for bilharzial cases (11.8:1) than for non-bilharzial (4.8:1), low-risk British (4.1:1) cases or high-risk Mozambican cases with exposure during field work (0.9:1)
Anthony (1974)	Uganda, referral hospital	Proportional frequencies	Frequency of schistosomiasis diagnoses	Bladder cancer, including squamous-cell cancers, unrelated to small foci of schistosomiasis	–	–
Bowry (1975)[a]	Kenya, referral pathology service	Proportional frequencies	Frequency of schistosomiasis diagnoses and school surveys	Cancer foci on coast and near Lake Victoria, both known foci of schistosomiasis	–	–
Malik *et al.* (1975)[a]	Sudan, referral hospital	Proportional frequencies	Ministry of Health records of 'highest endemicity'	Correspondence between frequency of bladder cancer and endemicity by province	–	–
Keen & Fripp (1980)[a]	South Africa (Transvaal)	Frequencies identified in regional surveys	None explicit	–	–	Wide variations in sex ratio (from 2:1 to 1:2) according to region and tribe
Lucas (1982)[a]	Africa	Proportional frequencies	Histological identification of *S. haematobium* eggs in bladder specimens	Geographical distribution of percentage of histologically *S. haematobium* egg-positive tumours correlated directly with percentage of all bladder cancers that are squamous-cell and inversely with the percentage that are transitional-cell tumours		

Table 2 (contd)

Reference	Location	Outcome index	Exposure index	Geographical correlations	Secular or occupational correlations	Correlated sex ratios or age distributions
Hanash (1984)	Saudi Arabia, referral hospital	Proportional frequencies	Known distribution of *S. haematobium* endemicity	Bladder cancer cases commonly come from endemic communities	–	–
Al-Fouadi & Parkin (1984)[a]	Iraq, urban hospitals	Registered cases	'Known distribution of *S. haematobium* endemicity'	Percentage of tumours that are squamous-cell and percentage of tumours that contain histologically identifiable *S. haematobium* eggs closely related to southern latitude [proximity to the river delta]	–	–
Kitinya *et al.* (1986)[a]	United Republic of Tanzania, referral hospital	Proportional frequencies	Known distribution of snail vectors in relation to altitude	Low proportion of squamous-cell tumours and low prevalence of *S. haematobium* at high elevations near Mt Kilimanjaro	–	–
Tawfik (1988)[a]	Egypt, referral hospital	Proportional frequencies	Histological identification of *S. haematobium* eggs in bladder specimens; records of control programme	–	High bladder cancer proportional frequency despite 20 years of successful control efforts (prevalence reduced from 60 to 10% in one province)	High sex ratio correlated with documented intensity of infection. As period of successful control efforts lengthens, mean age of bladder cancer increases.
Thomas *et al.* (1990)	Zimbabwe, referral hospital	Proportional frequencies	National prevalence surveys among schoolchildren	Estimated bladder cancer incidence correlated with prevalence of *S. haematobium* infection ($r = 0.87$; $p < 0.01$). Ratio of squamous-cell to transitional-cell tumours linked to *S. haematobium* prevalence: 12:1 where prevalence was 67%, 2:1 where prevalence was 17%	–	Sex ratio for squamous-cell tumours, 1.0; for transitional-cell tumours, 2.9:1.

[a]Correlation not formally tested

Whereas in the Nile Delta, where men do most of the agricultural work, the ratio of male to female cases of urinary bladder cancer with histological evidence of past infection may be as high as 12:1 (Makhyoun *et al.*, 1971), the sex ratio among those without such evidence approximates the 4:1 ratio seen in the United Kingdom (Prates & Gillman, 1959). In contrast, in Mozambique (Prates, 1963) and adjacent regions of the Transvaal in South Africa (Keen & Fripp, 1980), where women do most of the agricultural labour and are therefore more commonly infected, the sex ratios are reversed to 1:1.1 or even 1:2, even though ratios of 2:1 prevail among cases referred from nearby areas. The sex ratio of bladder cancer cases has also been linked to the histologically measured intensity of infection in tumour specimens, and ranged from 8.7:1 in heavily infected people, to 4:1 in those who are lightly infected, to 2:1 in those without eggs in Egypt (Tawfik, 1988).

In a community in Angola, where both males and females work in agriculture, the minimal age of infection with *S. haematobium* was 11 years. The mean age of patients with urinary bladder carcinomas associated with schstosomiasis was 44 years. The sex ratio was 1.6:1 for bladder carcinoma associated with schistosomiasis and 3.2:1 for bladder carcinoma not associated with schistosomal disease ($p \sim 0.05$) (da Silva Lopes, 1984).

It should be noted, however, that in Uganda, squamous-cell carcinomas of the urinary bladder are commoner than in Europe or North America in the absence of any relationship to known *S. haematobium* prevalence (Anthony, 1974).

Because of the lack of population-based cancer registration, the secular trends in incidence of squamous- or transitional-cell carcinomas of the urinary bladder have not been formally evaluated. In an area of the Nile Delta where the prevalence of *S. haematobium* infection was brought from a level of 60% in 1968 to 10% in 1988, no impact upon the rate of bladder cancer was clinically evident at the end of that period, although the mean age at diagnosis had increased (Tawfik, 1988).

2.1.2 *Schistosoma mansoni*

No description has appeared of the geographical occurrence of cancer in relation to the prevalence of *S. mansoni* infection. In relation to liver cancer, one observer pointed out that the pattern of occurrence in Africa and South America does not correspond to that which would be expected on the basis of a strong association with *S. haematobium* (Edington, 1979). The absence of any geographical relationship between colorectal cancer and colorectal schistosomiasis in Africa is even clearer. Despite wide variations in the geographical distribution of *S. mansoni*, colorectal cancer occurs in Africa with remarkable uniformity, insofar as the proportion of cases among all cancers provides pertinent information (Parkin, 1986). Moreover, reports from multiple centres in north, east, south and west Africa all indicate that evidence of schistosomal infection in colorectal tumour specimens is no commoner than would have been expected on the basis of the known prevalence of infection (Murray, 1967).

2.1.3 *Schistosoma japonicum*

The geographical co-occurrence of *S. japonicum* and cancer has been assessed formally (Table 3). Unfortunately, interpretation of the geographical patterns of occurrence of liver and colorectal cancers in Asia is difficult, because of known variations in the distribution of other causes of the same neoplasms, including hepatitis viral infection, dietary nutrients and carcinogenic dietary contaminants such as aflatoxins. In particular, a large correlation study from China assessed the association between mortality from schistosomiasis and from colorectal, liver, oesophageal and gastric cancers (Liu *et al.*, 1983). Correlations were calculated at two geographical levels: in 24 provinces of varying endemicity and in 10–98 counties within six provinces of high endemicity. [The Working Group noted that, in addition to the problems common to the interpretation of all correlation studies (see Preamble, p. 22), interpretation of studies correlating mortality from cancer and from schistosomiasis are complicated by the low diagnostic specificity of the latter cause of death; however, such misclassification of cause of death would probably lead to an underestimated correlation coefficient.]

(*a*) *Liver cancer*

In the study of Liu *et al.* (1983) in areas of high endemicity in China, significant correlations were found for both men and women in one province, while in four other provinces, the correlations were significantly positive only for women. No correlation was found in an analysis of 24 provinces, or in the seven endemic counties in Jiangsu Province (Guo *et al.*, 1984).

Within areas of Yamanashi Prefecture, Japan, classified on the basis of prevalence rates of schistosomiasis in 1958–62 [survey method not specified], the standardized mortality ratios for liver cancer on the basis of mortality in Japan were found to be significantly higher (at the 95% level) than those predicted in non-endemic areas and especially in aggregates of local endemic areas (Inaba *et al.*, 1977). Positive correlations were found between these prevalence rates and liver cancer rates in individual local areas in 1968–72, which were significant at the 95% level only for men (Table 3). The correlations for men increased in the period 1970–75, and while the correlation for women in that period became positive it remained compatible with chance. No adjustment was made for possible covariation with prevalence of hepatitis viral infection.

In a separate analysis analogous to that for liver cancer, Inaba (1982) assessed the frequency of mortality from other gastrointestinal malignancies in endemic areas by examining standardized mortality ratios in relation to those for Japan as a whole. No excess of cancer of the oesophagus, stomach, colon or rectum was noted for people of either sex, although the ratios of cancers of the bile duct and the pancreas in men were slightly but significantly elevated in endemic areas.

(*b*) *Cancers of the oesophagus and stomach*

In the study of Liu *et al.* (1983), significantly positive correlations were found for both stomach and oesophageal cancer for men and women in one province (Jiangxi), while the results for other provinces were inconsistent. No correlation was suggested in the analysis of 24 provinces with respect to stomach cancer. In another analysis (Guo *et al.*, 1984), no

Table 3. Descriptive studies of infection with *Schistosoma japonicum* and cancer

Reference	Population observed	Outcome index	Exposure index	Geographical correlations
Inaba *et al.* (1977)	Japan, Yamanashi Prefecture, localities	HCC mortality rate, 1968–72, 1970–75	Prevalence of schistosomiasis, both sexes, 1958–62	1968–72, males: 0.303*; females: -0.067 1970–75, males: 0.463*; females: 0.236
	Japan, Yamanashi Prefecture, endemic *versus* non-endemic areas	HCC mortality rate, 1970–75	Prevalence of schistosomiasis, both sexes, 1958–62	SMR, endemic males, 156 ± 21 females, 148 ± 26
				SMR, non-endemic males, 127 ± 17 females, 128 ± 21
Liu *et al.* (1983)	China, 24 provinces	Stomach cancer mortality rate	Schistosomiasis mortality rate	Not correlated
		Liver cancer mortality rate	Schistosomiasis mortality rate	Not correlated
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	Males, $r = 0.695, p < 0.001$; females, $r = 0.625, p < 0.005$
	China, 10–98 counties of six high endemicity provinces	Stomach cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in three provinces Females, positive correlation in four provinces ($p < 0.05$ in two)
		Oesophageal cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in two provinces Females, positive correlation in five provinces ($p < 0.05$ in one)
		Liver cancer mortality rate	Schistosomiasis mortality rate	Males, significant positive correlation in one province; Females, significant positive correlation in five provinces ($r = 0.22$, 0.24, 0.32, 0.39, 0.44)
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	Males, $r = 0.36$, 0.49, 0.58, 0.71, 0.81, 0.89 (all $p < 0.05$) Females, $r = 0.23$, 0.41, 0.44, 0.74, 0.85, 0.85 (all $p < 0.05$)

Table 3 (contd)

Reference	Population observed	Outcome index	Exposure index	Geographical correlations
Guo *et al.* (1984)	China, 7 counties of Jiangsu Province	Stomach cancer mortality rate	Schistosomiasis mortality rate	$r = -0.268, p < 0.001$ Inverse correlation with infection prevalence rate
		Oesophagus mortality rate	Schistosomiasis mortality rate	$r = 0.059, p \geq 0.20$
		HCC mortality rate	Schistosomiasis mortality rate	$r = 0.0053, p \geq 0.50$
		Colorectal cancer mortality rate	Schistosomiasis mortality rate	$r = 0.630, p < 0.001$ Direct correlation with infection prevalence rate
Xu & Su (1984)	China, 89 communes in 4 high-prevalence counties, Jiangsu Province 1977–79	Colorectal cancer mortality rate	Estimated *S. japonicum* infection prevalence rate	$r = 0.68, p < 0.01$
	24 communes, Haining county, Zhejiang Province	Colorectal cancer incidence rate	*S. japonicum* survey prevalence rate	$r = 0.60, p < 0.01$ (separately, colon, $r = 0.42$; rectum, $r = 0.48$)
Guo *et al.* (1985)[a]	China, Haining county, Zhejiang Province	Colorectal cancer mortality rate	*S. japonicum* survey prevalence rates	–
Li (1988)	China, 12 provinces in south	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 0.71, p < 0.01$
	10 counties of Jiaxing area of Zhejiang Province	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 0.90, p < 0.001$
	4 groups of counties in Jiaxing Prefecture	Colorectal cancer mortality	Incidence rate of schistosomiasis	$r = 1.00, p > 0.05$
Guo *et al.* (1993)	China, 49 rural counties selected on the basis of diversity of mortality from selected cancers	Colorectal cancer mortality rate	Schistosomiasis mortality rate	Univariate: males, $r = 0.395$, $p < 0.01$; females, $r = 0.538$, $p < 0.01$ Multivariate standardized: males, $r = 0.333, p < 0.01$; females, $r = 0.537, p < 0.01$

HCC, hepatocellular carcinoma; *, significant

[a]Correlation not formally tested

positive correlation between the prevalence of infection and mortality from either stomach or oesophageal cancer was found in the counties in Jiangsu Province.

(*c*) *Colorectal cancer*

In the study of Liu *et al.* (1983), mortality from colorectal cancer was correlated with that from schistosomiasis (r = 0.695 for men and 0.625 for women) in 24 Chinese provinces. In the analysis by county, significantly positive correlations were found for people of each sex in all six provinces (r, 0.23–0.89; median, 0.61).

Colorectal cancer mortality was correlated with 'prevalence of infection' (r = 0.63 for the two sexes combined) in seven counties in Jiangsu (Guo *et al.*, 1984); and the prevalence of infection was correlated with cancer mortality (r = 0.68) in the 89 communes of four high-prevalence counties in the Province (Xu & Su, 1984) and with cancer incidence (r = 0.42 for colon, 0.48 for rectum, 0.60 overall) in 24 communes of Haining County, Zhejiang Province (Xu & Su, 1984). Mortality from colorectal cancer was correlated with the incidence of schistosomiasis in 12 provinces of South China (r = 0.71), in 10 counties of the Jiaxing area of Zhejiang Province (r = 0.90) and in four county groups in Zhejiang Province (r = 1.00) (Li, 1988). Although in the latter analyses concern was raised about covariation between schistosomal infection and low levels of dietary selenium, in none of the above were dietary or other possible causes of colorectal cancer taken into consideration.

In a large correlation study from China, 65 rural counties were selected on the basis of the diversity of mortality rates from selected malignancies in an attempt to examine links between cancer mortality in 1973–75 and the dietary habits in 1983 of carefully selected, representative inhabitants (Chen *et al.*, 1990). The correlation between mortality rates for colorectal cancer and those for schistosomiasis was formally examined in a regression analysis, with adjustment for estimated consumption of individual nutrients and micronutrients. A significant association (r = 0.89, $p < 0.001$) was found. The correlation was significant for mortality from cancers of both colon (0.72) and rectum (0.88) when they were analysed in a subset of 49 counties. In both studies, the strength of the relationship between mortality from schistosomiasis and from cancer was as strong and consistent as that between mortality from schistosomiasis and any other variable. In a separate analysis of mortality from colon cancer by sex, significant associations with mortality from schistosomiasis were found for both men and women (Guo *et al.*, 1993).

While decades have passed since the first substantial efforts were made to control *S. japonicum* infection, no serious attempt has been made to assess the impact of eradication on the incidence of colorectal cancer. In one area, the continued high incidence of colorectal cancer has been attributed to the large number of people with controlled, advanced schistosomiasis (Guo *et al.*, 1985).

2.2 Case reports and case series

The first suggestion of a link between schistosomiasis and cancer came from careful assessment of clinical and pathological observations (Goebel, 1905; Ferguson, 1911; Kazama, 1921); however, as knowledge of the distribution and presentation of both schistosomiasis and cancer has accumulated, it has become apparent that case reports and

series cannot help in assessing cancer etiology. In endemic areas, substantial proportions of the population are infected. Moreover, evidence of infection is widely disseminated throughout the body, remains there throughout life and may or may not produce symptomatic disease. Under the null hypothesis of no association between infection and cancer occurrence, it is therefore to be expected that a substantial proportion of the population of all ages will have been among those with clinical or subclinical disease, that a substantial proportion of patients with newly diagnosed cancer will show evidence of past infection, that evidence of infection may appear in virtually any organ of the body, and that such evidence of infection may therefore be expected to be incorporated in or found adjacent to virtually any tumour. Nonetheless, cases and case series can add credibility to the evidence of a causal relationship between these infections and cancer by documenting the anatomical proximity of the effects of infection to the appearance of the malignancy and by illustrating changes in the clinical and pathological characteristics of malignancies as they appear in conjunction with the infection.

2.2.1 *Schistosoma haematobium*

Subsequent to the early reports, large series of cases of urinary bladder cancer have been reported in association with evidence of *S. haematobium* infection (see Box).

The case descriptions have repeatedly emphasized the preponderance of squamous-cell urinary bladder tumours among cases with evidence of schistosomal infection, the somewhat different distribution over the surface of the bladder (notably the rarity of occurrence in the trigone) in comparison with bladder tumours in developed countries, and the prevalence of metaplastic changes in conjunction with evidence of infection (da Silva Lopes, 1984). Clinically, the most notable and consistent feature described in these series is the relative youth of the cases with evidence of a link to *S. haematobium* infection. While this observation is made in almost all of the reports, and is usually interpreted as constituting evidence of etiological heterogeneity, the finding does not constitute strong evidence because evidence of the infection is known to decrease in frequency with age.

Other than urinary bladder cancer, the malignancies most frequently reported in association with *S. haematobium* infection are those of the female genitalia. A few dozen cases of squamous cervical carcinoma have been reported from endemic areas (Badawy, 1962; Youssef *et al.*, 1962; Berry, 1966; Sharma *et al.*, 1970; Youssef *et al.*, 1970; Bognel *et al.*, 1980; Schwartz, 1984; El Tabbakh & Hamza, 1989), and the same authors and others (Shafeek, 1957; Iskander & Kamel, 1968; Sunder-Raj, 1976; Al-Adnani & Saleh, 1982; El-Maraghy *et al.*, 1982) have reported certain other genital squamous malignancies, ovarian cystadenocarcinomas, Brenner tumours and teratomas. It has been alleged that breast cancers in men infected with *S. haematobium* constitute a relatively high proportion of all male breast cancers in Egypt (El-Gazayerli & Abdel-Aziz, 1963; Sherif *et al.*, 1980), but the reported numbers are small and cannot be evaluated. Relatively small numbers of other malignancies that have been reported in association with evidence of *S. haematobium* infection include hepatocellular carcinoma (Nkrumah, 1964; Hashem, 1971), bladder sarcoma (Alwan *et al.*, 1988) and lymphomas (Edington *et al.*, 1970; Cheever *et al.*, 1978).

Angola (da Silva Lopes, 1984)
Egypt (Mohamed, 1954; Mustacchi & Shimkin, 1958; El-Gazayerli & Khalil, 1959; Hashem *et al.*, 1961; Aboul Nasr *et al.*, 1962; Makhyoun *et al.*, 1971; El-Bolkainy *et al.*, 1972; Khafagy *et al.*, 1972; El-Sebai, 1980; El-Bolkainy *et al.*, 1981; Christie *et al.*, 1986a; Tawfik, 1988; Fukushima *et al.*, 1989)
Senegal (Quenum, 1967)
Zambia (Bhagwandeen, 1976; Elem & Purohit, 1983)
Nigeria (Attah & Nkposong, 1976), Malawi (Lucas, 1982b)
Sudan (Malik *et al.*, 1975; Sharfi *et al.*, 1992)
Kenya (Anjarwalla, 1971; Bowry, 1975)
Iraq (Al Adnani & Saleh, 1983; Al-Fouadi & Parkin, 1984)
Natal (Cooppan *et al.*, 1984)
South Africa (Transvaal) (Higginson & Oettlé, 1962; Hinder & Schmaman, 1969; Kisner, 1973)
Uganda (Dodge, 1962)
Saudi Arabia (Cutajar, 1983; Hanash, 1984; Khurana *et al.*, 1992)
Kuwait (Al-Shukri *et al.*, 1987)
Mozambique (Prates & Gillman, 1959; Gillman & Prates, 1962; Ebert, 1987)
United Republic of Tanzania (Kitinya *et al.*, 1986)
Zimbabwe (Houston, 1964; Gelfand *et al.*, 1967; Thomas *et al.*, 1990) and
Among immigrants in Europe (Wagenknecht, 1974; Pieron *et al.*, 1983; Delmas *et al.*, 1986) or visitors to Africa (Diaz Hernandez *et al.*, 1984).

2.2.2 *Schistosoma mansoni*

Cases of liver cancer have been reported in connection with evidence of *S. mansoni* infection from Egypt (Hashem, 1971), Mozambique (Prates & Torres, 1965), Brazil (Cheever & Andrade, 1967; Lyra *et al.*, 1976), Puerto Rico (Martinez-Maldonado *et al.*, 1965), Saudi Arabia (Nouh *et al.*, 1990) and Nigeria (Edington *et al.*, 1970). Similarly, cases of colorectal cancer have frequently been described from Egypt (Afifi, 1948; Dimmette *et al.*, 1956; Cheever *et al.*, 1978) and Lebanon (Uthman *et al.*, 1991). Andrade and Abreu (1971) reported the occurrence of eight giant follicular lymphomas in 863 spleens removed from patients with portal hypertension due to infection with *S. mansoni*; subsequently, six additional cases of this neoplasm were described (Paes & Marigo, 1981) in a similar series of 714 spleens. Of these 14 lymphomas, four were further confirmed in biopsy samples or at autopsy; the rest were lost to follow-up. Although other individual cases of diverse lymphomas have been reported in patients with schistosomiasis (Andrade & Abreu, 1971; Cheever *et al.*, 1978; de Andrade *et al.*, 1982; Chirimwami *et al.*, 1991), no reports of giant follicular-cell lymphoma have subsequently appeared.

Other malignancies that have been reported in association with evidence of *S. mansoni* infection include prostatic cancer (Alexis & Domingo, 1986; Godec *et al.*, 1992), ovarian

teratoma (Kahn *et al.*, 1978), uterine leiomyosarcoma (Joyce *et al.*, 1972), renal-cell carcinoma (Oro Ortiz *et al.*, 1991), rectal carcinoid tumour (Satti *et al.*, 1988) and cancer of the cervix (Coelho *et al.*, 1979; Wright *et al.*, 1982).

2.2.3 *Schistosoma japonicum*

Most of the cases or series of cases of liver cancers reported in association with *S. japonicum* infection have come from Japan (Iuchi *et al.*, 1971; Nakashima *et al.*, 1975; Kojiro *et al.*, 1986; Fujimoto *et al.*, 1989; Kitani & Iuchi, 1990; Uetsuji *et al.*, 1990). Within such series, cases of liver cancer have been reported to occur commonly in patients who responded positively to a skin test or were shown histologically to have *S. japonicum* infection (Iuchi *et al.*, 1971; Nakashima *et al.*, 1975; Kojiro *et al.*, 1986); in patients who had evidence of hepatitis viral infection (Nakashima *et al.*, 1975; Kitani & Iuchi, 1990; Kojiro *et al.*, 1986); and in those with schistosoma-associated cirrhosis (Iuchi *et al.*, 1971; Kitani & Iuchi, 1990). In one small series from an endemic area, *S. japonicum* was not found to be especially common in cases of liver cancer (Kamo & Ebato, 1982).

Series of cases of gastric cancer associated with histological evidence of *S. japonicum* infection have been reported from both Japan (Amano, 1980) and China (Wang, 1979; Qian & Yi, 1980; Feng & Shi, 1981; Wang & Kuang, 1983; Zhou, 1986).

Series of cases of colorectal cancer found in association with infection with *S. japonicum* have been reported from Japan (Shindo, 1976; Inoguchi *et al.*, 1978; Naito *et al.*, 1979; Amano, 1980; Hashimoto *et al.*, 1986; Sekiguchi *et al.*, 1989), the Phillipines (Abanilla, 1986) and China (Chen & Chen, 1957; Tsou & Ying, 1958; Wu *et al.*, 1960; Chuang *et al.*, 1979; Chen *et al.*, 1980; Chen *et al.*, 1981; Zhao & Wong, 1981; Liu *et al.*, 1983; Zhuang *et al.*, 1985; Chen, 1986). As in studies of bladder cancer, schistosomally infected patients are of younger average age in most series (Abanilla, 1986; Chen, 1986). This observation is difficult to interpret in the light of differences in the prevalence of infection with age.

Other malignancies that have been reported as individual cases in relation to *S. japonicum* infection include squamous-cell carcinoma of the skin (Ohtake *et al.*, 1991), malignant schwannoma (Schwartz, 1982), carcinoma of the parotid gland (Tangchai & Poshayalakshana, 1968), bronchogenic carcinoma (Ishihara *et al.*, 1984) and breast cancer (Zhou, 1983).

2.3 Cohort study

Inaba (1984) categorized all 2067 people native to a locality in Yamanashi Prefecture, Japan, endemic for *S. japonicum* infection into four classes, depending on whether they had resided before 1957 in that place for more than 50 years, 30–49 years, 10–29 years or fewer than 10 years (Table 4). Duration of residence was taken as an indicator of extent of exposure. They were then followed in the locality-based registers available in Japan, and all death certificates were collected. There were 26 deaths from liver cancer and 16 from colorectal cancer (nine from colon cancer). It was found that men who had lived for more than nine but less than 50 years in a community had a significantly high risk of liver cancer, and that women living in the community for 50 or more years had a significantly high risk of colorectal cancer. No adjustment was made for diet or for hepatitis viral infection.

Table 4. Cohort study of cancer based on death certificates for natives of a town in Yamanashi Prefecture, Japan, endemic for *S. japonicum* infection

Length of residence before 1957 (years)	Number of exposed subjects	Cancer	Number of cases	SMR	
				Males	Females
0–9	428	Liver	1	0.81	–
10–29	575		9	3.2[a]	2.5
30–49	655		10	2.9[a]	1.1
≥ 50	404		6	1.8	0.88
0–9	428	Colon	0	–	–
10–29	575		2	–	2.0
30–49	655		4	2.4	1.9
≥ 50	404		3	–	4.6[a]

From Inaba (1984); SMR, standardized mortality rate
[a] 95% confidence interval excludes 1.0

2.4 Case–control studies (with retrospective exposure assessment)

2.4.1 *Schistosoma haematobium*

Mustacchi and Shimkin (1958) identified 48 male and 7 female hospitalized patients with urinary bladder cancer in the Egyptian Nile Delta city of Tanta among 1472 consecutive admissions to the hospital. All patients were evaluated in relation to the presence of *S. haematobium* eggs in a urine sample taken at admission and to any subsequent evidence of *S. haematobium* infection [the latter but not the former could have been obtained on the basis of knowledge of the presence of bladder cancer]. After multivariate adjustment for age, sex and urban or rural origin, odds ratios of 2.1 ($p = 0.04$) were seen for the finding of eggs at the time of admission and 2.2 ($p < 0.01$) for any subsequent evidence of schistosomal infection.

Prates and Gillman (1959) compared 100 urinary bladder cancer cases in Maputo, Mozambique, with 185 cases found at autopsy in people over 40 years of age with respect to the frequency of identification of *S. haematobium* eggs in relation to the histological type of bladder cancer. Eggs were found in 33 of the cases found at autopsy and in 61% of controls [odds ratio, 0.3; 95% confidence interval (CI), 0.2–0.5]. Eggs were found in 56% of the 59 squamous-cell cancer patients but in none of the transitional-cell cancer patients. [The methods used to examine the biopsy and autopsy specimens were dissimilar, and there was no reconciliation of the high rate in cadavers, despite the absence of eggs in the bladders of people with transitional-cell cancer. The causes of death of the controls were not described, and no adjustment was made for differences in specific age or place of origin.]

Hinder and Schmaman (1969) compared the prevalence of histologically identified eggs in punch biopsy specimens from 79 patients with urinary bladder carcinoma in Johannesburg, South Africa, with the prevalence in two or more full-thickness biopsy specimens from 101 people over the age 15 who came to autopsy. Eggs were identified in 34.2% of the cases but in only 9.0% of the autopsied patients [odds ratio, 5.3; 95% CI,

2.3–12]. The causes of death of the controls were not provided, and no adjustment was made for differences in specific age or place of origin. When cases were analysed by histological type, 19% of transitional-cell carcinomas and 68% of squamous-cell carcinomas contained eggs.

Gelfand *et al.* (1967), in Harare, Zimbabwe, compared 33 patients with urinary bladder cancer with other hospital patients who had been 'submitted to similar investigation' and were matched on age, sex and race. Comparisons were made on the basis of the results of pelvic X-rays (33 pairs) and rectal biopsies (31 pairs). Among the 16 pairs discordant for calcified eggs identified by X-ray, the case was positive in 15, giving an odds ratio of [15; 95% CI, 2.0–114]; among the 15 pairs discordant for the results of rectal biopsy, the case was positive in 13, giving an odds ratio of [6.5; 95% CI, 1.5–29]. The diagnoses of disease in the controls were not described, and no adjustment was made for differences in smoking habits or place of origin.

In a project for cytological screening of urinary bladder cancer conducted from 1976 to 1979 in a location in the Nile Delta highly endemic for *S. haematobium*, participants over 20 years of age were characterized by occupation, on the presumption that the 4769 agricultural labourers in this age group had a higher prevalence of infection than 1112 people with other occupations (El-Bokainy *et al.*, 1982). All 10 cases of bladder cancer detected and confirmed histologically appeared among the agricultural workers [prevalence ratio, ∞]. Although the ages of the subjects were not analysed in detail, it was concluded that adults of this working class were at increased risk of bladder cancer.

In Zambia, Elem and Purohit (1983) compared the bladders of 50 patients who had died of urinary bladder cancer with bladders from age- and sex-matched cadavers (mostly trauma victims matched on age and sex to the decedent) by means of X-ray examination and digestion of tissues away from the eggs they contained. The bladders of the cases were [3.8] [95% CI, 1.4–10] times as likely to show schistosomiasis by X-ray and [14] [95% CI, 4.6–43] times as likely to contain *S. haematobium* eggs.

In the Bulawayo region of Zimbabwe, cancer registration procedures from 1963 to 1977 included collection of information about exposures, including past history of clinical schistosomiasis ('bilharzia' or 'blood in the urine') (Skinner *et al.*, 1993). Some difference in the availability of information about past schistosomiasis is evident between cases of urinary bladder cancer (61%) and cases of cancer of other types (50%). The exposures of 305 patients with bladder cancer were compared with those of 3145 other cancer patients, with and without exclusion of people with cancers known to be linked to smoking. The occurrence of bladder cancer was associated with place of origin, a lower level of education and a more menial occupation. No effect of smoking was found for squamous-cell cancers and only a modest effect (1.3) for other cancers. For a history of schistosomiasis in men, the odds ratio (using all other cancer cases as controls, relative to no such history and adjusted for age, tobacco use, province of origin, education and occupation) was 3.9 (95% CI, 2.9–5.1) for all types of cancer and 3.4 for both squamous-cell cancer and other specified carcinomas. When the cases of smoking-related cancers were excluded from the control group, the odds ratio for squamous-cell cancers increased to 3.9 and that for other cancers dropped to 3.1.

These studies are summarized in Table 5.

Table 5. Case–control studies of infection with *Schistosoma haematobium* and urinary bladder cancer

Reference	Location	Source of cases	Source of controls	Measure of exposure	No. of cases/ no. of controls	Cases/controls exposed (%)	Odds ratio	95% CI (or *p*)	Cases with squamous-cell tumours (%)
Mustacchi & Shimkin (1958)	Tanta, Nile Delta, Egypt		Other admissions to hospital	Eggs in first urine sample	55/1417	14.5/7.6	2.1[a]	0.04	Not specified
				All clinical evidence, including history and cystoscopy	55/1417	49.0/23.3	2.2[a]	< 0.01	
Prates & Gillman (1959)	Maputo, Mozambique		Autopsied people > 40 years	Eggs identified in histological sections	100/185	33/61.1	[0.3	0.2–0.5]	59 (56 with past exposure)
Hinder & Schmaman (1969)	Johannesburg, South Africa		Autopsied people > 15 years	Post-mortem punch biopsy sample	79/101	34.2/9.0	[5.3	2.3–12]	28 (68 with past exposure)
Gelfand *et al.* (1967)	Harare, Zimbabwe		Matched patients[b] of same age, sex, race, on different hospital ward	Pelvic X-ray	33/33	45.5/3.03	[15	2.0–114]	62 (62 with past exposure)
				Rectal biopsy	31/31	54.8/19.4 (discordant matched pairs 1) 15/1 2) 13/2)	[6.5	1.5–29]	
El-Bolkainy *et al.* (1982)	Dakahliya Governorate, Nile Delta, Egypt	Rural residents participating in a bladder screening programme subdivided by occupation		Occupation as farmer	10/5871	100/81	∞		50
Elem & Purohit (1983)	Lusaka, Zambia		Cadavers without malignancy (mostly traumatic death)	Digestion and centrifugation of bladder	50/50	94.0/40.0	[14	4.6–43]	72
				Pelvic X-ray	50/50	38/14	[3.8	1.4–10]	
Skinner *et al.* (1993)	Bulawayo, Zimbabwe	Cancer registry cases, males	Registry cases with other cancers	Self-reported history of bilharzia or blood in urine	305/3145	348/11.7	3.9[c]	[2.9–5.1]	71. No change when tobacco-related cancers excluded from controls

[a]Adjusted for age, sex and urban or rural residence

[b]Who were 'submitted to same procedure'

[c]Adjusted for age, period, province, drinking and smoking

Of interest is an additional case–control study of urinary bladder cancer, which was not performed to test the hypothesis of schistosomal etiology (Table 6). Makhyoun (1974) compared males admitted to hospital for urinary bladder cancer in Alexandria and Tanta, Egypt, with other admitted males, matched on age and smoking history, after stratification of cases and controls on the basis of history of clinical schistosomiasis. In 80% of people without such a history who had smoked heavily or moderately, the malignancies were strongly associated with cumulative smoking history. Only 23% of the schistosomiasis patients had smoked moderately or heavily, and the link between cancer and smoking in these subjects, while present, was weaker. [While the role of past clinical schistosomiasis in bladder cancer was not assessed within groups comparable for past smoking history, the low level of smoking among the patients with *S. haematobium*-associated cancer makes it extremely unlikely that the pattern of smoking could explain the strong links between infection and bladder cancer.]

Table 6. Case–control study of urinary bladder cancer in relation to smoking and history of infection with *Schistosoma haematobium* among males admitted to hospital

Infection status	Smoking index[a]	No. exposed		Odds ratio
		Cases	Controls	
History of *S. haematobium* infection	None	66	80	1.0
	Light (< 300)	149	145	1.3
	Moderate (300–600)	42	35	1.5
	Heavy (> 600)	21	18	1.4
	Moderate–heavy	63	53	1.4
No history of *S. haematobium* infection	None	15	23	1.0
	Light (< 300)	3	24	0.2
	Moderate (300–600)	41	27	2.3
	Heavy (> 600)	28	13	3.3[b]
	Moderate–heavy	69	40	2.6[b]

From Makhyoun (1974); odds ratios calculated by the Working Group.
[a]Daily number of cigarettes times number of years smoking
[b]Significantly different at $p < 0.01$

2.4.2 *Schistosoma japonicum*

In a comparison based on skin testing for antigens to *S. japonicum*, Iuchi *et al.* (1971) found that 85.2% of 52 cases of hepatocellular carcinoma and 68.2% of 217 other hospital in-patients over 40 years of age had antigens. No adjustment was made for evidence of past hepatitis viral infection.

Inaba *et al.* (1984) used skin testing and medical histories to compare 62 cases of liver cancer diagnosed in seven hospitals in an endemic area, Yamanashi Prefecture, Japan, in 1977–79 with age- and sex-matched hospital controls admitted for various diseases other than liver disease. While the univariate relative risk was 9.5 [95% CI, 2.2–41], restriction of the analysis to the 88 subjects seronegative for hepatitis B surface antigen and their controls gave a relative risk of [6.7; 1.5–30] for 39 alcohol users and of [4.7; 1.2–19] for 49 non-users.

Guo and Lu (1987) compared 166 patients who had died of liver cancer with 166 people who had died from other cancers and with 166 healthy people, both groups matched on age, sex and place of residence with respect to a history of *S. japonicum* infection. The matched odds ratio for schistosomal infection based on both series of controls was 2.2 ($p < 0.01$). Relative risks of [2.5; 95% CI, 1.4–4.4] and [2.3; 1.3–4.1] were found in relation to cancer decedents and healthy controls, respectively, after adjustment for smoking and family history of liver cancer but not for evidence of hepatitis viral infection. The relative risk estimates increased significantly with the interval since diagnosis of schistosomiasis, whether cancer or healthy controls were used. Dietary exposure to aflatoxins was considered not to be prevalent in this area.

Amano (1980) compared 362 patients with stomach cancer who were treated surgically in Yamanashi Prefecture, Japan, with 897 surgical cases with non-malignant disease of the stomach and duodenum, and found *S. japonicum* eggs [1.8] [95% CI, 1.3–2.6] times more frequently in the tissues of cases than in those of controls. No adjustment was made for potential confounders. In the same study, eggs were found [1.2] [0.62–2.5] times more often in the tissues of 103 colon cancer cases than in the 96 controls with benign disease of the colon. No adjustment was made for diet or other potential confounders.

In endemic Kunshan County in Jiangsu Province, China, Xu and Su (1984) gathered medical histories on schistosomiasis for all colorectal cancer patients and for patients with other cancers and from healthy neighbours, each matched on age, sex, occupation and work unit. While no significant association was found between colon cancer and past history, odds ratios of 8.3 and 4.5 were found for rectal cancer in comparisons with cancer controls and healthy controls, respectively. No adjustment was made for diet or other potential determinants of colorectal cancer.

In the same county, Guo *et al.* (1987) compared people who had died of colon cancer with those who had died of lung cancer and with healthy people, with respect to any medical history of early- or late-stage schistosomiasis. In relation to healthy controls, odds ratios of 2.4 [CI not given] were found for a history of early-stage infection and 5.5 [CI not given] for a history of late-stage schistosomal disease. After adjustment for smoking and a family history of colon cancer, but not for diet or exercise, significant associations were still found: 2.1 (95% CI, 1.1–3.8) and 4.2 (1.2–15) in relation to lung cancer controls for early- and late-stage disease, respectively, and 2.4 (1.1–5.0) and 5.7 (1.3–25) for the same exposures in relation to healthy controls. The risk was found to increase stepwise from 1.2 to 4.3 after < 10 years to > 30 cumulative years of infection [CI not given].

These studies are summarized in Table 7.

A number of studies have addressed the association between infections with *S. mansoni* and *S. japonicum* and cancer of the liver. The possible confounding of schistosomal infection with hepatitis viral infection (see IARC, 1994) in these studies has rarely been addressed empirically. A recent review of the coincidence of infection with hepatitis B virus and with *S. mansoni* and *S. japonicum* in population-based studies (Chen *et al.*, 1993) showed no significant increase in the prevalence of hepatitis B surface antigenaemia in people with these schistosomal infections. The prevalence of joint infection is, however, higher in hospital patients than in members of the corresponding general population; in particular, patients hospitalized with hepatosplenic schistosomiasis are more likely to be seropositive

Table 7. Case–control studies of infection with *Schistosoma japonicum* and cancer

Reference	Location	Source of cases	Source of controls	Measure of exposure	Number of cases/controls	Exposure in cases/controls	Odds ratio	95% CI
Liver cancer								
Iuchi *et al.* (1971)	Kofu, Yamanashi Prefecture, Japan	Previous diagnoses in hospital autopsies	Other in-patients	Skin test for *S. japonicum*	61/303	Prevalence of + 91.8%/53.1%	[9.9]	[3.9–25]
				Histology	61/21	91.8%/71.4%	[4.5]	[1.2–17]
Inaba *et al.* (1984)	Yamanashi Prefecture, Japan	Diagnoses in 7 hospitals, 1977–79	Patients matched on sex, age, hospital	Skin test for *S. japonicum*; medical history	62/62		9.5	[2.2–41]
						Negative for hepatitis B surface antigen, alcohol use	[6.7]	[1.5–30]
						Negative for hepatitis B surface antigen, no alcohol use	[4.7]	[1.2–19]
Guo & Lu (1987)	Kunshan County, Jiangsu Province, China	Liver cancer deaths, 1982–83	Deaths from other cancers 'Healthy people', matched on age, sex, county of residence	History of infection	166/166/166		Matched odds ratio, 2.2 ($p < 0.01$); unmatched [1.9 for cancer controls],	[1.1–3.3]
							[2.1 for healthy controls]	[1.2–3.7]
							After adjustment for smoking and family history of liver cancer, odds ratio of [2.5] for cancer controls	[1.4–4.4]
							and [2.3] for healthy controls	[1.3–4.1]
Stomach cancer								
Amano (1980)	Kofu, Yamanashi Prefecture, Japan	Surgically treated hospital cancer patients	Non-malignant cases	*S. japonicum* eggs in pathological specimens	362/897	15.2%/9.0% prevalence	[1.8]	[1.3–2.6]

Table 7 (contd)

Reference	Location	Source of cases	Source of controls	Measure of exposure	Number of cases/controls	Exposure in cases/controls	Odds ratio	95% CI
Colorectal cancer								
Amano (1980)	Kofu, Yamanashi Prefecture, Japan	Surgically treated hospital colon cancer patients	Non-malignant cases	*S. japonicum* eggs in pathological specimens	103/96	22.3%/18.8% prevalence. Much higher differential among those aged 40–49	[1.2]	[0.62–2.5]
Xu & Su (1984)	Kunshan County, Jiangsu Province, China	Colorectal cancer cases, 1973–79	Non-gastrointestinal cancer patients Neighbours, each matched on age, sex, occupation and production brigade or team	Medical history from patients, relatives, barefoot doctors	98/98/98 (colon) 154/154/154 (rectum)		Colon: odds ratio, 1.2 with other cancer controls; 0.64 with healthy neighbourhood controls Rectum: odds ratio, 8.3 with other cancer controls and 4.5 with healthy neighbourhood controls	[0.48–3.2] (triplets) [0.33–1.2] [3.1–22.6] [1.7–12.1]
Guo *et al.* (1987)	Kunshan County, Jiangsu Province, China	Colon cancer deaths, 1981–83	Lung cancer patients 'Healthy persons'	Medical history	197/205/200		Odds ratio, 2.4 (early-stage disease), 5.5 (late-stage disease) After adjustment for smoking and family history of colon cancer, but not diet or exercise, overall significant association remains: 2.1 and 4.2 for early- and late-stage disease with lung cancer controls, 2.4 and 5.7 with healthy controls After < 10, -20, -30, ≥ 30 years since diagnosis, 1.2, 1.9, 2.9, 4.3 duration–response effects	

for hepatitis B surface antigen than those with latent or intestinal schistosomiasis. These observations suggest that hepatitis B viral infection may confound the association between schistosomal infection and liver cancer in hospital-based studies of individuals. There are no similar data that would allow evaluation of the possibility of confounding between hepatitis C viral infection and schistosomal infection.

3. Studies of Cancer in Animals

3.1 Infection with *Schistosoma haematobium* alone

3.1.1 *Mouse*

Groups of 6–10 male C3H mice, two months old, received single subcutaneous injections of 1.5–10 mg of lyophilized *S. haematobium* eggs or worms in saline or tricaprylin. Another group received a single intraperitoneal injection of 4 mg of egg material, while a further group received two subcutaneous injections of 3 or 4 mg of egg material at an interval of three months. Animals were examined for the presence of tumours 13, 17 and 20 months after injection. The experiment was terminated at 20 months. No tumours were seen at the injection site. Of the 20 mice killed at termination, five had pulmonary tumours and three had hepatomas. The authors noted that the frequency of pulmonary and liver tumours was similar to that in historical controls (Shimkin *et al.*, 1955). [The Working Group noted the limited reporting and that an infectious agent was not employed.]

As part of an experiment on *S. haematobium* in combination with 2-acetylaminofluorene (see below), a control group of 20 Swiss mice [sex and age unspecified] was repeatedly treated by subcutaneous injection with cercariae [schedule unspecified] and kept for 44 weeks. Urinary bladder epithelial hyperplasia beginning as early as three weeks was observed in the majority of the mice. Hyperplasia was not observed in 100 untreated control animals (Hashem & Boutros, 1961). [The Working Group noted the absence of ova or worms in the bladder and the short duration of the study.]

A group of 30 male BALB/c mice, three to four weeks of age, received subcutaneous implants of ligated urinary bladder cysts from donor mice. Bladder cysts were prepared by distending bladders with 0.15 ml mineral oil containing 1000 lyophilized *S. haematobium* ova before ligation. The mice were observed for 44 weeks. A control group of 29 mice received donor bladder cysts containing 0.15 ml mineral oil alone. Hyperplasia of the bladder cyst epithelium was seen in 4/30 mice and 5/29 controls. One transitional-cell tumour and one squamous-cell tumour in the implanted bladder cyst [tumour pathology not described] were reported in the experimental group but not in controls (Al-Hussaini & McDonald, 1967). [The Working Group noted the unusual design of the experiment and the lack of significance of the tumour response.]

3.1.2 *Rat*

In a combination experiment, a group of 100 white rats [sex, strain and age unspecified], weighing 140–160 g, were exposed to water containing 2000 *S. haematobium* cercariae per

litre. The urinary bladders from half of the rats were examined after 12 months, and the remaining rats were examined at 24 months. No malignant change was reported; a few rats had bladder lesions reported as 'sessile polyps' (Gawish, 1975). [The Working Group noted the inadequate reporting and found no compelling evidence for sustained bladder infection.]

3.1.3 *Hamster*

In a combination experiment reported in a proceedings volume (James *et al.*, 1974), a group of 50 hamsters [sex unspecified] were exposed to 80 *S. haematobium* cercariae. No adverse pathological finding in the urinary bladder was reported in the 56-week experiment. [The Working Group noted the inadequate reporting on e.g. the presence of infection.]

A group of 18 male hamsters, eight weeks of age, was exposed to *S. haematobium* by immersion in water containing 250 cercariae for 1 h. Exposure was repeated three months later. The animals were killed 7–11 months after the first exposure, and the viscera were examined histopathologically. Eleven animals developed manifestations of schistosomal cystitis. In four animals, epithelial hyperplasia of the urinary bladder was related to sites of submucosal reaction to ova. In four other animals, the bladder epithelial changes consisted of both hyperplasia and squamous metaplasia (El-Morsi *et al.*, 1975). [The Working Group noted that hyperplasia of the bladder is unusual in untreated hamsters and that the duration of observation was short in comparison with the lifespan of the animals, so that tumours might have developed in the animals if they had been allowed to live longer.]

3.1.4 *Opossum*

Eight opossums (*Didelphis marsupialis*) were exposed to 1000–2000 cercariae of *S. haematobium* on the shaved skin for 30 min. Between 18 and 53 weeks after infection, two animals were reported to have mucosal fibrous plaques in the urinary bladder. A third animal had multiple epithelial lesions of the bladder that were variably described as hyperplastic, papillomatous, polypoid or tumourous. The presence of eggs was associated with the lesions in two animals, and all three animals had evidence of infection (Kuntz *et al.*, 1971).

3.1.5 *Nonhuman primate*

Young adult primates, including one talapoin (*Cercopithecus talapoin*), seven capuchins (*Cebus apella*), seven squirrel monkeys (*Saimiri sciureus*) and 11 African baboons (*Papio cynocephalus*), were exposed percutaneously to 1000–2000 cercariae of *S. haematobium* and observed for up to 24 months. Epithelial lesions of the urinary bladder, reported to be papillary transitional-cell carcinomas, were found in a talapoin monkey which died 21 weeks after infection and in a capuchin that was killed 56 weeks after infection. An epithelial lesion reported as a papilloma of the ureter was associated with the presence of schistosomal eggs in an African baboon killed one year after infection (Kuntz *et al.*, 1972).

In a further experiment, nine capuchin monkeys (*Cebus apella*) were exposed via the skin to 1000–2000 cercariae of *S. haematobium* and were examined for pathological changes in the urinary bladder by laparotomy and cystotomy 94–164 weeks after infection. Six of nine animals showed papillary hyperplasia with or without nodular hyperplasia. In two animals, only focal nodular hyperplasia was seen (Kuntz *et al.*, 1978).

In a study to detect C-type viral particles in tumours, it was reported that four of six capuchin monkeys that had been infected experimentally with *S. haematobium* developed lesions described as papillary carcinomas of the urinary bladder during periods of observation of 109–111 weeks. Three of the animals also had squamous metaplasia of the bladder epithelium (Kalter *et al.*, 1974). [The Working Group noted the lack of experimental details and of documentation of the pathological findings.]

Kuntz *et al.* (1975) described the pathological findings and parasitological and radiological observations in two gibbons (*Hylobates lar*) infected by skin application with 1000 cercariae of *S. haematobium*. Both animals developed evidence of infection, the most striking change being extensive calcification of the eggs in the urinary bladder. One animal had evidence of papillary and nodular transitional-cell hyperplasia of the bladder, and the other had similar lesions in the ureter. The lesions were described as morphologically similar to the grade-I and grade-II papillary transitional-cell carcinomas that are seen in the bladders of humans. [The Working Group noted the small number of animals and the equivocal diagnoses of the lesions.]

In combination experiments with baboons (*Papio* sp.) (Hicks *et al.*, 1980; Hicks, 1982), five animals were infected by an abdominal pouch method with 1000 cercariae of *S. haematobium* and kept for 2.5 years. Four animals had polypoid hyperplasia of the urinary bladder and one had endophytic papillary hyperplasia of the ureter. None of these lesions was considered to be a tumour.

3.2 Infection with *Schistosoma haematobium* in combination with administration of known carcinogens

3.2.1 *2-Acetylaminofluorene*

Mouse: Two groups of 20 Swiss mice [sex and age unspecified] were administered 0.2 ml of a 1.5% suspension of 2-acetylaminofluorene (2-AAF) in olive oil by stomach tube three times a week [duration unspecified]. One of the groups was repeatedly infected with *S. haematobium* cercariae by subcutaneous injection [dosing schedules and duration unspecified]. Animals were observed up to 44 weeks, at which time survivors were killed. A third group of 20 mice was infected with *S. haematobium* alone. Epithelial hyperplasia of the urinary bladder was observed in *S. haematobium*-infected mice. One of the 2-AAF-treated mice developed a benign villous papilloma of the bladder after 43 weeks. Four of the carcinogen-treated animals infected previously with *S. haematobium* developed bladder neoplasms at 36–44 weeks; one had an anaplastic infiltrating carcinoma and three had papillomas, two of which had malignant areas (Hashem & Boutros, 1961). [The Working Group noted the short duration, the lack of verification of infection and inadequate documentation of experimental details.]

Rat: A group of 100 white rats [sex, strain and age unspecified], weighing 160 g, were exposed to water containing 2000 *S. haematobium* cercariae per litre; 45 days after exposure, the rats received intraperitoneal injections of 50 mg/kg bw 2-AAF three times per week for four weeks, followed by a diet containing 0.06% 2-AAF and 1.6% indole for one year. A control group of 100 rats received the carcinogen alone. Ten rats were killed every two months and the bladders examined microscopically. In 80 rats in the combined group killed

after six months, all but five had transitional-cell carcinomas of the urinary bladder, as did 7 of the 10 control animals treated with 2-AAF and killed after 10 months (Gawish, 1975). [The Working Group noted the inadequate experimental design, the lack of verification of infection and the fact that the results for the two groups did not differ statistically.]

3.2.2 ortho-*Aminoazotoluene*

Hamster: In a study reported in a proceedings volume (James *et al.*, 1974), groups of 50 hamsters were exposed to 80 *S. haematobium* cercariae. Ten weeks later, 0.02 or 0.1% *ortho*-aminoazotoluene was incorporated into the diet. Administration of the carcinogen alone caused hyperplasia of the urinary bladder epithelium. In the combined group at the 0.1% dose level, malignant changes were seen in the bladder within 24 weeks . [The Working Group noted the inadequate reporting.]

3.2.3 N-*Nitrosamines*

Hamster: In a combination study reported as an abstract (Hicks *et al.*, 1977), groups of hamsters received a single intravesicular instillation of *N*-methylnitrosourea and were infected with *S. haematobium*. Urinary bladder tumours developed in 5/16 hamsters receiving the combined treatment, 0/26 uninfected controls [$p < 0.001$; Fisher exact test], 0/28 infected animals and 0/19 hamsters treated with *N*-methylnitrosourea alone. In groups of hamsters treated with *N*-nitrosobutyl-4-hydroxybutylamine (NBHBA), bladder tumours developed in 9/24 infected hamsters and 5/30 uninfected controls [$p = 0.057$; Fisher exact test]. [The Working Group noted the inadequate reporting.]

Nonhuman primate: In an experiment designed to simulate the possible proliferative stimulus of *S. haematobium* infection on cancer growth due to exposure to low doses of *N*-nitrosamines in humans, small groups of baboons (*Papio* sp.) were either infected through an abdominal pouch with 1000 cercariae of *S. haematobium* alone (five animals); received intramuscular injections of 5 mg/kg bw (two animals) or 50 mg/kg bw (three animals) NBHBA per week up to the end of the experiment; or were infected with *S. haematobium* and administered 5 mg/kg bw NBHBA per week throughout the experiment (10 animals). All surviving animals were killed after 2.5 years. No urinary bladder tumour was found in animals receiving either *S. haematobium* or NBHBA alone, but three of the baboons receiving the combined treatment had adenomatous lesions of the urinary bladder described by the authors as 'early or latent adenocarcinomas' and a fourth had a papillary carcinoma. Three baboons had papillary growths in the ureter (Hicks *et al.*, 1980; Hicks, 1982). [The Working Group had difficulty in interpreting some of the diagnostic terms used in these reports.]

3.3 Infection with *Schistosoma mansoni* alone

3.3.1 *Mouse*

Groups of eight male C3H mice, three months old, were injected subcutaneously with one, six or 10–16 lyophilized, immature worms of *S. mansoni* and were examined for palpable tumours at the injection site every two weeks until termination of the experiment at 21 months. No tumours were found at the injection site. The numbers of survivors were

19/24 at 12 months, 11/24 at 18 months and 9/24 at termination. Of the nine mice killed at termination, three had hepatomas and one had a single pulmonary tumour. The authors reported that the frequency of pulmonary and liver tumours in this strain of mice was similar to that in historical controls (Shimkin *et al.*, 1955). [The Working Group noted that an infectious agent was not employed.]

In several combination experiments in mice (Domingo *et al.*, 1967; Haese *et al.*, 1973; Haese & Bueding, 1976; Bulay *et al.*, 1977; El-Aaser *et al.*, 1978; Kakizoe, 1985) in which control groups of untreated mice or mice infected with *S. mansoni* only were used, no increase in the frequency of liver tumours was reported. Some of the experiments lasted less than 50 weeks (see section 3.4).

As part of an experiment to study the carcinogenic potential of hycanthone, groups of female Swiss-Webster mice, four weeks of age, were infected by intraperitoneal injection with 40 or 80 cercariae of *S. mansoni*. Eighteen months later, the incidences of livers with nodules were 15/60 [$p < 0.001$; Fisher exact test] in the group given 40 cercariae and 1/49 [not significant] in that given 80 cercariae. No nodule was found in uninfected paired groups of 61 and 54 animals (Yarinsky *et al.*, 1974). [The Working Group noted that histological examination was not performed.]

3.3.2 *Mastomys natalensis*

A group of 200 *Mastomys natalensis*, about three weeks of age, were injected intraperitoneally with 100 *S. mansoni* cercariae and maintained until death (up to 2.5 years). Infection was confirmed by examination of faeces for ova during life and examination of liver, gut and mesentery for ova and adult worms after death. At the end of the experiment, 106 animals with evidence of infection were available for evaluation. The incidence of adenocarcinomas of the glandular stomach (23/106) did not differ significantly from that expected in controls (~20%). [The common stomach tumours in *M. natalensis* were then described as adenocarcinoma but are now recognized as carcinoids.] In contrast, hepatomas were observed in 22 infected animals; such tumours had not been observed in several hundred historical controls. Two animals also developed reticulum-cell sarcomas of the ileum and colon, respectively, associated with schistosomal granulomas (Oettlé *et al.*, 1959).

3.3.3 *Hamster*

Groups of 35 male and 35 female Syrian golden hamsters were infected by intraperitoneal injection of 15 cercariae of *S. mansoni*. No increase in tumour incidence was observed over that in uninfected hamsters within 73 weeks (Bulay *et al.*, 1977). [The Working Group noted the lack of verification of infection.]

3.3.4 *Nonhuman primate*

One case report of a hepatocellular carcinoma in a 12-year-old female chimpanzee (*Pan troglodytes*) has been published. The animal had been captured in the wild in Sierra Leone when two years of age and had no hepatitis B surface antigen, no antibodies to hepatitis B surface or core antigens and no viral RNA of hepatitis C on arrival at the laboratory, although granulomatous inflammation was seen. After 10 years in captivity, during an

intervention before the start of a study of hepatitis, a firm white nodule was discovered in the liver which, upon histological examination, was found to be a well-differentiated hepatocellular carcinoma. No cirrhosis was present, but a severe granulomatous inflammatory reaction was apparent, with remnants of schistosomal egg capsules. On the basis of morphological examination, the eggs were considered to be *S. mansoni* (Abe *et al.*, 1993).

3.4 Infection with *Schistosoma mansoni* in combination with administration of known carcinogens

3.4.1 *2-Amino-5-azotoluene*

Mouse: A total of 410 female CBA mice, two months of age, were divided into four groups as follows: 80 untreated, uninfected animals, which served as controls; 95 mice that each received subcutaneous injections of 10 mg 2-amino-5-azotoluene in glycerol once a month for nine months; 100 mice that received a single subcutaneous injection of 30 cercariae of *S. mansoni*; and 135 mice that were infected with *S. mansoni* and received 2-amino-5-azotoluene eight weeks later. Between 24 and 52 weeks, six animals from each group were examined periodically for pathological changes in the liver; the remaining animals were maintained until death and were examined for gross liver tumours. At 24 weeks after the beginning of the study, the numbers of animals alive in the four groups were 69/80, 80/95, 31/100 and 35/135, respectively. The authors noted that the high mortality in infected animals was due to the infection. No hepatoma was observed in control animals or in those infected with *S. mansoni* alone. At 52 weeks of age, the incidence of hepatomas was 1/80 in the group treated with 2-amino-5-azotoluene alone and 13/35 in the group given the combined treatment [$p < 0.001$; Fisher exact test] (Domingo *et al.*, 1967; Liu *et al.*, 1969).

3.4.2 *2-Naphthylamine and 2-acetylaminofluorene*

Mouse: Groups of female Swiss albino mice, six to eight weeks of age, were divided at random into the following groups: one group of 45 mice served as untreated controls; one group of 46 mice was infected with *S. mansoni* by immersion [technique unspecified] for 1 h in water containing 20–30 cercariae per millilitre; one group of 20 mice received 1% 2-naphthylamine in the diet; a group of 20 mice received 0.06% 2-AAF in the diet; one group of 17 mice was infected with *S. mansoni* and treated with 1% 2-naphthylamine; and a further group of 22 mice was infected with *S. mansoni* and treated with 0.06% 2-AAF. Administration of the carcinogens was terminated after 30 weeks owing to severe toxicity. The other experimental groups were continued up to 70 weeks. No liver or bladder tumour was observed in any of the groups. All mice infected with *S. mansoni* showed granulomatous areas in the portal tracts of the liver and had ova in the faeces (El-Aaser *et al.*, 1978).

A total of 109 female ddY mice, four weeks of age, were divided into three groups: 45 mice received an intraperitoneal injection of 20 *S. mansoni* cercariae and four weeks later were fed a diet containing 0.03% 2-AAF; 32 mice were infected with *S. mansoni* and fed normal diets; and 32 uninfected mice were fed normal diet for four weeks and subsequently fed a diet containing 0.03% 2-AAF. A number of animals from each group were killed every 10 weeks for interim examination. The experiment was terminated after 40 weeks. No liver

tumour was found in the group infected with *S. mansoni* only. In the group fed 2-AAF only, the incidence of hyperplastic nodules in the liver was 2/32 (6.3%) at 40 weeks. In the group that was both infected and fed 2-AAF, the incidence of hyperplastic nodules was 9/45 (20%) [$p = 0.005$; Fisher exact test]. Hepatocellular carcinomas were found in 12/45 mice in the combined treatment group at weeks 29–40 and 0/32 in the group infected with *S. mansoni* [$p < 0.001$; Fisher exact test] (Kakizoe, 1985).

3.5 Infection with *Schistosoma mansoni* in combination with administration of compounds used or evaluated in the past as antischistosomal agents

A variety of studies were undertaken to determine the effects of hycanthone (Haese *et al.*, 1973; Yarinsky *et al.*, 1974; Haese & Bueding, 1976), niridazole (Bulay *et al.*, 1977) and SQ 18506 (Haese *et al.*, 1973; Dunsford *et al.*, 1984) on tumour induction in uninfected and *S. mansoni*-infected mice and hamsters. These chemicals were used in the past (hycanthone and niridazole) or evaluated for possible use (SQ 18506) as antischistosomal agents; none are currently in use clinically. The agents were studied by various methods and schedules of administration, and various non-tumour and tumour end-points were evaluated, including hyperplastic nodules of the liver, hepatomas, tumours of the stomach and other tumours. Both higher and lower tumour incidences were found with combined treatment than in animals only infected with *S. mansoni*. The lower tumour incidences were presumably due to lowering or elimination of infection. [The Working Group noted that hycanthone was previously categorized in Group 3 and niridazole in Group 2B (IARC, 1987).]

3.6 Infection with *Schistosoma japonicum* alone

Mouse: A group of 395 female SPF ddY mice, four weeks of age, were exposed after anaesthesia with phenobarbital to five or six cercariae of *S. japonicum* on the shaved abdomen; 163 were found to be infected 8–10 weeks after exposure, as shown by the presence of eggs in the faeces. More than half of the infected animals had died within 30 weeks after exposure, and 70 survived to the end of the experiment (50 weeks). Of a control group of 61 females undergoing anaesthesia only, 60 survived to the end of the experiment. Upon autopsy, 9/70 infected mice showed no presence of eggs in the liver or intestine and were excluded from the analysis. Of the 61 remaining treated animals, 48 were found to have hepatomas, whereas none were found in the surviving controls [$p < 0.001$; Fisher exact test] (Amano & Oshima, 1988).

3.7 Infection with *Schistosoma japonicum* in combination with administration of known carcinogens

3.7.1 *Dimethylaminoazobenzene*

Mouse: Three groups of mice [initial numbers, sex and age unspecified] were either infected with *S. japonicum* and received no further treatment; were uninfected and fed a diet containing 20 ml 3% dimethylaminoazobenzene in corn oil mixed with 1 kg of rice powder; or were infected with *S. japonicum* and, 60 days later, fed the diet containing dimethylamino-

azobenzene. Groups of mice were killed at various intervals up to 150 days. The authors reported that the mice that received the combined treatment developed severe liver cirrhosis and had faster hepatic cancer formation than the uninfected, carcinogen-treated mice (Shigefuku, 1943). [The Working Group noted the limited reporting of this early study].

3.7.2 *2-Acetylaminofluorene*

Mouse: Female ddY mice, four weeks of age, were divided at random into two groups. The first group (77 animals) was infected by immersion of the tail in water containing 40 *S. japonicum* cercariae and four weeks later were fed a diet containing 0.03% 2-AAF for 40 weeks; the second group (86 animals) was fed basal diet followed four weeks later by a diet containing 0.03% 2-AAF for 40 weeks. Interim killings of animals were made between weeks 9 and 40 of 2-AAF administration. The first liver tumours were observed 16 weeks after administration of 2-AAF in the infected group and at 37 weeks in the uninfected group. At 40 weeks, the incidence of liver tumours was 24/77 in carcinogen-treated, infected mice and 6/86 in carcinogen-treated, uninfected mice ($p < 0.005$, χ^2 test). The tumour types in the two groups, respectively, were: hyperplastic type 1 nodules, 6 and 4; hyperplastic type 2 nodules, 10 and 2 ($p < 0.01$, χ^2 test); and hepatocellular carcinomas, 8 and 0 ($p < 0.005$, χ^2 test) (Miyasato, 1984).

4. Other Data Relevant for Evaluation of Carcinogenicity and its Mechanisms

4.1 Pathology of infection

4.1.1 *Humans*

(*a*) *Schistosoma haematobium*

Many of the most severe pathological manifestations of schistosomiasis are due to a large extent to a physical and immunological response of the host to the eggs (Parra *et al.*, 1991). A periovular area of granulomas surrounded by an exudative cellular reaction consisting of many polymorphonuclear leukocytes, lymphocytes and eosinophilic cells is found to occur in most granulomatous areas (Nawar *et al.*, 1992; Lukacs *et al.*, 1993).

Clinical and pathological evidence for 'early stage of infection' (haematuria and dysuria) is seen in the majority of infected children and young adults (King *et al.*, 1988). In contrast, 'late stage of infection' may be less symptomatic but associated with structural urinary tract diseases. Asymptomatic infection may still be associated with urinary tract lesions (Abdel-Salam & Ehsan, 1978).

da Silva Lopes (1984) reported a pathological study of 210 malignant tumours (206 carcinomas) of the bladder in Luanda, Angola. Of the 164 carcinomas associated with schistosomiasis, 122 were of the 'spinocellular' type, 15 were 'urothelial', 13 were 'urothelial plus epidermoid metaplasia', 8 were adenocarcinomas and 16 were undifferentiated carcinomas. Of the 42 carcinomas not associated with infection, 30 were 'urothelial', 6 were 'urothelial plus epidermoid metaplasia', 3 were 'spinocellular' and 3 were undifferentiated carcinomas.

(i) *Early stage of infection*

The most significant pathophysiological disease sequelae of the early stage of *S. haematobium* disease occur in the ureters and urinary bladder. Eggs are deposited in particularly large numbers at the lower ends of the ureters. Ureteric lesions result in anatomical or functional stenosis, leading to hydroureters and hydronephrosis. At the site of egg deposition in tissues, circumoval granulomas, fibrosis and muscular hypertrophy may be demonstrated histologically. The same pattern of tissue involvement is seen in the urinary bladder (Smith *et al.*, 1974).

Two major autopsy studies—one in Ibadan, Nigeria (Edington *et al.*, 1970) and the other in Egypt (Smith *et al.*, 1974)—contributed significantly to our appreciation of the pathological changes in schistosomiasis caused by *S. haemotobium*. Edington *et al.* (1970) studied 673 unselected cadavers in Nigeria and found *S. haematobium* in 20%; 183 of the autopsies were performed on individuals under 19 years of age. In Egypt, Smith *et al.* (1974) examined specimens taken at 190 consecutive autopsies and found evidence of *S. haematobium* infection in 117 (61.6%).

The morphological findings in early active *S. haematobium* disease comprise polypoid granulomatous lesions surrounding the parasite eggs. In the urinary bladder, the pathological manifestations are polyposis and/or ulceration. *S. haematobium*-induced bladder polyps consist of large inflammatory masses containing schistosome eggs. The deposition of eggs may be apicocentric, basocentric or diffuse. Apicocentric ova deposition usually occurs at the apex and dome of the urinary bladder, whereas basocentric deposition occurs predominantly in the trigone and lower posterior wall (Christie *et al.*, 1986b). Bladder polyposis is responsible for the haematuria seen in the early stages of infection and in obstructive disease. The other major morphological lesion is bladder ulceration, which may be due to polyp sloughing. Histological examination of bladder tissue in the early stage of infection demonstrates hyperaemia, granulomas around nests of schistosome eggs and early fibrosis and hypertrophy of muscle. Urethelial hyperplasia, metaplasia and dysplasia were significant in all stages of the disease in the series of Smith *et al.* (1974), hyperplasia occurring in 38% of autopsied cases and 21% uninfected controls, metaplasia in 31.6% cases and 11.5% controls and dysplasia in 27.2% cases and 8.5% controls.

(ii) *Late stage of infection*

The change from early-stage to late-stage schistosomiasis caused by *S. haematobium* occurs with age, decrease in parasite load (as determined by urinary egg excretion) and diminished manifestations of acute inflammatory disease, e.g. haematuria. Morphologically, urinary bladder disease in late-stage infection manifests as schistosomal ulcers or sandy patches (Smith *et al.*, 1974). Chronic schistosome-related bladder ulcers usually occur in individuals with previous heavy infection. They are located mainly in the posterior part of the bladder. Sandy patches occur late in infection, most frequently in the trigone area and are covered by irregularly thickened or atrophic mucosa. Histologically, old granulomas may be found in the submucosa and muscularis surrounding disintegrating or calcified ova. In many instances, fibrosis and scanty round-cell infiltration may be seen. Differences between the early and late stages of infection are summarized in Table 8. The eggs of *S. haematobium* tend to calcify and to remain in tissues longer than those of *S. mansoni* (Cheever *et al.*, 1978).

Table 8. Differences between early and late stages of infection with *S. haematobium*

Feature	Early stage of infection	Late stage of infection
Adult worm pairs	Commonly present	Commonly absent
Oviposition	Commonly present	Commonly absent
Urinary egg excretion	Commonly present	Commonly absent
Important in transmission	Yes	No
Granulomatous host response	Present	Absent
Polypoid lesions	Present and possibly obstructive	Very rare
Sandy patches	Present in late active disease	Present and possibly obstructive
Schistosomal obstructive uropathy	Due to obstructive inflammatory polyps	Due to sandy patches obliterating ureteral muscle
Schistosomal ulceration	Uncommon	Frequent
Treatment	Antischistosomal chemotherapy	Surgical repair

Adapted from Smith & Christie (1986)

The concordance of lesions of chronic infection with those of urethelial cancer has been known for over a century. In a series of 1095 patients with urinary bladder cancer in Egypt, *S. haematobium* eggs were found in 82.4% of cases (El-Bolkainy *et al.*, 1981). Well-differentiated squamous-cell carcinomas of the bladder were seen predominantly in patients with eggs and at an earlier mean age than transitional-cell carcinomas. The morphological changes in the urinary bladder associated with the late stage of infection included a spectrum of hyperplasia, squamous metaplasia, dysplastic changes and predominance of squamous-cell carcinoma. Of the 798 squamous-cell carcinomas, 691 occurred in *S. haematobium*-positive samples and 107 in patients with no eggs. Of the 148 cases of transitional-cell carcinoma, 103 were in patients with eggs and 45 in those without.

Similarly, urethelial hyperplasia and squamous metaplasia have been associated with urinary schistosomiasis. Squamous-cell metaplasia of the bladder occurs at increased frequency in schistosomiasis patients and in young people in populations at high risk of squamous-cell carcinoma (Khafagy *et al.*, 1972). Although granulomas occur in both the ureter and bladder, carcinomas occur predominantly in the bladder. In 30 patients with bladder carcinoma in Egypt, the tissue surrounding the tumours usually contained a higher concentration of *S. haematobium* eggs than other areas in the bladder: The egg burden in tissue surrounding the tumour was almost twice the mean in the remainder of the urinary bladder (Christie *et al.*, 1986a).

Further pathological sequelae of *S. haematobium* infection can be seen almost anywhere in the body. The infection may also be associated with other clinical conditions, such as bladder calcification, urolithiasis and pyelonephritis. Most of these lesions are thought to be related to the inflammatory and subsequent fibrotic responses that follow egg deposition in tissues (Cheever *et al.*, 1978).

(*b*) *Schistosoma mansoni*

Infection with *S. mansoni* is often asymptomatic. In studies of populations in endemic areas, morbidity due to *S. mansoni*-induced schistosomiasis was found to be associated with

intensity of infection, particularly in the young (Arap Siongok *et al.*, 1976). Older individuals with light or no parasitologically demonstrable infection may also present with chronic sequelae of disease. Other factors, besides the age of the host, that may play an integral role in the pathogenesis of disease include the geographical strain of parasite, the genetic make-up of the host (Abdel-Salam *et al.*, 1986), water contact and other infectious and nutritional changes.

Disease due to schistosomiasis caused by *S. mansoni* may be classified according to the natural history of infection: cercarial invasion and dermatitis, maturing worms and acute schistosomiasis (Katayama fever) or established infection and intestinal–hepatic disease. Disease may also be classified into mild and severe forms according to its association with intensity of infection and the immunopathological responses of the host.

(i) *Early stage of infection*

Clinical and pathological changes during the acute phase of infection may manifest as cercarial dermatitis, Katayama fever and established intestinal, hepatosplenic and other features of morbidity. Cercarial dermatitis is a sensitization due to invasion of the skin by cercariae. Morphologically, the lesions are maculopapular eruptions, with oedema and round-cell and eosinophil infiltration. In most circumstances, cercarial dermatitis is self-limiting. Early-stage schistosomiasis may occur four to eight weeks after exposure, usually in infected individuals with a high worm load. Early infection is usually found in individuals with no prior exposure to schistosomes. Disease manifestations resemble those of serum-sickness syndrome and are characterized by hepatosplenomegaly, fever, lymphadenopathy and peripheral blood eosinophilia. The pathological features are nonspecific. Katayama syndrome is self-limiting in most circumstances; severe cases may be associated with heavy infection and may be fatal.

The morphological features that characterize acute established infection are related to the severe inflammatory response around mature eggs in tissues. Large periovular granulomas with prominent necrotic–exudative features are seen. Microscopically, mature eggs are surrounded by round-cell and eosinophilic infiltrations with necrosis and the development of fibrosis (Cheever *et al.*, 1978).

(ii) *Late stage of infection*

Hepatic disease is the best characterized feature of the late stage of *S. mansoni* infection (Kamel *et al.*, 1978). Granulomas around schistosome eggs first cause obstruction of the finest portal radicles at the periphery of the liver. With progression of inflammation, increased intrahepatic portal pressure occurs, leading to the opening up of fine collaterals around the main portal branches. Simultaneously, fibrosis follows inflammation, and the classical clay-pipe-stem fibrosis becomes the dominant feature, with its haemodynamic sequelae.

Colonic inflammatory pseudopolyposis [the Working Group noted that these lesions are not neoplastic] was described in 30 men in Egypt who were infected with *S. mansoni*, *S. haematobium* or both. Most of the pseudopolyps occurred in the rectosigmoid colon. Microscopically, the lesions contain mononuclear cells and eosinophils; the colonic glands show proliferation and distortion but no adenomatous change. Ulcers are frequently reported on the surface of colonic polyps (Smith *et al.*, 1977).

(*c*) *Schistosoma japonicum*

The pattern of infection and disease due to *S. japonicum* infection in general follows closely the sequence of events in schistosomiasis caused by *S. mansoni*: swimmers' itch (cercarial dermatitis), Katayama fever and progression of the disease, leading to established infection (Domingo *et al.*, 1980; Warren *et al.*, 1983). The major differentiating feature is the morphology of the host granulomatous response around the eggs. Granulomas around *S. japonicum* eggs usually occur around nests rather than isolated eggs. In early-stage infection, the lesions look like abscesses with central necrosis. Early-stage acute granulomas consist of eosinophils, lymphocytes and a few histiocytes. At the late stage, histiocytes become more prominent, with the formation of multinucleated giant cells phagocytosing pieces of egg shell. The end result is a fibrotic lesion with a certain degree of hyaline degeneration (Kurniawan *et al.*, 1976).

Chen *et al.* (1980) compared 289 cases of colorectal carcinoma associated with schistosomiasis with 165 cases not associated with the parasite in China. Well-differentiated adenocarcinomas accounted for 91.6% of the malignant tumours in patients with schistosomiasis and 69.1% in patients without schistosomiasis. Benign adenomatous and papillary polyps were found in 6.4% of patients with schistosomiasis and in 29% of patients without schistosomiasis. The same group of investigators (Chen *et al.*, 1981) conducted a retrospective review of specimens taken by colectomy from 60 patients with schistosomiasis. They described 36 lesions as dysplasia, which occurred in the flat mucosa, in pseudopolyps or in regenerative epithelium at the edges of ulcers. The incidence of dysplasia in the colon was not reported for people not infected with schistosomes. Another study from China (Yu *et al.*, 1991) included the results of mass screening for colorectal carcinoma, which led to the taking of 754 biopsy specimens from patients over 30; 320 polyps were studied histologically and were found to be distributed about equally between fibrous, mixed and epithelial polyps. Sialomucins and carcinoembryonic antigens were found more frequently in epithelial than in other types of polyps. [The Working Group noted that the terminology used is confusing and the relevance to carcinogenicity is uncertain.]

4.1.2 *Experimental systems*

(*a*) *Schistosoma haematobium*

Repeated attempts have been made to infect several species of experimental animals with *S. haematobium* (Kuntz *et al.*, 1972), but no satisfactory model that reproduces infection and disease as it occurs in humans has yet been described. Webbe *et al.* (1974) demonstrated that infection of baboons (*Papio anubis*) results in passing of viable eggs in urine and faeces. Macroscopic bladder lesions have been reported to vary from pinhead discoloured elevation of mucosa to gross polypoid masses. Eggs have been seen scattered throughout subepithelial layers and surrounded by a predominantly eosinophilic infiltrate. No evidence of malignant transformation was reported. Similar lesions were seen in the ureters. The pathophysiological sequelae included distorted ureters, hydronephrosis and ureteric calculi.

(*b*) *Schistosoma mansoni*

Animal models have made it possible to study the pathogenesis of granuloma formation and fibrosis due to this species of schistosome. For example, *S. mansoni* infection in mice

results in granuloma formation and disease in the intestines and liver. It was estimated that 63% of ova produced by the schistosome in the porto-mesenteric system were retained in the murine host. Egg deposition was followed by a delayed hypersensitivity granulomatous response which is central to the pathogenesis of disease in the intestine and liver (Warren, 1973). Hepatic egg granulomas are located in all the presinusoidal areas and result in hepatomegaly and destruction of portal blood flow. The haemodynamic consequences lead to portal hypertension, splenomegaly and oesophageal varices, which may bleed. Granulomas are finally replaced by fibrous tissue in the liver, resulting in a unique form of liver fibrosis (Olds *et al.*, 1989) in which hepatic parenchyma and perfusion are retained for a long time.

The regulation of granuloma formation has been carefully studied in the murine model (Warren, 1973; Henderson *et al.*, 1991, 1992). Parasite ova lodge in the small pulmonary vessels, and the host reacts to their presence by forming delayed hypersensitivity granulomas. These isolated lesions can be studied with respect to their composition, the basis of their induction and regulation and immunological reactions. The granuloma is made of lymphocytes, mononuclear phagocytes and eosinophils, but this rich cellular infiltrate is later replaced by scar tissue, with a marked reduction in cellularity. Several cytokines have been shown to be involved in the induction of granuloma, including interleukins 2 and 4 and interferon-γ (Henderson *et al.*, 1991, 1992; Lukacs & Boros, 1993). Granulomas that form in animals with chronic infection are smaller than those seen during the acute phase. This down-regulation or modulation of granuloma formation has been shown to be immunologically regulated and to be dependent on the interaction of Th1 and Th2 subsets of lymphocytes (Lukacs & Boros, 1993).

In baboons and chimpanzees infected with *S. mansoni*, the disease sequence closely resembles the features seen in infected humans (Warren, 1973).

(*c*) *Schistosoma japonicum*

Several species of subhuman primates and rodents exhibit a host–parasite relationship similar to *S. japonicum* infection in humans (Cheever, 1985).

4.2 Other observations relevant to the interpretation of carcinogenicity and mechanisms of carcinogenesis

4.2.1 *Humans*

Numerous explanations have been offered for the proposed association between schistosomiasis and human cancers. Generally, these can be categorized as involving: exogenous and endogenous agents which induce DNA damage (Abdel-Tawab *et al.*, 1968a,b; Fripp & Kean, 1980; Hicks, 1982; Gentile, 1991) or possible tumour promoting activity (Ishii *et al.*, 1989); altered host metabolism (El-Aaser *et al.*, 1982; Gentile, 1985; Gentile *et al.*, 1985); pathological changes leading to increased cell proliferation (Ishak *et al.*, 1967; Brand & Brand, 1980a,b; Rosin *et al.*, 1994); and immune reactions (Raziuddin *et al.*, 1991, 1992, 1993; Gentile & Gentile, 1994).

Endogenous agents may be introduced into schistosome-infected organs in several ways. For example, quantitatively altered tryptophan metabolism in *S. haematobium*-infected

patients results in higher concentrations of certain metabolites (e.g. indican, anthranilic acid glucuronide, 3-hydroxyanthranilic acid, L-kynurenine, 3-hydroxy-L-kynurenine and acetyl-L-kynurenine) in pooled urine (Abdel-Tawab *et al.*, 1966a, 1968b). Some of these metabolites have been reported to be carcinogenic to the urinary bladder in implantation experiments (Allen *et al.*, 1957; Bryan *et al.*, 1964; Bryan, 1969; Röhl *et al.*, 1969).

Other endogenous agents may be involved in secondary bacterial infection. Bacterial urinary tract infections such as those that occur subsequent to the late sequelae of *S. haematobium* infection may play an intermediary role in the genesis of squamous-cell carcinoma. Secondary bacterial infection of *Schistosoma*-infected bladders is a well-documented event (Laughlin *et al.*, 1978; Hill, 1979; El-Aaser *et al.*, 1982; Hicks *et al.*, 1982).

Nitrosamines formed by bacterial catalysis (or via urinary phenol catalysis) of the nitrosation of secondary amines with nitrites have been detected in urinary bladders from *S. haematobium*-infected patients; they may be carcinogenic to bladder mucosa (Hicks *et al.*, 1977, 1978, 1982; Tricker *et al.*, 1989, 1991). Mostafa *et al.* (1994) also demonstrated the presence of nitrates and nitrites in the saliva and increased concentrations of *N*-nitroso compounds in the urine of *S. mansoni*- or *S. haematobium*-infected people who were not on controlled diets. The etiological significance of these findings is, however, unclear in the light of the finding that urine from schistosomiasis patients is not mutagenic (Everson *et al.*, 1983).

Nitrosamines have been detected in the urine of paraplegic patients with urinary tract infections due to urinary stasis (Hicks *et al.*, 1977, 1978).

In a US case–control study in which 2982 urinary bladder cancer patients (97% with transitional-cell carcinomas) were compared with 5782 controls (Kantor *et al.*, 1984), odds ratios of 1.5 (95% CI, 1.3–1.8) in males and 1.2 (0.9–1.5) in females reflect an association with one or two past urinary tract infections, and odds ratios of 2.0 (1.6–2.6) in males and 2.1 (1.6–2.7) in females reflect an association with three or more such infections. For the 39 patients with squamous-cell carcinomas, odds ratios of 1.9 (0.7–4.8) for having had one or two infections and 4.8 (1.9–11.5) for three or more infections were found for the two sexes combined. Adjustments were made for race, age, smoking and, for squamous-cell cancer, sex.

On follow-up of 6744 British paraplegic patients (who are subject to frequent urinary tract infections), 25 urinary bladder cancers were identified (El Masri & Fellows, 1981). On the basis of information for an otherwise comparable population, 1.6% of these would have been expected to be of squamous origin, whereas 44% actually were (estimated relative risk, 49; 95% CI, 20–119). In Uganda, squamous-cell bladder cancers are commonly seen in the absence of *S. haematobium* infection but in the presence of other urinary tract abnormalities (Anthony, 1974).

One of the prevalent theories for the association between schistosomal infection and cancer is that elevated levels of the enzyme β-glucuronidase in the host could increase the release of carcinogenic metabolites from their glucuronides. No data are available at present to confirm this association, although schistosome-infected humans are known to have elevated β-glucuronidase activity in urine (Fripp, 1960; Abdul-Fadl & Metwalli, 1963; Fripp, 1965; Abdel-Tawab *et al.*, 1966b, 1968a; Norden & Gefland, 1972; El-Sewedy *et al.*, 1978;

El-Zoghby *et al.*, 1978; El-Aaser *et al.*, 1979). The cause of the increase in β-glucuronidase activity in individuals suffering from schistosomiasis is unknown.

Several studies provide evidence for genetic damage in schistosomiasis patients. Sister chromatid exchange and micronucleus frequencies are increased slightly in peripheral blood lymphocytes harvested from schistosomiasis patients (Shubber, 1987; Anwar, 1994), and micronuclei were more frequent in urothelial cells from chronic schistosomiasis patients than in controls (Rosin & Anwar, 1992). The mean frequency of micronuclei was reduced significantly after treatment with praziquantel, which may indicate that infection is involved in chromosomal breakage in the urothelium (Anwar & Rosin, 1993).

No mutation was detected at codon 12 of the H-*ras* oncogene in nine squamous-cell carcinomas associated with schistosomiasis (Fujita *et al.*, 1987). Mutations of the *p53* tumour suppressor gene were detected in six of seven squamous-cell carcinomas associated with *S. haematobium*; no specific pattern of mutation emerged, in contrast to the pattern seen in transitional-cell carcinomas related to tobacco smoking (Habuchi *et al.*, 1993). O^6-Methyldeoxyguanosine was detected in DNA from 44 of 46 Egyptian samples of bladder tissue, 38 from tumour tissue and eight from uninvolved bladder mucosa, and in 4 of 12 normal samples of bladder of European origin (Badawi *et al.*, 1992a).

4.2.2 *Experimental systems*

(*a*) *Schistosoma haematobium*

Capuchin monkeys (*Cebus apella*) and African baboons (*Papio cynocephalus*) were exposed to 500–3000 cercariae, which produced active schistosomiasis and associated pathological manifestations (Brown *et al.*, 1976). Analysis of urine samples collected when the infection was declared (5–8 months after infection) showed accumulation of high levels of 3-hydroxykynurenine and 3-hydroxyanthranilic acid, indicating altered tryptophan metabolism in the host.

Syrian hamsters infected with 200 cercariae of *S. haematobium* had elevated β-glucuronidase activity, and their livers had reduced competence to metabolize the urinary bladder carcinogen 3,3′-dichlorobenzidine. The mutagenic potential of this chemical to bacteria was significantly enhanced in the presence of urine from the infected animals, liver enzymes and β-glucuronidase (Gentile *et al.*, 1985).

(*b*) *Schistosoma mansoni*

The modified metabolic profiles of xenobiotics in parasite-infested hosts have been studied extensively (for a general review of altered xenobiotic metabolism in parasitic diseases, see Tekwani *et al.*, 1988). In most of these studies, mice were used as hosts and exposed to 100–200 cercariae. The xenobiotics studied include lindane (Mostafa *et al.*, 1984), *N*-nitrosodimethylamine (Mostafa *et al.*, 1984), 2-acetylaminofluorene (Siwela *et al.*, 1990) and aflatoxin B_1 (Daneshmend, 1984). The evidence suggests that alterations in the carcinogen metabolizing capacities of the liver of mice infected with *S. mansoni* lead to a decreased capability to process xenobiotics. Infected hosts also have enhanced enzymatic activity for some other enzymes, such as β-glucuronidase. O^6-Methyldeoxyguanosine was found in DNA of the liver (but not of other organs) of *S. mansoni*-infected mice, again implying an abnormal metabolic profile in infected livers (Badawi *et al.*, 1992a,b,1993).

(*c*) *Schistosoma japonicum*

Sequence homologies to the *env* gene of mouse ecotropic and xenotropic retroviruses were detected in the DNA of adult worms (Tanaka *et al.*, 1989). Iwamura *et al.* (1991) made similar findings in adult worms and in DNA isolated from eggs. Host (mouse)-related DNA sequences were identified in the subtegumental layer and inner tissues of adult *S. japonicum* by in-situ hybridization with ^{32}P-labelled probes (Irie & Iwamura, 1993).

Reduced levels of cytochrome P450 have frequently been reported in infected animals (see Tekwani *et al.*, 1988, for a review). These results were confirmed in mice infected with *S. japonicum* (Matsuoka *et al.*, 1989), and the same authors demonstrated that liver homogenate from *S. japonicum*-infected mice had a reduced mutagen activating potential for 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2). Hepatic fractions from infected mice had a lower mutagen-activating capacity than hepatic fractions from uninfected mice when Trp-P-2 was used as the substrate (Arimoto *et al.*, 1992). A similar observation was made with aflatoxin B_1: microsomes from infected mice were less effective at producing ^{3}H-AFB_1 covalent binding than microsomes from uninfected animals (Hasler *et al.*, 1986).

S. japonicum-infected mice, however, maintain higher levels of serum Trp-P-2 given intravenously than uninfected mice treated in the same way, suggesting that although infected animals have lowered metabolism increased retention of the mutagen can occur (Aji *et al.*, 1994). This persistence could result in Trp-P-2 complexes with haem *in vivo* (Arimoto *et al.*, 1980; Arimoto & Hayatsu, 1989).

The mutagenicity of the parasite itself was investigated in bacterial bioassays; extracts of neither eggs nor adults were mutagenic to *Salmonella typhimurium* or *Escherichia coli* (Ishii *et al.*, 1989).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Schistosomes are trematode worms that live in the bloodstream of human beings and animals. Three species (*Schistosoma haematobium*, *S. mansoni* and *S. japonicum*) account for the majority of human infections. People are infected by exposure to water containing the infective larvae (cercariae). The worms mature in the veins that drain the bladder (*S. haematobium*) or in the intestine (other species). The adults do not multiply in the body but live there for several years, producing eggs. Some eggs leave the body in the urine or faeces and hatch in water to liberate the miracidium larva, which infects certain types of freshwater snails. Within the snail, the parasites multiply asexually to produce free-swimming cercaria larvae, which infect people by skin penetration. Eggs remaining in the human body are trapped in the tissues, where they elicit hypersensitivity granulomas that cause disease in the urogenital system (*S. haematobium*) or in the liver and intestines (other species).

The diagnosis of infection with *Schistosoma* is based on simple qualitative and quantitative examinations of faeces and urine. *S. haematobium* infection is identified on the basis of a history of haematuria, observation of gross haematuria, detection of haematuria by chemical reagent strips or detection of eggs in urine by microscopy. *S. mansoni* and

S. japonicum infections are identified by the presence of eggs in faeces. All infections can be quantified by egg counts in urine (*S. haematobium*) and faeces (other species). The available immunodiagnostic tests are useful for detecting light infections. Absence of infection can be established with certainty only by use of a combination of diagnostic tests.

Schistosomiasis occurs in at least 74 countries where 600 million people are at risk, of whom over 200 million are infected. The distribution of infection corresponds to the distribution of the snail hosts. Within endemic areas, transmission may be focal and can be localized to specific water sources. The intensity and frequency of exposure to contaminated freshwater determine the occurrence of the heavy infection that leads to disease. Prevalence and intensity of infection are usually correlated in endemic areas and especially in children. Sex differences in intensity of infection have been linked to differences in exposure. Death may be caused by urinary tract disease in *S. haematobium* infection and by portal hypertension in *S. mansoni* and *S. japonicum* infection.

Infection with *Schistosoma* is not synonymous with clinical disease, and many infections are asymptomatic. The outcome of infection is influenced by genetic factors, the immune response of the host and concomitant infections (e.g. hepatitis). Clinical disease is a sequel of heavy infection. Treatment of all forms of schistosomiasis with safe, effective anti-schistosomal drugs (i) results in a high rate of resolution of infection, (ii) prevents development of disease in people with heavy infection, (iii) arrests progression of existing severe disease and (iv) reverses some disease manifestations, particularly in children. Control of schistosomiasis has been achieved in some countries through combined approaches to intervention, including health education, improved water supplies and sanitation, environmental management, snail control and treatment.

5.2 Human carcinogenicity data

Schistosoma haematobium

A number of studies from Africa have shown that the estimated incidence of urinary bladder cancer is higher in areas with a high prevalence of infection with *S. haematobium* than in areas with a low prevalence. For example, urinary bladder cancer as a proportion of all cancer appears to be 10 times commoner among men in Egypt than among men in Algeria. Several other observations support an association between the occurrence of urinary bladder cancer and *S. haematobium* infection: the estimated incidence of urinary bladder cancer was related to the proportion of cancerous urinary bladder specimens containing *S. haematobium* eggs or egg remnants; the sex ratio of urinary bladder cancer cases varied widely and corresponded to the relative involvement of men and women in agricultural work (a risk factor for *S. haematobium* infection); and squamous-cell cancers of the urinary bladder were proportionately commoner in populations with a high prevalence of infection with *S. hematobium* and a high proportion of urinary bladder cancers showing histological evidence of infection than in areas without these characteristics.

Many cases of urinary bladder cancer have been reported in association with schistosomal infection of the urinary bladder. Other cancers have been reported in association with infection with *S. haematobium* including, particularly, cancer of the cervix.

Seven case–control studies of the association between *S. haematobium* infection and urinary bladder cancer have been reported. *S. haematobium* infection was measured variously by presence of eggs in urine, pelvic X-ray, rectal biopsy, biopsy of the urinary bladder and digestion and centrifugation of urinary bladder tissue. All of the studies were hospital-based and in none was the correspondence between the population giving rise to the cases and that sampled for the controls demonstrated or addressed in the analysis. Possible confounding by age and sex was not considered in four studies. In three of these four studies, the method of measurement of past infection with *S. haematobium* differed between cases and controls. Possible confounding by smoking was considered in only one study. Six of the seven studies showed significant, positive associations between the occurrence of urinary bladder cancer and infection with *S. haematobium*, with estimated relative risks ranging from 2 to 14. Confounding is not likely to explain the strong associations seen in these studies.

Schistosoma mansoni

A number of cases of liver cancer, colorectal cancer, giant follicular lymphoma and some other cancers have been reported in association with *S. mansoni* infection.

Schistosoma japonicum

Mortality from liver cancer and prevalence of infection with *S. japonicum* have been found to be positively correlated in Japan but not consistently so in China. Mortality from and, in one study, incidence of colorectal cancer were strongly, consistently and significantly correlated with various measures of infection with *S. japonicum* in many studies across provinces, counties and communes in China.

In three case–control studies of liver cancer and infection with *S. japonicum* in Japan and China, the estimated relative risks for the association varied from 2 to 10. The relative risk remained elevated in patients who did not have antigens to hepatitis virus. The two studies giving the highest estimated relative risks were hospital-based and did not address the issue of correspondence between the population giving rise to the cases and that sampled for the controls. In one of these studies, possible confounding by age and sex was not controlled for.

In one hospital-based case–control study of gastric cancer in Japan, the estimated relative risk for *S. japonicum* infection, based on the presence of eggs in tissue, was 1.8 and was significant. Possible confounding by age and sex was not controlled for, and the issue of correspondence between the population giving rise to the cases and that sampled for the controls was not addressed.

Three case–control studies of colorectal cancer and infection with *S. japonicum* have been reported from China and Japan. In one, the estimated relative risks for cancer of the colon in association with the presence of eggs in tissue was about 2.5 and was significant. Possible confounding by age, sex, area of residence, smoking and family history of cancer of the colon was controlled for in this study. In the two other studies, the estimated relative risks were 1.2 for colon cancer in both studies and 8.3 for rectal cancer in one study with control for possible confounding by age, sex, place of residence and occupation.

5.3 Animal carcinogenicity data

Infection with *S. haematobium* has been studied in experiments in mice, rats, hamsters, opossums and nonhuman primates. In mice, hamsters and opossums, hyperplasia of the urinary bladder was observed; one tumour of the urinary bladder was reported in an opossum. The studies in rats were inadequate for evaluation. In nonhuman primates, hyperplasia of the urinary bladder and a few lesions described as tumours of the urinary bladder or ureter were reported. *S. haematobium* infection was also studied in animals treated with known urinary bladder carcinogens. Infection with the parasite increased urinary bladder tumour incidence in mice administered 2-acetylaminofluorene and in baboons treated with *N*-nitrosobutyl-4-hydroxybutylamine.

In one experiment with *Mastomys natalensis* infected with *S. mansoni*, an increased incidence of liver tumours was observed. One case report of a hepatocellular carcinoma in a chimpanzee with *S. mansoni* infection has been published. Infection with *S. mansoni* was studied in inadequate experiments in mice and hamsters. An increased incidence of liver tumours was seen in one experiment in mice infected with *S. mansoni* and treated with 2-amino-5-azotoluene and in one experiment in infected mice treated with 2-acetylaminofluorene.

Infection of mice with *S. japonicum* resulted in a significantly increased incidence of liver tumours in one experiment. Infection with *S. japonicum* enhanced the liver tumour incidence in mice treated with 2-acetylaminofluorene in one experiment.

5.4 Other relevant data

S. haematobium induces chronic inflammation of the lower urinary tract, leading to obstruction, squamous metaplasia, urinary retention and secondary bacterial infections.

Carcinomas of the urinary bladder seen in association with *S. haematobium* infection are more frequently of the squamous-cell type than of the transitional-cell type. Some characteristics of *S. haematobium* infections of the urinary tract may be relevant to the genesis of squamous-cell carcinoma of the bladder. Inflammatory changes are seen in the mucosa of the lower urinary tract. Endogenous mutagenic and carcinogenic products are detected in increased concentrations in the urine of people infected with *S. haematobium*. Recurrent bacterial infection of the urinary tract, even in the absence of *S. haematobium* infection, is strongly associated with the appearance of squamous-cell carcinomas of the urinary bladder. In a small series of patients, mutations at the *p53* gene in squamous-cell carcinomas found in association with *S. haematobium* infection were different from those in the transitional-cell malignancies of smokers.

S. mansoni and *S. japonicum* induce fibrosis of the liver and inflammatory lesions of the large bowel. There is some evidence that livers infected with *S. japonicum* (and other species) alter the metabolism of certain carcinogens.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of infection with *Schistosoma haematobium*.

There is *inadequate evidence* in humans for the carcinogenicity of infection with *Schistosoma mansoni*.

There is *limited evidence* in humans for the carcinogenicity of infection with *Schistosoma japonicum*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Schistosoma haematobium*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Schisotosoma mansoni*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Schistosoma japonicum*.

Overall evaluations

Infection with *Schistosoma haematobium* is carcinogenic to humans (Group 1).

Infection with *Schistosoma mansoni* is not classifiable as to its carcinogenicity to humans (Group 3).

Infection with *Schistosoma japonicum* is possibly carcinogenic to humans (Group 2B).

6. References

Abanilla, L.M. (1986) A report on the association of colonic cancer with *Schistosoma japonicum* infection. *J. Philipp. med. Assoc.*, **62**, 30–32

Abdel-Salam, E. & Ehsan, A. (1978) Cystoscopic picture of *Schistosoma haematobium* in Egyptian children correlated to intensity of infection and morbidity. *Am. J. trop. Med. Hyg.*, **27**, 774–778

Abdel-Salam, E., Abdel Khalik, A., Abdel-Meguid, A., Barakat, W. & Mahmoud, A.A.F. (1986) Association of HLA class I antigens (A1, B5, B8 and CW2) with disease manifestations and infection in human schistosomiasis mansoni in Egypt. *Tissue Antigens*, **27**, 142–146

Abdel-Tawab, G.A., Kelada, F.S., Kelada, N.L., Abdel-Daim, M.H. & Makhyoun, N. (1966a) Studies on the aetiology of bilharzial carcinoma of the urinary bladder. V. Excretion of tryptophan metabolites in urine. *Int. J. Cancer*, **1**, 377–382

Abdel-Tawab, G.A., El-Zoghby, S.M., Abdel-Samie, Y.M., Zaki, A. & Saad, A.A. (1966b) Studies on the aetiology of bilharzial carcinoma of the urinary bladder. VI. Beta-glucuronidases in urine. *Int. J. Cancer*, **1**, 383–389

Abdel-Tawab, G.A., El-Zoghby, S.M., Abdel-Samie, Y.M., Zaki, A.M., Kholef, T.S. & El-Sewedy, S.H.M. (1968a) Urinary beta-glucuronidase enzyme activity in some bilharzial urinary tract diseases. *Trans. R. Soc. trop. Med. Hyg.*, **62**, 501–505

Abdel-Tawab, G.A., Ibrahim, E.K., El-Masri, A., Al-Ghorab, M. & Makhyoun, N. (1968b) Studies on tryptophan metabolism in bilharzial bladder cancer patients. *Invest. Urol.*, **5**, 591–601

Abdel-Wahab, M.F. & Mahmoud, S.S. (1987) Schistosomiasis mansoni in Egypt. In: Mahmoud, A.A.F., ed., *Ballière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 2, *Schistosomiasis*, London, Ballière Tindall, pp. 371–395

Abdel-Wahab, M.F., Strickland, G.T., El-Sahly, A., Ahmed, L., Zakaria, S., El-Kady, N. & Mahmoud, S. (1980) Schistosomiasis mansoni in an Egyptian village in the Nile Delta. *Am. J. trop. Med. Hyg.*, **29**, 868–874

Abdul-Fadl, M.A.M. & Metwalli, O.M. (1963) Studies on certain urinary blood serum enzymes in bilharziasis and their possible relation to bladder cancer in Egypt. *Br. J. Cancer*, **15**, 137–141

Abe, K., Kagei, N., Teramura, Y. & Ejima, H. (1993) Hepatocellular carcinoma associated with chronic *Schistosoma mansoni* infection in a chimpanzee. *J. med. Primatol.*, **22**, 237–239

Abel, L., Demenais, F., Prata, A., Souza, A.E. & Dessein, A. (1991) Evidence for the segregation of a major gene in human susceptibility/resistance to infection by *Schistosoma mansoni*. *Am. J. hum. Genet.*, **48**, 959–970

Aboul Nasr, A.L., Gazayerli, M.E., Fawzi, R.M. & El-Sibai, I. (1962) Epidemiology and pathology of cancer of the bladder in Egypt. *Acta union int. contra cancrum*, **18**, 528–537

Afifi, M.A. (1948) *Bilharzial Cancer, Radiological Diagnosis and Treatment*, London, H.K. Lewis

Aji, T., Matsuoka, H., Ishii, A., Arimoto, S. & Hayatsu, H. (1994) Retention of a mutagen, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), in the liver of mice infected with *Schistosoma japonicum*. *Mutat. Res.*, **305**, 265–272

Al-Adnani, M.S. & Saleh, K.M. (1982) Extraurinary schistosomiasis in southern Iraq. *Histopathology*, **6**, 747–752

Al Adnani, M.S. & Saleh, K.M. (1983) Schistosomiasis and bladder carcinoma in southern Iraq. *J. trop. Med. Hyg.*, **86**, 93–97

Alexis, R. & Domingo, J. (1986) Schistosomiasis and adenocarcinoma of prostate: a morphologic study. *Hum. Pathol.*, **17**, 757–760

Al-Fouadi, A. & Parkin, D.M. (1984) Cancer in Iraq: seven years' data from the Baghdad tumour registry. *Int. J. Cancer*, **34**, 207–213

Al-Hussaini, M. & McDonald, D.F. (1967) Lack of urothelial topical tumorigenicity and cotumorigenicity of schistosome ova in mice. *Cancer Res.*, **27**, 228–229

Allen, M.J., Boyland, E., Dukes, C.E., Horning, E.S. & Watson, J.G. (1957) Cancer of the urinary bladder induced in mice with metabolites of aromatic amines and tryptophan. *Br. J. Cancer*, **11**, 212–228

Al-Shukri, S., Alwan, M.H., Nayef, M. & Rahman, A.A. (1987) Bilharziasis in malignant tumours of the urinary bladder. *Br. J. Urol.*, **59**, 59–62

Alwan, M.H., Sayed, M. & Kamal, M.M. (1988) Schistosomiasis and sarcoma of the urinary bladder. *Eur. Urol.*, **15**, 139–140

Amano, T. (1980) Clinicopathological studies on the gastro-intestinal schistosomiasis in the endemic area of Yamanashi Prefecture, with special reference to the carcinogenicity of schistosome infection. *Jpn. J. Parasitol.*, **29**, 305–312 (in Japanese)

Amano, T. & Oshima, T. (1988) Hepatoma formation in ddY mice with chronic schistosomiasis japonica. *Jpn. J. Cancer Res. (Gann)*, **79**, 173–180

Anderson, R.M. (1987) Determinants of infection in human schistosomiasis. In: Mahmoud, A.A.F., ed., *Ballière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 2, *Schistosomiasis*, London, Ballière Tindall, pp. 279–300

Andrade, Z.A. & Abreu, W.N. (1971) Follicular lymphoma of the spleen in patients with hepatosplenic schistosomiasis mansoni. *Am. J. trop. Med. Hyg.*, **20**, 237–243

Andrade, Z.A. & Van Marck, E. (1984) Schistosomal glomerular disease (a review). *Mem. Inst. Oswaldo Cruz*, **79**, 499–506

de Andrade, D.R., Ishioka, S., Camara-Lopes, L.H. & Meira, J.A. (1982) Schistosomiasis mansoni in association with histiocytic lymphoma. *Arq. Gastroent. S. Paulo*, **19**, 77–80 (in Portuguese)

Anjarwalla, K.A. (1971) Carcinoma of the bladder in the coast province of Kenya. *E. Afr. med. J.*, **48**, 502–509

Anon. (1992) *Parasitic Diseases in China*, Beijing, Ministry of Health, Department of Health and Endemic Prevention, Division of Parasitic Diseases

Anthony, P.P. (1974) Carcinoma of the urinary tract and urinary retention in Uganda. *Br. J. Urol.*, **46**, 201–208

Anwar, W.A. (1994) Praziquantel (antischistosomal drug): is it clastogenic, co-clastogenic or anticlastogenic? *Mutat. Res.*, **305**, 165–173

Anwar, W.A. & Rosin, M.P. (1993) Reduction in chromosomal damage in schistosomiasis patients after treatment with praziquantel. *Mutat. Res.*, **298**, 179–185

Arap Siongok, T.K., Mahmoud, A.A.F., Ouma, J.H., Warren, K.S., Muller, A.S., Handa, A.K. & Houser, H.B. (1976) Morbidity in schistosomiasis mansoni in relation to intensity of infection: study of a community in Machakos, Kenya. *Am. J. trop. Med. Hyg.*, **25**, 273–283

Arimoto, S. & Hayatsu, H. (1989) Role of hemin in the inhibition of mutagenic activity of 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2) and other aminoazaarenes. *Mutat. Res.*, **213**, 217–226

Arimoto, S., Ohara, Y., Namba, T., Negishi, T. & Hayatsu, H. (1980) Inhibition of the mutagenicity of amino acid pyrolysis products by hemin and other biological pyrrole pigments. *Biochem. biophys. Res. Commun.*, **92**, 662–668

Arimoto, S., Matsuoka, H., Aji, T., Ishii, A., Wataya, Y. & Hayatsu, H. (1992) Modified metabolism of a carcinogen, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), by liver S9 from *Schistosoma japonicum*-infected mice. *Mutat. Res.*, **282**, 177–182

Attah, E.D.'B. & Nkposong, E.O. (1976) Schistosomiasis and carcinoma of the bladder: a critical appraisal of causal relationship. *Trop. geogr. Med.*, **28**, 268–272

Badawi, A.F., Mostafa, M.H., Aboul-Azm, T., Haboubi, N.Y., O'Connor, P.J. & Cooper, D.P. (1992a) Promutagenic methylation damage in bladder DNA from patients with bladder cancer associated with schistosomiasis and from normal individuals. *Carcinogenesis*, **13**, 877–881

Badawi, A.F., Mostafa, M.H. & O'Connor, P.J. (1992b) Involvement of alkylating agents in schistosome-associated bladder cancer: the possible basic mechanisms of induction. *Cancer Lett.*, **63**, 171–188

Badawi, A.F., Cooper, D.P., Mostafa, M.H., Doenhoff, M.J., Probert, A., Fallon, P., Cooper, R. & O'Connor, P.J. (1993) Promutagenic methylation damage in liver DNA of mice infected with *Schistosoma mansoni*. *Carcinogenesis*, **14**, 653–657

Badawy, A.H. (1962) Schistosomiasis of the cervix. *Br. med. J.*, **i**, 369–372

Barreto, M.L. (1993) Use of risk factors obtained by questionnaires in the screening for *Schistosoma mansoni* infections. *Am. J. trop. Med. Hyg.*, **48**, 742–747

Barreto, M.L., França Silva, J.T., Mott, K.E. & Lehman, J.S. (1978) Stability of faecal egg excretion in *Schistosoma mansoni* infection. *Trans. R. Soc. trop. Med. Hyg.*, **72**, 181–187

Barreto, M.L., Smith, D.H. & Sleigh, A.C. (1990) Implications of faecal egg count variation when using the Kato–Katz method to assess *Schistosoma mansoni* infections. *Trans. R. Soc. trop. Med. Hyg.*, **84**, 554–555

Bassily, S., Strickland, G.T., Abdel-Wahab, M.F., Esmat, G.E., Narooz, S., El-Masry, N.A., Constantine, N.T. & Struewing, J.P. (1992) Efficacy of hepatitis B vaccination in primary school children from a village endemic for *Schistosoma mansoni*. *J. infect. Dis.*, **166**, 265–268

Bergquist, N.R. (1992) Present aspects of immunodiagnosis of schistosomiasis. *Mem. Inst. Oswaldo Cruz*, **87** (Suppl. IV), 29–38

Berry, A. (1966) A cytopathological and histopathological study of bilharziasis of the female genital tract. *J. Pathol. Bacteriol.*, **91**, 325–338

Bhagwandeen, S.B. (1976) Schistosomiasis and carcinoma of the bladder in Zambia. *S. Afr. med. J.*, **50**, 1616–1620

Blas, B.L., Cabrera, B.D., Santos, A.T., Jr & Noseñas, J.S. (1986) An attempt to study the case fatality rate in *Schistosoma japonicum* infection in the Philippines. *S.E. Asian J. trop. Med. public Health*, **17**, 67–70

Bognel, C., Prade, M., Charpentier, P. & Michel, G. (1980) Cancer of the cervix and bilharziasis. Study of 2 anatomo-clinical observations. *Gynécologie*, **31**, 513–517 (in French)

Boros, D.L. (1989) Immunopathology of *Schistosoma mansoni* infection. *Clin. Microbiol. Rev.*, **2**, 250–269

Bowry, T.R. (1975) Carcinoma of bladder in Kenya. *E. Afr. med. J.*, **52**, 356–364

Brand, G. & Brand, I. (1980a) Investigations and review of literature relating to carcinogenesis. I. Communication: Cancer from asbestos, schistosomiasis and cicatrization. *Zbl. Bakt. Hyg., I. Abt. Orig. B*, **171**, 1–17 (in German)

Brand, G. & Brand, I. (1980b) Investigations and review of literature relating to carcinogenesis. III. Communication: The results of experimental foreign-body carcinogenesis in relation to asbestos, schistosomiasis and cicatrization cancer in man. *Zbl. Bakt. Hyg., I. Abt. Orig. B.*, **171**, 544–73 (in German)

Brown, R.R., Kuntz, R.E., Arend, R.A., Moore, J.A. & Huang, T.-C. (1976) Experimental bilharzial bladder cancer: tryptophan metabolism in nonhuman primates experimentally infected with *Schistosoma haematobium*. *J. natl Cancer Inst.*, **56**, 101–104

Bryan, G.T. (1969) Role of tryptophan metabolites in urinary bladder cancer. *Am. ind. Hyg. Assoc. J.*, **30**, 27–34

Bryan, G.T., Brown, R.R. & Price, J.M. (1964) Mouse bladder carcinogenicity of certain tryptophan metabolites and other aromatic nitrogen compounds suspended in cholesterol. *Cancer Res.*, **24**, 596–602

Bulay, O., Urman, H., Clayson, D.B. & Shubik, P. (1977) Carcinogenic effects of niridazole on rodents infected with *Schistosoma mansoni*. *J. natl Cancer Inst.*, **59**, 1625–1630

Butterworth, A.E. (1993) Immunology of schistosomiasis. In: Jordan, P., Webbe, G. & Sturrock, R.F., eds, *Human Schistosomiasis*, Wallingford, Oxon., CAB International, pp. 331–366

Cheever, A.W. (1969) Quantitative comparison of the intensity of *Schistosoma mansoni* infections in man and experimental animals. *Trans. R. Soc. trop. Med. Hyg.*, **63**, 781–795

Cheever, A.W. (1985) A review: *Schistosoma japonicum*: the pathology of experimental infection. *Exp. Parasitol.*, **59**, 1–11

Cheever, A.W. & Andrade, Z.A. (1967) Pathological lesions association with *Schistosoma mansoni* infection in man. *Trans. R. Soc. trop. Med. Hyg.*, **61**, 626–639

Cheever, A.W., Kamel, I.A., Elwi, A.M., Mosimann, J.E., Danner, R. & Sippel, J.E. (1978) *Schistosoma mansoni* and *S. haematobium* infection in Egypt. III. Extrahepatic pathology. *Am. J. trop. Med. Hyg.*, **27**, 55–75

Chen, S.C. (1986) Carcinoma of the large bowel. Relationship between eggs of schistosome in large bowel and carcinoma of the large bowel. *Chin. J. Pathol.*, **15**, 69–70 (in Chinese)

Chen, M.G. (1989) Progress and problems in schistosomiasis control in China. *Trop. Med. Parasitol.*, **40**, 174–176

Chen, M.-C. & Chen, W.S.-C. (1957) Acute colonic obstruction in schistosomiasis japonica. A clinical study of 40 cases—14 associated with carcinoma. *Chin. med. J.*, **75**, 517–532

Chen, M.G. & Mott, K.E. (1989) Progress in assessment of morbidity due to *Schistosoma haematobium* infection. A review of recent literature. *Trop. Dis. Bull.*, **86**, R2–R56

Chen, M.-C., Chuang, C.-Y., Chang, P.-Y. & Hu, J.-C. (1980) Evolution of colorectal cancer in schistosomiasis. Transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens. *Cancer*, **46**, 1661–1675

Chen, M.-C., Chang, P.-Y., Chuang, C.-Y., Chen, Y.-J., Wang, F.-P., Tang, Y.-C. & Chou, S.-C. (1981) Colorectal cancer and schistosomiasis. *Lancet*, **i**, 971–973

Chen, J., Campbell, T.C., Li, J. & Peto, R. (1990) *Diet, Life-style, and Mortality in China. A Study of the Characteristics of 65 Chinese Counties*, Oxford, Oxford University Press

Chen, M.-G., Mott, K.E., Wang, Q.-H. & Kane, M. (1993) Hepatitis B and schistosomiasis: interaction or no interaction? *Trop. Dis. Bull.*, **90**, R97–R115

Chirimwami, B., Okonda, L. & Nelson, A.-M. (1991) Lymphoma and schistosomiasis due to *Schistosoma mansoni*. A case report. *Arch. Anat. Cytol. Pathol.*, **39**, 59–61 (in French)

Christie, J.D., Crouse, D., Kelada, A.S., Anis-Ishak, E., Smith, J.H. & Kamel, I.A. (1986a) Patterns of *Schistosoma haematobium* egg distribution in the human lower urinary tract. III. Cancerous lower urinary tracts. *Am. J. trop. Med. Hyg.*, **35**, 759–764

Christie, J.D., Crouse, D., Pineda, J., Anis-Ishak, E., Smith, J.H. & Kamel, I.A. (1986b) Patterns of *Schistosoma haematobium* egg distribution in the human lower urinary tract. I. Noncancerous lower urinary tracts. *Am. J. trop. Med. Hyg.*, **35**, 743–751

Chuang, C.-Y., Chang, P.-Y., Hu, J.-C. & Cheng, M.-C. (1979) Pathomorphologic observations on the relation between late schistosomiasis colitis and colorectal cancer. *Chin. med. J.*, **92**, 113–118

Coelho, L.H.M.R., Carvalho, G. & Carvalho, J.M. (1979) Carcinoma in situ and invasive squamous cell carcinoma associated with schistosomiasis of the uterine cervix. A report of three cases. *Acta cytol.*, **23**, 45–48

Cooppan, R.M., Bhoola, K.D.N. & Mayet, F.G.H. (1984) Schistosomiasis and bladder carcinoma in Natal. *S. Afr. med. J.*, **66**, 841–843

Corbett, E.L., Butterworth, A.E., Fulford, A.J.C., Ouma, J.H. & Sturrock, R.F. (1992) Nutritional status of children with schistosomiasis mansoni in two different areas of Machakos District, Kenya. *Trans. R. Soc. trop. Med. Hyg.*, **86**, 266–273

Cutajar, C.L. (1983) Urinary schistosomiasis in Saudi Arabia. *Saudi med. J.*, **4**, 67–76

Daneshmend, T.K. (1984) Aflatoxin, hepatocellular carcinoma, and schistosomiasis. *Lancet*, **ii**, 1393–1394

Darwish, M.A., Raouf, T.A., Rushdy, P., Constantine, N.T., Rao, M.R. & Edelman, R. (1993) Risk factors associated with a high seroprevalence of hepatitis C virus infection in Egyptian blood donors. *Am. J. trop. Med. Hyg.*, **49**, 440–447

Delmas, V., Dauge, M.C., Davody, A.P., Coulaud, J.P. & Moulonguet, A. (1986) Carcinoma of the bladder in urinary schistosomiasis. *Ann. Urol.*, **20**, 213–217 (in French)

Dessein, A.J., Abel, L., Carvallo, E.M. & Prata, A. (1992) Environmental, genetic and immunological factors in human resistance to *Schistosoma mansoni*. *Immunol. Invest.*, **21**, 423–453

Diaz Hernandez, A., Lopetegui, O.L., Perez, A.R., Garcia, A.R. & Avila, J.P. (1984) Schistosomiasis and travel cancer. *Rev. Cub. Med. trop.*, **36**, 258–263 (in Spanish)

Dimmette, R.M., Elwi, A.M. & Sproat, H.F. (1956) Relationship of schistosomiasis to polyposis and adenocarcinoma of large intestine. *Am. J. clin. Pathol.*, **26**, 266–276

Dodge, O.G. (1962) Tumours of the bladder in Uganda Africans. *Acta unio int. contra cancrum*, **18**, 548–559

Doehring, E., Ehrich, J.H.H. & Bremer, H.J. (1986) Reversibility of urinary tract abnormalities due to schistosoma haematobium infection. *Kidney int.*, **30**, 582–585

Domingo, E.O., Warren, K.S. & Stenger, R.J. (1967) Increased incidence of hepatoma in mice with chronic schistosomiasis mansoni treated with a carcinogen. *Am. J. Pathol.*, **51**, 307–321

Domingo, E.O., Tiu, E., Peters, P.A., Warren, K.S., Mahmoud, A.M.F. & Hauser, H.B. (1980) Morbidity in schistosomiasis japonica in relation to intensity of infection: study of a community in Leyte, Philippines. *Am. J. trop. Med. Hyg.*, **29**, 858–867

Dunne, D.W., Butterworth, A.E., Fulford, A.J.C., Kariuki, H.C., Langley, J.G., Ouma, J.H., Capron, A., Pierce, R.J. & Sturrock, R.F. (1992) Immunity after treatment of human schistosomiasis: association between IgE antibodies to adult worm antigens and resistance to reinfection. *Eur. J. Immunol.*, **22**, 1483–1494

Dunsford, H.A., Keysser, C.H., Dolan, P.M., Seed, J.L. & Bueding, E. (1984) Carcinogenicity of the antischistosomal nitrofuran *trans*-5-amino-3-[2-(5-nitro-2-furyl)viny]-1,2,4-oxadiazole. *J. natl Cancer Inst.*, **73**, 151–160

Ebert, W. (1987) Studies on the frequency and significance of biharziasis in the People's Republic of Mozambique. *Z. Urol. Nephrol.*, **80**, 625–628 (in German)

Edington, G.M. (1979) Schistosomiasis and primary liver cell carcinoma (Letter to the Editor). *Trans. R. Soc. trop. Med. Hyg.*, **73**, 351

Edington, G.M., von Lichtenberg, F., Nwabuebo, I., Taylor, J.R. & Smith, J.H. (1970) Pathological effects of schistosomiasis in Ibadan, Western State of Nigeria. I. Incidence and intensity of infection; distribution and severity of lesions. *Am. J. trop. Med. Hyg.*, **19**, 982–995

El-Aaser, A.A., Hassanein, S.M., El-Bolkainy, M.N., Omar, S., El-Sebai, I. & El-Merzabani, M.M. (1978) Bladder carcinogenesis using bilharzia-infested Swiss albino mice. *Eur. J. Cancer*, **14**, 645–648

El-Aaser, A.A., El-Merzabani, M.M., Higgy, N.A. & Kader, M.M.A. (1979) A study on the aetiological factors of bilharzial bladder cancer in Egypt. 3. Urinary β-glucuronidase. *Eur. J. Cancer*, **15**, 573–583

El-Aaser, A.A., El-Merzabani, M.M., Higgy, N.A. & El-Habet, A.E. (1982) A study on the etiological factors of bilharzial bladder cancer in Egypt. 6. The possible role of urinary bacteria. *Tumori*, **68**, 23–28

El-Bolkainy, M.N., Ghoneim, M.A. & Mansour, M.A. (1972) Carcinoma of bilharzial bladder in Egypt: clinical and pathological features. *Br. J. Cancer*, **44**, 561–570

El-Bolkainy, M.N., Mokhtar, N.M., Ghoneim, M.A. & Hussein, M.H. (1981) The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer*, **48**, 2643–2648

El-Bolkainy, M.N., Chu, E.W., Ghoneim, M.A. & Ibrahim, A.S. (1982) Cytologic detection of bladder cancer in a rural Egyptian population infested with schistosomiasis. *Acta cytol.*, **26**, 303–310

Elem, B. & Purohit, R. (1983) Carcinoma of the urinary bladder in Zambia. A quantitative estimation of *Schistosoma haematobium* infection. *Br. J. Urol.*, **55**, 275–278

El-Gazayerli, M.M. & Abdel-Aziz, A.-S. (1963) On bilharziasis and male breast cancer in Egypt: a preliminary report and review of the literature. *Br. J. Cancer*, **17**, 566–571

El-Gazayerli, M. & Khalil, H.A. (1959) Bilharziasis and cancer of the urinary tract. Some observations. *Alexandria med. J.*, **5**, 31–36

El Malatawy, A., El Habashy, A., Lechine, N., Dixon, H., Davis, A. & Mott, K.E. (1992) Selective population chemotherapy among schoolchildren in Beheira governate: the UNICEF/Arab Repubic of Egypt/WHO Schistosomiasis Control Project. *Bull. World Health Organ.*, **70**, 47–56

El-Maraghy, M.A., Elyan, A., El-Leithy, A.G., El-Tehewey, F.A., Abou Senna, I., El-Tawil, A. & Naguib, F. (1982) Bilharziasis of the female genital tract: new concepts. *J. Egypt. Soc. Parasitol.*, **12**, 179–186

El-Masri, W.S. & Fellows, G. (1981) Bladder cancer after spinal cord injury. Incidence, presentation, histology and prognosis compared with bladder cancer in the non-paralysed population. *Paraplegia*, **19**, 265–270

El Masry, N.A., Farid, Z., Bassily, S., Kilpatrick, M.E. & Watten, R.H. (1986) Schistosomal colonic polyposis: clinical, radiological and parasitological study. *J. trop. Med. Hyg.*, **89**, 13–17

El-Morsi, B., Sherif, M. & El-Raziki, E.S. (1975) Experimental bilharzial squamous metaplasia of the urinary bladder in hamsters. *Eur. J. Cancer*, **11**, 199–201

El-Rooby, A. (1985) Management of hepatic schistosomiasis. *Semin. Liver Dis.*, **5**, 263–276

El-Sebai, I. (1980) Carcinoma of the urinary bladder in Egypt: current clinical experience. In: El Bolkainy, M.N. & Chu, E.W., eds, *Detection of Bladder Cancer Associated with Schistosomiasis*, Cairo, Al-Ahram Press, pp. 9–18

El-Sewedy, S.M., Arafa, A., Abdel-Aal, G. & Mostafa, M.H. (1978) The activities of urinary α-esterases in bilharziasis and their possible role in the diagnosis of bilharzial bladder cancer in Egypt. *Trans. R. Soc. trop. Med. Hyg.*, **72**, 525–528

El Tabbakh, G. & Hamza, M.A. (1989) Carcinoma of the uterine cervix and schistosomiasis. *Int. J. Gynecol. Obstet.*, **29**, 263–268

Eltoum, I.A., Sulaiman, S., Ismail, B.M., Ali, M.M.M., Elfatih, M. & Homeida, M.M.A. (1992) Evaluation of haematuria as an indirect screening test for schistosomiasis haematobium: a population-based study in the White Nile Province, Sudan. *Acta trop.*, **51**, 151–157

El-Zoghby, S.M., El-Kholy, Z.A., El-Shrkawy, A., Rashad, M., El-Kilany, S., Abaza, H. & Gawish, Y.S. (1978) β-Glucuronidase in schistosomal intestinal polypi of the colon. *Acta vitaminol. enzymol.*, **32**, 7–11

Everson, R.B., Gad-el-Mawla, N.M., Attia, M.A.M., Chevlen, E.M., Thorgeirsson, S.S., Alexander, L.A., Flack, P.M., Staiano, N. & Ziegler, J.L. (1983) Analysis of human urine for mutagens associated with carcinoma of the bilharzial bladder by the Ames *Salmonella* plate assay. Interpretation employing quantitation of viable lawn bacteria. *Cancer*, **51**, 371–377

Feldmeier, H. & Poggensee, G. (1993) Diagnostic techniques in schistosomiasis control. A review. *Acta trop.*, **52**, 205–220

Feng, Y.Z. & Shi, Q.N. (1981) Gastric schistosomiasis associated with gastric cancer (report of 15 cases). *Natl med. J. China*, **61**, 469 (in Chinese)

Ferguson, A.R. (1911) Associated bilharziosis and primary malignant disease of the urinary bladder with observations on a series of forty cases. *J. Pathol. Bacteriol.*, **16**, 76–98

Forsyth, D.M. (1969) A longitudinal study of endemic urinary schistosomiasis in a small East African community. *Bull. World Health Organ.*, **40**, 771–783

Fripp, P.J. (1960) Schistosomiasis and urinary β-glucuronidase activity. *Nature*, **189**, 507–508

Fripp, P.J. (1965) The origin of urinary β-glucuronidase. *Br. J. Cancer*, **19**, 330–335

Fripp, P.J. & Keen, P. (1980) Bladder cancer in an endemic *Schistosoma haematobium* area. The excretion patterns of 3-hydroxyanthranilic acid and kynurenine. *S. Afr. J. Science*, **76**, 212–215

Fujimoto, H., Araki, T., Hihara, T., Karikomi, M., Kachi, K., Saito, Y., Hayashi, S. & Uchiyama, G. (1989) Hepatocellular carcinoma associated with schistosomiasis japonicum; CT and angiographic features. *Nippon Igaku Hoshasen Gakkai Zasshi*, **49**, 139–145

Fujita, J., Nakayama, H., Onoue, H., Rhim, J.S., El-Bolkainy, M.N., El-Aaser, A.A. & Kitamura, Y. (1987) Frequency of active *ras* oncogene in human bladder cancers associated with schistosomiasis. *Jpn. J. Cancer Res. (Gann)*, **78**, 915–920

Fukushima, S., Asamoto, M., Imaida, K., El-Bolkainy, M.N., Tawfik, H.N. & Ito, N. (1989) Comparative study of urinary bladder carcinomas in Japanese and Egyptians. *Acta pathol. jpn*, **39**, 176–179

Gawish, N. (1975) Parasites and cancer. *Egypt. J. Bilharzia*, **2**, 131–136

Gelfand, M., Weinberg, R.W. & Castle, W.M. (1967) Relation between carcinoma of the bladder and infestation with *Schistosoma haematobium*. *Lancet*, **i**, 1249–1251

Gentile, J.M. (1985) Schistosome related cancers: a possible role for genotoxins. *Environ. Mutag.*, **7**, 775–785

Gentile, J.M. (1991) A possible role for genotoxins in parasite-associated cancers. *Rev. latinoam. Genet.*, **1**, 239–248

Gentile, J.M. & Gentile, G.J. (1994) Implications for the involvement of the immune system in parasite-associated cancers. *Mutat. Res.*, **305**, 315–320

Gentile, J.M., Brown, S., Aardema, M., Clark, D. & Blankespoor, H. (1985) Modified mutagen metabolism in *Schistosoma hematobium*-infested organisms. *Arch. environ. Health*, **40**, 5–12

Gillman, J. & Prates, M.D. (1962) Histological types and histogenesis of bladder cancer in the Portuguese East African with special reference to bilharzial cystitis. *Acta unio int. contra cancrum*, **18**, 560–574

Godec, C.J., Grunberger, I. & Carr, G.A. (1992) Simultaneous presence of schistosomiasis and advanced cancer in prostate. *Urology*, **39**, 547–549

Goebel, C. (1905) Occurrence of bladder tumours due to bilharziasis, with particular attention to carcinomas. *Z. Krebsforsch.*, **3**, 369–513 (in German)

Guo, Z.R. & Lu, Q.X. (1987) Parasitic diseases. A case-control study on the relationship between schistosomiasis and liver cancer. *Chin. J. Parasitol. parasit. Dis.*, **5**, 220–223 (in Chinese)

Guo, Z.R., Ni, Y.C. & Wu, J.L. (1984) Epidemiological study on relationship between schistosomiasis and colorectal cancer. *Jiangsu med. J.*, **4**, 35 (in Chinese)

Guo, Z.R., Lu, Q.X., Wu, J.W., Xu, J., Yang, M.L. & Wang, D.W. (1985) Schistosomiasis factor in the formation of colorectal cancer. *Jiangsu med. J.*, **12**, 41–42 (in Chinese)

Guo, Z.R., Lu, Q.X., Zhao, L.P. & Zhang, Z.H. (1987) Schistosomiasis japonicum and colon cancer. An enquiry about the pathogenesis of colon cancer by using a logistic regression model. *Chin. J. Epidemiol.*, **8**, 21–24 (in Chinese)

Guo, W., Zheng, W., Li, J.-Y., Chen, J.-S. & Blot, W.J. (1993) Correlations of colon cancer mortality with dietary factors, serum markers and schistosomiasis in China. *Nutr. Cancer*, **20**, 13–20

Habuchi, T., Takahashi, R., Yamada, H., Ogawa, O., Kakehi, Y., Ogura, K., Hamazaki, S., Toguchida, J., Ishizaki, K., Fujita, J., Sugiyama, T. & Yoshida, O. (1993) Influence of cigarette smoking and schistosomiasis on p53 gene mutation in urothelial cancer. *Cancer Res.*, **53**, 3795–3799

Haese, W.H. & Bueding, E. (1976) Long-term hepatocellular effects of hycanthone and of two other antischistosomal drugs in mice infected with *Schistosoma mansoni*. *J. Pharmacol. exp. Ther.*, **197**, 703–713

Haese, W.H., Smith, D.L. & Bueding, E. (1973) Hycanthone-induced hepatic changes in mice infected with *Schistosoma mansoni*. *J. Pharmacol. exp. Ther.*, **186**, 430–440

Hafez, M., Aboul Hassan, S., El-Tahan, H., El-Shennawy, F., Khashaba, M., Al-Tonbary, Y., El-Morsi, Z., El-Sallab, S., El-Desoky, I., El-Shazly, A. & Eteba, S. (1991) Immunogenetic susceptibility for post-schistosomal hepatic fibrosis. *Am. J. trop. Med. Hyg.*, **44**, 424–433

Hagan, P., Blumenthal, U.J., Dunn, D., Simpson, A.J.G. & Wilkins, H.A. (1991) Human IgE, IgG4 and resistance to reinfection with *Schistosoma haematobium*. *Nature*, **349**, 243–245

Hanash, K.A. (1984) Carcinoma of the bilharzial bladder. *Progr. clin. biol. Res.*, **2**, 249–274

Hashem, M. (1971) The aetiology and pathogenesis of primary liver cancer and its relation to schistosomiasis. *Ain Shams med. J.*, **22**, 555–567

Hashem, M. & Boutros, K. (1961) The influence of bilharzial infection on the carcinogenesis of the mouse bladder. *J. Egypt. med. Assoc.*, **44**, 598–606

Hashem, M., Zaki, S.A. & Hussein, M. (1961) The bilharzial bladder cancer and its relation to schistosomiasis. A statistical study. *J. Egypt. med. Assoc.*, **44**, 579–597

Hashimoto, Y., Muratani, A., Nishiyama, H., Ashida, H., Kurogo, F., Souno, K., Murao, S. & Maeda, S. (1986) A case of colon cancer associated with schistosomiasis japonica. *Gan No Rinsho*, **32**, 815–818

Hasler, J.A., Siwela, A.H., Nyathi, C.B. & Chetsanga, C.J. (1986) The effect of schistosomiasis on the activation of aflatoxin B_1. *Res. Commun. Chem. Pathol. Pharmacol.*, **51**, 421–424

Hatz, C., Mayombana, C., de Savigny, D., MacPherson, C.N.L., Koella, J.C., Degrémont, A. & Tanner, M. (1990) Ultrasound scanning for detecting morbidity due to *Schistosoma haematobium* and its resolution following treatment with different doses of praziquantel. *Trans. R. Soc. trop. Med. Hyg.*, **84**, 84–88

Hatz, C., Jenkins, J.M., Meudt, R., Abdel-Wahab, M.F. & Tanner, M. (1992a) A review of the literature on the use of ultrasonography in schistosomiasis with special reference to its use in field studies. 1. *Schistosoma haematobium*. *Acta trop.*, **51**, 1–14

Hatz, C., Jenkins, J.M., Ali, Q.M., Abdel-Wahab, M.F., Cerri, G.G. & Tanner, M. (1992b) A review of the literature on the use of ultrasonography in schistosomiasis with special reference to its use in field studies. 2. *Schistosoma mansoni*. *Acta trop.*, **51**, 15–28

Hatz, C., Murakami, H. & Jenkins, J.M. (1992c) A review of the literature on the use of ultrasonography in schistosomiasis with special reference to its use in field studies. 3. *Schistosoma japonicum*. *Acta trop.*, **51**, 29–36

Hatz, C., Jenkins, J.M., Morrow, R.H. & Tanner, M. (1992d) Ultrasound in schistosomiasis—a critical look at methodological issues and potential applications. *Acta trop.*, **51**, 89–97

Henderson, G.S., Conary, J.T., Summar, M., McCurley, T.L. & Colley, D.G. (1991) In vivo molecular analysis of lymphokines involved in the murine immune response during *Schistosoma mansoni* infection. I. IL-4 mRNA, not IL-2 mRNA, is abundant in the granulomatous livers, mesenteric lymph nodes, and spleens of infected mice. *J. Immunol.*, **147**, 992–997

Henderson, G.S., Lu, X., McCurley, T.L. & Colley, D.G. (1992) In vivo molecular analysis of lymphokines involved in the murine immune response during *Schistosoma mansoni* infection. II. Quantification of IL-4 mRNA, IFN-γ mRNA, and IL-2 mRNA levels in the granulomatous livers, mesenteric lymph nodes, and spleens during the course of modulation. *J. Immunol.*, **148**, 2261–2269

Hiatt, R.A. (1976) Morbidity from *Schistosoma mansoni* infections: an epidemiologic study based on quantitative analysis of egg excretion in two highland Ethiopian villages. *Am. J. trop. Med. Hyg.*, **25**, 808–817

Hiatt, R.A., Cline, B.L., Ruiz-Tiben, E., Knight, W.B. & Berrios-Duran, L.A. (1980) The Boqueron project after 5 years: a prospective community-based study of infection with *Schistosoma mansoni* in Puerto Rico. *Am. J. trop. Med. Hyg.*, **29**, 1228–1240

Hicks, R.M. (1982) Nitrosamines as possible etiological agents in bilharzial bladder cancer. In: Magee, P.N., ed., *Nitrosamines and Human Cancer* (Banbury Report No. 12), Cold Spring Harbor, NY, CSH Press, pp. 455–471

Hicks, R.M., Walters, C.L., Elsebai, I., El Aasser, A.-B., El Merzabani, M. & Gough, T.A. (1977) Demonstration of nitrosamines in human urine: preliminary observations on a possible etiology for bladder cancer in association with chronic urinary tract infections. *Proc. R. Soc. Med.*, **70**, 413–417

Hicks, R.M., Gough, T.A. & Walters, C.L. (1978) Demonstration of the presence of nitrosamines in human urine: preliminary observations on a possible etiology for bladder cancer in association with chronic urinary tract infection. In: Walker, E.A., Castegnaro, M., Griciute, L. & Lyle, R.E., eds, *Environmental Aspects of* N-*Nitroso Compounds* (IARC Scientific Publications No. 19), Lyon, IARC, pp. 465–475

Hicks, R.M., James, C. & Webbe, G. (1980) Effect of *Schistosoma haematobium* and *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine on the development of urothelial neoplasia in the baboon. *Br. J. Cancer*, **42**, 730–754

Hicks, R.M., Ismail, M.M., Walters, C.L., Beecham, P.T., Rabie, M.F. & El Alamy, M.A. (1982) Association of bacteriuria and urinary nitrosamine formation with *Schistosoma haematobium* infection in the Qalyub area of Egypt. *Trans. R. Soc. trop. Med. Hyg.*, **76**, 519–527

Higginson, J. & Oettlé, A.G. (1962) Cancer of the bladder in the South African Bantu. *Acta unio int. contra cancrum*, **18**, 579–584

Hill, M.J. (1979) Role of bacteria in human carcinogenesis. *J. hum. Nutr.*, **33**, 416–426

Hinder, R.A. & Schmaman, A. (1969) Bilharziasis and squamous carcinoma of the bladder. *S. Afr. med. J.*, **43**, 617–618

Houston, W. (1964) Carcinoma of the bladder in Southern Rhodesia. *Br. J. Urol.*, **36**, 71-76

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity. An Updating of* IARC Monographs *Volumes 1–42*, Lyon, pp. 77–78

IARC (1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 59, *Hepatitis Viruses*, Lyon, pp. 45–164

Inaba, Y. (1982) A statistical study on the mortality in the endemic area of schistosomiasis japonica in Yamanashi Prefecture—with special emphasis on the malignant neoplasms of the digestive tract. *Jpn. J. Public Health*, **29**, 585–590 (in Japanese)

Inaba, Y. (1984) A cohort study on the causes of death in an endemic area of schistosomiasis japonica in Japan. *Ann. Acad. Med.*, **13**, 142–148

Inaba, Y., Takahashi, E.Y. & Maruchi, N. (1977) A statistical analysis on the mortality of liver cancer and liver cirrhosis in Yamanashi Prefecture, with special emphasis on the relation to the prevalence of schistosomiasis. *Jpn. J. public Health*, **24**, 811–815

Inaba, Y., Maruchi, N., Matsuda, M., Yoshihara, N. & Yamamoto, S.-I. (1984) A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. *Int. J. Epidemiol.*, **13**, 408–412

Inoguchi, T., Adachi, T., Yamauchi, Y., Isomoto, H., Takamori, K. & Shinohara, M. (1978) Relationship between chronic schistosomiasis japonica and carcinoma in the large intestine. *Acta med. Fukuoka*, **48**, 93–100 (in Japanese)

Irie, Y. & Iwamura, Y. (1993) Host-related DNA sequences are localized in the body of schistosome adults. *Parasitology*, **107**, 519–528

Ishak, K.G., Le Golvan, O.C. & El-Sebai, I. (1967) Malignant bladder tumours associated with bilharziasis, a gross and microscopic study. In: Mostofi, F.K., ed., *Bilharziasis*, New York, Springer-Verlag, p. 67

Ishihara, J., Sasaki, Y., Suzuki, D., Yokokawa, T., Noguchi, H., Ikeda, C., Narimatsu, H., Aita, S., Matsumura, K., Nakajima, H., Ide, H. & Takahashi, T. (1984) An autopsy case of bronchiolo-alveolar cell carcinoma with many eggs of *Schistosoma japonicum* in the involved lung. *Nippon Kyobu Shikkan Gakkai Zasshi*, **22**, 225–228 (in Japanese)

Ishii, A., Matsuoka, H., Aji, T., Hayatsu, H., Wataya, Y., Arimoto, S. & Tokuda, H. (1989) Evaluation of the mutagenicity and the tumor-promoting activity of parasite extracts: *Schistosoma japonicum* and *Clonorchis sinensis*. *Mutat. Res.*, **224**, 229–233

Iskander, S.G. & Kamel, R. (1968) Bilharziasis in a malignant Brenner-cell tumour of the ovary. *J. Egypt med. Assoc.*, **51**, 922–928

Iuchi, M., Nakayama, Y., Ishiwa, M., Yamada, H. & Chiba, K. (1971) Primary cancer of the liver associated with chronic schistosomiasis japonica. *Naika*, **27**, 761–766 (in Japanese)

Iwamura, Y., Irie, Y., Kominami, R., Nara, T. & Yasuraoka, K. (1991) Existence of host-related DNA sequences in the schistosome genome. *Parasitology*, **102**, 397–403

James, C., Hicks, M., Webbe, G. & Nelson, G.S. (1974) *Schistosoma haematobium* and bladder cancer (Abstract). *Parasitology*, **69**, viii–ix

Jenkins, J.M. & Hatz, C., eds (1992) The use of diagnostic ultrasound in schistosomiasis—attempts at standardization of methodology. *Acta trop.*, **51**, 45–63

de Jonge, N. (1992) Detection of the circulating anodic antigen for immunodiagnosis of *Schistosoma* infections. In: Bergquist, N.R., ed., *Immunodiagnostic Approaches in Schistosomiasis*, New York, John Wiley & Sons, pp. 111–124

de Jonge, N., Polderman, A.M., Hilberath, G.W., Krijger, F.W. & Deelder, A.M. (1990) Immunodiagnosis of schistosomiasis patients in the Netherlands: comparison of antibody and antigen detection before and after chemotherapy. *Trop. Med. Parasitol.*, **41**, 257–261

Jordan, P. & Randall, K. (1962) Bilharziasis in Tanganyika: observations on its effects and the effects of treatment in schoolchildren. *J. trop. Med. Hyg.*, **65**, 1–6

Jordan, P. & Webbe, G. (1993) Epidemiology. In: Jordan, P., Webbe, G. & Sturrock, R.F., eds, *Human Schistosomiasis*, Wallingford, CAB International, pp. 87–158

Joyce, P.R., Blackwell, J.B. & Charters, A.D. (1972) Schistosomiasis in gynaecology. Two cases in immigrants in Western Australia. *Aust. N.Z. J. Obstet. Gynaecol.*, **12**, 137–141

Kagan, I.G. & Pellegrino, J. (1961) A critical review of immunological methods for the diagnosis of bilharziasis. *Bull. World Health Organ.*, **25**, 611–674

Kahn, H.J., Stroud, B.J. & Berry, A.V. (1978) *Schistosoma mansoni* worm in ovarian cystic teratoma. A case report. *S. Afr. med. J.*, **54**, 673–674

Kakizoe, Y. (1985) The influence of *Schistosoma mansoni* infection on carcinogenesis of mouse livers initiated by *N*-2-fluorenylacetamide. *Kurume med. J.*, **32**, 169–178

Kalter, S.S., Kuntz, R.E., Heberling, R.L., Helmke, R.J. & Smith, G.C. (1974) C-Type viral particles in a urinary bladder neoplasma induced by *Schistosoma haematobium*. *Nature*, **251**, 440

Kamel, I.A., Elwi, A.M., Cheever, A.W., Mosimann, J.E. & Danner, R. (1978) *Schistosoma mansoni* and *S. haematobium* infections in Egypt. IV. Hepatic lesions. *Am. J. trop. Med. Hyg.*, **27**, 931–938

Kamel, M.A., Zakaria, E., Mabrouk, M.A., Zakaria, S., Hgazi, A.R.M. & El Raziky, E.H. (1984) HLA antigen frequencies in Egyptian patients with complicated schistosomiasis mansoni. *Trans. R. Soc. trop. Med. Hyg.*, **78**, 850–851

Kamo, E. & Ebato, T. (1982) A clinical analysis of primary carcinoma of the liver in relation with schistosomiasis japonica. *J. Yamanashi med. Assoc.*, 9, 23–37

Kantor, A.F., Hartge, P., Hoover, R.N., Narayana, A.S., Sullivan, J.W. & Fraumeni, J.F., Jr (1984) Urinary tract infection and risk of bladder cancer. *Am. J. Epidemiol.*, **119**, 510–515

Kazama, Y. (1921) Intestinal carcinoma due to schistosomiasis japonica; a genetic association between its origin and the parasites. *Gann*, **15**, 22–24 (in German)

Keen, P. & Fripp, P.J. (1980) Bladder cancer in an endemic schistosomiasis area: geographical and sex distribution. *S. Afr. J. Sci.*, **76**, 228–230

Khafagy, M.M., El-Bolkainy, M.N. & Mansour, M.A. (1972) Carcinoma of the bilharzial urinary bladder. A study of the associated mucosal lesions in 86 cases. *Cancer*, **30**, 150–159

Khafagy, E.Z., El-Hawary, M.F,, Galal, A.F., Salah, M.K., Shoeb, S.M., Ibrahim, K.B. & Omar, S. (1976) Leucine aminopeptidase, significance of serum elevation in bilharziasis. *Egypt J. Bilharzia*, **3**, 183–197

Khurana, P., Morad, N., Khan, A.R., Shetty, S., Ibrahim, A. & Patil, K. (1992) Impact of schistosomiasis on urinary bladder cancer in the southern province of Saudi Arabia: review of 60 cases. *J. trop. Med. Hyg.*, **95**, 149–151

Kimura, E., Moji, K., Uga, S., Kiliku, F.M., Migwi, D.K., Mutua, W.R., Muhoho, N.D. & Aoki, Y. (1992) Effects of *Schistosoma haematobium* infection on mental test scores of Kenyan school children. *Trop. Med. Parasitol.*, **43**, 155–158

King, C.H., Keating, C.E., Muruka, J.F., Ouma, J.H., Houser, H., Arap Siongok, T.K. & Mahmoud, A.A.F. (1988) Urinary tract morbidity in schistosomiasis haematobia: association with age, and intensity of infection in an endemic area in Coast Province, Kenya. *Am. J. trop. Med. Hyg.*, **39**, 361–368

King, C.H., Lombardi, G., Lombardi, C., Greenblatt, R., Hodder, S., Kinyanjui, H., Ouma, J., Odiambo, O., Bryan, P.J., Muruka, J., Magak, P., Weinert, D., Ransohoff, D., Houser, H., Koech, D., Arap Siongok, T.K. & Mahmoud, A.A.F. (1990) Chemotherapy-based control of schistosomiasis haematobia. II. Metrifonate vs. praziquantel in control of infection-associated morbidity. *Am. J. trop. Med. Hyg.*, **42**, 587–595

Kisner, C.D. (1973) Vesical bilharziasis, pathological changes and relationship to squamous carcinoma. *S. Afr. J. Surg.*, **11**, 79–87

Kitani, K. & Iuchi, M. (1990) Schistosomiasis japonica: a vanishing endemic in Japan. *J. Gastroenterol. Hepatol.*, **5**, 160–172

Kitinya, J.N., Laurèn, P.A., Eshleman, L.J., Paljärvi, L. & Tanaka, K. (1986) The incidence of squamous and transitional cell carcinomas of the urinary bladder in northern Tanzania in areas of high and low levels of endemic *Schistosoma haematobium* infection. *Trans. R. Soc. trop. Med. Hyg.*, **80**, 935–939

Kloetzel, K. (1964) Natural history and prognosis of splenomegaly in *Schistosoma mansoni*. *Am. J. trop. Med. Hyg.*, **13**, 541–544

Kojima, S., Yano, A., Sasazuki, T. & Ohta, N. (1984) Associations between HLA and immune responses in individuals with chronic schistosomiasis japonica. *Trans. R. Soc. trop. Med. Hyg.*, **78**, 325–329

Kojiro, M., Kakizoe, S., Yano, H., Tsumagari, J., Kenmochi, K. & Nakashima, T. (1986) Hepatocellular carcinoma and schistosomiasis japonica. A clinicopathological study of 59 autopsy cases of hepatocellular carcinoma associated with chronic schistosomiasis japonica. *Acta pathol. jpn.*, **36**, 525–532

Kuntz, R.E., Myers, B.J. & Cheever, A.W. (1971) *Schistosoma haematobium* infection in the opossum (*Didelphis marsupialis*): involvement of the urogenital system. *Bull. World Health Organ.*, **45**, 21–25

Kuntz, R.E., Cheever, A.W. & Myers, B.J. (1972) Proliferative epithelial lesions of the urinary bladder of nonhuman primates infected with *Schistosoma haematobium*. *J. natl Cancer Inst.*, **48**, 223–235

Kuntz, R.E., Cheever, A.W., Myers, B.J., Young, S.W. & Moore, J.A. (1975) Calcification of the bladder and papillary tumours of the bladder and ureters in gibbons (*Hylobates lar*) infected with *Schistosoma haematobium* (Iran). *Trans. R. Soc. trop. Med. Hyg.*, **69**, 494–502

Kuntz, R.E., Cheever, A.W., Bryan, G.T., Moore, J.A. & Huang, T.-C. (1978) Natural history of papillary lesions in the urinary bladder in schistosomiasis. *Cancer Res.*, **38**, 3836–3839

Kurniawan, A.N., Hardjawidjaja, L. & Clark, R.T. (1976) A clinico-pathologic study of cases with *Schistosoma japonicum* infection in Indonesia. *S.E. Asian J. trop. Med. public Health*, **7**, 263–269

Laughlin, L.W., Farid, Z., Mansour, N., Edman, D.C. & Higashi, G.I. (1978) Bacteriuria in urinary schistosomiasis in Egypt. A prevalence survey. *Am. J. trop. Med. Hyg.*, **27**, 916–918

Lengeler, C., de Savigny, D., Mshinda, H., Mayombana, C., Tayari, S., Hatz, C., Degrémont, A. & Tanner, M. (1991a) Community-based questionnaires and health statistics as tools for the cost-efficient identification of communities at risk of urinary schistosomiasis. *Int. J. Epidemiol.*, **20**, 796–807

Lengeler, C., Kilima, P., Mshinda, H., Morona, D., Hatz, C. & Tanner, M. (1991b) Rapid, low-cost, two-step method to screen for urinary schistosomiasis at the district level: the Kilosa experience. *Bull. World Health Organ.*, **69**, 179–189

Lengeler, C., Mshinda, H., Morona, D. & deSavigny, D. (1993) Urinary schistosomiasis: testing with urine filtration and reagent sticks for haematuria provides a comparable prevalence estimate. *Acta trop.*, **53**, 39–50

Li, Y. (1988) Geographical correlation analysis between schistosomiasis and large intestine cancer. *Chung Hua Liu Hsing Ping Hsueh Tsa Chih*, **9**, 265–268 (in Chinese)

von Lichtenberg, F. (1987) Consequences of infections with schistosomes. In: Rollinson, D. & Simpson, A.J.G., eds, *The Biology of Schistosomes. From Genes to Latrines*, London, Acadamic Press, pp. 185–232

de Lima e Costa, M.F.F., Correa Leite, M.L., Rocha, R.S., de Almeida Magalhães, M.H. & Katz, N. (1988) Anthropometric measures in relation to schistosomiasis mansoni and socioeconomic variables. *Int. J. Epidemiol.*, **17**, 880–886

Liu, L.B., Domingo, E.O., Stenger, R.J., Warren, K.S., Confer, D.B. & Johnson, E.A. (1969) An ultrastructural study of the toxic and carcinogenic effects of 2-amino-5-azotoluene on the livers of schistosome-infected and -uninfected mice. *Cancer Res.*, **29**, 837–847

Liu, B.C., Rong, Z.P., Sun, X.T., Wu, Y.P. & Gao, R.Q. (1983) Study of geographic correlation between colorectal cancers and schistosomiasis in China. *Acta acad. med. sin.*, **5**, 173–177 (in Chinese)

Lucas, S.B. (1982a) Squamous cell carcinoma of the bladder and schistosomiasis. *E. Afr. med. J.*, **59**, 345–351

Lucas, S.B. (1982b) Bladder tumours in Malawi. *Br. J. Urol.*, **54**, 275–279

Lukacs, N.W. & Boros, D.L. (1993) Lymphokine regulation of granuloma formation in murine schistosomiasis mansoni. *Clin. Immunol. Immunopathol.*, **68**, 57–63

Lukacs, N.W., Kunkel, S.L., Strieter, R.M., Warmington, K. & Chensue, S.W. (1993) The role of macrophage inflammatory protein 1α in *Schistosoma mansoni* egg-induced granulomatous inflammation. *J. exp. Med.*, **177**, 1551–1559

Lyra, L.G., Rebouças, G. & Andrade, Z.A. (1976) Hepatitis B surface antigen carrier state in hepatosplenic schistosomiasis. *Gastroenterology*, **71**, 641–645

Makhyoun, N.A. (1974) Smoking and bladder cancer in Egypt. *Br. J. Cancer*, **30**, 577–581

Makhyoun, N.A., El-Kashlan, K.M., Al-Ghorab, M.M. & Mokhles, A.S. (1971) Aetiological factors in bilharzial bladder cancer. *J. trop. Med. Hyg.*, **74**, 73–78

Malik, M.O.A., Veress, B., Daoud, E.H. & El Hassan, A.M. (1975) Pattern of bladder cancer in the Sudan and its relation to schistosomiasis: a study of 255 vesical carcinomas. *J. trop. Med. Hyg.*, **78**, 219–226

Martinez-Maldonado, M., Girod, C.E., de Arellano, G.R. & Ramirez, E.A. (1965) Liver cell carcinoma (hepatoma) in Puerto Rico. A survey of 26 cases. *Am. J. dig. Dis.*, **10**, 522–529

Matsuoka, H., Aji, T., Ishii, A., Arimoto, S., Wataya, Y. & Hayatsu, H. (1989) Reduced levels of mutagen processing potential in the *Schistosoma japonicum*-infected mouse liver. *Mutat. Res.*, **227**, 153–157

McGarvey, S.T., Wu, G., Zhang, S., Wang, Y., Peters, P., Olds, G.R. & Wiest, P.M. (1993) Child growth, nutritional status, and schistosomiasis japonica in Jiangxi, People's Republic of China. *Am. J. trop. Med. Hyg.*, **48**, 547–553

Mikhail, N.E., Tawfic, M.I., Abel Hadi, A. & Akl, M. (1988) Schistosomal orchitis simulating malignancy. *J. Urol.*, **140**, 147–148

Miyasato, M. (1984) Experimental study of the influence of *Schistosoma japonicum* infection on carcinogenesis of mouse liver treated with N-2-fluorenylacetamide (2-FAA). *Jpn. J. Parasitol.*, **33**, 41–48

Mohamed, A.S. (1954) The association of bilharziasis and malignant disease in the urinary bladder. Pathogenesis of bilharzial cancer in the urinary bladder. *J. Egypt. med. Assoc.*, **37**, 1066–1085

Mohamed, A.R.E.-S., Karawi, M.A.A. & Yasawy, M.I. (1990) Schistosomal colonic disease. *Gut*, **31**, 439–442

Mohamed-Ali, Q., Doehring-Schwerdtfeger, E., Abdel-Rahim, I.M., Schlake, J., Kardorff, R., Franke, D., Kaiser, C., Elsheikh, M., Abdalla, M.E.M., Schafer, P. & Ehrich, J.H.H. (1991) Ultrasonographical investigation of periportal fibrosis in children with *Schistosoma mansoni* infection: reversibility of morbidity seven months after treatment with praziquantel. *Am. J. trop. Med. Hyg.*, **44**, 444–451

Mostafa, M.H., El-Bassiouni, E.A., El-Sewedy, S.M., Akhnouk, S., Tawfic, T. & Abdel-Rafee, A. (1984) Hepatic microsomal enzymes in *Schistosoma mansoni*-infected mice: 1. Effect of duration of infection and lindane administration on dimethylnitrosamine demethylases. *Environ. Res.*, **35**, 154–159

Mostafa, M.H., Helmi, S., Badawi, A.F., Tricker, A.R., Spiegelhalder, B. & Preussmann, R. (1994) Nitrate, nitrite and volatile *N*-nitroso compounds in the urine of *Schistosoma haematobium* and *Schistosoma mansoni* infected patients. *Carcinogenesis*, **15**, 619–625

Mott, K.E. & Dixon, H. (1982) Collaborative study on antigens for immunodiagnosis of schistosomiasis. *Bull. World Health Organ.*, **60**, 729–753

Mott, K.E., Dixon, H., Osei-Tutu, E. & England, E.C. (1983) Relation between intensity of *Schistosoma haematobium* infection and clinical haematuria and proteinuria. *Lancet*, **i**, 1005–1008

Mott, K.E., Dixon, H., Osei-Tutu, E., England, E.C., Ekue, K. & Tekle, A. (1985) Indirect screening for *Schistosoma haematobium* infection: a comparative study in Ghana and Zambia. *Bull. World Health Organ.*, **63**, 135–142

Mott, K.E., Dixon, H., Carter, C.E., Garcia, E., Ishii, A., Matsuda, H., Mitchell, G., Owhashi, M., Tanaka, H. & Tsang, V.C. (1987) Collaborative study on antigens for immunodiagnosis of *Schistosoma japonicum* infection. *Bull. World Health Organ.*, **65**, 233–244

Murray, J.F., ed. (1967) Tumors of the alimentary tract in Africans. *Natl Cancer Inst. Monogr.*, **25**

Mustacchi, P. & Shimkin, M.S. (1958) Cancer of the bladder and infestation with *Schistosoma hematobium*. *J. natl Cancer Inst.*, **20**, 825–842

Naito, S., Isomura, T., Okabe, M., Kamishiro, M., Iwamoto, G. & Mizoguchi, M. (1979) A case of mucinous carcinoma of the descending colon associated with *Schistosoma japonicum* infection. *Gan No Rinsho*, **25**, 325–328 (in Japanese)

Nakashima, T., Okuda, K., Kojiro, M., Sakamoto, K., Kubo, Y. & Shimokawa, Y. (1975) Primary liver cancer coincident with schistosomiasis japonica. A study of 24 necropsies. *Cancer*, **36**, 1483–1489

Nawar, O., Akridge, R.E., Hassan, E., El Gazar, R., Doughty, B.L. & Kemp, W.M. (1992) The effect of zinc deficiency on granuloma formation, liver fibrosis, and antibody responses in experimental schistosomiasis. *Am. J. trop. Med. Hyg.*, **47**, 383–389

Nkrumah, F.K. (1964) Primary carcinoma of the liver and post-necrotic cirrhosis in a Ghanaian child with non-hepatic bilharziasis. *Ghana med. J.*, **3**, 129–133

Norden, D.A. & Gelfand, M. (1972) Bilharzia and bladder cancer. An investigation of urinary β-glucuronidase associated with *S. haematobium* infection. *Trans. R. Soc. trop. Med. Hyg.*, **66**, 864–866

Norfray, J.F., Schlachter, L., Heiser, W.J., Weinberg, P.E., Jerva, M.J. & Wizgird, J.P. (1978) Schistosomiasis of the spinal cord. *Surg. Neurol.*, **9**, 68–71

Nouh, M.S., Bashi, S.A., Laajam, M.A., Mofleh, I.A.A. & Al-Aska, A. (1990) Hepatitis B virus *vs* schistosomiasis and hepatocellular carcinoma in Saudi Arabia. *E. Afr. med. J.*, **67**, 139–145

Oettlé, A.G., de Meillon, B. & Lazer, B. (1959) Carcinomas of the glandular stomach and hepatomas in *Rattus* (*Mastomys*) *natalensis* infected with bilharzia mansoni. *Acta unio int. contra cancrum*, **15**, 200–202

Ohta, N., Edahiro, T., Ishii, A., Yasukawa, M. & Hosaka, Y. (1990) HLA-DQ-controlled T cell response to soluble egg antigen of *Schistosoma japonicum* in humans. *Clin. exp. Immunol.*, **79**, 403–408

Ohtake, N., Takayama, O., Uno, A., Kubota, Y., Shimada, S. & Tamaki, K. (1991) A case of cutaneous squamous cell carcinoma associated with sporadic porphyria cutanea tarda due to liver disorder after *Schistosoma japonicum* infection. *J. Dermatol.*, **18**, 240–244

Olds, G.R., El Meneza, S., Mahmoud, A.A.F. & Kresina, T.F. (1989) Differential immunoregulation of granulomatous inflammation, portal hypertension, and hepatic fibrosis in murine schistosomiasis mansoni. *J. Immunol.*, **142**, 3605–3611

Olveda, R.M. & Domingo, E.O. (1987) Schistosomiasis japonica. In: Mahmoud, A.A.F., ed., *Ballière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 2, *Schistosomiasis*, London, Ballière Tindall, pp. 397–417

Olveda, R.M., Tiu, E., Fevidal, P., Jr, de Veyra, F., Jr, Icatlo, F.C., Jr & Domingo, E.O. (1983) Relationship of prevalence and intensity of infection to morbidity in schistosomiasis japonica: a study of three communities in Leyte, Philippines. *Am. J. trop. Med. Hyg.*, **32**, 1312–1321

Oro Ortiz, J., Gonzalez Cabrera, L.A. & Rosado Lizano, P. (1991) Carcinoma and renal schistosomiasis. *Arch. Esp. Urol.*, **44**, 78–81 (in Spanish)

Paes, R.A.P. & Marigo, C. (1981) Giant follicular lymphoma and schistosomiasis mansoni. *Rev. Inst. Med. trop. São Paulo*, **23**, 287–292 (in Portuguese)

Parker, M. (1992) Re-assessing disability: the impact of schistosomal infection on daily activities among women in Gezira Province, Sudan. *Soc. Sci. Med.*, **35**, 877–890

Parker, M. (1993) Bilharzia and the boys: questioning common assumptions. *Soc. Sci. Med.*, **37**, 481–492

Parkin, D.M., ed. (1986) *Cancer Occurrence in Developing Countries* (IARC Scientific Publications No. 75), Lyon, IARC

Parra, J.C., Gazzinelli, G., Goes, A.M., Moyes, R.B., Rocha, R., Colley, D.G. & Doughty, B.L. (1991) Granulomatous hypersensitivity to *Schistosoma mansoni* egg antigens in human schistosomiasis. II. In vitro granuloma modulation induced by polyclonal idiotypic antibodies. *J. Immunol.*, **147**, 3949–3954

Phillips, S.M. & Lammie, P.J. (1986) Immunopathology of granuloma formation and fibrosis in schistosomiasis. *Parasitol. Today*, **2**, 296–301

Pieron, R., Mafart, Y., Thibault, B., Gattegno, B., Roland, J. & Vultat, M. (1983) Bladder bilharzioma and carcinoma in the schistosomal bladder. *Semin. Hôp. Paris*, **59**, 2479–2482 (in French)

Prata, A. (1987) Schistosomiasis mansoni in Brazil. In: Mahmoud, A.A.F., ed., *Ballière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 2, *Schistosomiasis*, London, Ballière Tindall, pp. 349–369

Prates, M.D. (1963) The rates of cancer of the bladder in the Portuguese East Africans of Lourenço Marques. In: Stewart, H. & Clemmensen, J., eds, *Geographical Pathology of Neoplasms of Urinary Bladder*, New York, S. Karger, pp. 125–129

Prates, M.D. & Gillman, J. (1959) Carcinoma of the urinary bladder in the Portuguese East African with special reference to bilharzial cystitis and preneoplastic reactions. *S. Afr. J. med. Sci.*, **24**, 13–40

Prates, M.D. & Torres, F.O. (1965) A cancer survey in Lourenço Marques, Portuguese East Africa. *J. natl Cancer Inst.*, **35**, 729–757

Proietti, F.A., Paulino, U.H.M., Chiari, C.A., Proietti, A.B.F.C. & Antunes, C.M.F. (1992) Epidemiology of *Schistosoma mansoni* infection in a low-endemic area in Brazil: clinical and nutritional characteristics. *Rev. Inst. Med. trop. São Paulo*, **34**, 409–419

Pugh, R.N.H., Jakubowski, A.W. & Gilles, H.M. (1979) Malumfashi endemic diseases research project. VI. Urinary schistosomiasis: abnormal urograms in infected males from the Malumfashi study area, northern Nigeria. *Ann. trop. Med. Parasitol.*, **73**, 37–44

Qian, S.L. & Yi, C.Q. (1980) Clinical and pathological observations on 15 cases of gastric schistosomiasis associated with gastric cancer. *Chin. J. int. Med.*, **19**, 365–370 (in Chinese)

Quenum, C. (1967) Cancers of the bladder and bilharzial endemy in Senegal. *Indian Pract.*, **20**, 171–178

Raziuddin, S., Shetty, S. & Ibrahim, A. (1991) T-Cell abnormality and defective interleukin-2 production in patients with carcinoma of the urinary bladder with schistosomiasis. *J. clin. Immunol.*, **11**, 103–113

Raziuddin, S., Shetty, S. & Ibrahim, A. (1992) Soluble interleukin-2 receptor levels and immune activation in patients with schistosomiasis and carcinoma of the urinary bladder. *Scand. J. Immunol.*, **35**, 637–641

Raziuddin, S., Masihuzzaman, M., Shetty, S. & Ibrahim, A. (1993) Tumor necrosis factor alpha production in schistosomiasis with carcinoma of urinary bladder. *J. clin. Immunol.*, **13**, 23–29

Rihet, P., Demeure, C.E., Bourgois, A., Prata, A. & Dessein, A.J. (1991) Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. *Eur. J. Immunol.*, **21**, 2679–2686

Robert, C.F., Bouvier, S. & Rougement, A. (1989) Epidemiology of schistosomiasis in the riverine population of Lagdo Lake, Northern Cameroon: mixed infections and ethnic factors. *Trop. Med. Parasitol.*, **40**, 153–158

Röhl, L., Hochberg, K. & Kochen, W. (1969) Characteristic appearance of ^{3}H-labeled-3-hydroxy-anthranilic acid in the urinary bladder of rats with or without bladder tumors. *Scand. J. Urol. Nephrol.*, **3**, 214–218

Rollinson, D. & Southgate, V.R. (1987) The genus *Schistosoma*: a taxonomic appraisal. In: Rollinson, D. & Simpson, A.J.G., eds, *The Biology of Schistosomes. From Genes to Latrines*, London, Acadamic Press, pp. 1–49

Rosin, M.P. & Anwar, W. (1992) Chromosomal damage in urothelial cells from Egyptians with chronic *Schistosoma haematobium* infections. *Int. J. Cancer*, **51**, 1–5

Rosin, M.P., Zaki, S.S.E.D., Ward, A.J. & Anwar, W.A. (1994) Involvement of inflammatory reactions and elevated cell proliferation in the development of bladder cancer in schistosomiasis patients. *Mutat. Res.*, **305**, 283–292

Rumjanek, F.D. (1987) Biochemistry and physiology. In: Rollinson, D. & Simpson, A.J.G., eds, *The Biology of Schistosomes. From Genes to Latrines*, London, Academic Press, pp. 163–183

Salam, E.A., Ishacc, S. & Mahmoud, A.A.F. (1979) Histocompatibility-linked susceptibility for hepatosplenomegaly in human schistosomiasis mansoni. *J. Immunol.*, **123**, 1829–1831

Sasazuki, T., Kaneoka, H., Nishimura, Y., Kaneoka, R., Hayama, M. & Ohkuni, H. (1980) An HLA-linked immune suppression gene in man. *J. exp. Med.*, **152**, 297s–313s

Satti, M.B., Al-Breiki, H. & Al-Quorain, A. (1988) A rectal carcinoid in a patient with intestinal schistosomiasis: an unusual association. *Trop. Gastroenterol.*, **9**, 18–22

Savioli, L. & Mott, K.E. (1989) Urinary schistosomiasis on Pemba Island: low-cost diagnosis for control in a primary health care setting. *Parasitol. Today*, **5**, 333–337

Savioli, L., Hatz, C., Dixon, H., Kisumku, U.M. & Mott, K.E. (1990) Control of morbidity due to *Schistosoma haematobium* on Pemba Island: egg excretion and hematuria as indicators of infection. *Am. J. trop. Med. Hyg.*, **43**, 289–295

Schwartz, D.A. (1982) Malignant schwannoma occurring with *Schistosoma japonicum*: a case report. *S.E. Asian J. trop. Med. public Health*, **13**, 601–605

Schwartz, D.A. (1984) Carcinoma of the uterine cervix and schistosomiasis in West Africa. *Gynecol. Oncol.*, **19**, 365–370

Scrimgeour, E.M. & Gajdusek, D.G. (1985) Involvement of the central nervous system in *Schistosoma mansoni* and *S. haematobium* infection. A review. *Brain*, **108**, 1023–1038

Sekiguchi, A., Shindo, G., Okabe, H., Aoyanagi, N., Furuge, A. & Oka, T. (1989) A case of metastatic lung tumor of the colon cancer with ova of *Schistosoma japonicum* in the resected lung specimen. *Jpn. J. thorac. Surg.*, **42**, 1025–1028 (in Japanese)

Shafeek, M.A. (1957) Primary carcinoma of the bilharzial vagina. *Gaz. Egypt. Soc. Obstet. Gynecol.*, **5**, 86–89

Sharfi, A.R.A., El Sir, S. & Beleil, O. (1992) Squamous cell carcinoma of the urinary bladder. *Br. J. Urol.*, **69**, 369–371

Sharma, S.D., Ziegler, O. & Trussell, R.R. (1970) A case of schistosomiasis (bilharziasis) hematobium of the cervix (Letter to the Editor). *Acta cytol.*, **14**, 305–306

Sherif, M., Ibrahim, A.S. & El-Aaser, A.A. (1980) Prostatic carcinoma in Egypt: epidemiology and etiology. *Scand. J. Urol. Nephrol.*, **Suppl. 55**, 25–26

Shigefuku, T. (1943) An experimental study on parasitic liver changes and liver cancer: early carcinogenesis by dimethylaminoazobenzene (Buttergelb) in murine schistosomiasis japonica. *Jikken Igaku Zasshi*, **27**, 356–365 (in Japanese)

Shimkin, M.B., Mustacchi, P.O., Cram, E.B. & Wright, W.H. (1955) Lack of carcinogenicity of lyophilized *Schistosoma* in mice. *J. natl Cancer Inst.*, **16**, 471–474

Shindo, K. (1976) Significance of schistosomiasis japonica in the development of cancer of the large intestine: report of a case and review of the literature. *Dis. Col. Rect.*, **19**, 460–469

Shubber, E.K. (1987) Sister-chromatid exchanges in lymphocytes from patients with *Schistosoma hematobium*. *Mutat. Res.*, **180**, 93–99

da Silva Lopes, C.A. (1984) *Cancerização Vesical e Schistosomíase* [Bladder Cancer and Schistosomiasis], Porto, Faculty of Medicine (thesis)

Siwela, A.H., Nyathi, C.B., Chetsanga, C.J. & Hasler, J.A. (1990) The effect of schistosomiasis on the covalent binding of 2-acetylaminofluorene to mouse liver macromolecules in vivo and in vitro. *Biochem. Pharmacol.*, **40**, 379–382

Skinner, M.E.G., Parkin, D.M., Vizcaino, A.P. & Ndhlovu, A. (1993) *Cancer in the African Population of Bulawayo, Zimbabwe, 1963–1977, Incidence, Time, Trends and Risk Factors* (IARC Technical Report No. 15), Lyon, IARC

Sleigh, A.C. & Mott, K.E. (1986) Schistosomiasis. *Clin. trop. Med. commun. Dis.*, **1**, 643–670

Smith, J.H. & Christie, J.D. (1986) The pathobiology of *Schistosoma haematobium* infection in humans. *Hum. Pathol.*, **17**, 333–345

Smith, J.H., Kamel, I.A., Elwi, A. & von Lichtenberg, F.V. (1974) A quantitative post-mortem analysis of urinary schistosomiasis in Egypt. I. Pathology and pathogenesis. *Am. J. trop. Med. Hyg.*, **23**, 1054–1071

Smith, J.H., Said, M.N. & Kelada, A.S. (1977) Studies on schistosomal rectal and colonic polyposis. *Am. J. trop. Med. Hyg.*, **26**, 80–84

Stephenson, L.S. (1993) The impact of schistosomiasis on human nutrition. *Parasitology*, **107**, S107–S123

Stephenson, L.S., Latham, M.C., Kurz, K.M., Kinoti, S.N., Odouri, M.L. & Crompton, D.W.T. (1985) Relationships of *Schistosoma haematobium*, hookworm and malarial infections and metrifonate treatment to growth of Kenyan school children. *Am. J. trop. Med. Hyg.*, **34**, 1109–1118

Stephenson, L.S., Latham, M.C., Kurz, K.M. & Kinoti, S.N. (1989) Single dose metrifonate or praziquantel treatment in Kenyan children. II. Effects on growth in relation to *Schistosoma haematobium* and hookworm egg counts. *Am. J. trop. Med. Hyg.*, **41**, 445–453

Sunder-Raj, S. (1976) Cystic teratoma of ovary associated with schistosomiasis. *E. Afr. med. J.*, **53**, 111–114

Talib, H. (1970) The problem of carcinoma of bilharzial bladder in Iraq (Critical review). *Br. J. Urol.*, **42**, 571–579

Tanaka, M., Iwamura, Y., Amanuma, H., Irie, Y., Watanabe, M., Watanabe, T., Uchiyama, Y. & Yasuraoka, K. (1989) Integration and expression of murine retrovirus-related sequences in schistosomes. *Parasitology*, **99**, 31–38

Tangchai, P. & Poshayalakshana, P. (1968) Schistosomal granuloma with muco-epidermoid carcinoma of parotid gland. *J. trop. Med. Hyg.*, **71**, 134–136

Taylor, M.G. (1987) Schistosomes of domestic animals: *Schistosoma bovis* and other animal forms. In: Soulsby, E.J.L., ed., *Immunology, Immunoprophylaxis and Immunotherapy of Parasitic Infections*, Boca Raton, FL, CRC Press, pp. 49–90

Tawfik, H.N. (1988) Carcinoma of the urinary bladder associated with schistosomiasis in Egypt: the possible causal relationship. In: Miller, R.W., Watanabe, S., Fraumeni, J.F., Jr, Sugimura, T., Takayama, S. & Sugano, H., eds, *Unusual Occurrences as Clues to Cancer Etiology*, Tokyo, Japan Scientific Societies Press, pp. 197–209

Tekwani, B.L., Shukla, O.P. & Ghatak, S. (1988) Altered drug metabolism in parasitic diseases. *Parasitol. Today*, **4**, 4–10

Thomas, J.E., Bassett, M.T., Sigola, L.B. & Taylor, P. (1990) Relationship between bladder cancer incidence, *Schistosoma haematobium* infection, and geographical region in Zimbabwe. *Trans. R. Soc. trop. Med. Hyg.*, **84**, 551–553

Tricker, A.R., Mostafa, M.H., Spiegelhalder, B. & Preussmann, R. (1989) Urinary excretion of nitrate, nitrite, and *N*-nitroso compounds in schistosomiasis and bilharzia bladder cancer patients. *Carcinogenesis*, **10**, 547–552

Tricker, A.R., Mostafa, M.H., Spiegelhalder, B. & Preussmann, R. (1991) Urinary nitrate, nitrite and *N*-nitroso compounds in bladder cancer patients with schistosomiasis (bilharzia). In: O'Neill, I.K., Chen, J. & Bartsch, H., eds, *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105), Lyon, IARC, pp. 178–181

Tsou, H.-W. & Ying, Y.-Y. (1958) A pathological study of intestinal schistosomiasis associated with cancer. *Chin. med. J.*, **77**, 244–253

Uemura, K., Kawaguchi, T., Sodeyama, T. & Kiyosawa, K. (1992) Antibody to hepatitis C virus in patients with chronic schistosomiasis. *Ann. trop. Med. Parasitol.*, **86**, 257–262

Uetsuji, S., Yamamura, M., Okuda, Y., Yamamichi, K. & Yamamoto, M. (1990) Primary liver cancer coincident with schistosomiasis japonica. *Gan No Rinsho*, **3**, 521–525 (in Japanese)

Uthman, S., Farhat, B., Farah, S. & Uwayda, M. (1991) Association of *Schistosoma mansoni* with colonic carcinoma (Letter to the Editor). *Am. J. Gastroenterol.*, **86**, 1283–1284

de Vlas, S.J. & Gryseels, B. (1992) Underestimation of *Schistosoma mansoni* prevalences. *Parasitol. Today*, **8**, 274–277

de Vlas, S.J., Gryseels, B., van Oortmarssen, G.J., Polderman, A.M. & Habbema, J.D.F. (1993) A pocket chart to estimate true *Schistosoma mansoni* prevalences. *Parasitol. Today*, **9**, 305–306

Wagenknecht, L.V. (1974) Carcinoma of the bladder in urogenital bilharziasis. *Urologe*, **A13**, 59–62 (in German)

Wang, J.S. (1979) Gastric schistosomiasis complicated by gastric cancer: a report of 15 cases. *Chin. J. int. Med.*, **18**, 465–467 (in Chinese)

Wang, C.W. & Kuang, C.J. (1983) Gastric and duodenal schistosomiasis. Report of 29 cases. *Natl med. J. China*, **63**, 302–304 (in Chinese)

Warren, K.S. (1973) The pathology of schistosome infections. *Helminthol. Abstr. Ser. A*, **42**, 592–633

Warren, K.S. (1978) Hepatosplenic schistosomiasis: a great neglected disease of the liver. *Gut*, **19**, 572–577

Warren, K.S., Mahmoud, A.A.F., Muruka, J.F., Whittaker, L.R., Ouma, J.H. & Arap Siongok, T.K. (1979) Schistosomiasis haematobia in Coast province, Kenya. Relationship between egg output and morbidity. *Am. J. trop. Med. Hyg.*, **28**, 864–870

Warren, K.S., Su, D.-L., Xu, Z.-Y., Yuan, H.-C., Peters, P.A., Cook, J.A., Mott, K.E. & Houser, H.B. (1983) Morbidity in schistosomiasis japonica in relation to intensity of infection: a study of two rural brigades in Anhui Province, China. *New Engl. J. Med.*, **309**, 1533–1538

Webbe, G., James, C. & Nelson, G.S. (1974) *Schistosoma haematobium* in the baboon (*Papio anubis*). *Am. J. trop. Med. Parasitol.*, **68**, 187–203

Weinstock, J.V. (1992) The pathogenesis of granulomatous inflammation and organ injury in schistosomiasis: interactions between the schistosome ova and the host. *Immunol. Invest.*, **21**, 455–475

Wei-min, C., Dong-chuan, Q. & Hatz, C. (1992) Studies on ultrasonographic diagnosis of schistosomiasis japonica in China—a review of selected Chinese studies. *Acta trop.*, **51**, 37–43

WHO (1993) *The Control of Schistosomiasis. Second Report of the WHO Expert Committee* (WHO tech. Rep. Ser. 830), Geneva

Wilkins, A. & Gilles, H. (1987) Schistosomiasis haematobia. In: Mahmoud, A.A.F., ed., *Ballière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 2, *Schistosomiasis*, London, Ballière Tindall, pp. 333–348

Wilson, R.A. (1987) Cercariae to liver worms: development and migration in the mammalian host. In: Rollinson, D. & Simpson, A.J.G., eds, *The Biology of Schistosomes. From Genes to Latrines*, London, Acadamic Press, pp. 115–146

Wishahi, M., El-Baz, H.G. & Shaker, Z.A. (1989) Association between HLA-A, B, C and DR antigens and clinical manifestations of *Schistosoma haematobium* in the bladder. *Eur. Urol.*, **16**, 138–143

Wright, E.D., Chiphangwi, J. & Hutt, M.S.R. (1982) Schistosomiasis of the female genital tract. A histopathological study of 176 cases from Malawi. *Trans. R. Soc. trop. Med. Hyg.*, **76**, 822–829

Wu, T.-T., Chen, T.-H. & Chu, C. (1960) The relationship of schistosomiasis to carcinoma of large intestine. *Chin. med. J.*, **80**, 231–242

Xu, Z. & Su, D.-L. (1984) *Schistosoma japonicum* and colorectal cancer: an epidemiological study in the People's Republic of China. *Int. J. Cancer*, **34**, 315–318

Xue, C.G., Taylor, M.G., Bickle, Q.D., Savioli, L. & Renganathan, E.A. (1993) Diagnosis of *Schistosoma haematobium* infection: evaluation of ELISA using keyhold limpet haemocyanin or soluble egg antigen in comparison with detection of eggs or haematuria. *Trans. R. Soc. trop. Hyg. Med.*, **87**, 654–658

Yarinsky, A., Drobeck, H.P., Freele, H., Wiland, J. & Gumaer, K.I. (1974) An 18-months study of the parasitologic and tumorigenic effects of hycanthone in *Schistosoma mansoni*-infected and noninfected mice. *Toxicol. appl. Pharmacol.*, **27**, 169–182

Youssef, A.F., Fayad, M.M. & Shafeek, M.A. (1962) The diagnosis of genital bilharziasis by vaginal cytology. *Am. J. Obstet. Gynecol.*, **83**, 710–714

Youssef, A.F., Fayad, M.M. & Shafeek, M.A. (1970) Bilharziasis of the cervix uteri. *J. Obst. Gynaecol.*, **77**, 847–851

Yu, X.-R., Chen, P.-H., Xu, J.-Y., Xiao, S. & Shan, Z.-J. (1991) Histological classification of schistosomal egg induced polyps of colon and their clinical significance. *Chin. med. J.*, **104**, 64–70

Zhao, E.S. & Wong, Y.H. (1981) Carcinoma of the large intestine with schistosomiasis. Analysis of 279 cases. *Chin. J. Oncol.*, **3**, 67–69 (in Chinese)

Zhou, K.M. (1983) Breast cancer associated with breast schistosomiasis. A case report. *Natl med. J. China*, **63**, 375 (in Chinese)

Zhou, X.-X. (1986) Relationship between gastric schistosomiasis and gastric cancer, chronic gastric ulcer and chronic gastritis: pathological analysis of 79 cases. *Chin. J. Pathol.*, **15**, 62–64 (in Chinese)

Zhuang, Q.Y., Zhang, P.Y., Shen, D., Kang, S.Y., Geng, P.C. & Zhang, H.S. (1985) Multifactor analysis of progressive regression pathological relationship between colorectal cancer and intestinal schistosomiasis: a study on 500 surgical specimens with intestinal cancer. *Acta Suzhou med. Coll.*, **2**, 36–38 (in Chinese)