



REPORT OF THE WHO INFORMAL CONSULTATION ON  
RESEARCH REQUIREMENTS FOR ECHINOCOCCOSIS/HYDATIDOSIS

Montreal, Canada, 13 August 1987

CONTENTS

	Page
1. Introduction .....	2
2. Parasite Biology .....	3
2.1 Background information .....	3
2.1.1 Strain differences of <i>Echinococcus granulosus</i> .....	3
2.1.2 Strain differences of <i>E. multilocularis</i> .....	3
2.1.3 <i>In vitro</i> culture and cryopreservation .....	3
2.1.4 Biochemistry and molecular biology .....	4
2.1.5 Egg differentiation .....	4
2.2 Major research requirements .....	4
3. Host-parasite relationship .....	4
3.1 Background information .....	4
3.2 Major research requirements .....	5
3.2.1 In humans .....	5
3.2.2 In animals .....	5
4. Immunology .....	5
4.1 Background information .....	5
4.1.1 Immunodiagnosis .....	5
4.1.2 Immunity and immunization .....	8
4.2 Major research requirements .....	9
4.2.1 Immunodiagnosis .....	9
4.2.2 Immunity and immunization .....	9
4.2.3 Other requirements .....	10

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	Page
5. Epidemiology .....	10
5.1 Background information.....	10
5.2 Major research requirements .....	11
6. Chemotherapy .....	11
6.1 Background information .....	11
6.1.1 Cestodocides .....	11
6.1.2 Metacestodocides .....	12
6.2 Major research requirements .....	12
6.2.1 Metacestodocides .....	12
6.2.2 Cestodocides .....	13
7. Control .....	13
7.1 Background information .....	13
7.2 Major research requirements .....	14
7.3 Other measures .....	14
8. General recommendations .....	14
Annex I List of participants .....	17
Annex II Acknowledgments.....	18
Annex III Bibliography .....	19

## 1. Introduction

In conjunction with the 12th Conference of the World Association for the Advancement of Veterinary Parasitology (WAAVP) an informal consultation was convened by the World Health Organization in Montreal, Canada on 13 August 1987 to assess echinococcosis research requirements.

Dr. K. Bögel, Chief, Veterinary Public Health, World Health Organization, Geneva, opened the meeting on behalf of the Director-General of WHO. Professor J. Eckert was elected Chairman. Professor R.C.A. Thompson served as Rapporteur. See Annex 1 for list of participants.

A meeting was held in 1981 to establish research requirements for echinococcosis/hydatidosis and taeniasis/cystercosis (WHO, 1981). In January 1987 the Veterinary Public Health unit contacted leading scientists in many countries for information on the status of echinococcosis research. This information was subsequently analysed and amalgamated by Professor Eckert. The informal consultation was convened in Montreal to:

- up-date research requirements considered previously by WHO (WHO, 1981);
- recommend further research and to identify priorities, taking into account the need for action-orientated programmes; and
- identify objectives and fields of international cooperation.

Scientific progress made during the last few years has opened new avenues and possibilities for surveillance, diagnosis, prevention and control of echinococcosis/hydatidosis. Examples are the development of highly sensitive and specific immunodiagnostic tests for sero-epidemiological surveys in areas with endemic alveolar echinococcosis, the mathematical modelling of control programs against Echinococcus granulosus and new methods of Echinococcus strain identification by means of DNA hybridization techniques. By strengthening of individual and institutional research on national and international levels, by improved international exchange of specialized experience and mobilization of funds, it should be attempted to apply the new knowledge to control of echinococcosis/hydatidosis which is still a serious human health hazard in many parts of the world.

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### Terms Used:

Cystic and alveolar echinococcosis (hydatidosis): Infections caused by metacestodes of Echinococcus granulosus and Echinococcus multilocularis, respectively

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1 Report on FAO/UNEP/WHO Meeting on Research requirements in Echinococcosis/Hydatidosis and Taeniasis/Cystercosis, Geneva, 29 April - 1 May 1981 (WHO document VPH/82.34).

## 2. Parasite Biology

### 2.1 Background information

#### 2.1.1 Strain differences of Echinococcus granulosus

Evidence from various parts of the world that biologically distinct strains of E. granulosus exist have been confirmed by further studies (Thompson, 1986). Considerable attention has been given during the last few years to characterizing various strains using a variety of criteria, such as developmental biology (both in vivo and in vitro), morphology and biochemistry (isoenzymes). In this way the dog/sheep, dog/cattle, dog/horse and dog/camel strains could be further characterized. Modern techniques, such as the DNA hybridization technique, have been introduced for strain identification. It was shown for example that the DNA hybridization patterns of the dog/horse strain are significantly different from the dog/sheep strain of E. granulosus.

The examination of DNA hybridization patterns appears to be a relatively simple method for identifying strain differences. It is now necessary to gain more experience with this technique and to employ it for extended epidemiological studies in various areas of the world. A major objective of such studies should be the elucidation of strain infectivity to humans.

There is clear evidence that the dog/sheep strain and the "northern form" (dog/wild ruminants) of E. granulosus are infective for man. The status of the other strains regarding infectivity to man is still unclear and requires further investigation. The new technique of DNA hybridization could play an important role in such studies.

There is some evidence that, not only do strains of E. granulosus of different host origins exist, but that more than one strain may affect the same host species. For example, there are at least two distinct strains of E. granulosus which occur in sheep; one on the Australian mainland and another in Tasmania.

#### 2.1.2 Strain differences of E. multilocularis

There is ample epidemiological evidence that E. multilocularis in Alaska, Europe, in the USSR, China and Japan is infective to humans, since clinical cases have been reported from all of these areas. Distinct morphological, biological and other differences between various E. multilocularis isolates have not yet been described but this aspect requires further investigation.

#### 2.1.3 In vitro culture and cryopreservation

In vitro culture has proved a most useful tool in (a) strain differentiation, (b) biochemical studies and (c) immunological investigations. The status of knowledge has been described in the VPH (82.34) Document (WHO, 1981) and in a review (Howell, 1986). Recently, the successful long-term in vitro maintenance for many months and the cryopreservation of E. multilocularis metacystodes, the in vitro production of E. granulosus and E. multilocularis eggs in intestinal stages previously fertilized in vivo and other progress has been reported. In vitro techniques are increasingly used for the collection of secretory/excretory antigens of larval cestodes.

Cryopreservation of E. multilocularis can now be used for the maintenance of living metacystode reference material derived from various isolates. This technique could facilitate

the establishment of "parasite banks" and the exchange of material between laboratories. Therefore, cryopreservation techniques should be improved and also applied to other Echinococcus stages.

#### 2.1.4 Biochemistry and molecular biology

Studies of the biochemistry of Echinococcus have lagged behind similar investigations of other parasite groups. However, recent new approaches (McManus and Bryant, 1986) have opened new ways of applying biochemical and molecular techniques to practical problems. Examples are the analysis of isoenzyme patterns for Echinococcus strain identification and the application of recombinant DNA technology for antigenic polypeptide synthesis (see 4.J.1.4).

#### 2.1.5 Egg differentiation

Using monoclonal antibodies oncospheres hatched from E. granulosus eggs could be specifically identified and differentiated from Taenia eggs. This technique could be successfully employed in a field survey in Kenya for the identification of the infection risk of humans at water holes and other places. An improvement/simplification of immunological tests for egg identification and/or the introduction of other methods, like DNA probing, is required.

#### 2.2 Major research requirements

- (a) Identification and characterization of Echinococcus strains with particular reference to biological features and the use of biochemical and molecular techniques, including isoenzyme analysis and DNA hybridization.
- (b) Evaluation of the extent of strain variation on a world-wide basis and determination of the influence of strain variability on parasite infectivity and pathogenicity to man and on epidemiology of echinococcosis.
- (c) In vitro maintenance and cultivation of various Echinococcus stages with special reference to mass production of Echinococcus eggs in vitro, identification of biochemical and physiological parameters influencing in vitro development, long-term maintenance and cultivation, maintenance and cultivation in chemically defined media, cultivation of parasite cells, application of in vitro systems for drug screening (see chapter 6.2).
- (d) Cryopreservation of Echinococcus stages.
- (e) Molecular biology and biochemistry of Echinococcus with special reference to E. multilocularis.
- (f) Identification and differentiation of Echinococcus eggs using DNA hybridization techniques (see also chapter 5).

### 3. Host-Parasite-Relationship

#### 3.1. Background information

Recent studies on chemotherapy of human echinococcosis (see chapter 6) have demonstrated considerable gaps in our knowledge on the natural history of the infection, pathogenesis and the immune responses of the host. These aspects should be studied and considered in relation to strain differences of Echinococcus.

In E. multilocularis new morphological data are available on the mode of metacestode proliferation and metastasis formation in the intermediate host. However, the basic question, how the parasite is able to evade the host's immune mechanisms, is still unsolved. The same applies to the role of immune mechanisms in pathogenesis. A similar situation exists with regard to E. granulosus.

Research in this field is difficult and partially inhibited by the lack of adequate animal models representative for human disease.

Special attention should be paid to the development of reliable diagnostic methods for identifying the viability status of metacestodes in vivo within the human host.

### 3.2. Major research requirements

#### 3.2.1 In humans

- (a) Re-evaluation of the natural course of E. granulosus, E. multilocularis and E. vogeli infections in humans with special reference to the use of modern diagnostic techniques such as computer assisted tomography (CT) ultrasound examination (US) and nuclear magnetic resonance (NMR). Special attention should be given to diagnostic procedures which could reflect the viability status of the parasite in the living patient.
- (b) Studies on mechanisms of pathogenicity (for example cytotoxicity and proliferative capacity of metacestodes), immune responses and immune suppression.
- (c) Studies on the response of the parasite to chemical injury and the nature of the processes of destruction or recovery.

#### 3.2.2 In animals

- (a) Evaluation of the normal course of infection and development of metacestodes, especially the control mechanisms leading to abortive infections. Studies are required to determine the nature of the distribution of metacestodes in intermediate host populations and the control mechanisms determining this.
- (b) Studies on mechanisms of pathogenicity (for example, cytotoxicity and proliferative capacity of metacestodes), immune responses and immune suppression.
- (c) Studies on the response of the parasite to chemical injury and the nature of the processes of destruction or recovery.

## 4. Immunology

### 4.1. Background information

#### 4.1.1 Immunodiagnosis

During the last few years significant progress has been made in immunodiagnosis of cystic and alveolar echinococcosis of humans and in related fields (Schantz and Gottstein, 1986; Rickard and Lightowers, 1986).

#### 4.1.1.1 Immunodiagnosis in humans

##### (a) Sero-epidemiology

New avenues for sero-epidemiology have been opened by the isolation of a species-specific antigen from metacestodes of E. multilocularis. This antigen, denominated as fraction Em<sub>2</sub>, exhibits a high sensitivity and specificity in the ELISA. Therefore, the ELISA employing this antigen (= Em<sub>2</sub>-ELISA) has a high predictive value in sero-epidemiological studies avoiding false-positive reactions and cross-reactions. The Em<sub>2</sub>-ELISA has recently been successfully used in large sero-epidemiological surveys of human populations in Switzerland, France and Alaska/USA.

The results show that:

- an early detection of alveolar echinococcosis in humans is feasible,
- the Em<sub>2</sub>-ELISA is a reliable technique for collecting of epidemiological baseline data on alveolar echinococcosis in human populations,
- the Em<sub>2</sub>-ELISA can be adapted for rapid diagnosis under field conditions.

##### (b) Differential diagnosis

Based on the simultaneous use of the species-specific Em<sub>2</sub>-antigen and a further antigen fraction (Em<sub>1</sub>) containing components of both E. multilocularis and E. granulosus an ELISA for the differential diagnosis (DD-ELISA) of human cases of alveolar and cystic echinococcosis has been developed. This test exhibits a high discrimination rate allowing a correct differential diagnosis between the two forms of the disease in 95 % of the cases. In various geographical areas identical discrimination rates have been obtained indicating that potential differences in Echinococcus strains do not influence the results of this test.

In the DD-ELISA the diagnosis of alveolar echinococcosis is highly specific and cross-reactions and/or false-positive reactions do not play a role. On the other hand, in the diagnosis of cystic echinococcosis such reactions cannot be excluded. Infections with Taenia solium metacestodes, with filariid and some other nematode groups as well as with trematodes may lead to cross-reactions. However, the latter can be (at least partially) clarified by the detection of the arc-5 precipitation line (exclusion of nematode and trematode infections, see 4.1.1.1, c), and the determination of antibodies specific for T. solium by a Western Blot technique (confirmation of T. solium cysticercosis).

The DD-ELISA is of proven value in the species-specific diagnosis of individual clinical cases and in sero-epidemiological surveys carried out in areas with sympatric occurrence of E. multilocularis and E. granulosus.

##### (c) Detection of arc-5

Using immunoelectrophoresis (IE), the arc-5 precipitation line can be detected in about 75 % and 60 % of the human cases with cystic and alveolar echinococcosis, respectively. Demonstration of arc-5 may be considered as diagnostic confirmation of either E. granulosus, E. multilocularis or E. vogeli infections in human patients. As arc-5 is also produced with 5-10 % of the sera from cysticercosis (T. solium) patients the detection of arc-5 can only be regarded as cestode group-specific.

Arc-5 counterimmunoelectrophoresis (CEP 5) can be carried out on agar gel or cellulose acetate and is more rapid and a slightly more sensitive test than conventional IE.

(d) Immunoglobulin classes

Specific IgE antibodies appear to be relatively sensitive indicators for surgical removal or death of Echinococcus metacestodes in humans. However, the exact relation of specific IgE levels and the viability status of the parasite is still unclear.

(e) Circulating antigens and immune complexes

Circulating antigens (CAG) have been detected in 33-85 % of the sera from patients with cystic echinococcosis, and immune complexes were demonstrated in 70-90 % of the cases. Positive results for CAG in antibody-negative patients indicate that a CAG-ELISA could be of value as an adjunct diagnostic test. The potential value of a CAG-ELISA for post-treatment (surgical and/or chemotherapeutical) evaluation has to be further assessed.

4.1.1.2 Immunodiagnosis in intermediate host animals

There is still no satisfactory immunodiagnostic system available for the specific diagnosis of larval E. granulosus infections in domestic herbivores.

However, some progress has been reported recently. An ELISA employing two antigens derived from E. granulosus cyst membranes and protoscolices, respectively, has been described as useful in detecting, on a flock basis, those agecohorts of sheep with high E. granulosus infection rates. In field situations, this test would be unable to detect the true prevalence of E. granulosus infection in individual sheep. There is some evidence that injection of antigen may provide a challenge resulting in elevated antibody titers in infected animals. These techniques could be useful for detecting infected flocks and/or individual animals.

4.1.1.3 Immunodiagnosis in final hosts

In a recent study with dogs experimentally infected with 200'000 protoscolices of E. granulosus serum antibodies against scolex excretory/secretory and protoscolex antigens could be detected beginning at 14 days post infection until the end of the experiment at day 75. These antibodies did not cross-react with antigens prepared from Taenia ovis, T. hydatigena, T. pisiformis and from important dog nematodes (Ancylostoma caninum, Trichuris vulpis and Toxocara canis).

Such a test system which is presently being evaluated under field conditions could be of great value for the identification of dogs infected with E. granulosus. A similar test would also be useful in identifying foxes, dogs and cats infected with E. multilocularis as this procedure would be simpler than parasite detection at necropsy. Also, potential health hazards involved in fox necropsies could be reduced by the introduction of an immunodiagnostic test.

An alternative way of identifying final hosts infected with intestinal stages of Echinococcus by detection of copro-antigens has apparently not yet been evaluated.

#### 4.1.1.4 Antigen purification and synthesis

As mentioned under 4.1.1.1. (a) a species-specific antigen has been isolated from metacystodes of E. multilocularis (Em<sub>2</sub>-antigen). This antigenic polypeptide (M<sub>r</sub> 54,000 and pI 4.8) has a high diagnostic sensitivity and species-specificity. Using recombinant DNA techniques, specific E. multilocularis antigens have recently been produced by bacteria in vitro.

The biotechnological production of large quantities of sensitive and specific E. multilocularis antigens for diagnostic purposes appears now to be feasible. Also, antigens of E. granulosus have been synthesized by Escherichia coli in vitro.

#### 4.1.2 Immunity and immunization

##### 4.1.2.1 Adult stages

Some studies suggest that after immunization with antigens derived from adult stages or protoscolices of E. granulosus, a proportion of dogs in a population may develop a certain degree of immunity against re-infection with protoscolices. This partial protection may result in decrease in numbers and size of worms and a reduced fecundity (Heath, 1986; Ito and Smyth, 1987). However, the results obtained so far are conflicting, which may be in part ascribed to the lack of hosts' immunity or unresponsiveness rather than the lack of immunogenicity of the parasite. Other work indicates that genetic factors may play an important role in resistance patterns of the host to adult cestode infections.

Dogs have been shown to develop antibodies against oncospherical antigens of Taenia hydatigena and T. ovis but this immune response failed to prevent challenge infections with metacystodes from either homologous or heterologous infection.

Virtually nothing is known on the immune reaction of final hosts against E. multilocularis.

##### 4.1.2.2 Metacystode stages

Immunity of sheep to E. granulosus cyst development can be naturally acquired or artificially induced. A single injection of E. granulosus oncospheres results in significant resistance to challenge infection, and after two injections a higher degree of resistance is detectable. A high degree of protective immunity is also induced by the injection of secretory products of oncospheres cultured into 14 day old cysts in vitro.

However, the limited availability of E. granulosus eggs preclude any development of large-scale immunization procedures. Therefore, it is necessary to synthesize the required antigen by recombinant DNA technology.

Many aspects of the mechanisms of the intermediate hosts' immune responses against Echinococcus metacystodes are unclear and have to be further studied, especially in view of artificial immunization of intermediate hosts.

##### 4.1.2.3 Immunological carrier systems

Recent information shows (Dougan et al., 1987) that live attenuated strains of Salmonella are showing promise as live oral vaccines against human typhoid fever and other Salmonella infections of man and animals. Attenuation can be achieved by introducing genetically defined, non-reverting mutations into specific genes on the Salmonella chromosome. These mutations inhibit the ability of the bacteria to multiply in vivo, and strains carrying such

lesions are effective vaccines against salmonellosis. Genetic determinants coding for the expression of potentially protective antigens from heterologous, non-Salmonella pathogens, can be readily introduced into these attenuated Salmonella strains. The prospects for the use of live Salmonella vaccines as a carrier for delivering Echinococcus spp. antigens should be intensively evaluated in final and intermediate hosts.

#### 4.2. Major research requirements

##### 4.2.1 Immunodiagnosis

- (a) Mass production of species-specific E. multilocularis Em<sub>2</sub>-type antigens by recombinant DNA technologies.
- (b) Development of a species-specific and sensitive test for the immunodiagnosis of larval E. granulosus infections in man and farm animals (cattle, sheep, swine, horses, camels, etc.) for monitoring the progress of control programmes, including mass production of a specific antigen using recombinant DNA methods for in vitro synthesis.
- (c) Collection and/or production of defined human and animal reference sera containing antibodies against Echinococcus spp., Taenia and other helminth parasites. These sera are necessary as references for standardization of immunodiagnostic techniques and for use in studies on the specificity of cloned Echinococcus antigens.
- (d) Development of an immunodiagnostic "exposure" test for humans in endemic zones based on the detection of anti-oncospherical antibodies.
- (e) Development of simple immunodiagnostic tests for field application.
- (f) Extensive sero-epidemiological surveys for human alveolar and cystic echinococcosis in endemic areas using species-specific and sensitive antigens in the ELISA system with high predictive value.
- (g) Elaboration of biomathematical models and instructions for national and international sero-epidemiological surveys.
- (h) Identification of final hosts (dogs, foxes, cats, etc.) infected with Echinococcus spp. by immunodiagnostic techniques (detection of serum antibodies and/or copro-antigens).
- (i) Immunodiagnostic identification and differentiation of Echinococcus and Taenia eggs using molecular and immunodiagnostic procedures.

##### 4.2.2 Immunity and immunization

- (a) Identification of specific antigenic poly-peptides involved in immunoprotection against Echinococcus infections in intermediate and final hosts. Study of the immune evasion phenomenon in larval Echinococcus infections. Elaboration of basic data on the interaction of larval and adult Echinococcus spp. and the humoral and cellular immune systems of the hosts. Studies on the potential of immunotherapy in protection against metacestodes.
- (b) Molecular cloning of Echinococcus genes for in vitro production of protective antigens.

- (c) Development of vaccines against larval cestode infections in farm animals.
- (d) Studies on the possibilities of vaccination of final hosts against Echinococcus spp. infections.
- (e) Special attention should be given to new possibilities of using immunological carrier systems for vaccination against Echinococcus. (see chapter 4.1.2.3)
- (f) Determination of the degree of acquired immunity against E. granulosus or E. multilocularis of animal populations in endemic areas (see chapter 7).

#### 4.2.3 Other requirements

- (a) Establishment of national immunodiagnostic reference centers.
- (b) Supplies of reference sera and antigens.
- (c) Collection and distribution of sera from humans with echinococcosis, cysticercosis, taeniasis and other parasitic infections to assist research workers in developing new methods.
- (d) Set up a mechanism for new specific antigens (eg. cloned recombinant DNA products) to be tested under different conditions in different countries.
- (e) Organisation of training courses for immunodiagnostic techniques.

### 5. Epidemiology

#### 5.1. Background information

Since the publication on echinococcosis research requirements in 1981 (WHO, 1981) significant advances in the conceptual and technical understanding of the transmission dynamics of E. granulosus infections have been achieved, particularly in mathematical modelling of the life cycle of E. granulosus and of Taenia species (Cermell et al., 1987). It could be demonstrated that the "basic reproductive rate" ( $R_0$ ) is the major factor that determines the dynamics of transmission, and hence the stability of the parasites' life cycle. If the reproductive rate of an Echinococcus species and the degree of acquired immunity stimulated in the intermediate host population are known, then the amenability to control can be calculated. In E. multilocularis seasonal changes and fluctuations of host abundance have also to be considered. The application of a mathematical model to the epidemiological situation of E. granulosus has enhanced our knowledge of the transmission process and explained why it is relatively easy to destabilize the transmission cycle and to achieve effective control in contrast to Taenia ovis and T. hydatigena infections.

The present possibilities of mathematical modelling and the increase of related knowledge should be used for intensive studies of the specific epidemiological key factors in various parts of the world.

There are big gaps in our knowledge on epidemiological base-line data, like prevalence rates of echinococcosis in human and animal populations, on parasite-host-assemblages, specific ways of transmission, immune status of the host populations and others.

## 5.2 Major research requirements

- (a) Preparation of a computer program for standardized collection and evaluation of epidemiological base-line data on E. granulosus, E. multilocularis and E. vogeli infections in human and animal populations.
- (b) Assignment of national and regional centers for standardised data collection on human cases of echinococcosis, periodical assessment and publication of these data.
- (c) Establishment of national and/or regional reference centers for immunodiagnostic techniques which may take over coordinative functions in sero-epidemiological surveys.
- (d) Preparation of instructions for standardized techniques of Echinococcus strain identification.
- (e) Sero-epidemiological surveys on human alveolar echinococcosis in various endemic areas using an ELISA system with high predictive value, aiming at early diagnosis and treatment of cases and better understanding of epidemiological factors.
- (f) Similar surveys on E. granulosus infections as soon as species-specific and highly sensitive antigens are available. Animal populations should be included, provided that adequate test systems would be available.
- (g) Identification of Echinococcus strains, clarification of their developmental cycles, infectivity to humans and their epidemiological significance in various regions.
- (h) Determination of epidemiological key factors, such as the "basic reproductive rate" (Gemmell et al., 1987) for E. granulosus and E. multilocularis, using recently developed mathematical models (Gemmell et al., 1987). There is a special need for research on E. multilocularis. In this case knowledge on fox ecology gained from rabies research and on population dynamics of rodents has to be included and complemented by new research. As a prerequisite to the construction and application of such mathematical models, there is an urgent need for studies on the reproductive and developmental biology of Echinococcus (including egg production/fecundity, patent periods, egg "laying" behaviour and mode of egg release, longevity of adult worms).

## 6. Chemotherapy

### 6.1. Background information

Since the publication of the VPH Report No. 82.34 in 1981 (WHO, 1981), relatively little progress has been made in chemotherapy.

#### 6.1.1 Cestodocides

Medicated dog food containing praziquantel as a safe and effective anthelmintic against E. granulosus, E. multilocularis and other cestode species is now available. However, experience in its extensive use in control programmes against Echinococcus spp. infections in domestic and wild carnivores is still very limited. Apparently, progress in the development of slow release devices and of new drugs was not made.

### 6.1.2 Metacestodicides

In 1981, the WHO Parasitic Diseases Programme launched a series of coordinated, multi-centric clinical studies on the treatment of human echinococcosis with benzimidazolecarbamates. The patients were treated according to a WHO protocol. Preliminary data for the period 1982 to 1984 were published by Davis et al. (1986). Treatment of 85 patients with mebendazole for cystic echinococcosis was successful in only 8 ( 9.4%) patients and partially successful in 4 (4.7%) others, while clinical improvement was stated in 40 (47.1%) patients. Treatment of 30 further patients with albendazole exhibited slightly better results.

In 54 patients with alveolar echinococcosis it was confirmed that long-term treatment with mebendazole stabilized or improved the clinical condition in 38 (70.4%) of the patients. This may be indicative for arrestment of the parasites. Review of the present knowledge (Eckert, 1986) indicates that adequate animal models for primary drug screening are available and a broad methodological knowledge has been accumulated in chemotherapy of human cases. Although the available drugs, like mebendazole and albendazole, appear to be partially effective in a certain proportion of human cases (see above) they are not optimal. Therefore, there is an urgent need for drug screening programmes and the development of an effective chemotherapy for treatment of human echinococcosis.

The use of drugs against E. granulosus metacestodes in farm animals in control programmes could only be feasible if anthelmintics with a high efficiency at a single dose would be available.

## 6.2. Major research requirements

### 6.2.1. Metacestodicides

- (a) Development of reliable in vitro systems for screening drug efficacy against larval Echinococcus and other cestodes.
- (b) Intensive screening for new drugs against larval cestodes using the available models for primary drug screening (see WHO, 1984). Improvement of animal models for secondary drug screening.
- (c) Basic studies on a rational approach to chemotherapy against Echinococcus metacestodes, including cyst permeability, targeting moieties that can be used to affect specific delivery of drugs to the parasite, molecular mechanisms of antiparasitic drug efficacy.
- (d) Improved systems for drug delivery against Echinococcus metacestodes such as liposomes, slow-release devices and mini-osmotic pumps.
- (e) Studies on the influence of drug formulation on efficacy of benzimidazoles and other drugs against larval cestodes and on bioavailability in hosts. .
- (f) Improvement of methods for the assessment of drug efficacy against Echinococcus metacestodes in man, with special reference to the viability status of the parasite (see also chapter 3).
- (g) Evaluation of possible side-effects of long-term treatment of human echinococcosis patients with benzimidazole compounds.

(h) Studies on the role of chemotherapy in the prevention of secondary hydatid cysts following surgery.

(i) Studies on the factors (host and parasite) responsible for variation in the response to chemotherapy.

#### 6.2.2 Cestodocides

(a) Attention should be given to the evaluation of drugs with the potential for prolonged release in the definitive host and particular attention given to any new drugs with ovicidal effects.

### 7. Control

#### 7.1. Background information

In several areas, like New Zealand, Tasmania and Cyprus, control strategies have resulted in a substantial reduction of E. granulosus in final hosts, intermediate hosts and human populations (Gemmill et al., 1987). The control strategies applied in the various regions differed but were mainly based on (a) chemotherapy of infected dogs, (b) prevention of dogs in gaining access to raw offal containing cysts and (c) control of dog populations. Theoretically, these control measures appear to be relatively simple and easy to apply. In practice, however, highly efficient control authorities and structures, the necessary epidemiological base-line data, considerable experience and financial sources are required to achieve successful control.

There are now a number of countries that are considering developing programmes for the control of echinococcosis. In the past, many years had to elapse before it could be determined whether or not the right control methods had been selected. This hampered or even prevented the introduction of control in some cases. This problem can now be solved because new technology is available for the prior selection of the most cost-effective option. Such are the costs of developing and sustaining a successful control programme, that a well documented cost estimation may be found to be a prerequisite for convincing the legislature to support any project.

The technology involved includes (a) collection of base-line data and quantification of health and economic problems, (b) preparation of project proposals to the stage at which they can be submitted to the legislature for funding, (c) identification of cost-effective methods before and during the course of the campaign and (d) development of appropriate computer surveillance programmes (Gemmill et al., 1987).

The Hydatid Research Unit in New Zealand has had many years of international practical experience in these fields. It now offers a service through the New Zealand Government to countries contemplating, embarking on or wanting to upgrade their control programmes.

In spite of this progress it has to be kept in mind that control schemes as described above are difficult to apply to special epidemiological situations like the wild-life cycle of E. granulosus or to the sylvatic cycle of E. multilocularis because of the complex epidemiological situation.

Therefore, research opening new ways of control, like immunization of final and intermediate hosts, is urgently needed (see chapter 4).

### 7.2. Major research requirements

- (a) Appropriate new educational techniques with a view to changing established behaviour patterns that have exposed humans to infection.
- (b) Operational research for optimal control strategies and programmes.
- (c) The need for pilot control projects using sentinel animals should be emphasised, in order to assess the applicability of established control programmes.
- (d) Application of established control strategies against E. granulosus (chemotherapy of infected dogs, prevention of dogs in gaining access to infective cysts, regulation of dog populations) using computerized surveillance and evaluation programmes and expert advice in countries with health problems from cystic echinococcosis.
- (e) Research on new methods for E. granulosus control should be emphasized. For example, the use of biotechnological procedures in the development of vaccines and immunodiagnostic tests for intermediate and definitive hosts.
- (f) New strategies for E. multilocularis control have to be developed. For example, methods for controlling of echinococcosis in foxes by "baiting" or other means of "self-application" of drugs should be studied. Expertise gained from vaccination of foxes against rabies should be considered in this connection. Moreover, the prospects of immunizing foxes and other final hosts against E. multilocularis have to be evaluated. In this respect the modern systems of immune carriers for heterologous antigens should be exploited.

### 7.3 Other measures

- (a) Advanced training courses for management of control programs.

## 8. General recommendations

The foregoing lists of research requirements are not exhaustive but cover some of the major areas of actual interest. From these items the following general recommendations can be deduced:

- (a) Urgency should be given to research on molecular biology of Echinococcus, especially to DNA hybridization techniques for the identification and differentiation of Echinococcus eggs and strains and to gene cloning with subsequent in vitro synthesis of species-specific antigens for diagnostic and immunization purposes.
- (b) In view of the existing possibilities of gene technology, the production of vaccines against Echinococcus metacestode infections of intermediate hosts seems to be feasible. The prospects for immunizing final hosts against Echinococcus should be further studied. In both cases the potential of using attenuated Salmonella strains as carriers for heterologous antigens may offer new avenues for vaccination of final and intermediate hosts. Related research should be given a high priority.
- (c) Successful vaccine development is depending on progress of research in various fields, such as in vitro cultivation of Echinococcus and the safe mass production of

eggs for immunization trials, elucidation of the major mechanisms of immune protection and natural resistance as well as of a detailed knowledge of epidemiological key factors.

- (d) Recent progress in the development of a species-specific ELISA (Em<sub>2</sub>-ELISA) for the detection of E. multilocularis infections in human populations offers new perspectives for the early diagnosis of the infection and the collection of base-line data by extensive sero-epidemiological surveys on national and international levels. The mass production of Em<sub>2</sub>-type antigens, the wide application of the Em<sub>2</sub>-ELISA and the development of similar test systems for E. granulosus should be enhanced.
- (e) In epidemiology the identification and characterization of Echinococcus strains by means of advanced techniques, such as DNA hybridization, and the use of mathematical models for determining epidemiological key factors, such as the "basic reproductive rate", have to be regarded as important research requirements. Special attention should be given to E. multilocularis.
- (f) For surveillance and control new methods (possibly based on detection of serum antibodies and/or copro-antigens), for the identification of infected final hosts are urgently required.
- (g) The further development and evaluation of ultrasound examination for the early detection of E. granulosus infection in human populations should be supported.
- (h) Recent research results indicate that chemotherapy of larval cystic and alveolar echinococcosis in animals and man is principally possible but the presently available drugs are not sufficiently active in the treatment of human cases. Therefore, all aspects of basic and applied research on chemotherapy of echinococcosis should be given a high priority. Other methods for effective therapy, for example immunotherapy, should be supported.
- (i) Recently developed mathematical models of the life cycle of E. granulosus have opened new possibilities of epidemiological research and improved control by means of established techniques, such as mass drug treatment of dogs. The applicability and potential of these models and of the existing expertise in further endemic areas of the world is recommended.
- (j) Moreover, the development of new concepts of echinococcosis control is an urgent requirement, especially with regard to E. multilocularis. As mentioned above (8.b), immunization of intermediate hosts of E. granulosus and of final hosts of E. granulosus and E. multilocularis might be part of new conceptual strategies.
- (k) WHO should assist research groups, especially in activities for multi-disciplinary and international approaches by means of the following measures:
  - Assignment of "WHO Working Groups on Echinococcosis" responsible for the periodical up-dating of the echinococcosis research requirements and for encouraging the coordination and collaboration of research activities.
  - Development of a network of national centres for research, data collection and immunodiagnostic techniques.
  - Assistance in the coordination of clinical studies.

- Assistance in the dissemination of information and specimens.
  - Technical support in implementing control programmes in various countries.
  - Technical assistance with the collection and distribution of sera from humans with echinococcosis, cysticercosis, taeniasis and other parasitic infections to assist research workers in developing new methods.
  - Technical assistance in the establishment of a mechanism for new specific antigens (eg. cloned recombinant DNA products) to be tested under different conditions in different countries.
- (1) The World Association for the Advancement of Veterinary Parasitology (WAAVP) should cooperate with WHO in organizing regular symposia on echinococcosis during the WAAVP conferences.

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\*Invited but unable to attend.

## ANNEX II

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## ANNEX III

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