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FOURTEENTH (14th) SEMINAR ON TROPICAL

MEDICINE

INSTITUTE OF TROPICAL MEDICINE

YONSHEI UNIVERSITY - SEOUL, KOREA

A Report Prepared by:

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Executive Summary.

The Fourteenth Seminar on Tropical Medicine was conducted under the auspices of the Institute of Tropical Medicine, Yonsei University and supported by the Ministry of Health and Social Affairs, Republic of Korea, The Korea Medical Association and the Korean Overseas Construction Association. The Conference was held at Chiang, Kee Won Memorial Hall, Yonsei University, Seoul, Korea on 9-11 June, 1983.

The main theme of the seminar was "Control of Currently Important Tropical Diseases". The seminar consisted of the presentation of review papers and original free papers, and two panel discussions. Attendees at the seminar included scientists from various countries (see appendix A) who are engaged in research in basic and applied medical sciences concerning parasitic and microbial diseases and in public health and epidemiological studies.

The seminar consisted of four (4) main sections: 1). advances in immunodiagnosis, 2). new developments in treatment of tropical diseases, 3). biological control of vectors and intermediates of tropical diseases and 4). other scientific free papers.

This consultant acted as a resource person serving as a member of the organizing committee, presenting two (2) scientific papers (see Introduction and Methodology section), serving as moderator for section on "Biology and Control of Intermediates" and sharing presentation of paper entitled Bulinus truncatus in Jordan with Dr. A. Buck in absence of originally scheduled presenter, Dr. E. Saliba.

Several timely and important scientific presentations were made during the seminar. These included: 1) recent advances in immunodiagnosis of tropical diseases, by Dr. John H. Cross, Scientific Director, U. S. Naval Medical Research Unit. No. 2 (NAMRU-2) APO S.F. CA. 96528, 2) treatment of trematode

infections by Dr. Han-Jong Rim, Professor, Department of Parasitology, Korea University College of Medicine, 3) Epidemiology of concomitant disease by Dr. Alfred Buck, Tropical Disease Advisor, Office of Health, Agency for International Development, Washington, D.C., 4) The emerging problem of drug resistance in treatment of schistosomiasis by Dr. John I. Bruce (this consultant), Professor of Biological Sciences, and Director of Center for Tropical Diseases, University of Lowell, Lowell, MA, 5) Control of Schistosomiasis throughout Japan today by Dr. George W. Hunter, III, Clinical Professor, Department of Community and Family Medicine, Division of Epidemiology, University of California School of Medicine, California and 6) Biological control of vectors and intermediates in Southeast Asia by Dr. Chamlong Harinasuta, Professor, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

The special session on Hepatitis B virus infection highlighted the Republic of Korea's efforts in producing and testing of the new Hepatitis B virus vaccine with information concerning the problems and logistics of immunization procedures. Information concerning certain aspects of the disease in Thailand, Uganda, Philippines and Taiwan were also presented.

The two panel discussion sessions, namely session I; Biological Control of Vectors of Tropical Diseases and session II; Strategy in Health Problems were especially well organized and provided current and up to date information which was valuable to conference participants.

The series of Tropical Medicine seminars organized under the leadership of Dr. Chin-Tak Soh of Korea since 1969 has served as an important forum and source of current information for scientists in Southeast Asia and Asia proper. The annual seminar brings together scientists from Asia at a site which is economical and convenient for them to reach. Many young scientists from Asia have been given an opportunity to attend these meetings and to meet with senior scientists whom they would never have the chance to meet otherwise. The annual seminar is therefore a very important event for the scientific community of Asia.

I. Introduction.

A. Purpose of the Assignment.

The purpose of the assignment was to attend "The Fourteenth Seminar on Tropical Medicine" for the purpose of serving as a resource person with particular reference to schistosomiasis.

B. Scope of work task.

The assignment consisted of serving as a member of organizing committee, presenting two (2) scientific papers, serving as moderator for the afternoon session dealing with the "Biology and Control of Intermediates", filling in when appropriate for scheduled participants who were unable to attend the conference and aid during a post-conference period the organization of documents for publication of conference proceedings.

C. Itinerary.

June 8 - Pre-conference meeting with members of organizing committee. Assisted in rearrangement of certain conference sections due to absence of scheduled participants, 2) planned post-conference meeting to discuss organization of seminar proceedings publication.

June 9 - Attendance at seminar.

June 10 - Shared in presentation of scientific paper No. 26 entitled "Bulinus truncatus in Jordan".

Presented scientific paper No. 27 A entitled "The Emerging Problem of Drug Resistance in Treatment of Schistosomiasis".

Presented scientific paper No. 31 entitled "Recent Advances in the Biological Control of Snail Intermediate Host of Trematode".

Served as moderator for entire afternoon session entitled "Biological Control of Intermediates".

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- June 11 - Attendance at seminar.
- June 12 - Post-Conference working meeting to organize seminar proceedings publication at Yonsei University.
- June 13 - Meeting with chairman of organizing committee and staff of Institute of Tropical Medicine at Yonsei University.

D. Methodology.

The assignment consisted of serving as resource person at the seminar. The methodology in this instance involved the presentation of scientific papers and serving as moderator for an afternoon session.

The scientific papers presented were as follows.

1. The Emerging Problem of Drug Resistance in the Treatment of Schistosomiasis.
2. Bulinus truncatus in Jordan (summary of subject shared with Dr. A. Buck in absence of scheduled participant, Dr. Saliba from Jordan).
3. Recent Advances in the Biological Control of Snail Intermediate Host of Trematodes.

The complete text of each of the above presentations are enclosed in Appendix B.

2. Conclusion

The Fourteenth Seminar on Tropical Medicine was well organized and of substantial quality. The quality of many of the papers presented was excellent, timely and of current contents. Several of the presentations and/or panel discussions were considered to be very outstanding both in content and of relevance to the seminars theme.

The seminar is considered to be of relevant scientific importance to the scientific community of Asia.

Appendix A
List of Seminar Participants

LIST OF PARTICIPANTS

Fourteenth Seminar on Tropical Medicine

June 9-11, 1983

Name	Position	Address
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Appendix - B

Papers Presented at Seminar

1. The Emerging Problem of Drug Resistance in Treatment of Schistosomiasis.
2. Bulinus truncatus in Jordan.
3. Recent Advances in the Biological Control of Snail Intermediate Host of Trematodes.

1. THE EMERGING PROBLEM OF DRUG RESISTANCE IN TREATMENT OF SCHISTOSOMIASIS

Drug resistance can be defined as the transitory or permanent loss of the initial sensitivity of microorganisms or mammalian cells to the effect of substances which interfere with vital functions of these structures. It manifests itself after the exposure to the agent in vitro or in-vivo. More recent developments in this area might justify a further simplification of this statement in the words of Lamy as the "sudden or gradual, permanent or transient loss of the originally present susceptibility to a chemical compound".

The first observation that certain microorganisms could become resistant to drugs which they were formerly sensitive was made by Ehlich for trypanosomes. Subsequently, many microorganisms such as bacteria, viruses, spirochetes, fungi, rickettsia and protozoa such as malaria, entameba, coccidiosis among others were shown to be able to develop resistance to therapeutic agents. The problem of drug resistance also occurs among arthropods.

During this century, the widespread use of drugs to treat and control infectious organisms has almost invariably led to the development of drug resistance. In man, this problem has been a very persistent one in regard to the treatment of bacteria and protozoa such as malaria, trypanosomiasis and more recently leishmaniasis. Constant vigilance is maintained for the occurrence of new resistant strains among protozoa and bacteria as compared to no effort for the helminths which infect man.

Among the helminths, drug resistance has occurred from the widespread use of anthelmintics to treat nematode infections in domestic animals. Considerable concern has arisen in the veterinary industry in Australia because of drug resistance in nematodes of sheep. The problem has already progressed beyond the situation as reviewed recently by Prichard, to one where in some areas the two major types of anthelmintics used no longer kill some species of nematodes. The phenomenon of nematode drug resistance is not confined to Australia. In the opinion of many scientists, the problem is now growing worse in America.

Based on the farmers experiences with anthelmintics especially in Australia and reports of new cases, the problem with drug resistance in nematodes is likely to persist. In fact, users of nematode anthelmintics are now seeking alternative ways of controlling these drug-resistant nematode worms.

Drug resistant strains of nematodes have been produced experimentally (in both in vivo and in vitro systems) in the laboratory with such anthelmintics as carbendazole, thiabendazole, and levamisole. For carbendazole and thiabendazole, resistance has been brought about by selection of a naturally drug-resistant population and the progressive elimination of drug sensitive worms. In the case of levamisole and benzimidazole resistance, Caenorhabditis elegans worm was first exposed to a mutagen and then selected with these drugs.

The problem of drug resistance among helminths is not limited only to nematodes. The literature contains many references which refer to the wide variation in results obtained from drug trials both clinically and under experimental conditions concerning the susceptibility of Schistosoma mansoni from various geographical regions. The results of these observations showed that strains of S. mansoni originating from the same region can also differ in this sensitivity to anti-schistosomal drugs.

References to the occurrence of resistant S. mansoni strains have been reported by various investigators as a result of laboratory experimentation or from a combination of field and laboratory observations. These include the reports by Rogers and Bueding, 1971, Katz et al 1973, Compos et al 1976, Jasma et al 1977, Dias et al 1978, and Dias et al 1982. It appears that from some of the reported data that the lack of susceptibility observed in some strains of S. mansoni cannot be solely ascribed to previous administration of anti-schistosome drugs and thus further studies are required to elucidate this phenomena.

Rogers and Bueding and Jasma et al showed the occurrence of genetically transferred resistance to hycanthone for several strains of S. mansoni in mice. It should be pointed out that the relative ease by which resistance to hycanthone was produced under experimental conditions may be due to the highly



mutagenic nature of this compound. Development or selection of resistant strains may not occur as readily with other antischistosomal agents.

The occurrence of drug-resistant S. mansoni as a result of treatment of patients was first suggested by Davis during a program in upper Egypt in 1966. It was observed by clinicians that the cure rate was lower in those patients undergoing a second course of treatment with niridazole than in those receiving treatment for the first time, thus suggesting that perhaps drug resistance was developing in the retreated group.

Since that time, nearly all of the reports concerning information relative to the occurrence of drug resistant S. mansoni in the field from patients treated with various drugs have come from Brazil.

In view of the current situation, there seems to be little reason to think that the same problem is not occurring in other regions of the world where antischistosome drugs are being used to treat patients both in clinics and on a mass scale.

Although the rate of occurrence of drug resistant strains will depend on the length of the parasite life cycle and the selection pressure used, this in turn will depend on the percentage of the population treated, the frequency of dosing and the efficacy of the treatment. Drugs with 100% efficacy should not select for resistance, but in practice few treatments for schistosomiasis give a complete cure of egg production. Whether those worms that survive are present due to the pharmacology of the schistosomicide and thus the effectiveness of the therapy varying between patients, or because of a natural variation in susceptibility of worms to drugs is not known. If all cases were due to the former reason, there would be no reason for concern, but if the latter, then drug resistance could be expected to emerge. In practice both situations may be expected to occur in the field.

There is at present no information on the significance of drug resistance in schistosomiasis anywhere in the world. Clearly this situation must be remedied as resistance and could become a very serious problem in the control of schistosomiasis. Before detailed epidemiology of resistance can be undertaken,

as has been performed for nematodes of sheep, basic information needs to be collected. This must include a description of what resistant strains already exist in the field and to what drugs these strains are resistant. This is a prerequisite for the optimal clinical therapy of patients harboring resistant strains. It needs also determining whether strains failing to respond to more than one type of drug are present. This has been described in the nematode haemonchus contortus in Australia and may be widespread. It could presumably occur with S. mansoni as well.

In addition to searching for resistance and trying to relate cure rates to presence of drug-resistant worms, we should look for alternative methods of detecting resistance. The present method to be used for infection of snails with eggs from patients' feces-then-mice-with cercariae-from snails and then treatment of mice with drugs takes at least 12 weeks and uses large numbers of animals. Alternative tests using infected snails, cercariae or schistosomula should be investigated.

Observations concerning drug resistance S. haematobium has not been made. Only one laboratory study by Hsu suggests drug resistance may occur with S. japonicum worms.

In view of the occurrence of drug resistant schistosome following treatment of patients with hycanthone, oxamniquine and niradizole, this could conceivably occur with compounds which may be developed in the future. This problem then poses great difficulty in the eventual development of anti-schistosomal agents.

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2. BULINUS TRUNCATUS IN JORDAN

The possibility of schistosomiasis occurring in Jordan was thought to be minimal prior to 1975 (Saliba et al., 1976, 1980; Salaba and Salameh, 1981; and Saliba et al., 1981). This view was based on (1) the fact that the patients who had been diagnosed as having schistosomiasis had encountered the disease outside of Jordan, presumably in neighboring countries, and (2) a result of the limited surveys of Abdel Azim and Gismann (1956) and Chu (1969) in which no snail vectors for the human schistosomes were found.

In 1975 a case of urinary schistosomiasis was diagnosed at a hospital by the Royal Jordanian Medical Services. Interrogation of the patient revealed that he had resided primarily in the Jordan Valley and that he had never left the country. Despite the fact that the autochthony of the case was questionable, urine samples from 3,000 Jordanians were collected while they were outpatients at the clinics in the Jordan Valley (Saliba et al., 1980). The results of the examination of these samples for Schistosoma haematobium ova were negative (unpublished data).

Despite the fact that there are annually 75,000 - 120,000 migrant workers from countries with endemic areas of schistosomiasis, there is no evidence that transmission is occurring in Jordan at the present time (personal communication, Ministry of Health). During the period between March 1979 and April 1982, a total of 42,600 urine samples were collected from migrant workers and examined for S. haematobium ova, and 10,011 were found to be positive. The percent of infection was thus found to be 23.5%. A total of 7,005 of the 10,011 migrant workers who were scheduled to work at various agricultural tasks in the Jordan Valley were treated with the antischistosomal drug, praziquantel. The remaining 3,006 infected persons were scheduled to work in the greater Amman urban area and some of these were treated with ambilhar and others were not treated (personal communication, Dr. M.R. Tawfiq, Ministry of Health). In addition to urinary schistosomiasis, some migrant workers undoubtedly suffer from intestinal schistosomiasis, since this form of the disease is also present in their respective homelands.

The foreign agriculture workers who reside in Jordan pose a special threat in that they represent a pool of infected persons who may act as a source of schistosome eggs (if those infected are not successfully treated) which can be disseminated into Jordanian waters. Likewise, vacationers from countries with endemic schistosomiasis also pose a special public health threat. In many instances, there is an absence of proper sanitary facilities in vacation areas and the possibility exists that water in these areas will be contaminated with human wastes harboring viable eggs.

Snail Intermediate Hosts for Schistosomiasis in Jordan and their Ecological Considerations.

Because of the increased development of new water resources in Jordan, significant changes in the natural hydrographic topography of Jordan are presently underway. The ancient scheme of rapid movement of surface waters from the mountains to the barren Dead Sea are now being compromised by water resource improvements such as the East Ghor Canal and its extension, the King Talal Dam, and fish farming operations. The current development of an extensive system of secondary and tertiary canals to distribute water for irrigation in the Jordan Valley will provide good potential habitats for the establishment of vector snail populations. Chemical analyses for pH, (Saliba et al., 1980) temperature, turbidity, color and alkalinity of many Jordanian water resources were observed to be within the same range found in snail-infested Nile River sites (Saliba et al., 1980 and Mallett and Bruce, in preparation). It has been noted that those areas which recently have become high probability areas for the establishment of Bulinus snails are also among those areas most frequented by foreign workers who have had previous exposure to Schistosoma haematobium. These areas, along with other developed water resources, must be regarded as potential high risk areas.

The key factor in the absence of schistosomiasis in Jordan has been the lack of snail intermediate hosts in the country. Vector snails had not been found during earlier limited surveys for schistosome intermediate hosts in Jordan (Azim and Gismann, 1956 and Chiu, 1969). However, in spite of the absence of vector snails, it was felt at that time that some areas seemed favorable for the establishment of Bulinus truncatus (e.g., Azraq and the

Jordan Valley), and that future exploitation of the waters of the Yarmouk and the Jordan rivers would change ecologic conditions so as to favor establishment of the snails and schistosomiasis might then be introduced (Rey, 1977 and Bruce et al., 1978).

In 1975, and after the discovery of the presumed indigenous Jordanian case of schistosomiasis mentioned previously, the waters of 64 localities in the Jordan Valley (excluding the Jordan River itself) were surveyed for snails. The species collected were mainly members of the genera Fossaria, Melanoides, Melanopsis, Physella, Radix, and Theodoxus. The snail vector for urinary schistosomiasis in the Middle East, Bulinus truncatus, was found at only one locality. This was a cemented reservoir in the Muthalath Al-Masri area about 13 km south of Dair Alla village (Saliba et al., 1974). The reservoir received water periodically from the East Ghor Canal. No other Bulinus snail foci were found in the Jordan Valley during that survey or the subsequent limited surveys carried out in 1977 by a team from the Ministry of Health or the brief survey in 1977 and 1978.

In 1979, a new focus of B. truncatus was located about 1.5km west of the town of Jerash in a spring pool and in its drainage canal carrying water to irrigate farms on the outskirts of the town (Saliba and Salameh, 1981). The potential for snail dispersal from this area to other water bodies is high since water from the pool overflows in winter to the Wadi of Jerash, then to the Zarqa River and the King Talal Dam, and subsequently to the Jordan Valley.

In 1980, following construction and subsequent filling of the King Talal Dam, snails identified as Bulinus truncatus, the intermediate host for S. haematobium in the Middle East, were discovered in large numbers throughout the dam and even in drainage or leakage areas adjacent to the dam (Saliba and Rida, unpublished data).

Subsequent to the above discovery, Bulinus snails have been found at four sites in the Jordan Valley. The sites are as follows: Shaikh Hussain, Zour Al-Hamman, Tal Salman and Ain Taha (Saliba and Rida, unpublished data). Bulinus shells were also recovered from two other sites in the Jordan Valley, at Ain Abu Fareed and Al-Mahchia (Malaka springs).

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3. RECENT ADVANCES IN THE BIOLOGICAL CONTROL OF SNAIL INTERMEDIATE HOST OF TREMATODES.

As a result of the increasing resistance against the use of chemicals to control disease vectors, biological control involving the use of predators, competitors, microorganisms, and certain vertebrates has assumed a high level of importance during the past decade.

A review of the literature dealing with biological control of snail intermediate hosts reveals that there are more than several hundred species of various forms which have been considered as potential competitors, or predators such as pathogens, parasites and invertebrates and vertebrates. The efficiency of using these various life forms as control agents has rarely been tested outside the confines of the laboratory.

Comprehensive reviews discussing various aspects of biological control of snail intermediate hosts have been published by Michelson (1957), Ferguson (1972, 1978) Harrston et al, 1975 and McCullough (1981). For this presentation, the more promising biocontrol techniques will be summarized.

Among the various groups of predators which have been described, only two species, fish and insects merit serious consideration for possible use in control schemes. There are several fish species which deserve mentioning (Serranochromis sp., astatoreochromis alluaudi, Tilapia melanopheura, clarias sp. and various others) as possible predators. Nearly all of the observations concerning effect of fish on snail populations have been made in East and Central Africa and none can be regarded as conclusive and therefore there is a need for further investigation.

The insect most frequently cited as a possible control organism for snails is the sciomyzid flies which are obligatory feeders of mollusc larvae, especially in gastropods. As reviewed by Berg (1964) and Harrston et al (1975), there are several hundred which exist with a wide range of predator/prey activity.

Pointier (1979) conducted field studies in Guadeloupe concerning the natural enemies of Biomphalaria glabrata in a series of diverse habitats. Pointiers concluded that in nature, co-existing predators such as leeches, insects,

crustaceans do play a very crucial role in governing snail host population densities particularly in small, well developed, static waterbodies as well as in situations where natural enemies exist in combinations with each other. The role of these organisms in reducing or eliminating schistosome transmission is not one of absolute value.

Significant progress is being made in the use of certain species of bacteria to control insects and interest now exists on the part of some investigators to determine if there are species of bacteria which can be used as control agents for schistosome vector snails. Studies of microspordia hyperparasites of schistosome larva is in the basic exploratory stage of investigation.

The antagonistic and/or predacious interaction of the larval stages of certain trematodes infecting the same snail have been studied in detail by Lin and Heyneman (1972) and Lie (1973). These studies have shown that schistosome sporocysts cannot survive the antagonism exhibited by redia-producing trematode such as echinostomes. Small scale field studies were successfully conducted while others were not successful. Research is still needed to determine if this method is feasible, if other trematodes can be used and if cost-effective methods for mass culture are possible.

The principle of competitive interactions which result in exclusion and/or displacement of another species by one which is similar but stronger is a very attractive approach. Before this approach can become successful, more information should be obtained concerning snail-population densities and transmission dynamics.

Various species of freshwater snails (Marisa cornuaretis, Helisoma duryi, Pomacea hanstru Physa sp., Melanopsis sp., Thiara granifera, Potamopyrgus jenkinsi and certain species of Bulinus) have been recognized as having potential for use as competitors against schistosome vector snails. The species M. cornuaretis has been studied the most extensively and found to be a competitive feeder and incidental predator on the eggs and junevile of B. glabrata in Puerto Rico. M. cornuaretis has also been shown to be a predator on Bulinus sp. in experiments conducted in outside concrete troughs in Egypt.

The Marisa snail was placed into a small dam in Tanzania where heavy populations of B. pfeifferi, Bulinus tropicus and Lymnea natalensis existed and after twenty-four months the three pulmonate species had been eliminated.

The snail species Melanopsis has been shown to competitively replace B. truncatus in irrigation canals during a three year study in Algeria.

Various investigators have suggested that the snail species, Helisoma duryi appears to have possibilities as an effective competitor when present in certain types of habitats. In many instances it has been observed that the snail vectors for schistosomes are noticeably absent when H. duryi is present. This possibility is thought to exist in certain areas of Egypt where H. duryi is present in large numbers. More studies concerned with the competitive ability of this species is warranted.

The hydrobiid snail P. jenkinsi has been shown to apparently displace B. truncatus from its natural habitat in Corsica. These observations need to be confined and extended if possible to other areas where P. jenkinsi may exist.

Recent observations by several investigators have indicated that B. straminea and B. tenagophila can competitively reduce and/or eliminate populations of B. glabrata. The possibility of using these species in Brazil and Martinique to at least reduce transmission is a possibility. It is obvious from this presentation that all of the biological agents discussed must be exhaustly tested for their efficacy in reducing and/or eliminating the target species to a threshold below which transmission ceases to be a health problem. In addition, the safety of these successful predators and competitors to man and other non-target biota must be proven without a doubt. The selected species must be used at a level which is cost-effective in the context of the local situation. None of the discussed species meet any of the above criteria.

A scheme devised by Arata (1975) and WHO (1975) for screening and evaluating the most promising organisms for biological control of insects vectors should be adapted for use in attempts to develop a biocontrol of the schistosome snail vectors. What is needed now, is support for purposes of evaluating and subsequent safety and cost effective determinations under carefully defined field conditions.

The recent resurgence of interest in the use of plant molluscicides deserves mention here even though it is in reference to chemical control. Many vegetable molluscicides (e.g., the bark of Entada phaseoloides, the roots of Derris elliptica and etc.) have been reported as having potential effectiveness against snails but they are also harmful to other life forms. The most studied molluscicide of plant origin is from the berries of the plant endod, the Ethiopian name for the climbing plant (Phytolacca dodecandra). A review and list of recent literature pertaining to endod has been prepared by Lemma, Heyneman and Kloos. Other plant molluscicides which deserve mentioning here are Croton tiglium and C. macrostachys, Ambrosia maritima and the seeds of Jatropha curcas.

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