20 YEARS OF PROGRESS IN SCHISTOSOMIASIS RESEARCH

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Preliminary studies of schistosomiasis in Indonesia were made in the late 1930's and the early 1940's. The first human case of *S. japonicum* was discovered by Muller and Tesch from the Lindu valley of Central Sulawesi (Celebes). Early epidemiological studies prior to World War II demonstrated that, in addition to man, wild deer and domestic dogs served as reservoir hosts, and subsequent microscopic examination of adult worms from these mammals confirmed them to be *S. japonicum*. Although extensive snail surveys were conducted at that time, the molluscan host was not found. The schistosomiasis problem in Lindu Valley virtually remained dormant until the 1970s[1-4].

In the 1970's there was a resurgence of interest in the epidemiology of schistosomiasis in Indonesia. A new schistosomiasis area in the Napu valley was discovered. During this period, the intermediate host, *Oncomelania hupensis* was found in the Lake Lindu valley. This confirmed that the disease situation in Indonesia was, in fact, a form of classical oriental schistosomiasis similar in its biology and transmission to that found in the Philippines, Japan, and China. The molluscan host of *S. japonicum* in the Lake Lindu Valley was subsequently described as a new species, *O. h. lindoensis*, and is most similar to *O. h. quadrasi*, the vector host in the Philippines. The disease occurs now only in two very isolated areas, the Lake Lindu valley and Napu valley in Central Sulawesi[5-7].

DESCRIPTION OF THE LINDU AND NAPU VALLEYS

Detailed descriptions of both these valleys were given by Clarke *et al.* and Carney *et al.* However, it will be useful to summarize some of the salient features of the areas.

The Lindu valley is located in the highlands of Central Sulawesi. The valley has an area of approximately 100 km^2 in the Takolekadju mountain range. In the northwestern portion of the valley lies Lake Lindu, which is 10 km in length and average 5-6 km in width. Numerous streams originating from the surrounding mountains empty into the lake. At the northwest corner, the Gumbasa River, which is the only outlet, flows into the adjoining Palu valley. There are flat stretches of low-lying marshy areas on the eastern and northern sides as well as at the northwest corner of the lake. These open swampy areas are utilized by the village population for cultivating rice and grazing cattle. Climatologically the Lindu valley is situated in a tropical rain forest characterized by high temperatures and humidity. Human population numbering about 1,500-2,000 are spread among the villages there, most of which

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lie on the western shore of the lake[8]. Napu valley is also located in the highlands of Central Sulawesi, about 50 km southeast of Lake Lindu. The valley lies between the Takolekedju mountains on the west and the Tineba mountains on the east, and is now a dried-out lake bed of more than 1,000 km^2. It is surrounded by tropical rain forest characterized by high temperatures and humidity. The valley floor is a well-drained grassy plain. A small body of water, Lake Wanga, is situated 5 km south of Wuasa, the district capital. The Napu valley is drained by the Lariang River which empties into the Strait of Makassar. Presently more than 4,000 people inhabit the Napu valley in villages located along the Lariang River and its tributaries[5].

ECOLOGY OF ONCOMELANIA SNAILS AND INFECTIVITY

Following the discovery of a single specimens of *Oncomelania* snail in 1971 by Carney *et al.*, further intensive surveys revealed over 70 foci of this snail were found on the lowlands surrounding the lake Lindu area and 15 foci in Napu valley about 50 km southeast of Lindu. The ecology of this snail is well documented by these investigators, and later also by Pinardi Hadidjaja and Sudomo[10]. The subspecific status of the *Oncomelania* in the Napu valley has not been determined as yet, and is presently referred to at the Napu geographic strain of *O. hupensis*[6,9-11].

In the Lake Lindu valley, most of the *Oncomelania* colonies isolated have been found on the western and northern side of the lake. Colonies of this snail were found near cultivated fields, abandoned farming areas and in the uncultivated virgin forests surrounding the lake[9].

In the Napu valley, the habitats are mainly swampy fields with dense, short or tall marsh grasses, usually adjacent to actively worked paddy fields. Forested areas, or along the edge of the forest, have not yet been searched for the snails[5].

Potential *Oncomelania* habitat in Napu valley is far greater than that available in Lindu valley. In Lindu valley less than 50 km^2 are low lands or moors for *O. hupensis* habitat, whereas in Napu valley there are 7,500 km^2 of such terrain.

Infection rates of *S. japonicum* in *O. h. lindoensis* varied considerably between foci and between sampling periods. The overall average infection rate in the Lindu valley was 2.4% in large disturbed focus, and about 7.0% in small natural focus bordering the lake shore or in the virgin lowland forests. Infection rates were higher in females (2.7%) than in male snails (1.95%). By age (length) snail infection rates were quite consistent in snails two months of age or older[9].

EXPERIMENTAL INFECTION STUDIES

Studies on experimental animals, using mice, Wistar rats, long Evans rats, Mongolian gerbils, wild rats (*Rattus norvegicus*), hamsters and guinea pigs showed that mice were found to be the most susceptible experimental host for the Indonesian strains of *S. japonicum*.

Experimental studies on subspecies of *O. hupensis* exposed to infection with zoophilic and anthropophilic strains of *S. japonicum* to determine the ability of geographic strains of the parasite were carried out by Cross *et al.*[12] The snails, *O. h. quadrasi* from Philippines, *O. h. formosa* and *O. h. chiui* from Taiwan, *O. h.*

nosophora from Japan, and *O. h. lindoensis* from Indonesia were used for these experiments. Anthropophilic strains of *S. japonicum* from Philippines, China, Japan and Indonesia, and zoophilic strains from Taiwan were used to infect the different geographic strains of snails. The results showed the diversity specificity of *O. hupensis* subspecies to infection with geographic zoophilic and anthropophilic strains of *S. japonicum*. Most species of snails can be infected with geographic strains of the parasite from other areas, but usually in low numbers. Others such as *O. h. quadrasi* from Philippines and *O. h. formosa* from Taiwan are essentially resistant, but *O. h. chiui* from Taiwan seems to be a universal host easily becoming infected with all strains of *S. japonicum*. These experimental studies clearly show that the anthropophilic strains of *S. japonicum* from Indonesia can infect a wide diversity of geographic strains of *Oncomelania* snails[12].

Subsequent experimental studies on four subspecies of *O. hupensis*, namely, *O. h. lindoensis, O. h. hupensis, O. h. nosophora* and *O. h. quadrasi* exposed to miracidia of four geographic strains of *S. japonicum* (i.e. Chinese, Japanese, Philippines and Indonesia) were carried out by Sudomo. He found that *O. h. lindoensis* from Indonesia and *O. h. hupensis* from China to be the most susceptible among all the four geographic strains of *S. japonicum* while *O. h. quadrasi* from the Philippines were susceptible to the Philippines strains of *S. japonicum*, and refractory to the other three strains of *S. japonicum*[13].

The results of this study differs from Cross *et al.* in that the *S. japonicum* strains of Indonesia were shown not to be a good experimental host for *O. h. hupensis* from China, while the reverse was found in Sudomo's experimentation[12,13].

The survival infectivity of the Indonesian strains of *S. japonicum* to its natural host, *O. h. lindoensis*, at different temperatures was carried out by Sudomo. He showed the miracidia were active and infective at three different temperatures (18°C, 23°C, and 18°C) from 0-8 hours. At 18°C the miracidia were still active at 24 hours, but the infection rate was comparatively low. At 23°C the miracidia were still active and infective at 12 hours, whereas at 28°C miracidia were not able to withstand the temperature longer than 8 hours[14].

MAMMALIAN RESERVOIR HOSTS

Man, of course, is one of the predominant mammals in the Lake Lindu valley serving as a reservoir host. Surveys on wild mammals revealed *S. japonicum* naturally infected 13 of the 23 mammalian species examined. They are the field and forest rats: *R. exulans, R. hoffmanni, R. chrysocomus rallus, R. marmosurus, R. celebensis*, wild deer (*Cervus timorensis*), wild pigs (*Sus scrofa*), wild civet (*Viverra tangalunga*), forest shrew *Crocidura nigripes*, domestic cow, dog, horses, and water buffalo. Mammal studies determined the distribution and infection rates in rodents, principally *R. exulans*, which inhabit the cultivated lowlands in the Lindu area. Wild and domestic mammals were shown to be significant in the transmission of this disease, because they frequent areas, which harbour the molluscan host and leave their excreta in its amphibious habitat[9].

DISEASE PREVALENCE IN HUMANS

The distribution of schistosomiasis throughout the Indonesian archipelago was studied extensively in the 1970's, especially on the island of Sulawesi. Although more than 50,000 stools specimens were examined and extensive surveys conducted *S. japonicum* and *Oncomelania hupensis* appear limited in their respective distribution to two contiguous drainage systems of Central Sulawesi, i.e. the Lindu valley, 1,000 meters in elevation at the headwaters of the Gumbasa River drainage system and the Napu valley, more than 1,000 meters in elevation at the headwaters of the Lariang River drainage system. Carney speculated that at least 7,000 individuals are continuously exposed to schistosomiasis in confirmed endemic areas[15,16]. In Lindu valley 93.9% of 1,515 inhabitants among the villages surveyed in 1971, 1972, 1974, the infection rates were 53%, 37.9% and 37.5% respectively. In the Napu valley, a coverage of 50.4% of 1,843 inhabitants surveyed in 1972, 1974, and 1980, the infection rates were 43%, 31% and 65.9%. The results showed that the prevalence rates vary at different periods of surveys, and they are relatively high for each of the period examined[5,8,9,15-18]. It is important to emphasize that these numbers and percentages refer to persons passing schistosome eggs in their stools, a much smaller percentage of persons who are really clinically compromised by this infection.

In Palu valley which is in the same drainage system as Lake Lindu the 2,433 stools from an estimated population of 18,700 in the seven villages along the Palu drainage system were examined in 1971. Less than 1.0% of these stool were positive with *S. japonicum* eggs and these were from two of the seven villages. In 1973, the Rampi and Seko valleys of South Sulawesi with similar mountain valleys and geological history to that of the Lindu and Napu valleys, seven villages were surveyed for human parasites (3 in Seko village and 4 in Rampi village). Only six persons of 640 inhabitants in the 3 villages at Seko valley were found with *S. japonicum* eggs in their stools. A follow-up investigation of these positive cases in the Seko valley by these investigators, revealed that all had recently migrated from the Napu valley, a confirmed schistosomiasis area[19,21].

Liver biopsies of 52 patients from the Lindu valleys with stools positive for *S. japonicum* eggs were performed by Kurniawan *et al.* in 1974. The individuals did not show signs and symptoms of terminal stage and 96% showed eggs in the liver biopsy. This study indicated that liver biopsy is a valuable method of diagnosis[22].

CONTROL PROGRAM

Since 1975, there have been a number of developments that have changed the epidemiological picture some for the better and some, regrettably, for the worse.

A pilot control project was initiated by the National Institute of Health Research and Development (NIHRD) in conjunction with the World Health Organization (WHO). This pilot project which focused on the Paku-Anca area, involved selective mass treatment, agroengineering, molluscicide, improved sanitation and health education. The results were good as the prevalence of schistosomiasis was reduced from 70% to 25% in the intervention area over a two year period. Regrettably,

however, the control effort has not been maintained and one indicator of increased transmission, the prevalence of infection in rodents, suggests that the disease will return to its previous level of endemicity in a short period[18,23,24].

Other schistosomiasis control projects were conducted throughout the Lindu valley during the same time frame and subsequent to the NIHRD-WHO pilot control projects. The non-intervention area of one study was accidentally "controlled" by another project, obviously compromising the results of both studies. In addition 4-5 villages in the Lindu valley were treated by a number of agencies on more than one occasion using more than one anti-schistosomal compound making it difficult to determine who had been treated, with what, by whom, or when.

DRUG TRIALS

Mass and selective treatments with different anti-schistosomal compounds such as niridazole, stibophen and praziquantel were carried out by various investigators at different time periods in the focus area. The results showed that 11 patients treated with stibophen did not pass ova in their stools 2 and 6 months after treatment, but 11 months post treatment follow-up, one out of 10 patients passed ova. In the case of niridazole treatment of 31 patients, 4 passed ova after 2 to 6 months post treatment, and at the 11 month follow-up treatment 5 were still observed to pass ova[25]. Mass treatment of 708 people in three villages of Napu valley with praziquantel showed significant reduction of the prevalence rate from an average of 15% pretreatment to 2% six months post treatment. The side effects of the 3 anti-schistosomal drugs, showed praziquantel has the least side effects. It was apparent from these studies, praziquantel is the drug of choice for the treatment of *S. japonicum* in the endemic area of Indonesia[20].

Intensive mass treatments were then initiated by Directorate General of Communicable Disease Control and Environmental Health (CDC&EH) in 1981 using praziquantel with a single dose of 30 mg/kg BW twice a day. The results were good. The prevalence rates were reduced from an average of 17% pretreatment to 1.7% after 12 cycles of treatment in Lindu valley and from an average of 33.8% pretreatment to 1.51% after 11 cycles of treatment in Napu valley. Although the treatments were successful, transmission remained high. In 1988 the average infection rate in the snails was 0.30% in Lindu and 4.0% in Napu with average snail densities of 30.08/m^2 in Lindu and 55.02/m^2 in Napu. The average infection rate in the domestic animals was 2.55% and 17.45%, respectively for Lindu and Napu, while in rats it was 3.3% and 26.0% respectively (20, CDC unpublished report).

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