STUDIES ON HUMAN HYDATIDOSIS

IN KENYA

BY

GIDEON BARAK AGEMBO OKELO, M.B.B.S., M.R.C.P.,
D.T.M. & H. (LIVERPOOL)

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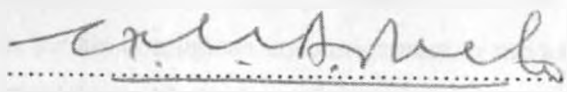
DECLARATION

This is a thesis of original work done by me in the Department of Medicine, Faculty of Medicine, College of Health Sciences, University of Nairobi and the Kenyatta National Hospital from 1978 to 1984. This work has not been presented to any other institution or University for the purpose of getting a degree.



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ABSTRACT

This thesis is concerned with studies on the diagnosis and the chemotherapy of human hydatid disease in Kenya. Prior to this work there was no chemotherapy being undertaken in this disease in Kenya and there was only a small amount of work being conducted on the diagnosis of hydatid disease.

A literature review revealed that human hydatidosis is a major global economic and health problem. It also revealed that Kenya has the highest endemicity for human hydatidosis, in the Turkana District n the north-western part of the country. Occasional hydatid cases have also been seen among the Masai, Luo, Kikuyu and Kalenjin people. In Kenya, increasing documentation of human hydatidosis has featured more prominently since the late sixties because of an increased awareness and interest in the disease. Prior to that, hydatidosis was not considered a major health problem as compared to other diseases such as malaria, schistosomiasis, tuberculosis, malnutrition and diarrhoea.

This study was made on 150 cases of surgically proven hydatidosis. In these, the immunoelectrophoresis test was carried out so as to evaluate its use as a diagnostic tool for human hydatidosis in Kenya as this would be useful in clinical practice. Its specificity for hydatidosis was also assessed (evaluated) by carrying out the tests in 60 controls consisting of normal, kalazar cases and schistosomiasis cases. This was thought necessary since any corss-reactivity would reduce the value of this test in clinical practice in Kenya. The test was found to be specific for human hydatidosis with a sensitivity of 62%, with no cross reactions in any of the control sera. The finding of 38% false negatives and the possibility of such factors as circulating immune complexes and circulating Echinococcus granulosus antigens in this group of patients is postulated and discussed. The factors currently known about the causative organism of hydatidosis in Kenya such as its strain characteristics are discussed in the light of the results obtained. The value of the immunoelectrophoresis test in Kenyan patients in this study is compared to the results of this test in Caucasian subjects with hydatidosis and the differences noted. The sensitivity of the immunoelectrophoresis test at 62% limits its routine clinical application. However, it many be of special value in specialist centers like Kenyatta National Hospital and Provincial Hospitals for use in the follow up of cases after medical and/or surgical treatment and also for follow up of control measures especially in young people to see if these measures are successful or not. The recently formed Hydatid Control Committee in the Ministry

of Health, Kenya, is initiating a pilot control programme in part of the Turkana District and this project will need several parameters for assessing the value of the control measures. In such a situation the immunoelectrophoresis test may be useful for the follow up of a selected group of patients.

Although ultrasonography has been previously tried on a very small scale prior to this study, it was decided to evaluate it in the 150 cases, as this would enable us to assess its cost-effectiveness compared to serology in clinical practice in Kenya. Ultrasonography is non-invasive, cheap, safe with no radiation hazard and is suitable for a developing country with limited financial resources. This study confirms that ultrasound examination is very useful in abdominal hydatidosis.

Radiology was included in the work because it was not available in Turkana at the beginning of this study. Prior to the study, a case had died in Turkana following chest aspiration without any x-ray examination of the case because it was assumed to be having pleural effusion. This emphasizes the value of x-ray examination. Moreover mass radiography may also reveal many more cases than can be diagnosed clinically and is therefore useful in prevalence studies. In Uruguay for instance the use of mass miniature radiography revealed a much higher prevalence of hydatidosis than had ever been suspected previously.

The development of chemotherapy for human hydatidosis in Kenya did not start until the present study was undertaken. Prior to that there was no properly controlled clinical trial going on and the treatment was entirely surgical. Since inoperable hydatidosis is an important clinical problem in Kenya, as it account for 30% of the cases, it was thought justified to undertake the present work. Mebendazole was selected since it had shown promise in human hydatidosis at the time. Later in the study, when Albendazole became available it was included in the study. The initial work on Mebendazole in Kenya was discouraging since none of the cases responded to it. In the preliminary work, a small dose of 40 mg. Per kilogram of body weight was used. However, when it became possible later on in the study to estimate the serum mebendazole levels in Kenya, a preliminary pharmacokinetics study was undertaken to confirm if fat influenced the absorption of this drug in Kenyan hydatidosis patients, and also to estimate the drug level using the radioimmunoassay method since it became known that the optimal drug level is 100 mg/ml. The study also investigated if mebendazole enters hydatid cysts in Kenyan patients as this had not been established in this country previously. The pharmacokinetics study

confirmed that fat greatly enhanced the absorption of mebendazole in Kenyan hydatidosis patients. This study also confirmed that mebendazole enters hydatid cysts in Kenyan patients and this is in agreement with previous reports by Morris on British patients. Thus following this pharmacokinetics study, it was decided to treat cases with hydatidosis so as to assess if when the drug level was around 100 ng/ml, it was effective in this disease. These cases were initially treated medically and then all underwent laparotomy and the protpscoleces removed were all subjected to viability studies, which included flame cell activity studies, evagination tests and the Eosin exclusion test. The results of this work show that in all the patients some of protoscoleces were structurally damaged, probably by the drug mebendazole. In all cases the optimal serum drug level of 100 ng/ml was achieved at one time or another during the treatment. Thus mebendazole has worked in this study and this could be a useful tool in future for the clinician looking after inoprablehydatid disease.

Albendazole is showing early promise since the few cases treated so far show cyst regression on ultrasound. However, its clinical evaluation is still going and audit is still too early to draw any firm conclusions.

Thus in the absence of a better alternative regime for inoperable human hydatidosis in Kenya, it may be justified to give either mebendazole or albendazole. In using the former drug the serum levels should be monitored.

In conclusion, human hydatidosis is a major economic and health problem in Kenya and its diagnosis and the medical treatment for inoperable cases still need further evaluation. Early diagnosis is desirable with a view to appropriate treatment. This study emphasizes the fact that chemotherapy is necessary in Kenya and the results here show that drug treatment can actually be effective and for the present, mebendazole or albendazole should be used until there is a better alternative. There is also a need in Kenya to establish the precise incidence of hydatidosis especially n Nyanza, Central and Rift Valley Provinces since sporadic cases come from those areas.

Finally, as a result of this study there is work going on currently in Kenya on circulating antigens in surgically proven cases with false negative immunoelectrophoresis test. Also following this work, it is now possible to do the Radioimmunoassay estimations of mebendazole levels in the Department of Medicine, Kenyatta National Hospital for hydatid patients receiving chemotherapy.

INTRODUCTION

This work was undertaken between 1978 and 1984. The interest in this work arose out of the realization that human hydatidosis was a major health problem in Kenya (1). Until that time, very little work was being done on the clinical aspects of this disease. The African Medical and Research Foundation (AMREF) was providing some surgical service in Turkana, but there was no work being done, on the diagnosis and medical treatment of human hydatidosis at that time. A look at the literature revealed that North-West Kenya had the highest endemicity in the world for human hydatidosis (1). There were 100 operations being performed annually for hydatic disease in Turkana, with around 15 in Masailand (2) and about five operations performed every month for hydatodosis in Marsabit District Hospital (personal communication from M.O.H. Marsabit). Moreover, there were a number of sporadic cases from the other parts of Kenya presenting at the out-patient departments of the Kenyatta National and other Government Hospitals.

HISTORICAL BACKGROUND

The Ministry of Health statistics did not show human hydatidosis as a major health problem in Kenya, until 1958 when Wray who was the Medical Officer of Health in Kitale published records of 117 cases most of whom were Turkana patients (3). But Nelson and Rausch (4) in 1963 published cases from King George VI (now Kenyatta National Hospital) records. In 1958 – 1961 they published 55 cases. Schwabe in 1969 made the first estimate of the incidence of human hydatidosis in Turkana based on hospital records from Kitale and Lodwar (5). Irving in 1974 (6) also reported cases from Lokori hospital records. More recently Rottcher who was a Flying doctor with AMREF and therefore visited certain areas particularly Turkana and Masai also reported some cases (2).

O'Leary (the Medical Officer of Health at Lodwar in 1976 published a very large number of cases over a five year period in the Turkana District (1). A later study in Masailand in 1978 by Eugster who was a District Veterinary Officer in Kajiado District showed that hydatidosis is a problem among these pastoral people (7). As a result of the realization that hydatid disease was a major health problem in Turkana, AMREF developed an interest and posted a full time doctor to take charge of their hydatid project there in 1976. In 1982 French and Nelson reviewed the problem in Turkana especially in relation to the geography of the district and the way of life of the Turkana people (8). But the possibility of cases coming from elsewhere in Kenya, outside Turkana and Masailand was not taken seriously because of lack of interest or suspicion, until the present work began in 1978 when an initial prospective study over a three year period at the Kenyatta National Hospital revealed that the disease was prevalent among other communities in Kenya such as Luos, Kikuyus, Kalenjins (9). It was therefore felt necessary to do more work on the clinical aspects of human hydatidosis in Kenya.

Until the present work was done, surgery was the only form of treatment for all the cases but it soon became apparent that recurrence was a major problem because it is recorded in 30% of cases and in any case some 20% of patients are primarily unsuitable for surgery (10). Therefore surgery is only possible in 50% of patients presenting clinically (10). Moreover, attempts to isolate cysts and to use scolicidal agents have not been altogether satisfactory. It was therefore

felt necessary to look at the possibility of chemotherapy with special attention being given to inoperable cases.

Diagnosis in the late 1970's was based entirely on clinical grounds. It was there felt necessary to look at the clinical aspects of human hydatidosis especially with regard to its diagnosis and treatment since earlier diagnosis might reduce the number of inoperable cases and medical treatment for inoperable cases was becoming a possibility at the time (11, 12, 13). The aim was to assess the most appropriate way of diagnosis and treatment of hydatidosis in Kenya. Prior to this study very little information had been published on the diagnosis and medical treatment of hydatidosis in this country. It was also felt that even if hydatidosis in Kenya were controlled, it would still be necessary to treat recurrent and inoperable cases for many years to come. Also, because of the long incubation period (three or more years) and the slow course of the disease, hydatidosis will continue as a major problem even after control is effective. For diagnosis it was felt necessary to evaluate ultrasonography in this disease because the technique is simple, safe, non-invasive and after the initial capital cost of purchasing the equipment, is fairly cheap to run and thus appropriate for a developing nation such as Kenya. For serological diagnosis, the immunoelectrophoresis test was selected because it was the standard test at the time and was thought to be specific for hydatidosis (14). Radiology was included in this study because it could reveal any pulmonary hydatids, which do not show up on an ultra scanner. For the treatment of inoperable hydatid disease it was decided to evaluate the clinical efficacy of mebendazole in Kenya since this drug had shown some promise at the time (11, 12, 13). Later when methods for the estimation of serum levels of mebendazole became available the opportunity was also taken to study the pharmacokinetics of the drug in Kenyan hydatid patients. The therapeutic effect of this drug was assessed by studies of the response of patients to treatment and by tests on the viability and morphological changes on the protoscoleces removed at operation from treated patients. This work is intended to provide information that will be available for use in order to improve the management of human hydatidosis in Kenya.

CHAPTER ONE

2.

2.1 THE PARASITE AND ITS LIFE CYCLE

2.1.1. INTRODUCTION

(a) Hydatidosis and echinococcosis are terms used to refer to infections by the metacestode (larval) and strobular (adult) stages of Echinococcus, which is a parasite of major public health and economic importance in all the continents. The causative agent of hydatidosis (echonococcosis) in Kenya is Echinoccoccus granulosus (E. granulosus) (4). This parasite is a member of the cyclophyllidae belonging to the family Taeniidae. This contains many parasites of pathological and economic importance to man. They are characterized by a life cycle in which the adult stage is in a "definitive" host where sexual reproductive occurs, and a larval stage in an "intermediate" host where a sexual reproduction may take place. Rudolph in 1801 coined the word "vesicular echinococcosis" to describe hydatid disease and he classified the causative organism in the genus Echinococcus to which his name is still attached as Echinococcus (Rudolph 1801 (15). Hydatid disease is referred to in the Talmud as "Water-bladder" (16) and Hypocrites mentioned it in his aphorisms and Galen referred to it (16). The complete life cycle was described by Leuckart in 1863 (17).

2.1.2 THE QUESTION OF SPECIATION IN ECHINOCOCCUS

There is considerable dispute over the division of the genus into species, subspecies and strains, and the taxonomic difficulties are considerable. Three species pathogenic to man, E. granulosus, E. multilocularis and E. vogeli are regarded with E. oligarthrus as being valid taxonomically (18). The taxonomic validity of the numerous subspecies and variants that have been described remains controversial, and until their biological status has been clarified should be referred to as strains. In fact it has been suggested that a continuum of strains exists with E. granulosus at one end and E. multilocularis at the other (19). In Africa the sub-species, E.g. granulosus, E.g. africanus, E.g. felidis, E.g. lycaontis, E.g. ortleppi have been recorded, though the validity of these is doubted by most modern authorities (20). In the past these distinctions were thought to be largely

academic and to have little significance. However, they may be of considerable importance with regard to virulence for man and response to treatment. Since E. multilocularis does not occur in Kenya it will only be referred to when comparison is of interest.

2.1.3 LIFE CYCLE OF ECHINOCOCCUS GRANULOSUS

Hydatid disease is a zoonosis. The adult worm (Fig. 1) inhabits the upper part of the intestinal tract of the definitive host, usually the dog in Kenya. In other parts of the world wolves, foxes, cape-hunting dogs, lions, golden jackals and silver-backed jackals also act as definitive hosts. The adult parasite is small measuring 3 – 8 mm in length and consists of a scolex and usually three to five proglottids or segments. As the terminal proglottid is shed further proglottids are produced behind the scolex. The proglottids are hermaphroditic, however, it is thought that cross fertilization may possibly occur (21).

The ova develop into eggs which mature until they become "infective". These are shed into the environment and are disseminated by various agents such as wind, water, flies, beetles etc. There is evidence that Taeniid eggs can be dispersed over large areas (22). Eggs, once in the environment may survive for many years or only for hours, depending on the ambient conditions (22). The factors inimical to the survival of eggs Include:-

FIG. 1 Echinococcus granulosus adult worms lying in the bottom of a dissecting dish with a beer bottle top illustrating their small size.

(a) Extremes of temperatures.

(b) Low humidity and low temperatures.

(c) Desiccation.

(d) Ageing of the eggs, which leads to loss of infectivity.

The dynamics of the important factors influencing egg transmission from the definitive to the intermediate hosts have recently been reviewed (22). When an intermediate host ingests eggs, the oncosphere hatches from the embryophone due to the action of bile. The oncosphere penetrates the gut wall and is believed to enter the blood stream, from where it is passively transported to almost any part of the body. The liver is the first organ encountered and is, in most intermediate host species, the most frequently affected. The oncosphere trapped may develop into the cystic (larval) stage. The larval stage (Fig. 2) comprises an inner germinal layer, which is surrounded by host reaction (ectocyst) (Fig. 3). From the germinal layer develop larvae (protoscoleces) (Fig. 4), which bud off, and fall into the cyst fluid. The larvae are usually grouped in brood capsules.

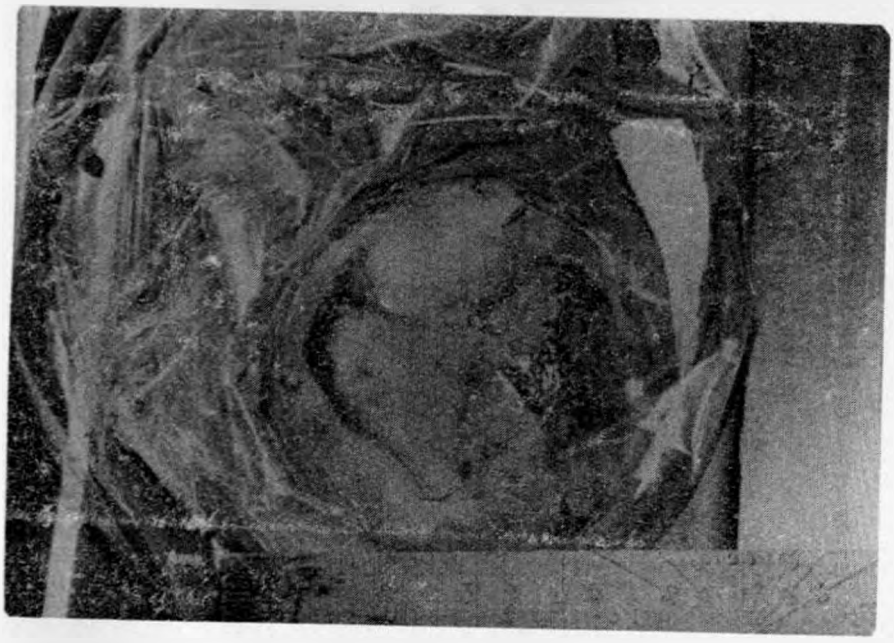


FIG. 2 Photograph of a hydatid cyst removed intact from a patient.

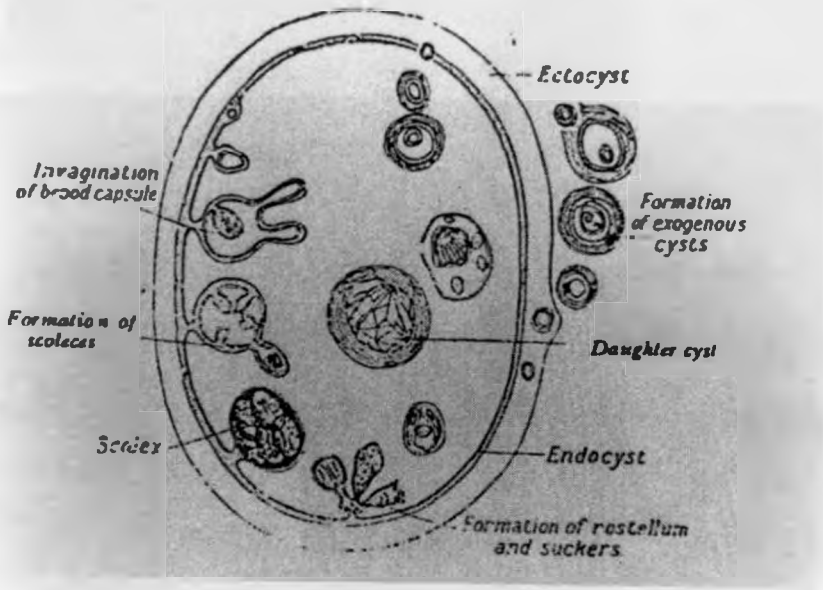


FIG. 3 Structure of a hydatid cyst showing its various layers.

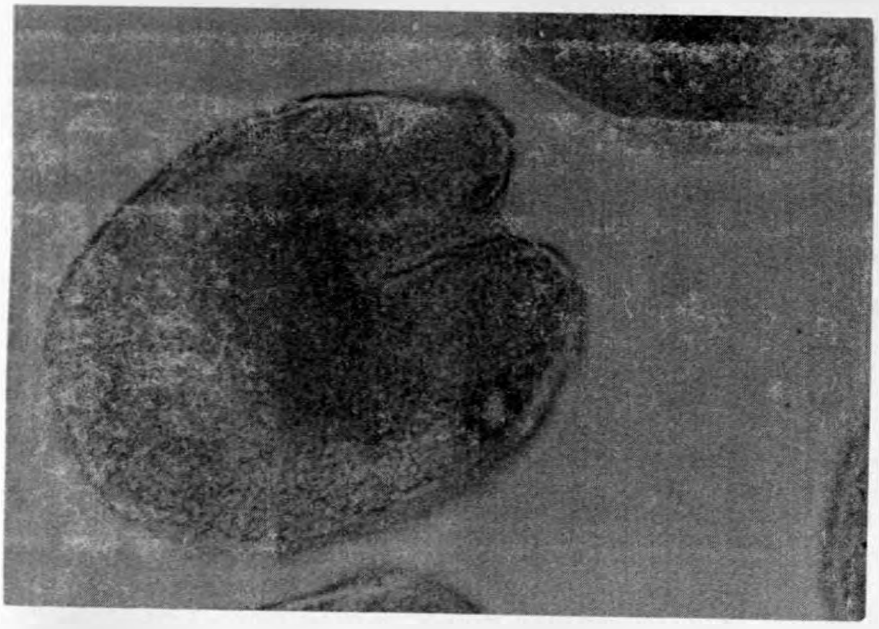


FIG. 4 Photograph of a normal protoscolex of Echinococcus granulosus.

Smaller cysts or daughter cysts sometimes develop inside the main cyst. In man, hydatid cysts can grow very large and may cause so much damage to the surrounding tissues that death may occur.

The larval stage of this parasite is remarkable in that it can develop either into an adult worm or into a cyst depending on its environment. With surgical spillage or rupture, released protoscoleces may develop into new cysts causing more severe multiple infections. When larvae are ingested by a definitive host such as the dog, the protoscoleces are stimulated to evaginate by the action of bile and the evaginated larvae attach to the surface of the dog's intestine. The time from the establishment of the parasite in the definitive host to the production of infective eggs is called the "prepatent period" and this varies between 40 – 56 days. After this, proglottids (Fig. 5) from the parasite in the definitive host begin to be released in the faeces and the life cycle of the parasite is completed. Cysts develop in different locations, sites and numbers depending on the intermediate host species.

In the Scandinavian reindeer, cysts spontaneously regress during winter and these animals must be re-infected during summer time if the infection with the parasite is to persist (23).

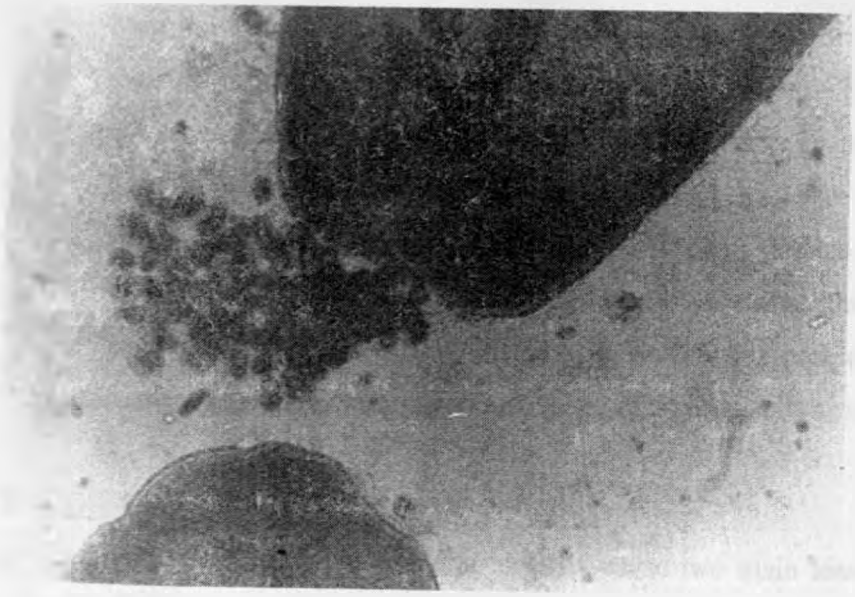


FIG. 5 Photograph of a proglottid with mature ova extruding from its end.

2.2 REVIEW OF THE GLOBAL PROBLEM OF HYDATIDOSIS

2.2.1 INTRODUCTION

(a) Hydatidosis is a zoonotic disease of cosmopolitan distribution wherever man, livestock and dogs coexist. E. granulosus is responsible for human cases of the disease although other species with sylvatic cycles are known to exist. Man may manifest the disease some years after exposure, while usually animals show practically no ill effects from invasion. E. granulosus is usually maintained in a simple domestic cycle but may go through a variety of wild animals with different susceptibilities such as the Australian Kangaroo (24). The recent appearance of hydatid disease in parts of the world previously free of it has created an entirely new global problem of increasing significance. For instance in Kuwait this problem has resulted from internal trade with rapid movements of humans and animals (25).

2.2.2 LOSSES CAUSED BY ECHINOCOCCOSIS

Zoonotic infections such as echinococcosis cause two main losses to man and animals namely:-

2.2.2.1 Man

Deterioration in human health, leading to shortening of life span of the person affected and reducing the working capability to earn one's own livelihood.

2.2.2.2 Animals

The disease in animals results in loss of high quality foods, so exacerbates problems of malnutrition in rural communities with food shortages such as Turkana. There is a heavy economic loss of high quality wool and protein foods (meat, milk etc). This economic loss is worldwide since echinococcosis occurs in both developing and developed countries. Twenty five per cent of sheep are affected by hydatidosis in England, 20 – 22% in India and Ethiopia, so, 55 and 67% in Iraq, Greece and Argentina respectively. 18% of cattle are affected with echinococcosis produce less meat, milk and wool because of growth and

development retardation. A lot of their organs (livers, lungs) have to be rejected (26).

The milk yield of the cows may drop by 50%. 1000 cows affected yield 4.4 tons of meat less than healthy ones. Millions of tons of wool, meat, fat, livers, hump, milk and lamb are lost every year despite the global food shortage especially in third world countries. In any case the products not rejected from these animals is usually of inferior quality. Annual figures for these economic losses are £400,000 in England, U.S $700,000 in Greece, USSR Roubles 30 millions in Kazakhstan, U.S. $150 – 300 million in Iran and US $30 millions in Latin American countries. Condemnation of carcasses may have serious consequences in countries relying on meat export as a means of earning much needed foreign exchange (26).

2.2.3 WORLD REVIEW

Hydatidosis as a global problem has been recently well reviewed (Fig. 6) (25). Iceland was the first country and the only one in the world which has successfully eradicated hydatid disease and the last human case was seen in 1960 (27, 28, 29).

2.2.3.1 Europe

In Europe, hydatidosis is a common problem. The disease is prevalent in Spain, Switzerland, Sweden, Britain, Italy, Hungary, Belgium, Cyprus, Czechoslovakia, France, Germany, Holland, Norway, Poland, Romania and U.S.S.R. The problem in these countries has been recently reviewed (25).

2.2.3.2 Middle East

In the Middle East and Mediterranean countries hydatidosis is well recognized in Turkey, Iraq, Iran, Syria, Lebanon, Jordan, Israel, Cyprus, Kuwait, Oman, and Saudi Arabia (25).

2.2.3.3 Asia

In Asian countries, hydatidosis is a problem in Afghanistan, Pakistan, Bangladesh, India, Sri Lanka, Malaysia, Sabah, Sarawak, Indonesia, Laos, Kampuchea, Thailand, Vietnam, Japan, China and Korea (25).

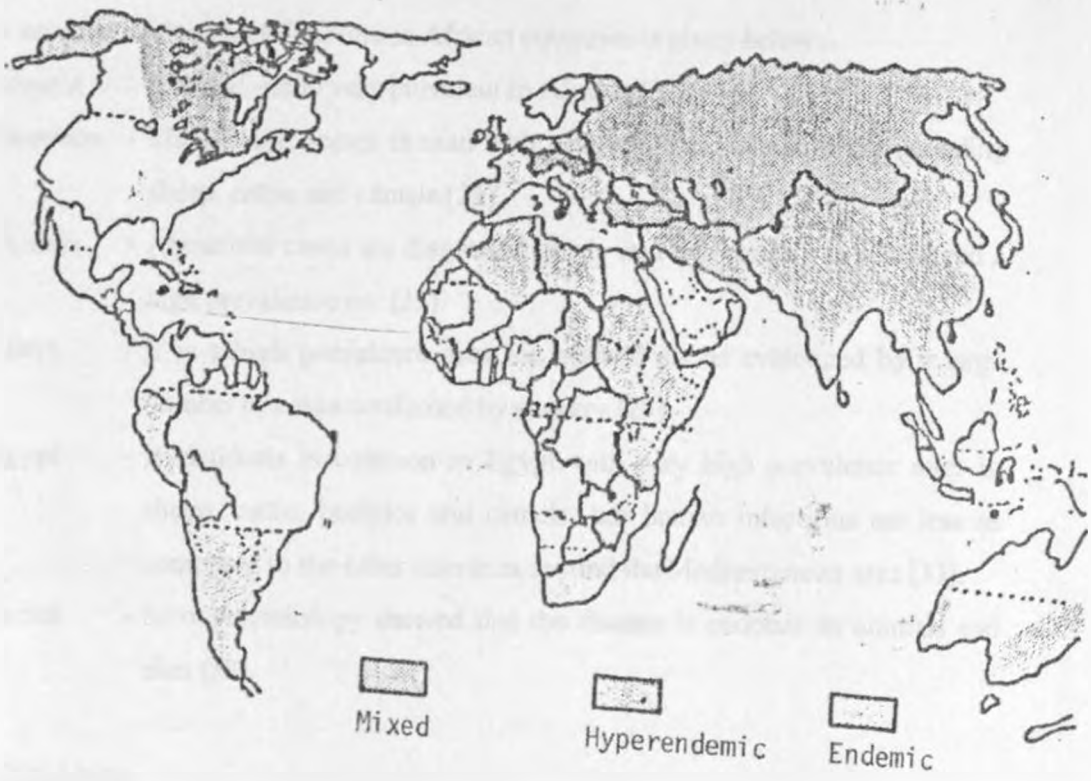


FIG. 6 Global distribution of human and animal hydatidosis. Single lines represent Echinococcus granulosus and crossed lines the coexistence of both E. granulosus and E. multilocularis infections.

2.2.3.4 America (30)

The problem of hydatidosis in Latin America has been recently reviewed (31). Some of the countries are free of infection while others have sporadic infections and a few have heavy infections (31).

2.2.3.5 Australasian

Australia (include Tasmania) and New Zealand have been high prevalence areas for hydatidosis as evidenced by a recent review (25).

2.2.3.6 Africa

A resume' of the hydatid picture in African countries is given below:-

Algeria - Hydatidosis is very prevalent in Algeria (32).

Morocco - The disease occurs in man with heavy infections in animals including sheep, cattle and camels (25).

Tunisia - About 600 cases are diagnosed yearly and this country is considered a high prevalence are (25).

Libya - It is a high prevalence area for hydatidosis as evidenced by a large number of cases confirmed by surgery (25).

Egypt - Hydatidosis is common in Egypt with very high prevalence rates in sheep, cattle, buffalos and camels, but human infections are less as compared to the other countries around the Mediterranean area (33).

Sudan - Seroepidemiology showed that the disease is endemic in animals and man (33).

West Africa

Little information is available from West Africa on hydatid disease, except in Nigeria which is discussed below. However reports from Senegal confirm the presence of hydatidosis there (34).

Nigeria - Hydatid cysts have been detected in cattle, sheep, pigs, goats and camels. Human hydatidosis has also been recorded in the Sudan zone of Nigeria. The infection in the Sudan zone in camels was 55.5%,

cattle 14.7%, sheep 11.4% goats 26.4% while in the Guinea zone of Nigeria the infection rate in camels is high at 50%, while it is lower in the livestock. Both camel and goat cysts were found to be very fertile. Echinococcus infections have also been detected in stray dogs and there is a high prevalence of hydatid cysts in livestock in parts of Nigeria, thus putting populations in those areas at special risk (35)

Central Africa

Very little information on hydatidosis is available from most central African states except Zimbabwe (see below).

Chad - Reports indicate the occurrence of human cases and endemicity in animals (camels) (25).

Zimbabwe - Human infections are rare and echinococcosis is found in cattle (36, 37)

South Africa

Animal infection is widely scattered with regional differences, and both jackals and domestic dogs are important in the transmission. However, human infections are not common (38).

Eastern Africa

Uganda - In 1921 the camel was noted as an intermediate host by the Veterinary Department. Human cases have been reported in Uganda, in its provinces adjoining the Turkana District of Kenya and southern Sudan. Hydatid cysts are present in cattle from all over Uganda (39).

Somalia - The disease has a low prevalence in man in Somalia although it is endemic in animals. This was shown by a seroepidemiological study in animals and man (40).

Ethiopia - Clinical and serological studies show that hydatidosis is highly prevalent in parts of Ethiopia (41).

Tanzania - Hydatid disease has been recognized in Tanzania (42).

Kenya - The problem of hydatidosis in Kenya will be discussed in Chapter two.

2.3 REVIEW OF GLOBAL CONTROL MEASURES

Since hydatidosis is a global problem, various countries have initiated national control programmes aimed at interrupting the transmission of the disease in their countries. Iceland successfully eradicated hydatid disease (29). The status of hydatid control programmes has recently been reviewed (30). Hydatidosis should not be regarded as merely a problem of dogs and livestock. It must be regarded as a problem of people. People must be educated about the disease and motivated to help in the control of the disease. For a control measure to be effective, it must be based on the education of the population affected, on how the disease is transmitted. All the successful control programmes have had education as the major component as shown in the summary below.

Control measures are aimed at interrupting the transmission by not allowing dogs to eat infected raw offal from sheep, goats, camels or any other intermediate hosts, and also by education of the public about the disease, of how it is transmitted and maintained. People must be motivated to help in the control of the disease.

2.3.1 ICELAND CONTROL PROGRAME

The only country that has successfully eradicated hydatid disease is Iceland (29) but New Zealand and Tasmania have undertaken control programmes with considerable success (30). The control programme in Iceland, which was then a colony of Denmark, took advantage of the 100% literacy rate and the education of the public on the nature and cause of the disease, the life cycle of the parasite and the means of prevention, in a pamphlet written by a Danish doctor (Professor Krabbe) and distributed to every family in Iceland in 1864 (43). The pamphlet was read by the entire Icelandic population including school children. This enabled the population to voluntarily undertake to reduce the disease prevalence.

Eventual compulsory measures by the Government merely added the momentum tot their determination to eradicate hydatid disease. Other factors for their success included the change from wool to fat lamb production, and the fact that their sheep were also slaughtered at a much younger age so that cysts in these animals did not get enough time to mature to the infective stages of the parasite for the dogs (29).

2.3.2 NEW ZEALAND CONTROL PROGRAMME, which was devised as a result of the Styx Valley pilot programme (44) consisted of:-

(i) Registering all dogs above six months of age.

(ii) All dogs were given Batamidine bromide (now praziquangel), six times a year at central dosing stations.

(iii) All the dog faeces were collected and examined and any worms found were identified.

(iv) In all cases, and in reinfected dogs, the authorities were given the powers to deal with the dog owners.

(v) All the farmers were instructed never to feed raw offal to their dogs.

These measures were supervised by the Hydatid Eradication Council. All these measures have resulted in a great reduction in the prevalence of hydatid in sheep and humans. It is an example of a control programme based on an effective health education programme. Unfortunately, the effect has been less spectacular in the less well educated Maori population, who keep fewer dogs (45).

2.3.3. TASMANIAN CONTROL PROGRAMME (46) was also similarly based on educating the farmers and the public about the disease transmission, the danger of feeding dogs on offal, and the prompt disposal of dead sheep. The dogs were examined periodically, and dosed with arecoline if thought necessary. The education was reinforced when the flocks of a farm having an infected dog were quarantined, resulting in financial loss to the farmer (46).

2.3.4. CYPRUS CONTROL PROGRAMME (47)

A similarly successful programme has been undertaken in Cyprus. All the above control programmes in Iceland, New-Zealand and Tasmania emphasize the value of a mass education campaign in hydatid disease control. The education enables the dog and livestock owners to understand how the disease is spread and how best to co-operate in controlling it. In the Iceland programme the control was initially voluntary before being made compulsory later on when farmers and the general public had understood the issue fully. The compulsory part consisted of a tax on every dog to limit the numbers owned, a law forbidding the feeding of raw offal to dogs, and that the dogs had to be treated regularly with a vermifuge. Stray dogs had to be destroyed. Dogs were banned from certain areas e.g. towns. Regular dosing requires a reliable vermifuge. Arecoline hydrobromide has proved erratic in that the dosing may have to be repeated many times. Droncit (R) Bayer (Praziquantel) is now the drug of choice (18).

The control of slaughter houses by centralization facilitates government supervision.

In conclusion, hydatidosis remains an important global problem. Iceland is the only country in the world in which this disease has been totally eradicated (29). In Tsamnia, New Zealand and Cyprus the disease has been brought under effective control (45). However, in all the other countries of the world the control programmes have been in operation for too short a time for meaningful results to have been obtained.

Perhaps a greater understanding of the disease and the parasite is needed for these measures to succeed.

CHAPTER TWO

3 REVIEW OF HYDATIDOSIS IN KENYA

3.1 INTRODUCTION

In Kenya (Fig. 7) hydatid disease poses both a medical and an economic problem. The medical problem relates to the lack of satisfactory chemotherapy, the unsatisfactory results of surgical treatment and an overall poor prognosis with an almost invariably fatal outcome for all the cases that are not successfully treated.

The first known records of hydatidosis in Kenya were made in 1915 when hydatid cysts were found in camels (48). In 1925 it was reported that cysts were rare in sheep in Kenya (49). In 1926 the larval or cystic stages of parasite E. granulosus, were found in Kenyan sheep and cattle (50) while in 1934 it was reported that this parasite was occasionally seen in cattle, sheep and pigs in Kabete (51). For the next twenty years there was no mention of hydatidosis. In 1956 it was noted that Kenya had no statistical data to show the incidence of hydatidosis in the slaughter animals throughout the country (52). After the establishment of the Kenya Meat Commission (KMC) central abattoir at Athi River in 1955 the first two annual reports of its veterinary services showed a very high incidence of echinococcosis in cattle,

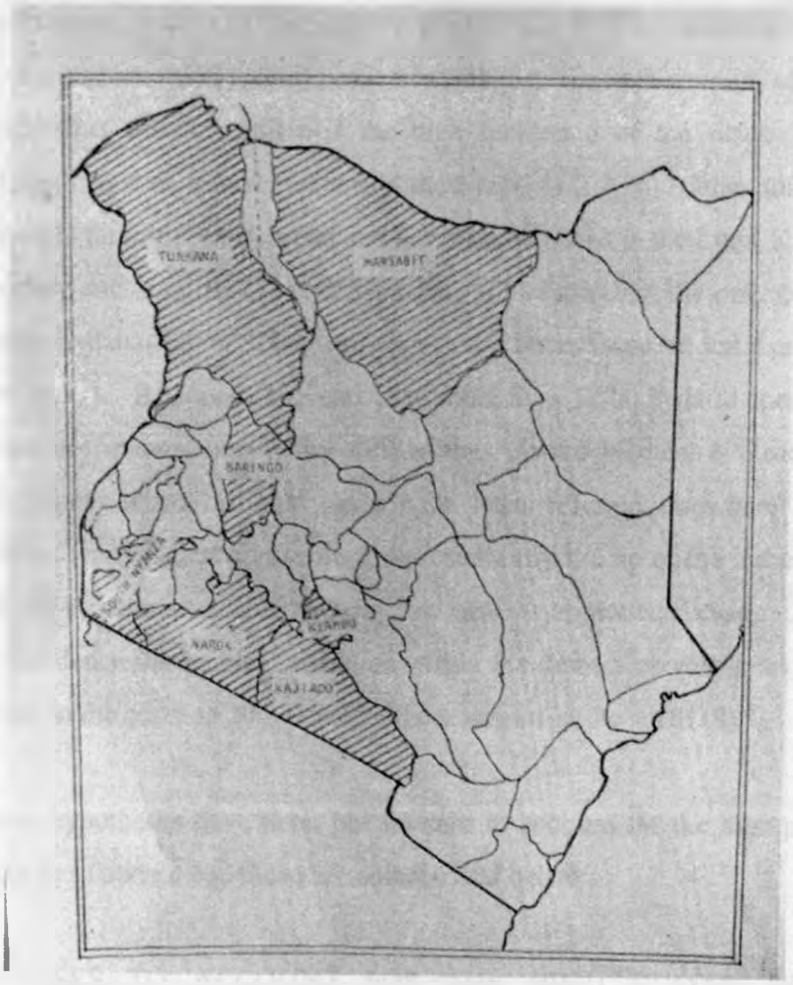


FIG. 7 A map of Kenya showing Turkana District and Masailand (the two endemic foci for hydatidosis in Kenya) as well as the areas, with sporadic cases (South Nyanza, kiambu and Baringo).

Sheep and goats (53) and these reports were later confirmed by other workers (54, 55)

3.2 HYDATIDOSIS IN MAN IN KENYA

The first record of human hydatidosis in Kenya was given by Wray (3) who noted the disease to occur mainly in the pastoral groups, the Turkana and to a lesser extent, the Masai. He also recorded a single case in a Suk (3). Since this report, several others have been published which confirmed the high incidence of the disease in the Turkana (1,2,3,4,5,6,8) and to a lesser extent in the Masai (1,2,7,56) Other studies indicate that the disease is far more widespread and has been recorded in the Luos, Kalenjins, Kikuyus (9), Rendille and Shagilla (1) and Samburu (56). However, the only surveys conducted on human hydatidosis in Kenya to date have been those undertaken in the Turkana Districts (8,57). Between 1965 and 1984 more than 1,700 hydatid operations have been conducted in Turkana, mainly by staff of the African Medical & Research Foundation (AMREF), and some difficult cases have been referred elsewhere for management (58,59,60). This surgical figure must represent only the tip of the iceberg for it does not account for those not seeking surgery and also asymptomatic cases. Interestingly, the disease incidence shows great variation within the district varying from 200 per 100,000 per annum in the north to 20 per 100,000 per annum in the south (8).

Numerous hypotheses have been put forward to account for the high prevalence of the disease in the Turkana and these are summarized below.

3.3 HYPOTHESES TO ACCOUNT FOR THE HIGH HUMAN INCIDENCE ON HYDATIDOSIS IN TURKANA

3.3.1 INHERENT VARIATIONS IN THE PATHOGENICITY OF THE TURKANA PARASITE (8).

Ecological separation of a species of a parasite can, on occasion, lead to the parasite developing differences infectivity and pathogenicity to the definitive and intermediate hosts. The polyembryony of E. granulosus in its cystic stage would facilitate the development or evolution of variants and the wide dispersal of these mutants (20). The situation in the Turkana District may have encouraged a genetic selection of a local parasite to which man has become unusually susceptible since dead human bodies are

very rarely buried deeply in the ground and dogs and other carnivores have easy access to human hydatid cysts so that a local parasite with an unusually high infectivity and pathogenicity for man may have been selected over the years (64). Evidence has been obtained from isoenzyme and biochemical and in vitro growth studies of hydatid material from man and animals in the Turkana District that there may be intraspecific variants or strains in this area (56,61,62,63,64,65).

3.3.2 HUMAN BEHAVIOURAL AND ENVIRONMENTAL FACTORS (8)

These factors undoubtedly play an important role in maintaining a high prevalence of a disease. For instance, hydatidosis was found to be more prevalent among Lebanese shoe workers who tan leather by using dog faeces than the rest of the Lebanese population (66) In Iceland, the high prevalence of hydatidosis was attributed to the habit of keeping dogs indoors during the long winters and the cleaning of utensils contaminated by dog faeces. This latter task was performed by women and probably accounted for the higher prevalence in females (43). A hypothesis has been advanced that the high incidence of the disease in Turkana is due to the very close contact between dogs and children and women of childbearing age and the use of dogs for general cleaning and also to clean babies. The incidence of the disease is much higher in females than males and this may be due to closer contact with dogs (61,67).

The habit of eating partially cooked or uncooked intestines of jackals has also been forwarded as a hypothesis to account for the ingestion of the infective eggs (57,69). The eating of dogs has never been proved and the Turkana themselves claim this would never occur (57,68,69).

3.3.3 THE TURKANA ATTITUDE TO THE DOG:

The Turkana like to keep large numbers of dogs for various reasons. Some of these include the use of dogs as guards against animals and human strangers, children's love for dogs as pets and the use of dogs to clean infant's vomit and faeces because of the lack of water. All these lead to very close man/dog contact and an increased chance of the ingestion of infective eggs. Moreover dogs sleep inside the house ("akai") with humans

(57). The role of the dog in the lifestyle of the Turkana has been recently reviewed (69,70).

3.3.4 USE OF DOG FAECES IN MEDICINE

Traditional medicine men, the world over, have used all sorts of mixtures to make concoctions for medicinal purposes. These practices may give rise to an increased exposure to various diseases. For example, the Icelandic medicine men used dog faeces for treating rheumatism and this practice contributed to the high prevalence of hydatidosis in that country. This has also been observed in South Africa (71). One of the hypotheses put forward for the high incidence of hydatidosis in Turkana is the use of a mixture of dog faeces, berries, soil or charcoal and leaves for the treatment of wounds by the traditional medicine men (57).

3.3.5 USE OF DOG FAECES AS LUBRICANT

Turkana women are fond of wearing heavy necklaces, which may have been accumulated over a long period (Fig. 8). As these may damage the skin around the neck, lubricants are used for the protection of the skin while mud is for decoration, any of which may be contaminated with dog faeces. The handling of the substances contaminated with dog faeces and their contact with the skin may increase the chance of infective eggs getting into the body (57).

FIG.8 A photograph of a Turkana female wearing a lot of necklaces.

3.3.6 CONTAMINATION OF DRIED MILK

The same skins used as bedding at night are also occasionally used to dry milk during the daytime. Dogs have access to the milk that is left on the skins and may thus contaminate the skins with infective eggs (57). Although E. granulosus eggs are very resistant and the scorching heat of Turkana may destroy most of them, there is a chance of the infective eggs reaching suitable intermediate hosts through such means (57).

3.3.7 CONTAMINATION OF WATER

Dogs and other carnivores have easy access to water-holes dug in dry river beds (Fig. 9). They can easily contaminate the water supply with infective E. granulosus eggs which may survive longer in such a wet environment. Up to 800 Taeniid eggs per litre have been found in such water-holes (72). Another source of infection is from contaminated berries that have fallen on the ground, roots and herbs (57).

3.3.8 POOR IMMUNOLOGICAL REASPONSE TO INFECTIONS BY E. GRANULOSUS

Anaphylactic shock is uncommon among the Turkana following the spillage of cyst material at operation. Moreover the finding of a lot of false negatives for the presence of arc 5 in cases of surgically proven hydatid disease may indicate an inability to mount an immune response to the disease. The high rate of false negatives, provides difficulties for the use of serology in diagnosis (73). In addition to the above factors, there may be many

FIG.9 Water-hole in Turkana. Water-borne transmission(s) thought to be a possible route of transmission to man and his animals in the hot/dry Turkana environment.

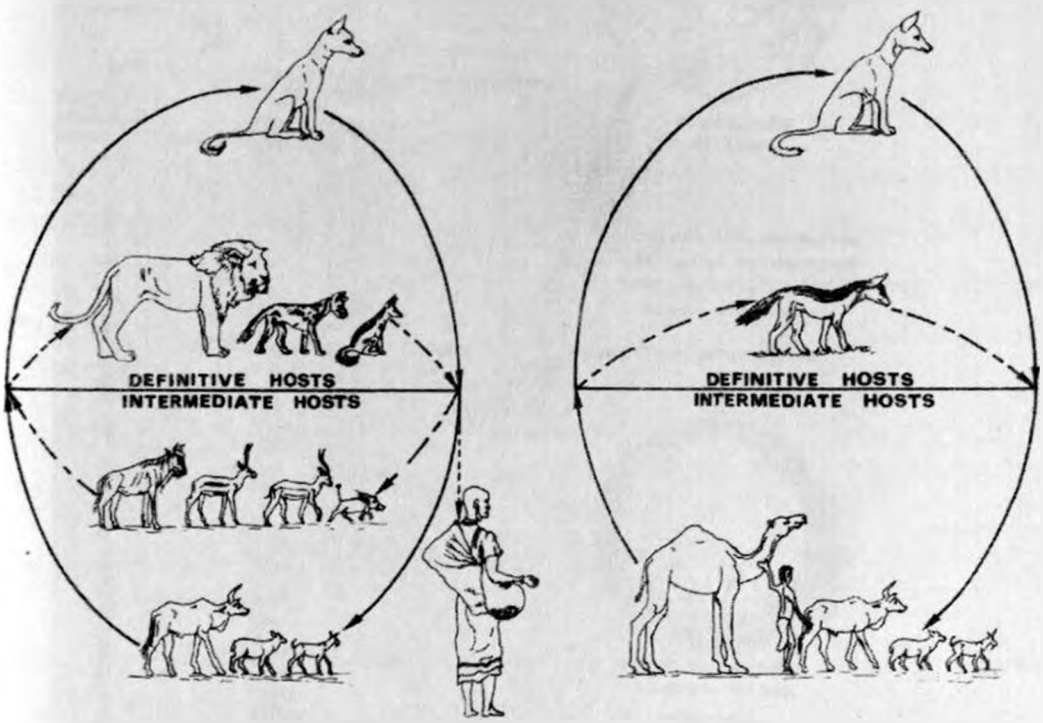


FIG. 10 The life cycle of Echinococcus granulosus in Masailand (left) and Turkana (right) after Macpherson et al 1983.

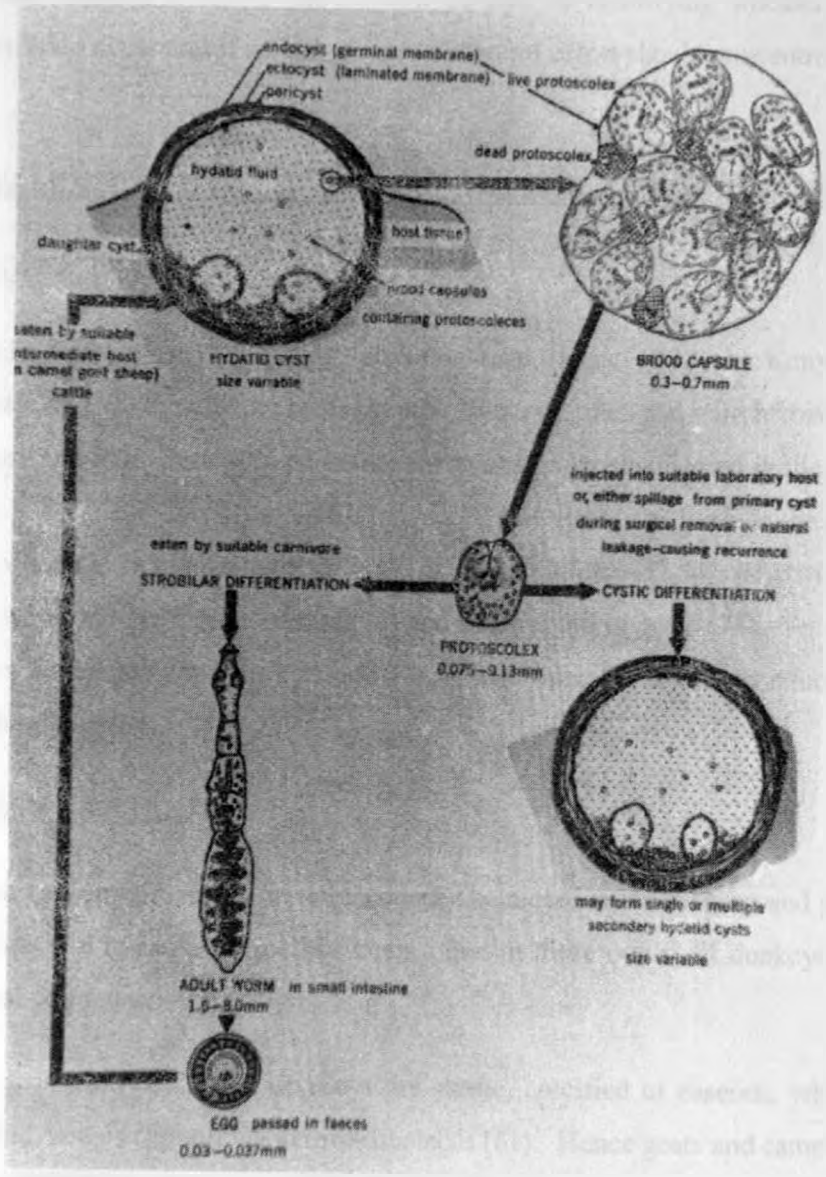


FIG.11 Diagrammatic life cycle of Echinococcus granulosus.

Other reasons for the high incidence of hydatidosis in Turkana and more studies are required. Special attention should now be paid to identifying whether foci of disease transmission occur and if so, any proposed control effort should concentrate on these.

3.4. PREVALENCE OF HYDATIDOSIS IN DOMESTIC ANIMALS IN KENYA

3.4.1 INTRODUCTION

The life cycle of E. granulosus affecting man (Figs. 10,11) in Kenya involves the domestic dog, wild carnivore and domestic livestock, man and wild herbivores, (7,56,68). 20 years ago more than 30% of cattle, sheep and goats slaughtered in the central abattoir of the K.M.C. at Athi River had hydatid cysts in either the liver or the lungs, and that there was an even greater infection rate in rural abattoirs (52,54). Hydatis were reported to be common in domestic animals (4) and widespread in goats (74). To date only a few surveys have been done on a regional basis and these have been conducted in Turkana and Masailand (69),

3.4.2 TURKANA DISTRICT

The most recently reported prevalence is 7.4% in cattle, 2% in sheep and goats, and 64% in camels and hydatid disease has been found in three out of 14 donkeys (Macpherson, personal communication).

Most cysts from cattle and donkeys are sterile, calcified of caseous, while those from goats and camels contain viable protoscoleces (61). Hence goats and camels are the main intermediate hosts of the parasite in Turkana (56). Although the problem of speciation is still being investigated, it is now recognized that there is a human, common goat and sheep strain of the parasite, which is the most widespread strain; the cattle strain is slightly different isoenzymatically and biochemically as is the camel and the less common goat strain (56,61,62,63,75). The physiological requirements of the larvae from all these animals hosts however, are surprisingly similar. The similarity of all the various strains may partially explain the high human incidence of the disease in Turkana. In Britain horse strain does not appear to be infective (76).

3.4.3 MASAILAND

Eugster (7) found that in Kajiado District between 1969 and 1976, 676 out of 1446 (46.7%) cattle, 14 out of 44 (29.5%) sheep and nine out of 100 (9%) goats harboured hydatid cysts. More recently Macpherson (77) has given the 1979 to 1984 incidence figures for Masailand as 8.9% in 1499 cattle, 8.1% in 1798 sheep and 7.1% in 2020 goats. The difference in the cattle prevalence with that of Eugster is due mainly to Eugster's inclusion of small calcified lesions in his data.

3.5 ECHINOCOCCOSIS IN DOMESTIC DOGS

Until 1962 it was thought that wild carnovores were the only hosts of adult E. granulosus in Kenya (3,52). However, in 1963 E. granulosus was found in dogs from Nairobi and Turkana District (4). Only light infections were found in wild carnivores (4). The dog was therefore regarded as the most important definitive host of the parasite in Kenya (8). The three surveys so far undertaken in Kenya for the examination of E. granulosus in domestic dogs are summarized in the table below:

TABLE I. PREVALENCE OF E. GRANULOSUS IN DOMESTIC DOGS IN KENYA

REGION	REFERENCE PERIOD	SURVEY PERIOD	NUMBER EXAMINED	NUMBER INFECTED	PER CENT INFECTED
Masai land	Nelson & Rausch 1963 (4)	1960	16	8	50.0
Turkana	Nelson and Rausch 1963 (4)	1960	27	19	70.4
Kajiado	Eugster 1978 (7)	1970-76	165	45	27.3
Turkana Total		1979-83	695	274	39.4
North-West Turkana		1979-83	263	167	63.5
North-East Turkana	Macpherson et al (in press)	1979-83	91	21	31.9
Central Turkana		1979-83	247	32	13
South Turkana		1979-83	94	46	48.9

During severe droughts in the past when both livestock and many people died, it has been noted that the incidence of dog infections dramatically increased and this has been thought to be due to the fact that the dogs have had access to animal and human corpses inadequately buried (69). It is considered that the dogs get a lot of their infection from goats which are slaughtered in very large numbers, although the infection rate among these animals is much lower compared to that in camels. Only a few camels are

slaughtered. Although the incidence of human hydatidosis is much higher in the north than in the south of Turkana District, the prevalence of dog infections is similar in both regions but the human/dog contact is greater in the north than in the south because of the large dog population in the north (70). There are about 50,000 dogs in the district (70) with a human population estimated at about 156,000 people (57).

The other focus of hydatidosis in Kenya is in Masailand (7). Although the Masai keep dogs for guarding their livestock at night but it has been noted that the man/dog contact is very low compared to that among the Turkana because Masai elders to not allow dogs into their houses (7).

3.6 WILDLIFE CYCLE OF E. GRANULOSUS IN KENYA

Awareness of the existence of wildlife cycles of Echinococcus infections is important from a public health point of view. Thus awareness of the existence of a wildlife cycle and its possible infection to man and his domestic livestock is necessary for an effective control programme. The first wild definitive host of E. granulosus found in Kenya was a jackal (52). It was the proposed that jackals and hyenas might be the main hosts in Kenya (78). Of the jackals, hyenas and a variety of other carnivores and herbivores examined, it was found that there were only light infections in silver-backed jackals Canis mesomelas), three spotted hyenas (Crocuta Crocuta) and Cape hunting dogs and Cape hunting Lyacon pictus plus hydatid cysts in one wildebeest Connochaetes taurinus) and it was concluded that the main cycle of transmission in Kenya was between dogs and domestic livestock (4). This hypothesis was supported by later studies (79). Although silver-backed and golden jackals are infected by scavenging on livestock and possibly human corpses but since no cysts were found in any of the wild herbivores examined in Turkana, including 64 did-dik, 56 hares, four warthogs, 38 Grant's gazelle, two baboons and 28 squirrel, there is no evidence suggesting a separate wild life cycle in Turkana (68).

On the other hand, in Masailand, Echinococcus adults have been found in lions, Cape hunging and jackals 4,7,68,80). Infection has also been noted in wildebeest which harbour fertile cysts. Hence it has been postulated that a true wild life cycle (Fig. 10) involving mainly lions, jackals and wildebeests occurs in Masailand (68).

CHAPTER THREE

4 STUDIES ON THE DIAGNOSIS OF HYDATID DISEASE IN KENYA

4.1 INTRODUCTION

Hydatidosis is a parasitic infection in which the diagnosis depends on the clinical and investigative methods and not on the demonstration of the parasite in the stool or urine. Moreover there is a great danger due to spillage from aspiration for diagnostic purposes as this may lead to anaphylaxis. The clinical diagnosis is unsatisfactory as it can only lead to a suspicion of the possibility of the patient having the diseases. Therefore more definitive diagnostic tests are often required for decisions on the most appropriate form of treatment. In developed countries, the diagnosis of human hydatidosis can now be undertaken using radio-isotope scanning, ultrasonography, computerized axial tomography (CAT scan) and serological tests. In those countries it is now possible to select suitable cases for medical or surgical treatment and to monitor the progress of the disease over a very long period. However in Kenya at the time of this study there were no reliable routine diagnostic methods and surgery was still used both for diagnosis and treatment resulting in a very high recurrence rate of hydatidosis for whom there is no treatment (10) AMREF surgeon, personal communication. Moreover, there was not precise and adequate information on the specificity and sensitivity of the different screening tests in Kenya and only two seroepidemiological surveys (73,81) had been undertaken at the time. It was therefore felt that there was a need to undertake this study on the diagnosis of human hydatidosis in Kenya. The immunoelectrophoresis (I.E.P.) test was selected because it was reported as the most specific test at that time (14) and preliminary studies in Kenya confirmed this (73,81). Since ultrasound had shown early promise in a small preliminary study in Kenya (82), it was also selected for this study in order to assess its value on a large scale study. During the greater part of this study there were no x-ray facilities in Turkana and it was therefore felt necessary to include radiology in this study in order not to miss any pulmonary cysts.

In this study these investigative procedures are evaluated, discussed and appropriate conclusions reached and recommendations made relating to the problem of human hydatidosis in Kenya.

4.2 MATERIALS

4.2.1 SOURCE OF PATIENTS

One hundred and fifty cases of human hydatidosis which at some stage were proven surgically were included in this study. 104 were females which 46 were males and the average age was 27 years. Sixty cases without hydatid disease were also included, 30 had kalazar, 10 had schistosomiasis, 20 normals as controls. All were referred to the Kenyatta National Hospital (K.N.H) for management. Some of the cases had had previous surgical treatment while others had primary hydatid diseases and were later sent for surgery as the only treatment available at the time. The majority of the cases were from Turkana District while the rest included Kalenjins, Masais, Kikuyus and Luos. The Kalenjin cases were from Kajiado, Narok and Ngong areas. The Kikuyus came from Kiambu District, Mau Narok and Laikipia. The Luo cases came from South Nyanza District. Details can be seen in the table below. (Table 2).

The Turkana cases were mostly brought directly from the district by AMREF and a few were referred from the Nakuru Provincial General Hospital by the Provincial Physician and surgeon.

The following case histories and clinical summaries of some cases may help illustrate the problems related to the diagnosis of human hydatidosis in this country.

TABLE 2 LIST OF THE 150 CASES STUDIED USING SEROLOGY, ULTRASOUND AND RADIOLOGY

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
1	15	F	Turkana	Primary	+ve
2	25	F	"	"	+ve
3	28	F	"	"	"
4	19	F	"	"	"
5	22	F	"	"	"
6	23	F	"	"	"
7	21	F	"	"	-ve
8	27	M	"	"	"
9	28	F	Turkana	"	+ve
10	32	F	"	"	"
11	35	F	"	"	"
12	27	F	"	"	"
13	30	F	"	"	"
14	27	M	"	Secondary	-ve
15	27	F	"	"	"
16	25	M	"	"	+ve
17	19	M	"	Primary	"
18	18	M	"	"	-ve
19	17	F	"	"	"
20	14	F	"	"	+ve
21	16	F	"	"	"
22	15	F	"	"	"
23	22	F	"	"	"
24	18	F	"	"	"
25	19	F	"	"	"
26	17	M	"	"	"

Table 2 (cont.)

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
27	25	M	Turkana	Primary	+ve
28	24	M	"	"	-ve
29	23	F	"	"	+ve
30	28	F	"	"	+ve
31	29	F	"	"	+ve
32	27	F	"	"	-ve
33	26	M	"	"	+ve
34	24	M	"	"	-ve
35	32	F	"	"	-ve
36	33	M	"	"	+ve
37	34	F	"	"	+ve
38	35	M	"	"	+ve
39	32	F	"	"	"
40	30	M	"	"	"
41	29	F	"	"	"
42	27	F	"	"	"
43	31	F	"	"	"
44	32	F	"	"	"
45	31	F	"	"	-ve
46	33	M	"	"	+ve
47	35	M	"	"	+ve
48	19	M	"	"	+ve
49	28	F	"	"	-ve
50	27	F	"	"	+ve
51	25	F	"	"	+ve
52	26	F	"	"	+ve
53	27	F	"	"	+ve

Table 2 (cont.)

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
54	28	F	Turkana	Secondary	-ve
55	29	F	"	"	-ve
56	33	M	"	"	-ve
57	33	M	"	"	+ve
58	30	F	"	"	+ve
59	29	M	"	"	+ve
60	28	F	"	"	-ve
61	24	M	"	"	+ve
62	29	F	"	"	+ve
63	28	F	"	"	-ve
64	27	F	"	Primary	+ve
65	25	F	"	"	-ve
66	26	F	"	"	-ve
67	28	M	"	"	+ve
68	27	F	"	"	+ve
69	28	F	"	"	-ve
70	29	F	"	"	+ve
71	32	F	"	"	+ve
72	31	F	"	"	+ve
73	19	F	"	Secondary	+ve
74	22	F	"	"	+ve
75	25	F	"	"	-ve
76	22	F	"	"	-ve
77	23	F	"	"	-ve
78	23	F	"	Primary	+ve
79	24	M	"	Secondary	-ve
80	18	M	"	Primary	-ve
81	25	F	"	"	-ve
82	26	M	"	"	+ve

Table 2 (cont.)

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
83	27	F	Turkana	Primary	-ve
84	28	F	"	"	-ve
85	29	F	"	"	+ve
86	32	M	"	"	-ve
87	31	F	"	"	-ve
88	33	F	"	"	-ve
89	30	F	"	"	-ve
90	28	F	"	"	+ve
91	27	M	"	"	+ve
92	26	F	"	"	-ve
93	25	M	"	"	-ve
94	24	M	"	"	-ve
95	25	F	"	"	+ve
96	28	F	Luo	"	+ve
97	30	F	"	"	+ve
98	35	M	"	"	-ve
99	32	F	Kalenjin	"	-ve
100	36	F	"	"	-ve
101	40	F	"	"	+ve
102	42	M	"	"	+ve
103	30	F	"	"	+ve
104	27	M	Luo	"	+ve
105	25	F	Luo	"	-ve
106	17	F	Kikuyu	Secondary	+ve
107	60	F	"	Primary	-ve
108	35	F	"	"	-ve
109	20	F	"	"	+ve
110	38	M	"	"	-ve

Table 2 (cont.)

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
111	49	M	Kikuyu	Primary	+ve
112	28	M	Turkana	"	+ve
113	25	M	"	"	-ve
114	26	M	"	"	-ve
115	50	F	"	"	+ve
116	10	F	"	"	-ve
117	18	F	"	Secondary	+ve
118	18	F	"	"	-ve
119	7	F	"	"	+ve
120	11	M	"	"	-ve
121	28	M	"	"	+ve
122	19	F	"	Primary	+ve
123	30	F	"	"	-ve
124	25	F	"	"	+ve
125	18	F	"	"	+ve
126	34	F	"	"	-ve
127	18	F	"	"	+ve
128	18	F	"	"	+ve
129	44	F	"	"	-ve
130	30	M	"	"	+ve
131	45	M	"	"	-ve
132	50	M	"	"	+ve
133	28	F	"	"	-ve
134	22	M	"	"	+ve
135	30	F	"	Secondary	+ve
136	24	F	"	"	+ve
137	30	F	"	"	+ve
138	32	M	"	"	-ve

Table 2 (cont.)

Case No.	Age	Sex	Tribe	Primary or secondary cysts	IEP Test
139	32	F	Turkana	Secondary	-ve
140	26	M	"	Primary	-ve
141	23	F	"	"	+ve
142	17	F	"	"	-ve
143	40	F	"	"	+ve
144	25	F	"	"	+ve
145	38	M	Masai	"	+ve
146	14	M	"	"	+ve
147	19	F	"	"	+ve
148	6	M	"	"	-ve
149	36	F	"	"	+ve
150	17	M	"	"	+ve

4.2.2. ILLUSTRATIVE CASES

Case No. 1

J.L. a 27 year old Turkana male who presented in 1983 with abdominal distension and pain, of very slow onset and progression. He gave a history of dry cough. He had had three abdominal laparotomies, one in 1968 and two in 1971 for removal of hydatid cysts and he had then felt only temporary relief. The physical examination revealed a young man in good general condition with the main findings being in the abdomen and chest. He had hepatosplenomegaly with multiple cystic masses which were non-tender. In the right lower chest he had stony dullness with reduced vocal resonance and fremitus and the breath sounds were reduced vesicular at the right base. Chest x-ray showed a well defined rounded opacity in the right lung and ultrasound showed disseminated small cysts in the abdomen with a large liver and spleen. The spleen had two cysts. Serology confirmed the presence of arc 5 in this case. He was given chemotherapy since no further surgery was possible. It would have been easy to suspect hydatid disease in him because of this being a Turkana and the remarkably good general condition. It also illustrates the fact that recurrence is a problem in Kenya (Fig. 12, Fig. 13. Fig. 14).

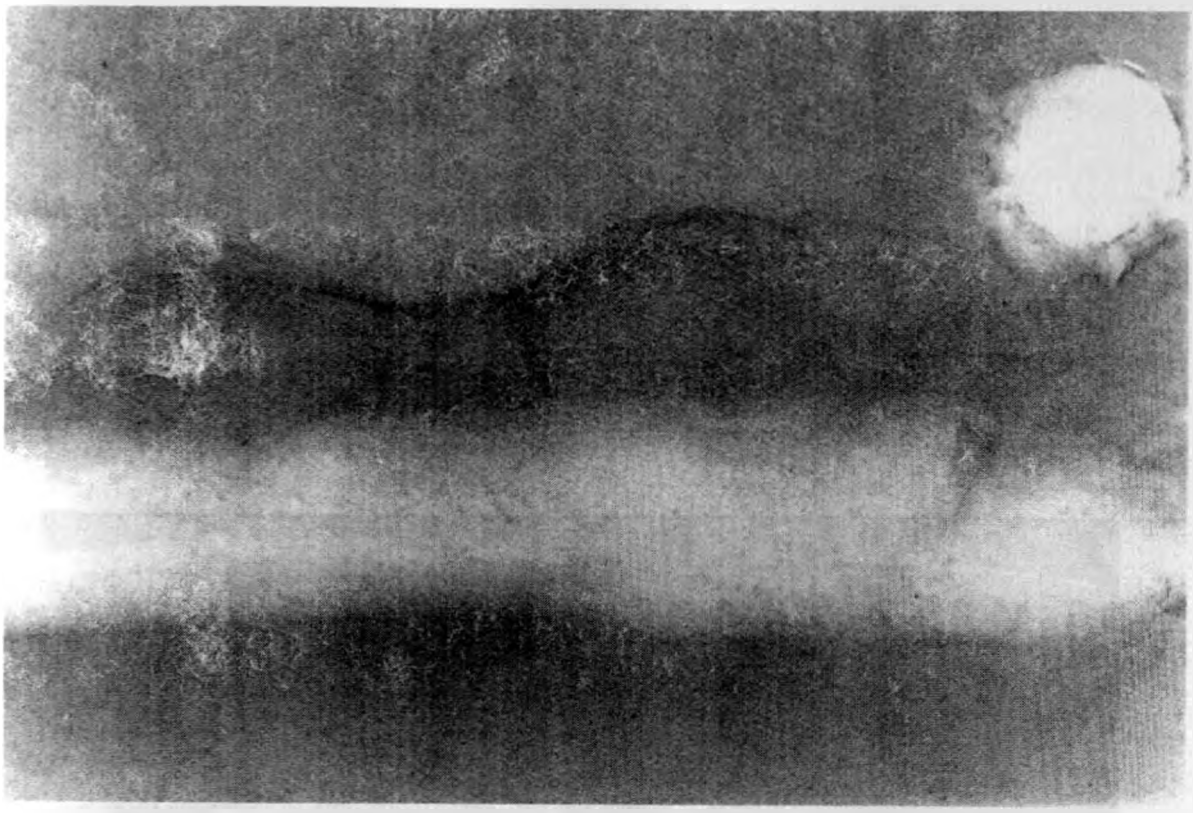
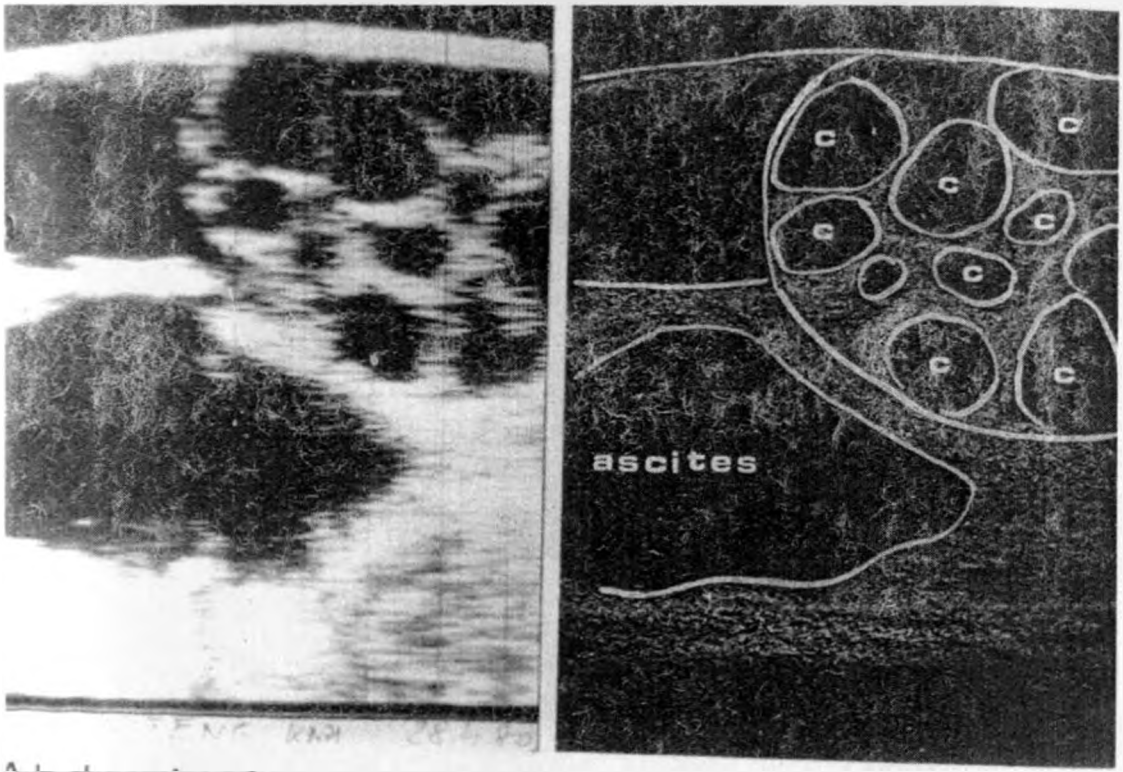


FIG. 12 Immunoelectrophoresis test arc 5 of Case one.



Abdominal scan. Hydatid cysts

FIG. 13 Ultrasound picture of case one.

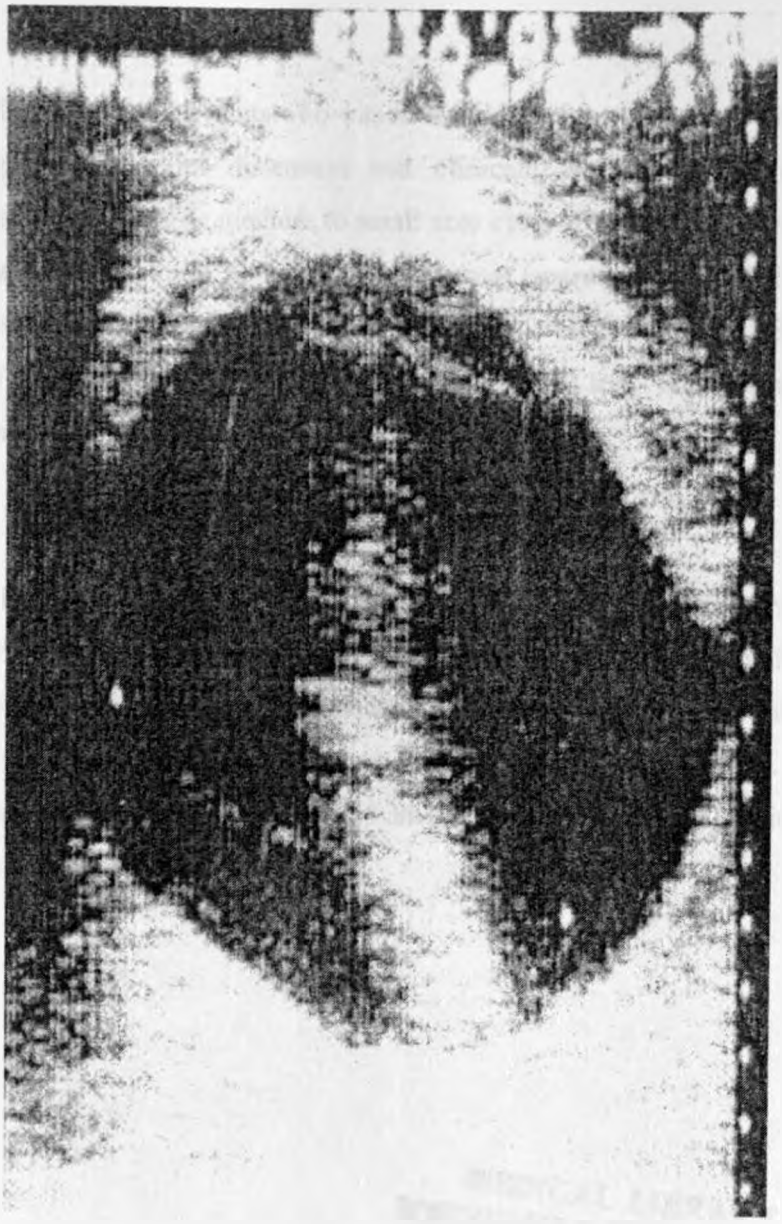


FIG. 14 Chest x-ray of case one showing a right pulmonary hydatid cyst.

Case Two

M.E. was a male Turkana aged 25 years who was referred here for treatment in 1979. He presented with gross abdominal distension and clinically he was wildly wasted. Ultrasound confirmed uncountable medium to small size cysts in the peritoneum and the liver. Prior to his admission here he had four abdominal laparotomies in 1973, 1978, 1979 for hydatidosis. He had a classical arc 5 on the immuno-electrophoresis (IEP) test. His serum is now used to standard anti um for running the IEP test. He illustrates the classical presentation of hydatid disease (Fig.15, Fig.16, Fig.17)

Case Three

Is a 17 year old Kikuyu lady who lives at Ngong. She is seen at Kenyatta National Hospital in early 1979 with multiple abdominal hydatids and hepatomegaly. In 1977 she had laparotomy for removal of hydatid cysts and now presented with secondary disease. She was followed up with repeated ultrasonography and the EIP test was positive. She is one of the first cases of human hydatidosis noted among the Kikuyus and it confirms the view that hydatidosis is widespread in Kenya (9).

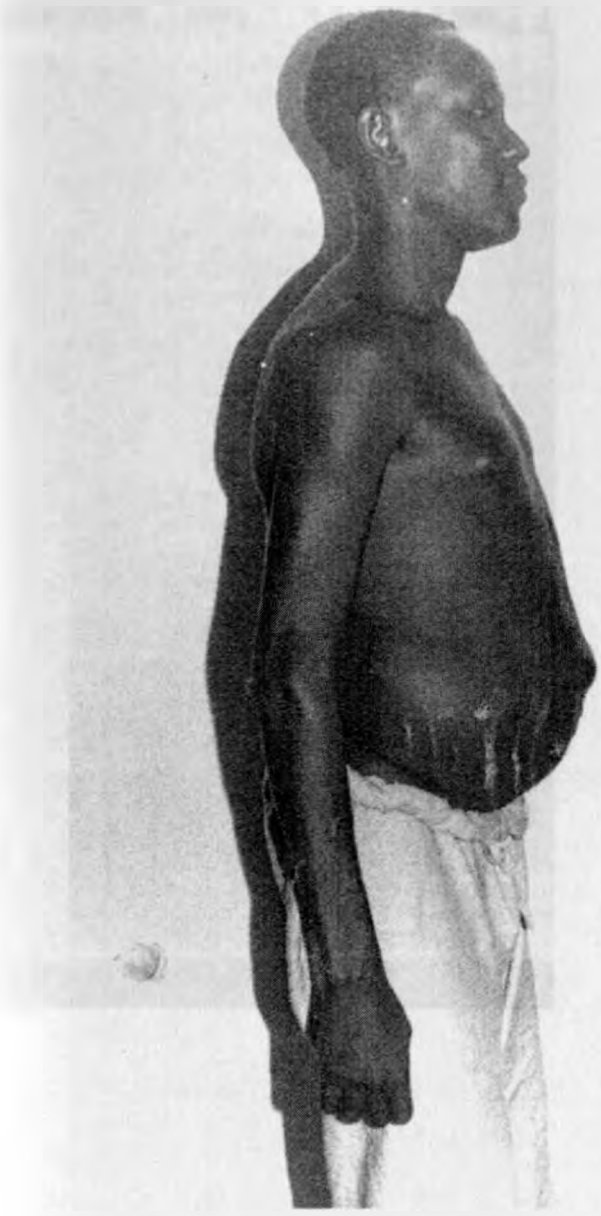


FIG. 15 Photograph of a typical appearance of a Turkana male with abdominal cysts.

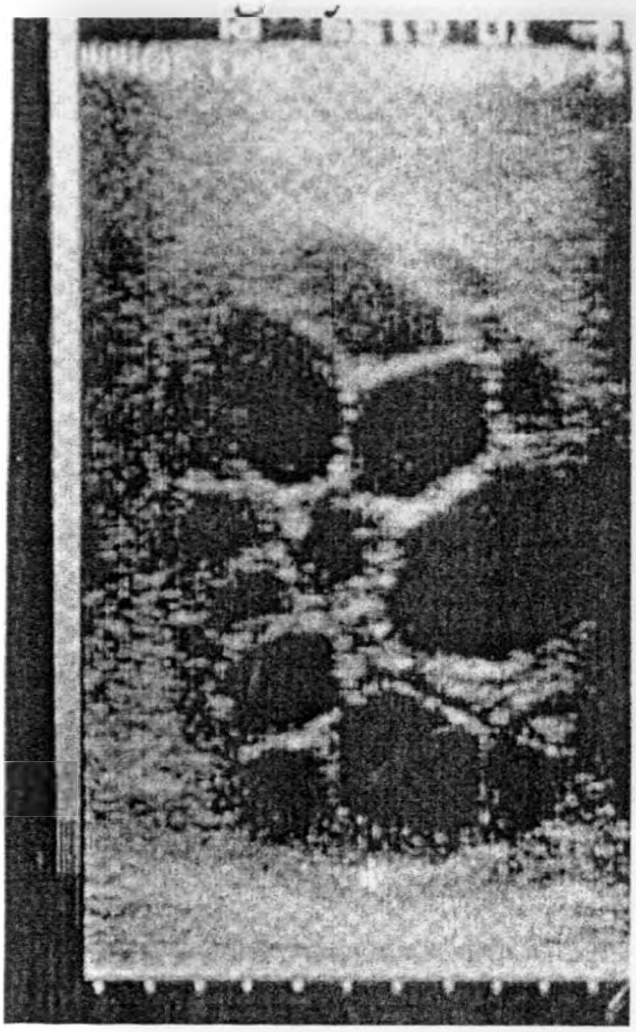


FIG. 16 Ultrasound film of case two

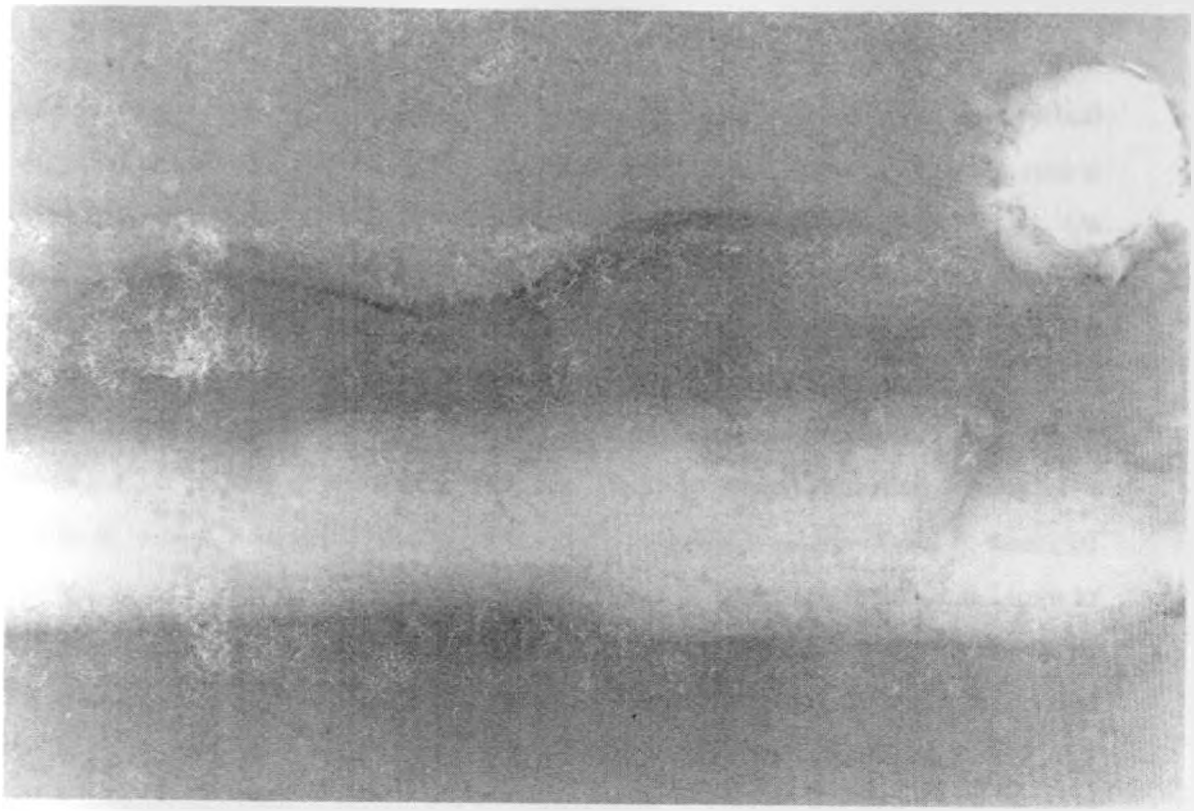


FIG. 17 Immunoelectrophoresis test arc 5 from case two

Case Four

A.M. is a 6 year old Masai boy who presented in 1983 with protrusion of the right eyeball and blurring of vision. The ophthalmologist who referred him suspected a cyst on retinal ultrasonogram and sent him for the IEP test to check if the patient had a hydatid cyst. On the physical examination, the boy looked small for his age and he had exophthalmos of the right eye with gross papilloedema of the right fundus. Both the left eye and left fundus were normal and the rest of the systems did not reveal any abnormality. Both ultrasound and chest x-ray did not disclose any cysts in the abdomen or chest respectively. He had an arc 5 on the IEP test. He was treated with Albendazole for 8 weeks at a dose f 10mg per kilogram daily in two doses. After about 8 weeks of chemotherapy, the right eye got bigger and the A – P diameter increased from 24mm to 37mm and the eye looked red and inflamed. The ophthalmologist confirmed a rupture of the cyst and the patient was given systematic and local steroids and the eye was operated on the eye has continued to get smaller in size. This case illustrates a very rare presentation of hydatid disease. It would be unwise to remove any eye before hydatid disease is excluded by serology, ultrasonography and/or exploration (Fig. 18, 19).

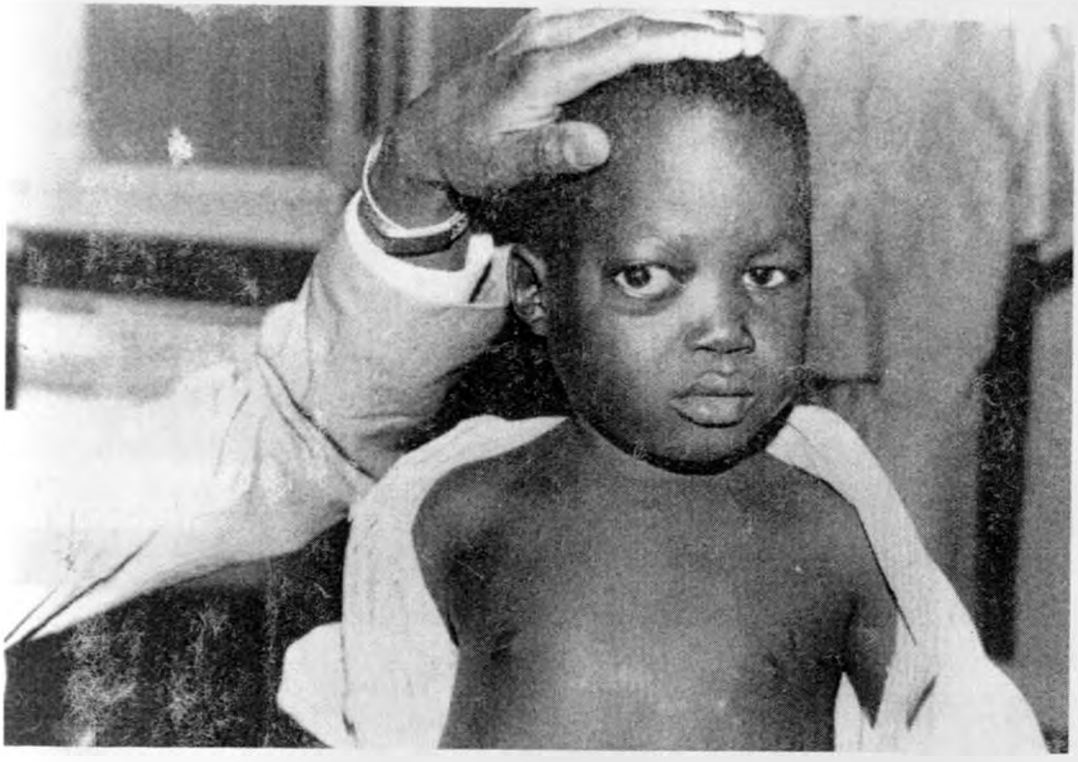


FIG. 18 Photograph of case four showing a retro-orbital hydatid.

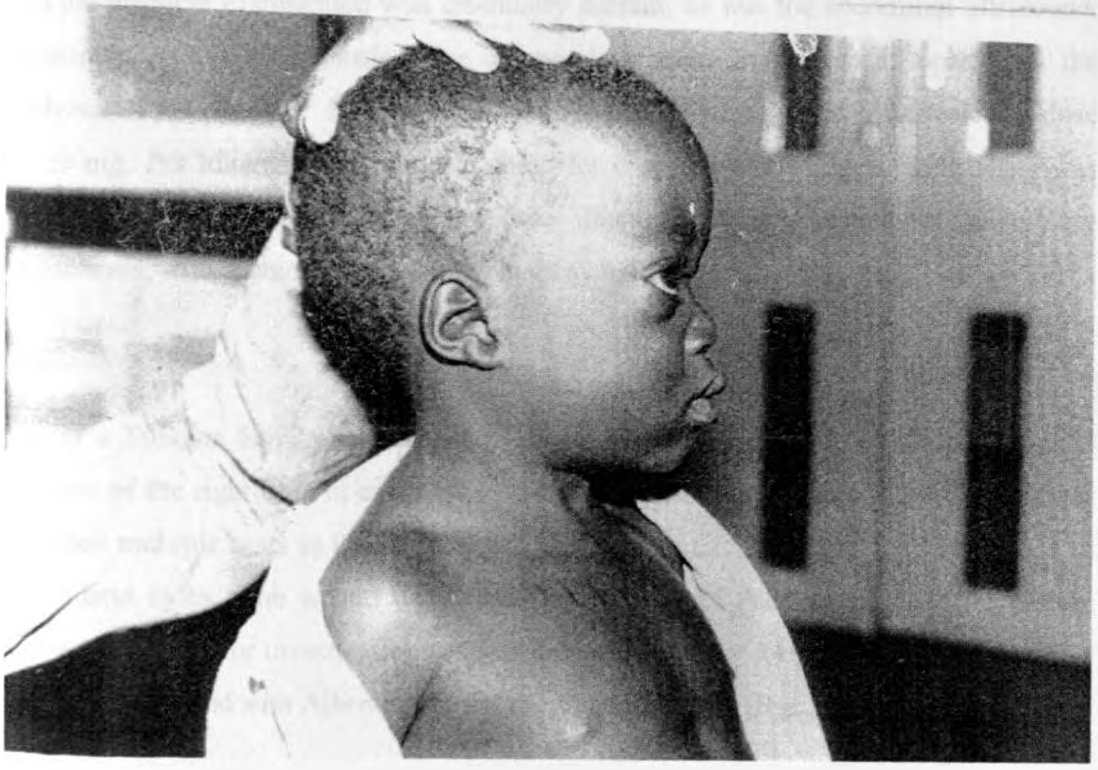


FIG. 19 Case four in profile.

Case Five

M.K. is an adult male Turkana who works as an enrolled nurse in Turkana District. He spoke fluent Turkana language and was often used as an interpreter by non-Turkana speaking doctors. He as referred here in 1983 by the medical officer of health at Lodwar and Dr. French (former head of hydatid unit at Lodwar) because he had coughed up blood stained sputum mixed with some cystic materials which were later found to be hydatid cysts. He was otherwise in excellent health with an unremarkable past medical history and the physical examination was essentially normal, as was the abdominal ultrasound. Investigations for tuberculosis were unrewarding apart from a small opacity in the midzone of the left lung. His arc 5 was positive and he was given Albendazole at a dose of 10 mg. Per kilogram daily in two doses for 8 weeks and a repeat chest x-ray was normal and was discharged. This case illustrates a presentation of pulmonary hydatidosis, with haemoptysis being the main symptom.

Case Six

E.E is a Turkana female aged about 25 years who had presented with a pathological fracture of the right tibia in early 1983. Surgical exploration of the fracture in Lodwar revealed multiple cysts in the bone around the fracture site and these were confirmed to be hydatid cysts. The wound was closed and plaster of Paris applied and the patient flown to Nairobi for investigations and treatment. Serology for arc 5 was positive. The patient was treated with Albendazole and the fracture healed (Fig. 20).

Case Seven

S.W. was an adult Kikuyu female aged about 32 years. She was admitted in 1983 with chronic pain in the right hypochondrium for a period of about 1 year. It was of insidious onset. On the general physical examination she was in good general condition and had a tender large pyriform shaped mass situated in the gall bladder area and moving with respiration. It measured about 3 cm long and about 2 cm across. The patient was no jaundiced and the liver was not palpable. All other systems were normal. A clinical impression of an enlarged gall bladder was made and since cholecystogram could not be

done for technical reasons it was decided to do a laparotomy at which a large hydatid cyst was found partially pressing on, and connected to the gall bladder which itself was normal. Her serology for arc 5 was positive but during her follow up no cysts were noted on either the chest x-ray or ultrasonogram. Gall bladder cysts are very rare and this case was therefore unusual.

N.B: Other cases are described in later sections (16 cases on Page 99, 10 cases on page 109, 10 cases on pate 116 and 12 cases on page 119).

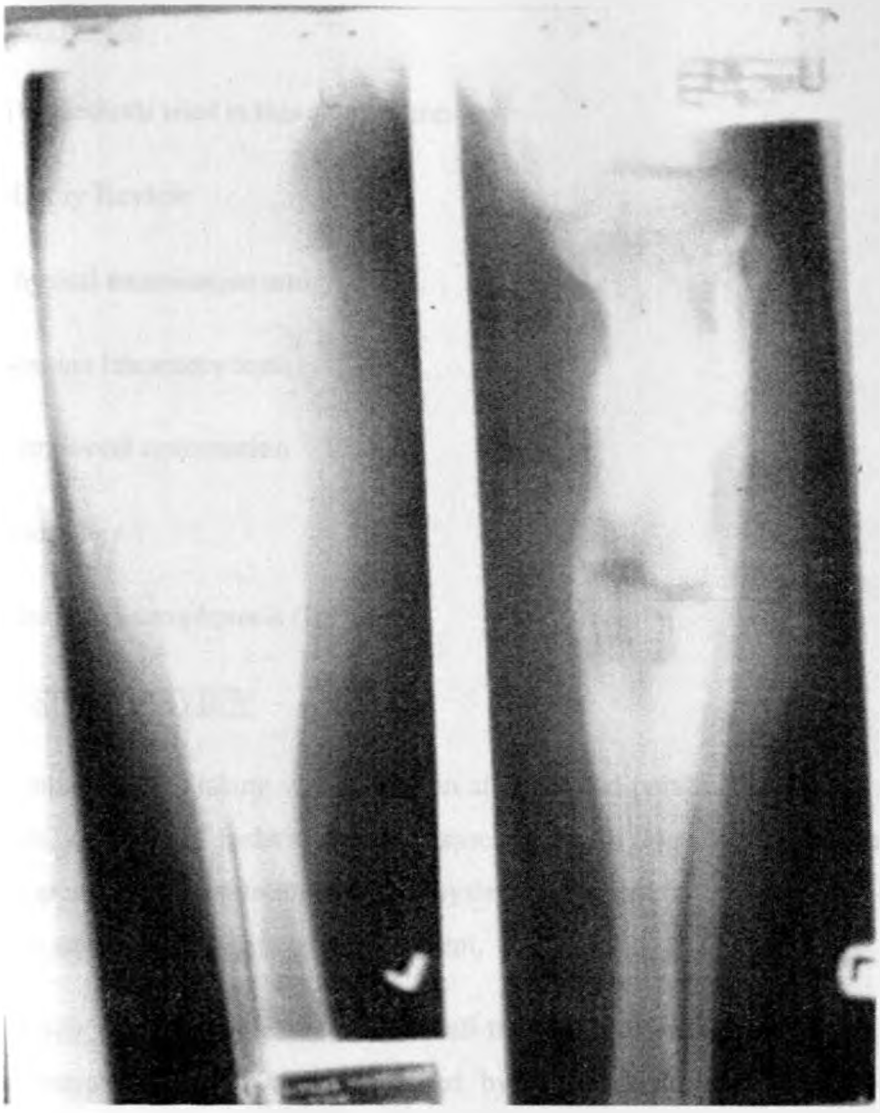


FIG. 20. X-ray of right tibia showing a pathological fracture due to hydatid cysts. The picture on the right shows the fracture before treatment and on the left after treatment, showing union.

4.3 METHODS

The methods used in this study were:

4.3.1 History Review

4.3.1.1 Physical examination and

4.3.1.2 Routine laboratory tests.

4.3.2 Ultrasound examination

4.3.3 Radiology

4.3.4 Immunoelectrophoresis (IEP) test.

4.4 HISTORY REVIEW

Routine history taking was carring in all cases and particular enquiries were made about family history of hydatid disease, association with dogs, area of residence and previous surgical or medical treatment. All systems were carefully reviewed in the history. Age was assessed if not given by the patient.

4.4.1.1 Physical Examination was done in all the cases and abnormal findings recorded. The abdomen and chest were examined by the standard routine methods of palpation, percussion and auscultation.

4.4.1.2 Routine Laboratory tests were carried out in all the cases and these included Urinalysis, Haemogram, stool for ova and cysts, urea, electrolytes and liver function tests.

4.4.2 ULTRASOUND EXAMINATION

All the patients were examined with a Siemens Vidoson Real-time scanner. The transducer, to which jelly had been applied, was situated on the abdomen and all the abdominal viscera were systematically visualized. The numbers, sizes and sites of any cysts in the abdomen were demonstrated and pictures of these recorded (Fig 21).

4.4.3 RADIOLOGY

Routine chest x-ray was done in all the 150 cases.

4.4.4 IMMUNOELECTROPHORESIS (IEP) TEST

This test was carried out in all the 150 cases and the controls. Both the antigen and anitserum were prepared as outlined below and then the IEP test was carried out according to the method of Varella Diaz (14).

4.3.4.1 Antigen Preparation (14) – Hydatid fluid, was aspirated from cysts in human cases, goats and sheep at the Athi River abattoir, by means of a needle and syringe. It was collected in a graduated cylinder. It was left in the cylinder to allow coarse particles such as protoscoleces, brood capsules, daughter cysts and membrane portions to sediment. The fluid was decanted, transferred to centrifuge tubes and was then centrifuged at 1000g. for 30 minutes. The supernatant fluid was then immediately frozen for storage (-20^{o} C).

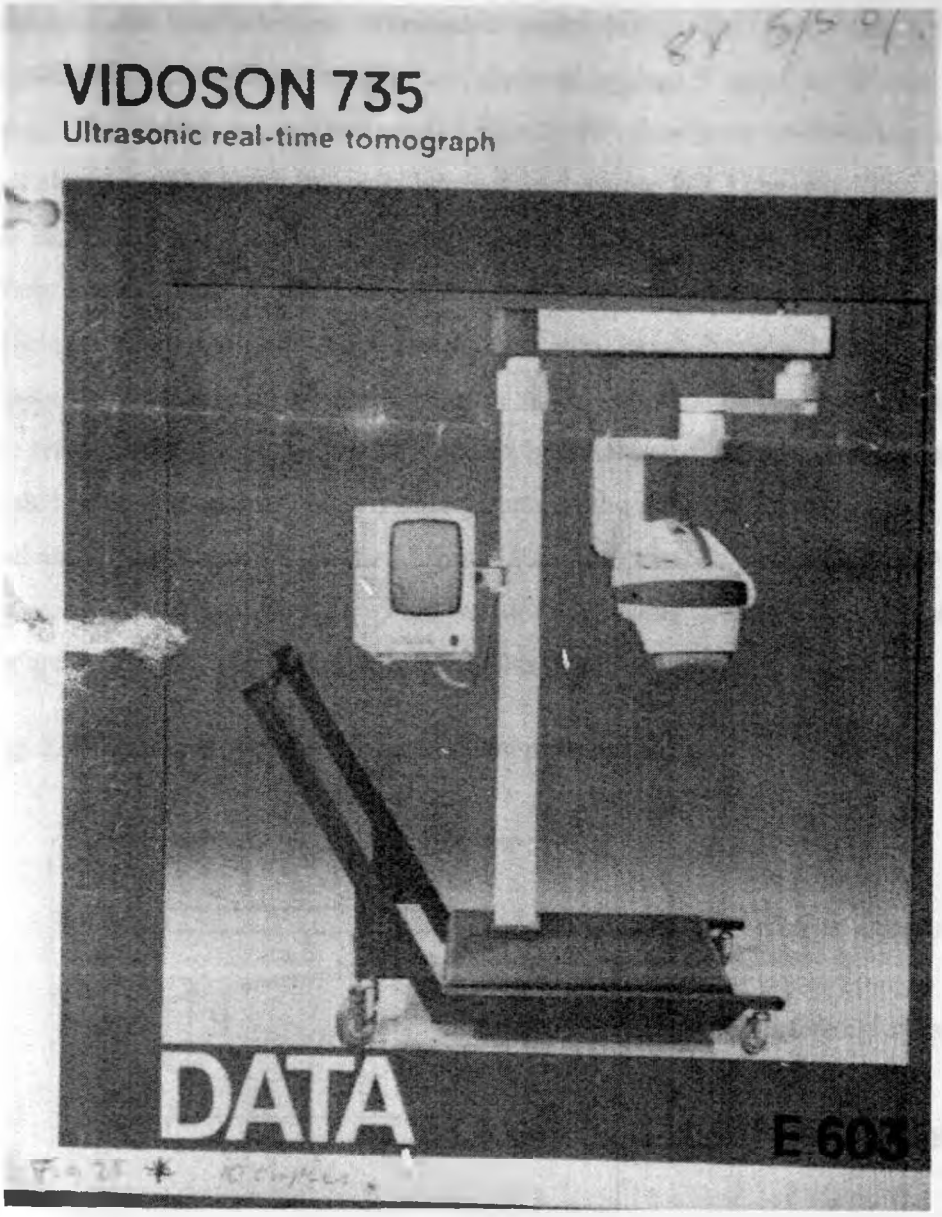
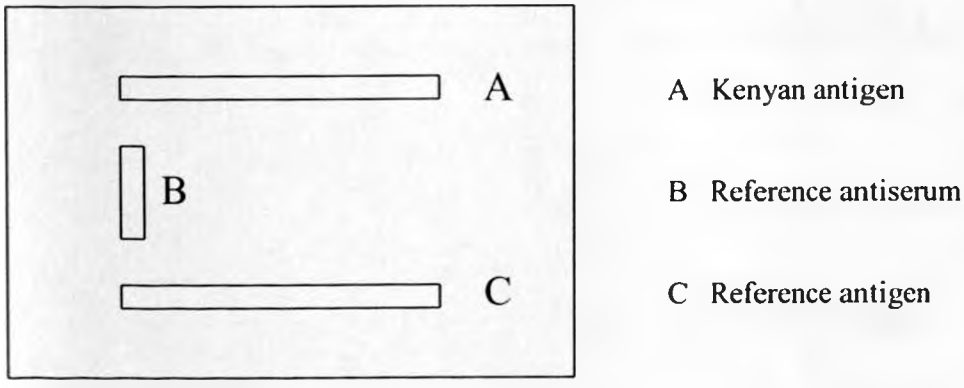


FIG. 21 Photograph of Siemens-Vidoson Real-time scanner used in the study.

Dialysis and lyopholization were next undertaken. The fluid was defrosted and transferred to dialysis tubing and was dialysed against 5 times its volume of distilled water. The dialysis water was changed 5 times with four hours intervals between the first two changes and 8 hours intervals between each of the last 3 changes. The dialysis fluid (or dialysate) was then transferred to bottles of appropriate sizes for Lyopholization. These bottles were ¼ filled to allow for subsequent freezing so as to allow for an efficient lyopholization. After distribution into lyopholization bottles the fluid was frozen by rotation in an alcohol/dry ice bath. Lyopholization was then undertaken with the temperature not exceeding 20°C. The lympholized fluid was then stored in tightly sealed vials in a cool dry place ready for use as the antigen. The quality of the antigen and antiserum obtained from the Director, Pan American Zoonoses Centre PAHO/WHO, Buenos Aires, Argentina (14). This was done by doing the immunoelectrophoresis test for arc 5. The arc 5 formed should be similar in all respects.

Fig. 22 Technique of standardization of the prepared antigen



4.3.4.2 Preparation of standard antiserum

The local antiserum was raised in rabbits and the validity of the results confirmed by comparison with those using material from Centro-Panamericanode zoonoses Buenos Aires (14).

Lyopholized hydatid fluid antigen prepared by the above method was used. Each animal was inoculated intramuscularly at weekly intervals at the hindquarters and shoulders

alternately. 5 mg. dry weight of lyophilized hydatid fluid antigen was used for each of the first two inoculations (14).

Subsequent inoculations were made using 20 mg. of the antigen. Each dose was dissolved in 0.5ml of physiological saline and emulsified in 0.5 ml. of Freund's complete adjuvant (14).

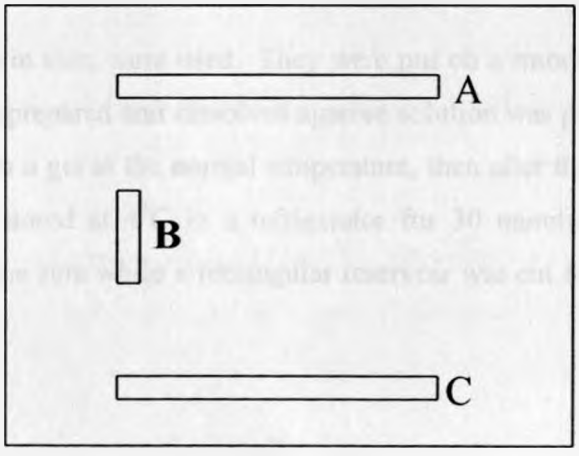
After 8 to 10 inoculations the first bleeding was done and the serum examined in the IEP test using standard antigen to verify the effectiveness of the immunization (14). The sera used were undiluted, as well as sera diluted 1:2, 1:4 and 1:8 together with 200 mg. dry weight of the antigen. This is shown below:-

Fig. 23 Standardisation of antiserum

A Bleeding serum

B Hydatid fluid antigen

C Reference antiserum



An effective immunization schedule is confirmed by the presence of arc 5 in both cases similar in all respects (morphologically), at 1:4 and 1:8 dilutions. The animals were then killed and serum is decanted, centrifuged and examined for arc 5 as above, the if satisfactory it is stored in vials at – 20° C.

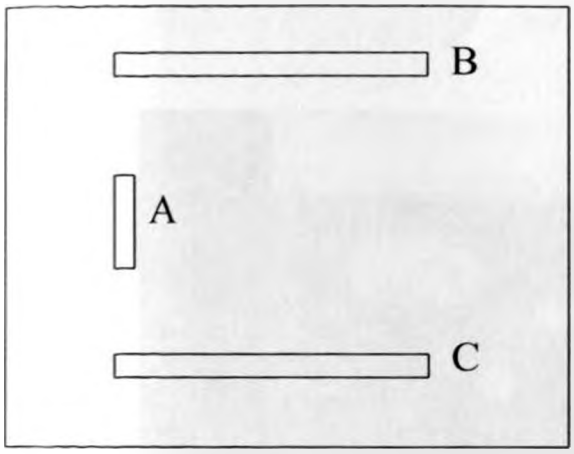
4.3.4.3 The Immunoelectrophoresis (IEP) test (14)

A 0.9% agarose suspension in veronal buffer pH 8.2 (which was made by dissolving 10.309 gm of sodium veronal or 5-5 di-ethyl sodium barbiturate), and 100 mg. of merthiloate powder in 800 ml. of distilled water were used. The pH was adjusted to 8.2 with IN HCI and the volume made to 1 litre and then kept in a refrigerator at 4°C. The hydatid fluid antigen required was weighed out and dissolved in veronal buffer in such a way as to get a concentration of 200 mg. dry weight per ml and this was used within 10 days.

Blood samples from the patients were collected in the morning before breakfast. It was collected using renous puncture and then allowed to stand and coagulate at the normal room temperature after which the clot was removed and the serum was centrifuged at 100g. for 10 minutes. The supernatant part of the serum was then collected and stored, frozen in quantities of 0.3 ml.

Dry and clean glass slides, 12 x 75 mm in size, were used. They were put on a smooth dry clean table surface and 3 ml. of the prepared and dissolved agarose solution was put over each slide and then allowed to form a gel at the normal temperature, then after that the slides covered with agarose were stored at 4°C in a refrigerator for 30 minutes. Lateral troughs were cut in the gel for the sera while a rectangular reservoir was cut for the antigen.

Fig. 24 TECHNIQUE FOR THE IMMUNOELECTROPHORESIS TEST



B - Trough for Patient's serum.

A - Rectangular reservoir for the antigen.

C - Trough for Reference serum.

The hollow rectangular reservoir was then filled with the prepared antigen at concentration of 200 mg. dry weight per ml. A drop of bromphenol blue is placed below the edge of the reservoir using a capillary tube. All the slides containing the antigen were then placed in the electrophoresis tray Figure 25. A filter paper, the same size as the slide is soaked in the veronal buffer and placed at each end of the slide to enable electrical continuity between the buffer and the slides. The marking on the slides is at the anode or positive (+) electrode.

A current was then passed not exceeding 10 milli-Amps per slide at a potential difference of 20V between both ends of the slide during the course of the electro-phoresis, which was done for 90 minutes or until the bromphenol blue dye had migrated at a distance of 35mm. from the antigen reservoir.

The gel in the lateral cuts was now removed and the resulting troughs were then filled with the serum at the normal (neat) concentration in 100 ul, and the slide was placed in the humid chamber. About 15 – 20 minutes later another 100 ul. neat serum was added to each trough, and again in 60 minutes later another 100 ul. neat serum was added to each trough. Thus the total volume of the neat serum was 300 ul. the slides were then incubated in a humid chamber for 40 hours at room temperature.

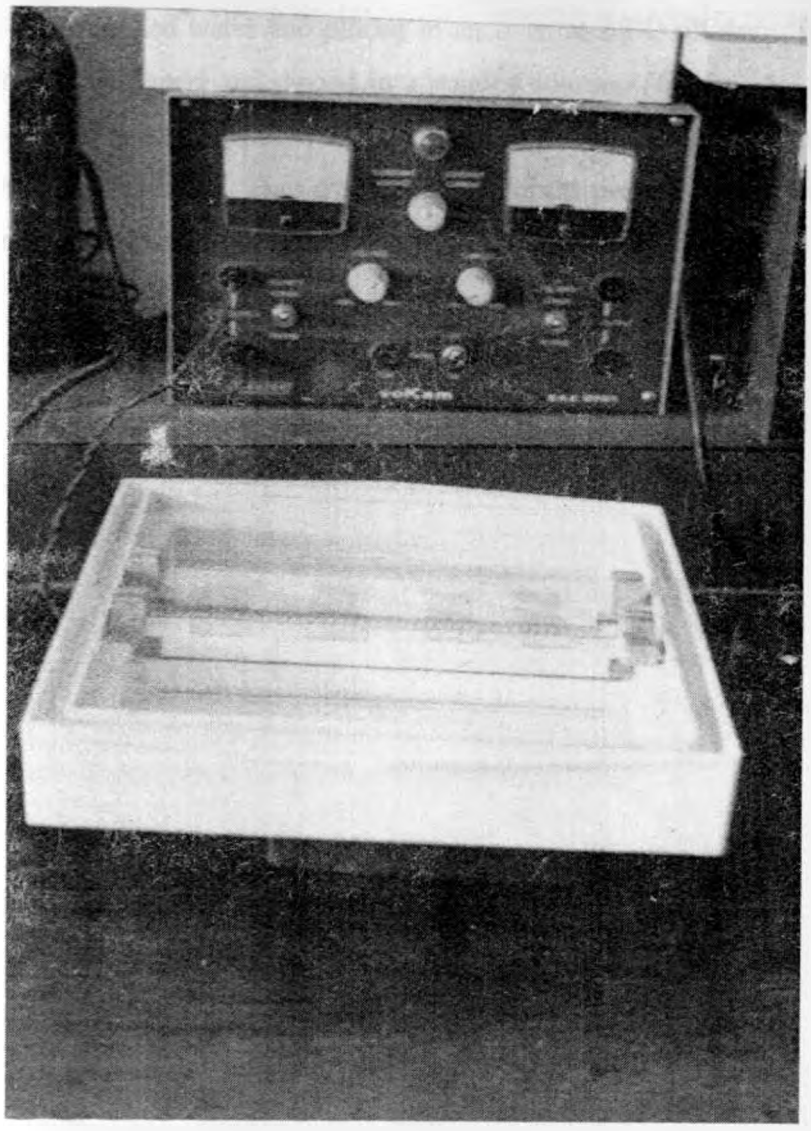


FIG. 25 Photograph of Immunoelectrophoresis tray of the type used in this study.

After the incubation the slides were immersed in a 5% sodium citrate solution for 10 minutes to dissolve the percipitates not resulting from antigen and antibody reaction. The slides were later washed in physiological saline by immersion for 36 hours at room temperature at 7 hourly intervals. After the 36 hours the slides were wrapped inside Whatman No. 1 filter paper moistened with distilled water and placed in an oven at 37°C till dry. The slides were then removed from filter papers and dipped in a staining solution (14) for 15 – 20 minutes at room temperature. They were then rinsed with distilled water, drained and then immersed in a clearing solution for 30 – 40 minutes. They were then read for the presence of arc 5 and compared to the control or reference serum from Buenos Aires (14).

4.4 RESULTS

4.4.1 RESULTS OF THE CLINICAL ASSESMENT

The results of the clinical examination and the total is summarised in the table below (examples of cases 1 to 7 have already been given). Clinical examination was more useful in cases with abdominal disease and pulmonary disease. Retro-orbital hydatid was clinically diagnosed because the boy was a Masai.

Table 3 Results of the clinical, Radiological and ultrasound assessment of the 150 cases.

SITES OF CYSTS	NUMBER OF CASES
Abdominal	117
Pulmonary	22
Others - Mixed (Abdominal & Pulmonary	6
- Ovary	1
- Retro-orbital	1
- Kidney	1
- Spleen	2
TOTAL	150

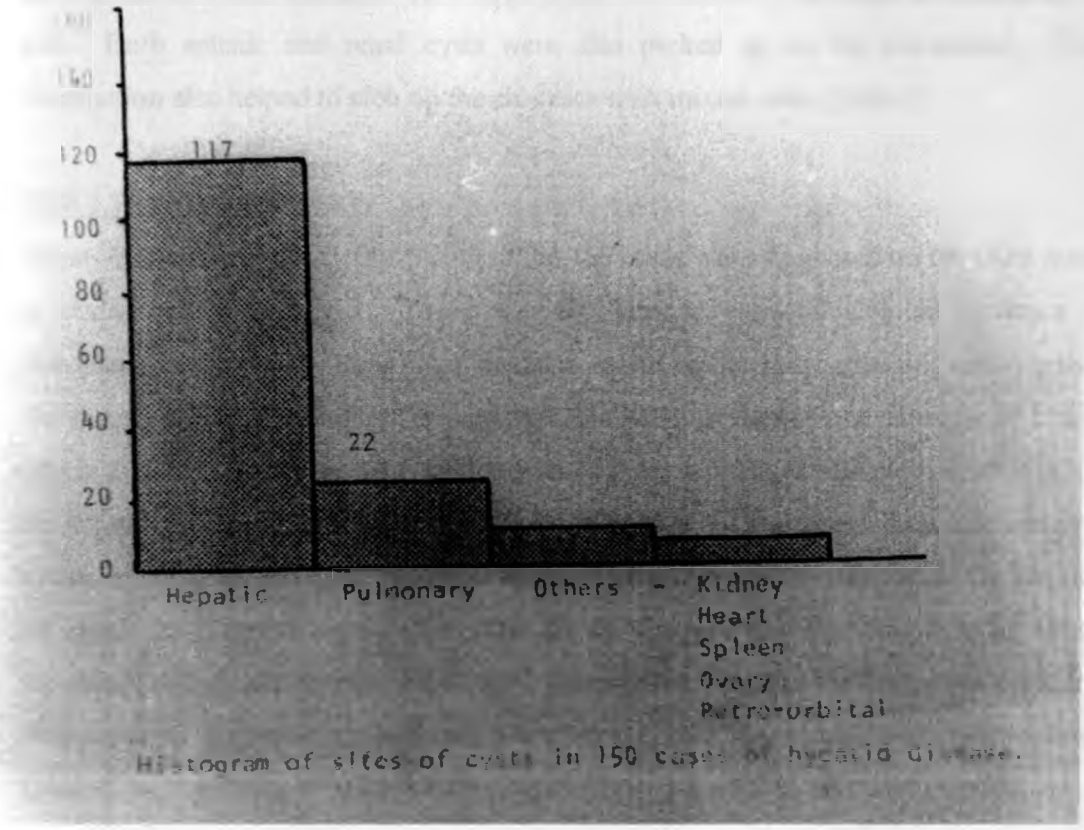


Fig. 26 A histogram showing the distribution of cysts.

4.4.2 RESULTS OF ULTRASOUND EXAMINATION

Of the 150 cases, 117 cases or 74.66% were diagnosed by ultrasound as having abdominal cysts (both hepatic and peritoneal). Ultrasound was able to measure cysts down to about 2 mm and upto very large sizes. Collapsed cysts could be picked up as well. Both splenic and renal cysts were also picked up on the ultrasound. This examination also helped to pick up the six cases with mixed cysts (Table 3).

4.4.3 RESULTS OF RADIOLOGY

Twenty two cases or about 1407% out of the 150 cases were diagnosed on the chest x-ray as having pulmonary cysts. None was noted to haveany raionlogical evidence of pulmonary tuberculosis. Radiology was also useful in diagnosing the six mixed cases. The importance of radiological examination can be illustrated by the example of a case seen in Lodwar. The patient (T.T.D) presented there with signs of a pleural effusion on the left side. The differential diagnoses entertained were the tuberculous effusion or a hydatid cysts in the left lung. As no x-ray facility was available it was decided to aspirate the chest for diagnostic purposes. The patient died of a severe anaphylactic shock following spillage during aspiration with widespread dissemination of daughter cysts and protoscoleces. Had it been possible to x-ray her chest that death could perhaps have been avoided.

(MOH Lodwar, personal communication)

4.4.4 RESULTS OF IEP TEST

Table 4 RESULTS OF THE IEP TEST IN BOTH THE PATIENTS AND CONTROL SUBJECTS.

Total	150 cases
Positive for arc 5	93 cases (62%)
False negatives	57 cases (38%)
Controls in the study	60 cases
These consisted of :-	
Kalazar	30 cases from Machakos Hospital.
Schistosoma Mansoni	10 cases
Normal healthy Medical Students	20 cases

The IEP test was negative in allt he control cases.

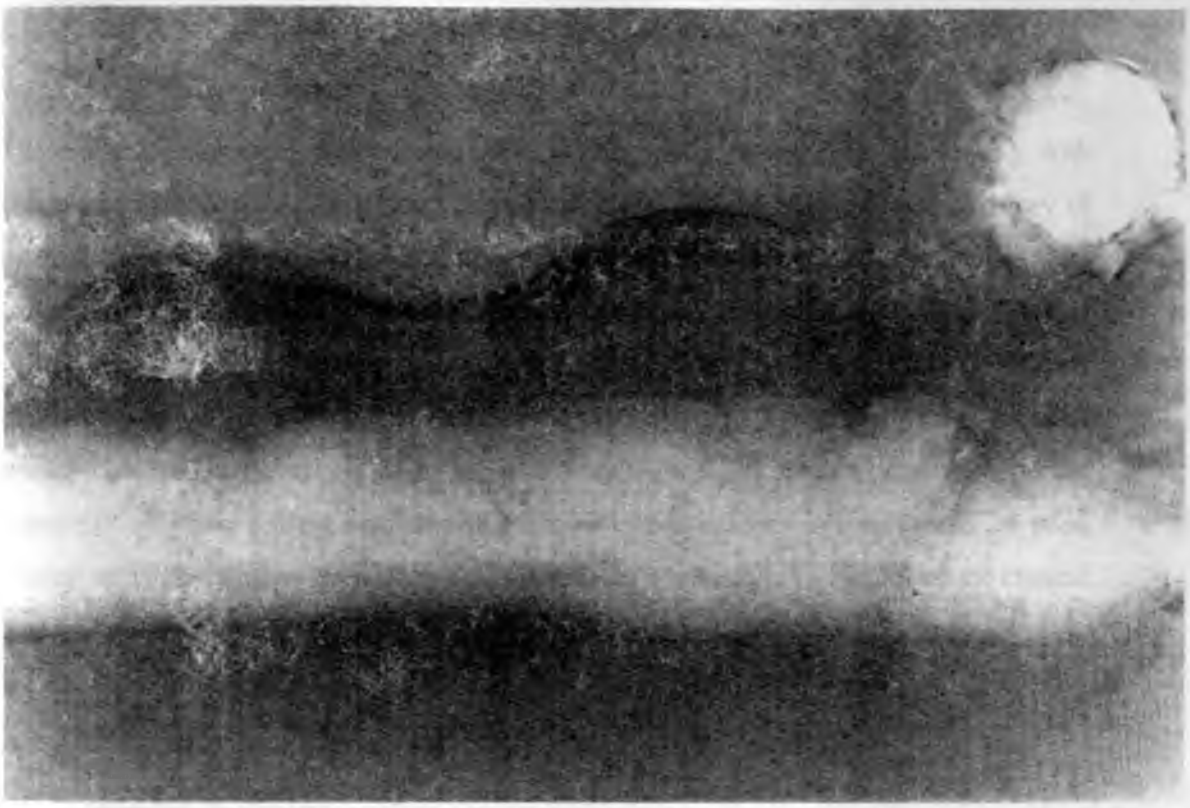


FIG. 27 A typical arc 5 formed in the positive cases.

4.5 DISCUSSION OF THE RESULTS AND CONCLUSIONS.

4.5.1 VALUE OF THE CLINICAL ASSESSMENT

The clinical assessment was of some use in this study in the cases presenting with abdominal hydatidosis. It could not have lead to a definitive diagnosis but a history of gradual onset of painless swellings in the abdomen not usually associated with significant weight loss, in this country should suggest the possibility of hydatidosis. This is particularly true in the Turkana district and Masailand. However, this study has shown that human hydatidosis is also prevalent in the other parts of Kenya (9). In the classical presentation as in case two (Fig 14, M.E.) hydatidosis is usually easily suspected especially when the patient has lived in a known endemic focus of the disease. A good clinical assessment often leads onto a decision to do a laparotomy. However, the clinical assessment of very limited use when the cysts are small and not palpable.

4.5.2 VALUE OF ULTRASOUND EXAMINATION

Ultrasound examination was very useful in this study. The numbers, sizes and location of the cysts were demonstrated with confidence in the 117 cases with abdominal cysts and in the cases with splenic and renal cysts as well as in the 6 cases who had mixed (abdominal and pulmonary) cysts. Ultrasonography of the retina was also useful in diagnosis the retro-orbital cyst. In this study ultrasonography was useful in obviating unwarranted liver biopsies or abdominal aspiration for diagnosis, because these latter procedures would have been of very great danger to the patients, resulting in anaphylaxis and dissemination of the disease from the spillage of daughter cysts.

Ultrasound was also of great value because of its advantages of being non-invasive, lacking any radiation hazard and it is much cheaper than computerized axial Tomography (CAT scan) and it is therefore much more suited to a developing country like Kenya with limited resources. Unfortunately, it cannot be used for thoracic studies because of shelding by ribs and in such cases standard x-rays have to be used.

In conclusion. ultrasonography can therefore be recommended for routine use in Kenya for the diagnosis of abdominal hydatid disease and for epidemiological surveys and for the follow up of cases after treatment to detect recurrent cases.

At the time of this study no compound had been proven as a therapeutic agent against hydatidosis. Ultrasound is the obvious method of assessing the value of any such agent particularly in Kenya where the demand for treatment is so high. In this study some investigations on the value of mebendazole and albendazole are reported and with the advent of ultrasound the value of assessment by a painless and harmless technique such as ultrasound must increase.

4.5.3 A SIMPLE CHEST X-RAY was found to be very useful in this study since all cases with pulmonary hydatid cysts could be detected and pulmonary tuberculosis and other conditions were confidently excluded. During the greater part of this study there were no x-ray facilities in Turkana. The "waterlily" sign which is pathognomonic of pulmonary hydatids may be picked up on the chest x-ray. Although Radiology is potentially more dangerous than ultrasound, the cases mentioned above illustrates that the use of chest x-ray may help avoid the disastrous consequences of an attempted drainage in the mistaken belief that there was pleural effusion (person communication. from Dr. C.M. French of case T.T.D. who died after such an accident).

4.5.4 VALUE OF THE IEP TEST

In this study the IEP test was positive in 93 (62%) of the 150 cases of surgically confirmed hydatidosis. However, there were false negatives in 38% of surgically proven cases of hydatidosis a finding which is in agreement with previous work in Kenya (73, 81). The sensitivity of the test in this study was 62% which is low when compared to the values obtained elsewhere (81). The reasons for this finding are not yet definitely established but a number of explanations are being investigated in an attempt to explain it. Isoenzyme studies and in vitro cultural characteristics of the parasite in Kenya indicate the existence of a different strain of E. granulosus (62).

It has been postulated that there are inhibitors in the serum and these together with immune complexes may be playing an important role (81). High levels of circulatinga immune complexes were found in Turkana patients (81). Turkana patients often have very large cysts (several titres) which may be a source of large quantities of antigens being released into the serum. Those cysts may be so large as to remove all the antibody and their role in immune response on the part of hydatid patients inthis country needs further elucidation. Circulating antigen has recently been detected in more than 80% of patients with hydatidosis, both from U.K. and Kenya (Craig, P.S. & Nelson, G.S., Personal communication). Hence the detection of circulating antigens other than antibodies may be of value in this country for the serological diagnosis of human hydatidosis since the IEP test was of limited value in this study. The 38% false negatives in this study may represent a group of infected people that have little or no detectable antibodies and in them the detection of circulating antigens would perhaps be of much more value in diagnosis and follow up after chemotherapy.

The cost effectiveness of the IEP test which can only detect approximately 62% of positive cases in Kenya is much higher compared to the x-ray or ultrasound. When funds are scarce it is probably not justified to set up this test but it may be of value in following the response to surgical and/or medical treatment, so it would be justified to make it available in a few specialist centers for this purpose and also for research. Serological tests are of even more value in epidemiological surveys and for assessing control measures. They can be used to find and select areas of high prevalence and direct control measures to these high risk areas. It can be used in the follow up of control measures especially in younger age groups to find out if the prevalence is diminishing in that group when the infection rate is reducing. In view of its cost and requirement of special facilities, the IEP test in probably unsuitable for use in large field surveys. A simpler cheaper test such as the I.D.H (Indirect haemaglutination test), although not quite so specific, is equally sensitive and therefore would probably be preferred for such surveys in Kenya (83).

STUDIES ON THE CHEMOTHERAPY OF HUMAN HYDATID DISEASE IN KENYA

INTRODUCTION

Surgery is still the main form of treatment with a high success rate in uncomplicated cases of hydatid disease. These are cases in which the cysts are either accessible by operation and organ and have not caused any other problems due to pressure on vital structures, or are not so numerous as to make total removal impossible. Many different methods of treatment have been tried including resection of liver lobe, injection into the cyst at surgery, of substances believed to devitalize the cyst tissue such as silver nitrate, formalin or hypertonic saline, but systemic complications may occur. Nowadays the relatively less toxic 0.5% cetrimide is used in an attempt to kill cysts and daughter cysts that burst there during surgery. This technique is however in its infancy and not all operators accept its safety (54). Although surgery to prevent spillage, this is often impossible and surgery may be followed by extensive secondary cystic hydatid disease which chemotherapy is needed. Chemotherapy also has the potential of prevention of cyst disease by treating early cases and it may be the only hope in patients with multiple pulmonary cysts where surgery is impossible. At the time of the present study only mebendazole was known to have any therapeutic value in human hydatidosis (11, 12, 13). However, recently Albendazole has become available more recently and has shown promise in hydatid disease (85, 86, 87).

ACTION OF MEBENDAZOLE

The structure of mebendazole is shown on the figure below (Figure 13). Mebendazole has been used for a long time in Kenya in the treatment of intestinal helminthes, such as Ascaris lumbricoides, Ancylostoma and Taenia Saginata (88).

CHAPTER FOUR

5 STUDIES ON THE CHEMOTHERAPY OF HUMAN HYDATID DISEASE IN KENYA

5.1.1 INTRODUCTION

Surgery is still the main form of treatment with a high success rate in uncomplicated cases of hydatid disease. These are cases in which the cysts are either accessible by position and organ and have not caused any other problems due to pressure on vital structures, or are not so numerous as to make total removal impossible. Many different methods of treatment have been tried including resection of liver lobe, injection into the cysts, at surgery, of substances believed to devitalize the cyst tissue such as silver nitrate, formalin or hypertonic saline, but nectrotic complications may occur. Nowadays the much less toxic 0.1% centrimide is used in an attempt to kill cysts and daughter cysts spilled from these during surgery. This technique is however in its infancy and not all authorities accept its safety (84). Although surgery to prevent spillage, this is often impossible and surgery may be followed by extensive secondary cystic hydatid disease for which chemotherapy is needed. Chemotherapy also has the potential of prevention of clinical disease by treating early cases and it may be the only hope in patients with multiple primary cysts where surgery is impossible. At the time of the present study only mebendazole was known to have any therapeutic value in human hydatidosis (11, 12, 13), however, since then Albendazole has become available more recently and has shown promise in hydatid disease (85, 86, 87).

5.1.2 REVIEW OF MEBENDAZOLE

The structure of mebendazole is shown on the figure below (Figure 33). Mebendazole has been used for a long time in Kenya in the treatment of intestinal halminths, such as Anklosomiasis, Ascariasis and Taenia Sarginatta (88).

FIG. 2

The efficacy of this drug against larval form of Echinococcus has be reported from Australia, the Soviet Union and the United States and particularly Alaska for E. multilocularis (89). Initial reports on the efficacy of mebendazole in hydatidosis were very encouraging (11,12,13) but other reports have shown less favourable results (89). There are big variations on the daily dosage and the duration of chemotherapy and this has made it difficult to define failed or successful chemotherapy. The controversy currently related to the treatment of human hydatidosis will not be answered until properly controlled clinical trials and precise pharmacokinetics studies (for individual patients) of the drug have been undertaken. For example the drug is often not absorbed from the gut and blood levels above 100 ng/ml have to be attained for effective therapy (90). In this study it was decided to investigate these factors in the Kenyan hydatidosis patients.

5.1.3 REVIEW OF ALBENDAZOLE IN HYDATIDOSIS

Albendazole has been shown to be very effective in the treatment of nematodes and cestodes in Kenya (91). There is some early evidence of its possible value in human hydatidosis (85,86,87). Since initial reports were encouraging it was decided to investigate its value in human hydatidosis in Kenya. However, the drug only became available towards the end of this study and therefore it has been possible to carry out only the preliminary studies.

Although much has been achieved in the last few years regarding the chemotherapy of human hydatidosis, the situation in Kenya as for the rest of the world, is unsatisfactory because there is still no effective treatement for inoperable or secondary hydatid cysts. The following reports are the result of a study on the chemotherapy of human hydatidosis in Kenya. It was felt justified to dot he study in view of the fact that recurrent and inoperable hydatid disease is a major problem since the recurrence rate in Kenya is estimated at around 30% following surgical treatment (1,10).

5.2 METHODS AND MATERIALS

The study was undertaken in four parts. These are discussed as outlined below:-

16 patients - treated on the original regime of 40 mg/kg/day of mebendazole for a period of 4 weeks.

Introduction.

Mebendazole regime.

16 cases histories.

Pharmacokinetics study of Mebendazole

Introduction.

Principles of R.I.A. test and preservation of sera.

10 brief case histories.

Ten cases - treated with dose controlled by the estimation of serum mebendazole levels.

Introduction.

Mebendazole regime with dates of blood drawing.

10 cases histories.

Albendazole study

Introduction.

Monitoring Response

Twelve case histories.

5.2.1 SIXTEEN PATIENTS

Introduction

Since mebendazole has shown some promise at the time (11,12,13) in hydatid disease, it was decided to treat 16 cases with proven hydatid disease in Kenya to see if they would respond to the drug. The treatment method was based on the original standard regime at that time.

Mebendazole was supplied in 500 mg tablets by Janssen Pharmaceutical. The dosage used was 40 mg. per kilogram of body weight daily in three divided doses for 4 weeks. The cases in this study were all referred to Kenyatta National Hospital. At the time of

this initial study there were no facilities for estimating serum mebendazole levels. Their medical and social histories were reviewed, followed by a complete physical examination of all the systems. Each case had the weight recorded. None of the cases had some other serious medical conditions like tuberculosis, diabetes, asthma etc. Chest x-ray was done as routine in all the cases. Routine tests included harmogram, urinalysis, stool for ova and cysts, liver function tests and urea and electrolytes in all the cases. Pregnancy test was done in all female patients from the age of 12 years onwards and it was negative in all the cases included in the study. All had abdominal ultrasound examination done before and after treatment and in each case a few larger cysts were selected and their measurements taken before and after treatment. All the cases were on the ordinary ward diet at the Kenyatta National Hospital.

Case Summaries

Case No. 1

A 14 year old Turkana female who had presented to out-patient department with non-tender abdominal masses and hepatomegaly. The masses were cystic and fluctuant. She had had surgical treatment for these, 3 years previously in Turkana. Both double diffusion (DD) and the immunoelectrophoresis tests (IEP) were positive and in view of her secondary disease and the fact that ultrasound examination showed very many cysts, she was accepted for the study. Similarly the serological tests were done before and after treatment (Fig. 29,30).

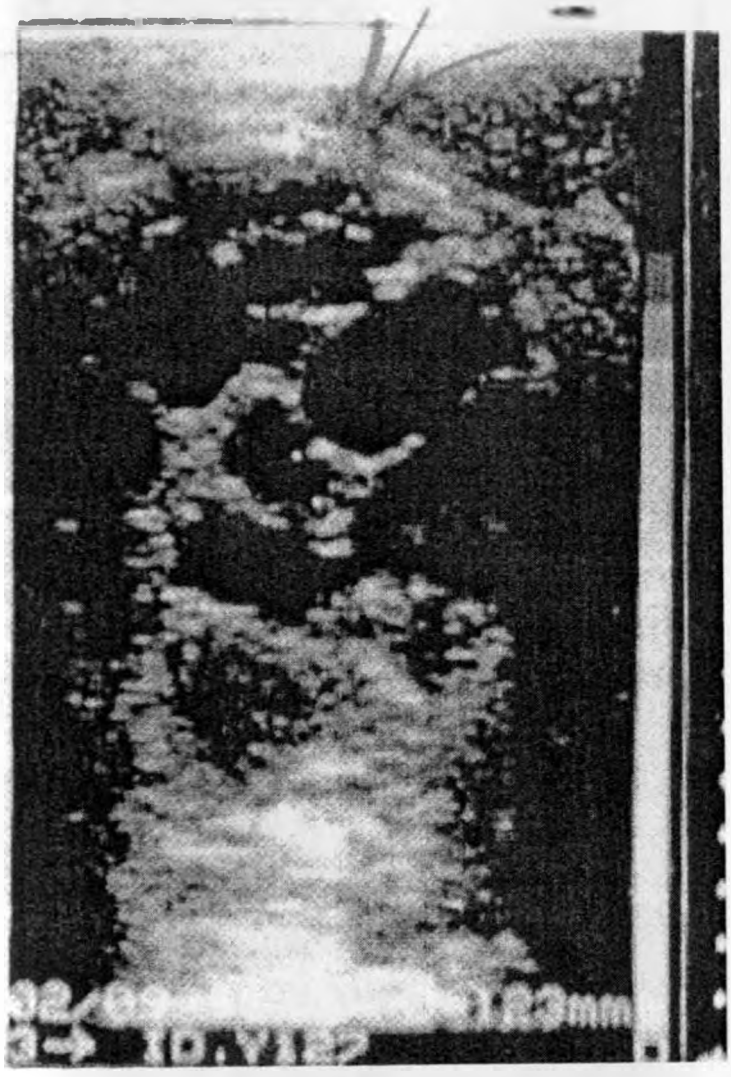


FIG. 29 Ultrasound before treatment of case one showing multiple cysts.

FIG. 30 Ultrasound of case one after treatment showing no change.

Case No. 2

A 60 year old Turkana male who had had previous surgical treatment for abdominal hydatids and now presented at Kenyatta National Hospital with secondary hydatids of the abdomen. Ultrasound showed multiple cysts and both DD and IEP tests were positive.

Case No. 3

A 35 year old Turkana female who had had previous surgery for abdominal hydatid disease and now presented with multiple cysts shown on abdominal ultrasound. Although both DD and IEP tests were negative, she was similarly treated.

Case No. 4

A 20 year old Turkana female who presented with multiple cystic masses in the abdomen and an irregular cystic liver. She had not had any previous surgery. Ultrasound confirmed several small cysts in the liver and peritoneum. Both DD and IEP tests were positive. Surgery was thought unsuitable since the cysts were numerous and not very large.

Case No. 5

A 28 year old Turkana male who presented with hepatomegaly which was non-tender and about 8 cm enlarged. She had had no previous surgery. Ultrasound confirmed multiple intra-hepatic cysts and both DD and IEP tests were positive.

Case No. 6

A 25 year old Turkana male with (surgically) proven abdominal hydatid disease in whom ultrasound showed several small cysts unsuitable for further surgery. Both DD and IEP were negative.

Case No. 7

A 26 year old Turkana male with multiple fluctuant abdominal masses confirmed as multiple cysts by ultrasound and surgeons were unwilling to accept him for surgery. Both DD and IEP tests were positive.

Case No. 8

A 60 year old female with non-tender hepatomegaly and abdominal masses. No previous surgery. Both DD and IEP confirmed hydatid disease. Ultrasound confirmed multiple cysts.

Case No. 9

A 10 year old female who had had previous surgical treatment for abdominal hydatid cysts which now recurred after 3 years. Serological tests were negative but ultrasound confirmed many small cysts in the abdomen.

Case No. 10

A 13 year old female with a history of previous surgery of the abdomen for hydatid disease, now presenting with multiple cystic masses confirmed as cysts by ultrasound. Both DD and IEP were negative.

Case No. 11

An eleven year old female operated previously for abdominal hydatid cysts and now presented with recurrent disease unsuitable for surgery. Ultrasound showed several cysts and both DD and IEP tests were positive.

Case No. 12

A 7 year old female child operated upon at the age of about 5 years for abdominal swellings which were found to be hydatid cysts. Had recurrent cysts confirmed by ultrasound but DD and IEP tests were negative.

Case No. 13

An eleven year old male with recurrent abdominal cysts who had had hydatid cysts removed 3 years previously. Ultrasound showed multiple cysts and both serological tests were positive.

Case No. 14

A 28 year old male with multiple small fluctuant masses in the abdomen with hepatosplenomegaly. No previous surgery had been done. Ultrasound confirmed numerous small cysts and both DD and IEP tests were positive. Because of the size of the cysts surgery was thought unsuitable.

Case No. 15

A 19 year old female with no history of previous surgery and presented with painless abdominal masses confirmed as cysts by ultrasound. Both DD and IEP tests were positive. The patient refused surgery.

Case No. 16

A 35 year old male who presented with hepatosplenomegaly and multiple fluctuant abdominal masses. He had had previous laparotomies in Turkana the last one having been done 3 years prior to his presentation at the Kenyatta National Hospital. Because of the history surgical treatment was precluded. Ultrasound showed a very large number of cysts of all sizes but none very big. Both DD and IEP tests were positive.

5.2.2 PHARMACOKINETICS STUDY

Introduction

After a method, (RIA), for estimating serum mebendazole levels became available in 1982 (92) and since there had been no therapeutic effect of mebendazole in the intial 16 cases studied (93) it was therefore decided that a pharmacokinetics study in Kenya was essential. This was not intended to be a therapeutic study but a preliminary kinetic study to determine a suitable mebendazole regime.

RIA (92) is a method of estimating the serum level of a drug. Its principle is based on the fact that an antibody against the substance, in this case mebendazole, can be raised as a haptene in rabbits. To the sample a known amount of radioactive substance (mebendazole) is added followed by the antibody again in a known amount. The radioactivity bound by this quantity of antibody will depend on the amount of unlabelled substance in the sample. Thus if there is no substance in the sample, almost all the radioactive compound will be extracted and maximal counts will be obtained. As more and more of the compound is in the sample, so dilution will occur and the counts will fall. A graph is prepared empirically from samples of known concentrations and from this the concentration of the unknown samples can be determined (92).

Initial treatment of inoperable hydatid disease using mebendazole in the earlier part of this study was disappointing (93).

Mebendazole absorption in normal persons is known to be enhanced by fat (94). It was felt necessary to confirm if this is true in Kenya hydatidosis patients. In order to do this 12 patients with confirmed hydatid disease were selected and they gave their informed consent.

Materials

Twelve adult Turkana patients were admitted to the study. Three Turkana interpreters had explained to them about the study and as a result the patients had understood it and agreed to give their consent to participate in the study. They were all admitted to the Lodwar Hospital.

Methods

The twelve cases were divided into two groups by the order of selection as "Odds" and "Evens". Two patients (Nos. 3 and 9) were eventually excluded from the study because of their refusal to have repeated venepunctures. Ten continued in the study. After fasting overnight each group was given 2 gram dose of mebendazole. "Odds" were given the drug with water only, while "Evens" with a margarine sandwich. Following this, bloods

were taken at 0,2,4,7 and 10 hours and estimations done for the serum mebendazole levels by the Radioimmuno-assay technique (RIA) (92), supplied by Janssen Pharmaceutical, Belgium. All had stool and urine examined. In addition, in two of these patients operation was required and the opportunity was taken the following day to obtain cysts fluid for estimation of mebendazole fluid levels as this would confirm it the drug enters hydatid cysts in human patients in Kenya. These two cases who were operated had been given 4 gm of mebendazole about three hours before operation, and because of anaesthetic safety no fat could be given. The cyst fluid was collected during operation for estimation of the drug level. The fluid was stored at 20°C until mebendazole concentration was assayed. Both intact daughter cysts and primary cysts material were removed from case sevem and six respectively. Examination of protoscoleces was done immediately after operation. Protoscoleces and brood capsules were allowed to sediment with centrifugation from fluid obtained from cysts. They were examined intact, after rupture of brood capsule by gentle pressure, over a cover slip for:-

i. Motility under the microscope.
ii. Evagination test (at 37°C) of protoscole immediately and after 20 minutes.
iii. Bosin exclusion test to see if they took up eosin stain.
iv. Morphology – by microphotography of the surgically removed protoscoleces.

Brief Case Histories

Two cases (3 and 9) refused venepunctures and were excluded from the study.

Case One

J.L.J. was a 36 year old Turkana male. He was admitted in 1983 and found to have a hydatid cyst of the chest (Pulmonary hydatid disease). He was given mebendazole with water only (no fat). His weight was 57 kg.

Case Two

A.M. was a 17 year old male weighing 30 kg. who presented with hydatid cysts of the liver.

Case Four

A.K. was 36 year old male whose weight was 31.9 kg. and had a pulmonary cyst. His height was 152 cm.

Case Five

A.M. an eight year old male, weighing 22.9 kg. and height 118 cm. He had recurrent multiple hydatids of the abdomen.

Case Six

B.L. a 24 year old female weighing 48.5 kg. and height was 158 cm. Had a retrohepatic cyst. She was operated on after dosing. Cyst ruptured and fluid was collected for estimation of drug level in cyst fluid.

Case Seven

L.E. an 18 year old female whose weight was 56 kg. and height was 174 cm. She had recurrent hydatid. Drug level was estimated in the cysts removed.

Case Eight

A.L. was a female who could not give her age. Her height was 154 cm. and weight 38 kg. She had a liver cysts.

Case Ten

N.A.A. 18 year old female whose weight was 44.5 kg. and height160 cm. had secondary hydatid disease of the abdomen.

Case Eleven

K.L. a 16 year old female with retrohepatic cyst found postoperatively. Her weight was 40 kg. and height 163 cm.

Case Twelve

K.L. a 38 year old female weighing 44 kg. and height 159 cm. who had recurrent hydatid disease of the abdomen.

5.2.3 TREATMENT OF TEN CASES

INTRODUCTION

As a result of the confirmation during the pharmacokinetics study of ten cases that fat enhanced mebendazole absorption in Kenyan hydatidosis patients, it was felt justified to proceed with mebendazole treatment of patients with proven hydatid disease in Kenya provided the drug was given with fat and the serum level monitored to attain the desired serum level of 100 ng/ml. The RIA technique (92) was used for the estimation of serum level of the drug.

Materials and Methods.

A group of 12 well informed (giving their informed consent) Turkana patients were selected for the study. Two were rejected (i.e. case No. 7 and Case No. 12). Case No.7 had a chest neoplasm and was excluded; while case No. 12 turned out to have liver carcinoma. Thus ten patients continued in the study. Their case histories are summarized below. Each case required operation and each was started on 60 mg. per kilogram of body weight daily and this was increased in each case so as to achieve a serum level (of the drug) of about 100 ng/ml. Each case had the drug with a maize oil enriched meal during treatment. After variable lengths of time of treatment (depending on the requirement of the patient in each case), all the cases were operated upon. Table 5 shows mebendazole regime dates and also it summarizes the dose in tablets, dates of operation and the operative findings in each of the cases. Treatment with mebendazole for all cases was started on 14th April 1983 and continued to 5th July 1983 during which time surgery was performed as indicated by the patient's general condition.

Blood samples were taken for estimation of serum mebendazole levels on 16.4.83, 22.4.83, 28.4.83, 20.5.83, 3.6.83, 22.6.83, and 2.7.83 in all the cases and table 6 shows the serum level of the drug in each case. In each case creatinine clearance, liver and renal function tests were done.

TABLE 5 MEBENDAZOLE REGIME (DOSES AND DATES OF ADJUSTMENT OF DOSES) AND DATES OF OPERATION WITH OPERATIVE FINDINGS IN EACH OF THE TEN CASES

Patient	No. of Tablets and dates			Date of Operation	Operative findings
		1st Series	2nd Series		
1	5 tablets	14.4.83	23.4.83	25.5.83	Abdominal cyst full of pus
2	4 tablets	"	"	23.2.83	Right liver cyst. 2 separate simple cysts, one with daughter cyst.
3	8 tablets	"	12 tablets	17.6.83	Previous surgery on 4.2.83 Liver cavity found
4	8 tablets	"	"	30.5.83	Right liver cyst. No daughter cyst.
5	8 tablets	"	"	25.5.83	Very large liver abscess infected cyst. More than 5 litres of pus.
6	7 tablets	"	"	23.5.83	Left liver lobe single cyst. No daughter cysts.
8	8 tablets	"	"	27.5.83	Left liver lobe cyst with a daughter cysts. No viable protoscoleces
9	8 tablets	"	"	7.6.83	Three mesenteric cysts. All over 1 litre with daughter cysts.
10	8 tablets	"	"	23.5.83	Recurrent case. 1st operation in 1970. 100-1000 cysts in the omentum
11	5 tablets	"	"	27.5.83	Posterior hepaticcyst. Large and ruptured

SERUM LEVELS OF MEBENDAZOLE IN THE TEN CASES TREATED

Patient's No.	Serum level on 16.4.83	Serum level on 22.4.83	Serum level on 28.4.83	Serum level on 7.5.83	Serum level on 20.5.83	Total No. of days of treatment before operation	Serum level on 3.5.83	Serum level on 22.6.83	Serum level on 2.7.83
1	22	56	97	Not done	125	40 Φ	35	110	103
2	58	64	108	Not done	Not done	38 Φ	83	155	77
3	23	12	62	Not done	94	Not done	Not done	84 Φ	124
4	20	Not done	Not done	100	72	45 Φ	Not done	74	Not done
5	21	58	Not done	71	Not done	40 Φ	Not done	Not done	150
6	52	93	Not done	135	102	38 Φ	70	94	Not done
7	32	101	Not done	71	+	42 Φ	68	70	105
8	28	Not done	Not done	Not done	70		131	55 Φ 83	152
9	62	75	Not done	81	81	38 Φ	Not done	80	142
10	21	84	Not done	Not done	Not done	42 Φ	109	Not done	69

Φ = Operated on between tests

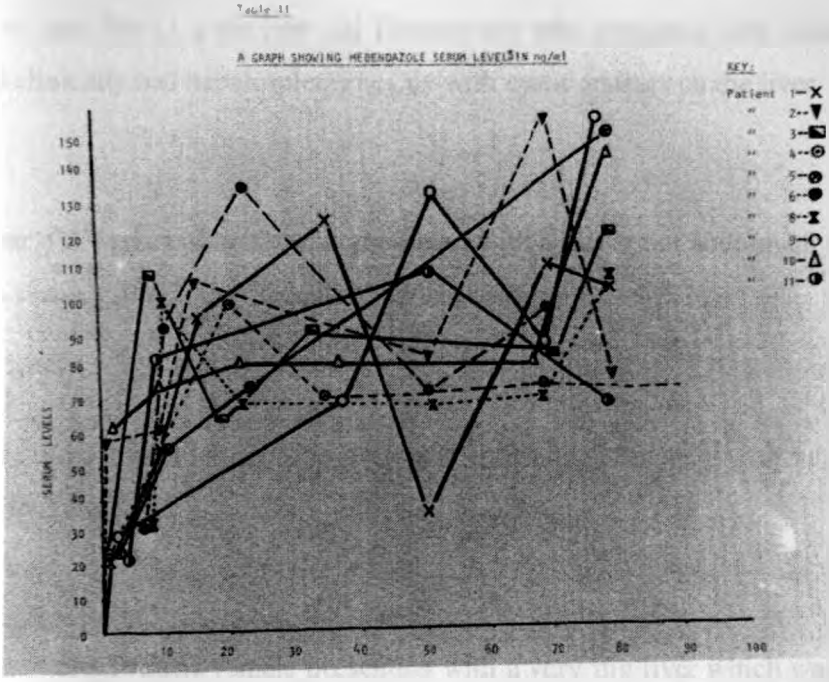


FIG. 31 A graph showing the serum levels of mebendazole.

Case No. 1

L.I. (sister of case No. 2, I.I.), a nine year old Turkana female presented with one large Abdominal hydatid cyst. She had had no previous surgery.

Case No. 2

I.I. (brother of case No. 1), a six year old Turkana boy who presented with history of abdominal swelling and clinically had hepatosplenomegaly with cystic masses on the liver.

Case No. 3

O.L. a 28 year old Turkana female who presented with a history of abdominal swelling and had had previous surgery of 4.2.83. Clinically had hepatomegaly.

Case No. 4

A.L., 35 years old Turkana female who presented with a hepatomegaly with a cystic mass on the right lobe of the liver.

Case No. 5

M.M. a 29 year old Turkana female presenting with a very big liver which was non-tender and cystic in consistency.

Case No. 6

I.T. 36 year old Turkana female presenting with hepatomegaly and a cystic feel of left lobe of the liver.

Case No. 8

L.L., a 33 year old Turkana female who presentd with a large non-tender liver with a cystic mass over the right lobe.

Case No.9

A.E. 4 year old Turkana female presenting with abdominal swellings and clinically had three non-tender cystic masses in the abdomen.

Case No. 10

L.L., a 32 year old Turkana female who had her first operation in 1970 and presented with recurrent abdominal swelling and cystic masses palpable. She had 100 to 1000 cysts in the omentum found at operation.

Case No. 11

E.L., a 10 year old Turkana male presenting with hepatomegaly.

2.4 ALBENDAZOLE

INTRODUCTION

Albendazole became available towards the end of this study. It was decided to change to it because it is much easier than mebendazole to administer to patients and initial reports had shown very encouraging results in human hydatidosis (85,86,87). It was therefore felt justified to try it in Kenya in patients with inoperable hydatid disease.

Albendazole is a newly released benzimidazole derivative which belongs to a class of substances with potent anthelmintic activity. It is Methyl – (5-propylthiol-H-benzimidazol-2-y^{l}) carbomate (see Fig. 32).

FIG. 32 The structure of Albendazole

The study on Albendazole was done in late 1983 and early 1984.

Materials and Methods

Twelve Turkana cases with surgically proven hydatid disease were admitted to the study. Arrangements were made with AMREF to fly them to Nairobi for admission to the Kenyatta National Hospital. Albendazole was supplied by Smith Kline and French in a strength of 100 mg. tablets. Each patient was given 10 mg per kilogram of body weight daily in two doses for 8 weeks (85,86,87). Each case had ultrasonography done before treatment and after 8 weeks. Chest x-ray was done in all cases. Drug toxicity was monitored by doing weekly haemograms, Urea. Electrolytes, liver function tests, and urinalysis and stool was checked for ova and cysts as routine. Pregnant women were excluded after a pregnancy test. The other cases excluded were those with epilepsy and any other serious illness e.g. tuberculosis or anybody on a regular medication.

Case Summaries

Case One

E.E. an 18 year old Turkana lady who had presented with pain in left leg and inability to walk, in Lodwar. There was no history of trauma. A fracture was suspected and she was taken to theatre and a pathological fracture of the right tibia with multiple cysts was noted. The cysts were confirmed as hydatid cysts and she was referred here for medical treatment. She was treated with Albendazole and all her cysts disappeared and the fracture healed and she was discharged home. Her chest x-ray and ultrasound were normal (Figure 20).

Case Two

J.M.K., a 15 year old Kikuyu male from Kiambu who was referred from Nakuru Provincial Hospital where he had undergone a laparotomy for abdominal masses at which he was found to have pulmonary and abdominal hydatid cysts. He was now presenting with recurrent disease. He had an old abdominal scar and hepatomegaly and ultrasound showed two large hepatic cysts. The chest x-ray was normal. He was treated and the cysts all cleared on the ultrasound. He is still being followed up.

Case Three

J.W., a 24 year old Kikuyu female from Dagoretti, Nairobi who presented with a slightly painful swelling below the liver. Ultrasonography confirmed two cysts below the liver and two other large cysts removed surgically, and had Albendazole for the smaller ones which all cleared on the ultrasound.

Case Four

This 6 year old boy with retro-orbital cyst was already discussed on pate 67.

Case Five

L.A., 50 year old Turkana herdsman admitted on 5.3.1984 as a referral from Lodwar District Hosptial with a three month history of pain on left side of the chest and haemoptysis. Pulmonary tuberculosis had been excluded. Physical examination revealed rhonchi in the left chest anteriorly and the chest x-ray (Fig. 34) showed a left pulmonary hydatid cyst. The patient was started on Abendazole 10 mg per kilogram of body weight daily in two doses for 38 days. A repeat chest x-ray done on 184.1984 (Fig. 34) showed that the cyst was very much smaller and collapsing and had almost completely disappeared as a result of the chemotherapy.

Case Six

N.M. is a 6 year old Masai boy who was referred on 5.4.1983 from Ward 13 at the Kenyatta National Hospital where he had had a right pneumonectomy for a hydatid cyst. On this occasion he presented with hepatomegaly and ultrasonography showed multiple liver cysts (8 in number). The immuno-electrophresis test for arc 5 was positive. However put on Albendazole 10 mg per kilogram in two doses daily for 8 weeks. Repeat ultrasonography showed shrinkage and collapse of all the cysts in the liver. He was discharged home and follow up by ultrasonography six months later showed that they arc hardly discernible and they remain collapsed and very shrunken.

Case Seven

N.K., a 30 year old Turkana housewife para 3+0 referred from Lodwar District Hospital on 5.3.1984 with a 1 year history of gradual abdominal swelling. Had had laparotomy in 1979 for hydatid disease. On examination the abdomen was grossly distended with an old surgical scar. The liver was large and there were also several masses palpable. Ultrasound scan done on 13.3.1984 showed large hydatid cyst on the right side with multiple daughter cysts extending below the liver margin.

Investigations: Liver Function, Renal Function test and stool for ova and cysts and urinalysis were all normal. She was started on Albendazole 400 gm bd on 5.3.1984. Repeat ultrasound scan on 8.5.1984 showed much smaller and collapsing cysts. Clinically she improved and there were no adverse effects noticed during the course of therapy.

Case Eight

S.O.D., a 7 year old Masai gal admitted to ward 28 on 22.2.1984 with a one year history of progressive swelling of the abdomen accompanied with slight pain especially when coughing. At examination the abdomen was distended with a hepatomegaly of 6 cm.

Investigations done: Haemogram, Urea and Electrolytes Urinalysis, Stool for Ova and Cyst were all normal. Ultrasound scan done on 28.2.1984 showed 2 hydatid cysts in the right liver lobe. She was started on Albendazol 200 mg bd on 22.2.1984. She has tolerated treatment well and the liver is much smaller clinically. Ultrasound scan done on 8.5.1984 showed that the smaller cyst has disappeared and the bigger cyst is much smaller.

Case Nine

A.L., a 28 year old Turkana female admitted to Ward 28 on 5.3.1984 as a referral from Lodwar District Hospital. She had presented at Lodwar with a 3 month history of right sided chst pain and productive cough of yellowish sputum. Chest x-ray done at Lodwar showed a cyst in the right lung. An intercostals drainage tube was inserted. The fluid obtained suggested a hydatid cyst. At examination expansion was found to be decreased on right chest with decreased air entry and bronchial breathing posteriorly. The liver was 4 cm below subcostal margin at mid clavicular line. He was started on Albendazole 400 mg twice daily. Ultrasound scan done on

15.3.1984 showed a single cyst in the right chest. She was already put on penicillin and metronidazole tablets. Urea and electrolytes, urinalysis, sputum microscopy and haemogram were all normal. The cough decreased and chest pain disappeared. Repeat ultrasound scan has showed regression of the cyst.

Case Ten

M.M. an 18 year old Turkana girl admitted as a referral from Lodwar District Hospital on 1.2.1984 with history of a laparotomy during early childhood for removal of intra abdominal hydatid cysts.

During the last few years she had gradually developed swelling of the abdomen accompanied with pain and vomiting at times. At examination she was found to have a grossly distended abdomen with an old laparotomy scar and very many nodular masses. Tab. Albendazole 400mg twice daily was started on 2.3.1984 and the Ultrasound scan done on 9.2.84 showed multiple (about 23) hydatid cysts spread all over the peritoneum and involving nearly the whole liver. Repeat Ultrasound scan on 5.4.84 showed tremendous improvement with collapsing cysts.

Investigations: Liver function tests, Urea and Electrolytes, Stool for ova and cysts, Urinalysis did not show a significant abnormality. She was discharged on 28.4.1984 for follow up at Lodwar District Hospital.

Case Eleven

E.E., a 16 year old Turkana boy from Lokogollio admitted to Ward 28 from Nakuru Provincial Hospital as a case of recurrent abdominal hydatitd disease. He had had laparotomy for abdominal hydatidosis when he was a small child and was well until a few years ago when he noticed a gradual swelling of the abdomen.

On examination the abdomen was grossly distended with an old laparotomy scar, a large firm liver was palpable and small cystic masses were also present.

Investigations: Stool and Urine examination were both normal. Alkaline phosphatase was 49.6 K.A. Units (normal 2-12)

Albumin SGOT and SGPT were normal.

Haemogram was 9.9 gm % with peripheral film suggestive of iron deficiency.

Ultrasound scan done on 19.1.84 showed one large cyst in the liver and many small cysts in the abdomen. He was started on Albendazole 400mg bd on 16.1.84 and repeat Ultrasound scan done on 3.4.84 showed only a large cyst below posterior aspect of the liver. Clinically the abdomen is much smaller and the masses are greatly reduced in size.

Case Twelve

L.J., a 27 year old Turkana herdsman admitted to Ward 28 from Lodwar District Hospital with a history of gradual swelling of the abdomen and cough productive of yellowish sputum sometimes stained with blood.

He had been operated three times for recurrent intra-abdominal hydatidosis.

On examination he had 3 laparotomy scars, splenomegaly with a mobile mass above it and the chest was dull on the right side with reduced air entry. Clinical impression was recurrent abdominal hydatid disease and chest infection.

Ultrasound scan on 28.10.83 showed a large cyst in the left lobe of the liver and 4 cysts in the peritoneal space.

Investigations: Liver and Renal Function tests were normal.

Hb 8 gm/dl – peripheral film showed hypochromia.

Urinalysis was normal.

Sputum for AFB and Stools for ova and cysts were negative.

Albendazole 400 mg twice daily was started on 26.10.84 and antibiotics and physiotherapy for chest infection. Repeat Ultrasound on 18.12.84 did not show much improvement and Albendazole was increased to 800 mg bd on 16.1.84. Repeat Ultrasound scan on 28.2.84 showed that all cysts were collapsing.

3 RESULTS

3.1 SIXTEEN PATIENTS

None of the 16 cases treated with 40 mg of mebendazole per kilogram of body weight daily for 4 weeks responded to the drug (93). There was no change on the ultrasound before and after treatment and the cyst sizes remained the same despite treatment. The serological tests remained positive even after treatement as shown on the table below (Table 7). Liver function, urea, electrolytes, urinalysis and haemogram remained normal throughout the study.

TABLE 7 SIXTEEN CASES TREATED WITH MEBENDAZOLE 40MG. PER KG. OF BODY WEIGHT DAILY FOR 4 WEEKS

Case No.	Sex	Age	Previous Treatment	Pre-Treatment		Post Treatment	
				IEP	DD	IEP	DD
1	F	14	Surgical	+	+	+	+
2	F	60	Surgical	+	+	+	+
3	M	35	Surgical	-	-	-	-
4	F	20	Primary disease	+	+	+	+
5	M	28	Primary disease	+	+	+	+
6	M	25	Surgical	-	-	-	-
7	M	26	Primary	+	+	+	+
8	F	60	Primary	+	+	+	+
9	F	10	Surgical	-	-	-	-
10	F	13	Surgical	-	-	-	-
11	F	11	Surgical	+	+	+	+
12	F	7	Surgical	-	-	-	-
13	M	11	Surgical	+	+	+	+
14	M	28	Primary	+	+	+	+
15	F	19	Primary	+	+	+	+
16	M	35	Surgical	+	+	+	+

3.2 RESULTS OF THE MEBENDAZOLE PHARMACOKINETICS STUDY IN KENYA

(a) The group that received the fat as margarine sandwich ("Evens") achieved significantly higher serum mebendazole levels than the group ("odds") that did not receive fat and also the time to reach peak values was longer. The results are shown below. Peak serum mebendazole levels and time to peak in the two groups of patients is shown below:-

TABLE 8 RESULTS OF MEBENDAZOLE PHARMACOKINETICS STUDY IN KENYA SHOWING PEAK SERUM LEVELS AND TIME TO PEAK IN TWO GROUPS OF PATIENTS

	Peak hour	Time to peak ng/ml
Without fat 4 patients	2.76±0.78	27.3±11.5 Range 17.4 to 43
With fat 6 patients	3.15±0.48	43.1±25.0 Range 25.1 to 125.9

(b) TABLE 9 LEVELS OF MEBENDAZOLE IN THE SERUM AND CYST FLUIDS

Patient	Serum level at operation	Cyst fluid level of Mebendazole	Daughter cyst fluid level of the drug
A Fat given	41.5 ng/ml	6.0 ng/ml	No daughter cyst obtained
B No fat	24.1 ng/ml	2.0 ng/ml	3.07 ng/ml

(c) This confirms that mebendazole enters hydatid cysts in patients in Kenya and this finding is in agreement with experience elsewhere (95).

3.3 RESULTS OF THE 10 CASES TREATED WITH MEBENDAZOLE:

(a) In all of the 10 cases treated the recommended optimal therapeutic level of mebendazole of 100ng/ml (90) was achieved, but not on all occasions as shown on the table below (Table 10).

(b) No serious toxic effects (in particular renal and hepatic of the drug were noted in the present series although particular attention was paid to the former since 5 cases of suspected glomerulonephritis have been previously reported (96). Particular attention was paid to liver functions and renal functions.

(c) The use of RIA (98) to monitor the blood levels enabled the use of large oral doses of the drug in order to achieve more effective therapeutic levels without danger of toxic levels occurring.

(d) Increase in the number of abnormal protoscoleces varying from 50% - 80%, was noted after treatment. Also some of these abnormarlities have not been seen previously in Turkana (Okelo, unpublished data). Hence it is reasonable to conclude that these abnormal protoscoleces were due to damage by the drug. Fig. 33 shows damage to protoscoleces which was noted in all the 10 cases. No motility was noted on any of the protoscoleces examined microscopically from the 10 cases. Hence they were probably dead.

Evagination test at 37°C showed that no protoscoleces evaginated after 20 minutes as compared to 0 minutes when they were initially examined for evagination. This negative evagination test shows that the protoscoleces were probably dead.

The Eosin exclusion test showed that the eosin stain was taken up by the protoscoleces thereby indicating that they were dead.

Morphological changes shown in Figure 33 above confirms damage to the protoscoleces probably by the drug. Fig. 35 shows complete damage to the cell wall.

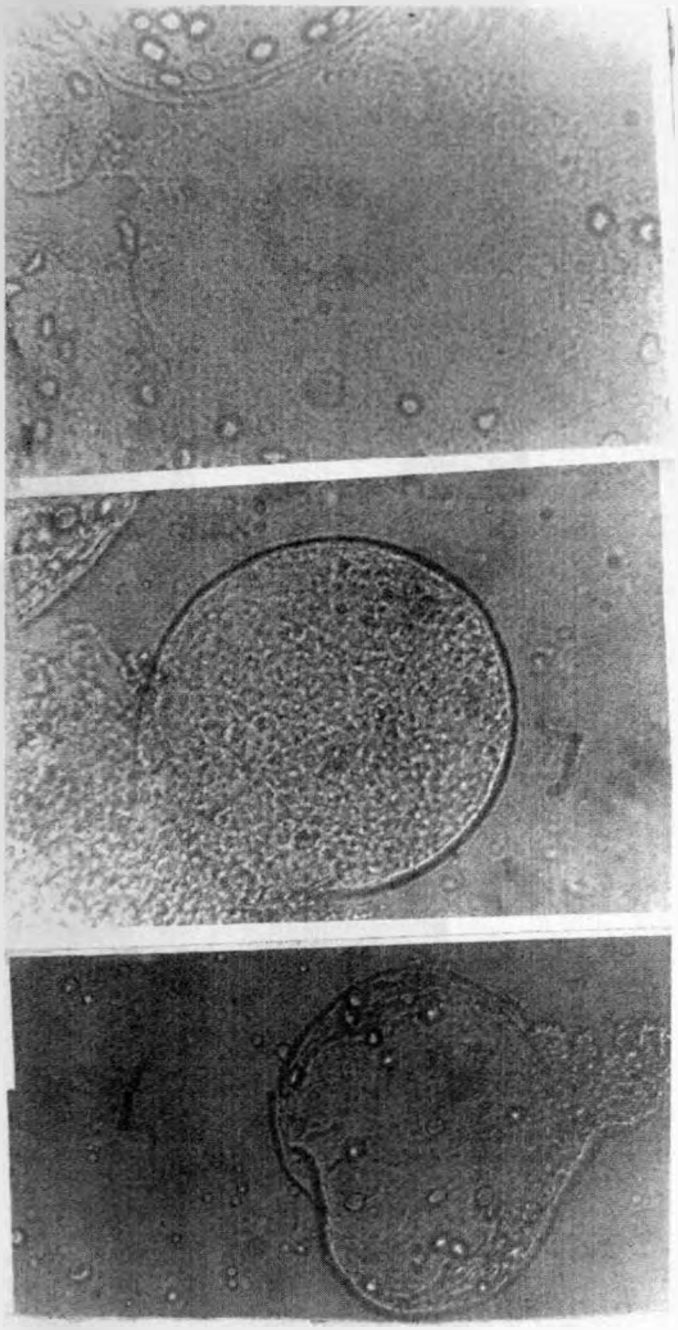


FIG. 33 Photograph showing damage protoscoleces in the ten cases treated. Damage was shown in all of the ten cases.

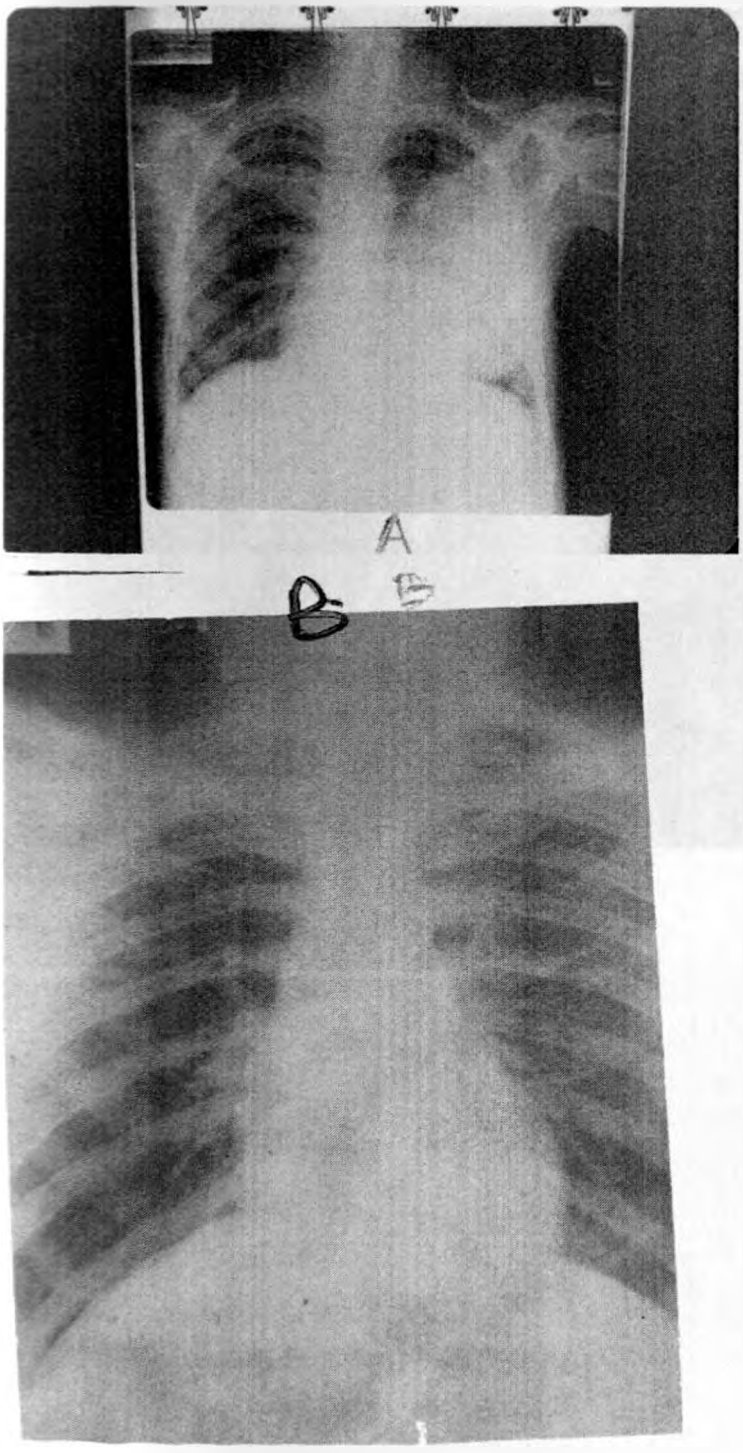


FIG. 34 Photograph of chest x-ray of case five before treatment (A) and after treatment (B) showing dramatic reduction in size of the cysts.

FIG. 35 The protoscolex was completely destroyed in this case and only loose hooklets were noted without any cellular structure around them.

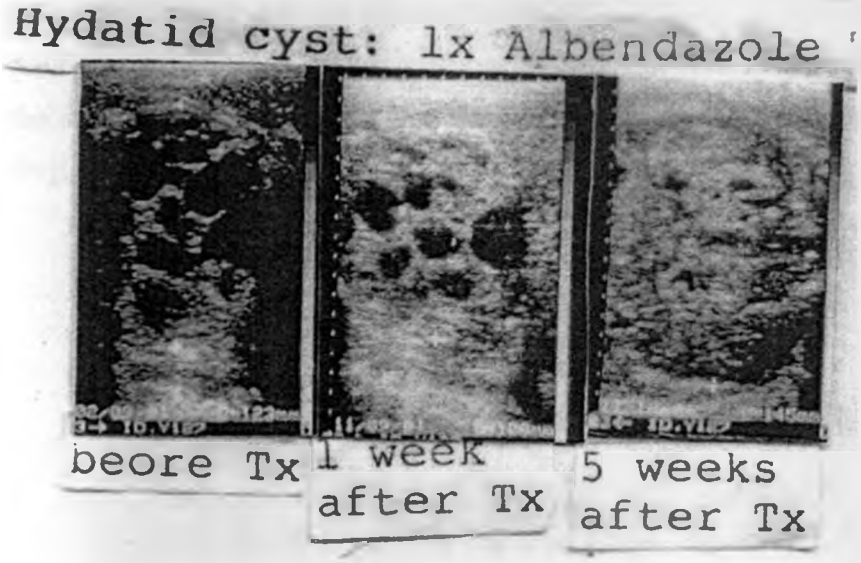


FIG. 36 Ultrasonography before treatment (A) and after treatment showing response to Albendazole therapy (B).

Albendazole Results

(a) No serious toxicity was noted during the study.

(b) All the cases treated showed regression, collapse and even disappearance of the cysts on the ultrasound thus indicating that the drug is effective in human hydatidosis in Kenya (Fig. 36 A & B).

5.4 DISCUSSION OF RESULTS AND CONCLUSIONS

In the initial study involving 16 patients treated with mebendazole no special diet was given and the dose of 40 mg/kg/day used can now be considered as on the lower side. It was impossible at the time to estimate the blood levels of mebendazole for technical reasons. It was therefore impossible to know if the drug was being absorbed. It is therefore difficult to define that part of the study as a true failure. However there was no immediate response by any of the 16 cases (93). However, in a long term follow up of 132 cases decreased recurrence rates have been reported (French, C.M. personal communication)

The fact that fat enhances the absorption of mebendanzole and that mebendazole penetrates the cysts (95) has here been confirmed as being true in Kenya. This finding should be utilized when this drug is being used in this country in future.

The five cases reported previously as having glomerulonephritis (96) may actually have been due to the deposition of massive amounts of antigens released especially during chemotherapy when the cyst is dying and its wall getting disintegrated resulting in leakage of large quantities of antigen thus causing antigenaemia. It is noteworthy that one of these patients had not received any mebendazole for 9 months prior to the changes being noted (96). Currently there is work being undertaken at the Kenyatta National Hospital to estimate the levels of circulating Echinococcus antigens before, during and after chemotherapy of human hydatidosis. This study may help in cases of hydatidosis in whom the IEP test is falsely negative.

When serum levels are monitored it is more likely that a therapeutic effect can be obtained and the great increase in the number of abnormal (devitalized or killed) protoscoleces in the 10 cases in this study is an important finding because no abnormal protoscoleces have been noted before in the Turkana. The protoscolex wall was destroyed and in some cases loose hooklets were noted without any cellular structures around them (Fig. 35). Viability studies by motility, evagination and Eosin exclusion tests all confirmed that the protoscoleces fromall the patients were dead. The finding in this study that the suggested optimal serum level of mebendazole of 100 ng/ml (90) results in damage to the protoscoleces will probably have an influence on future work in Kenya. Although the oral dose of mebendazole used in this study is large it would seem

that this is necessary to reach the blood level at which the drug worked in the 10 treated cases. In the absence of a better alternative treatment for inoperable hydatid cysts, it may be reasonable to use this drug.

However, Albendazole is showing a lot of promise. It is more soluble and therefore easier to administer than mebendazole. In the current on-going study it is still too early to draw any firm conclusions about its long term use in this disease.

CHAPTER FIVE

6 SUMMARY AND CONCLUSIONS

It is possible to summarise some important findings and facts arising from this study and relate them to future approach to human hydatidosis in Kenya especially in relation to clinical diagnosis and treatment and to a control programme now that the Kenya Government has set up a national Hydatid Control Committee based in the Ministry of Health. This committee is looking at the entire problem of hydatidosis (its management and control) in Kenya.

A few facts can now be summarized and conclusions drawn from the present study.

6.1 The literature review in Chapter one confirms that hydatidosis is a major global problem in increasing importance. The global control measures are clearly still lagging behind despite the great socio-economic impacts of hydatidosis which have not yet been fully assessed.

6.2 Hydatidosis is an important problem in Kenya both in man and his livestock as well as in the dog. The cases of non-Turkanas (e.g. Luos, Kikuyus, Kalenjins) reported in this study (9) emphasizes the widespread nature of this disease in this country. It shows that what we are seeing clinically anywhere is Kenya may be just the tip of the iceberg. Obviously in the other part of Kenya where the index of suspicion is low they may be under-diagnosing this disease. Surveys are needed for the on-going control which is being undertaken by the hydatid control committee in the Ministry of Health.

6.3 Ultrasonography of the abdomen can justifiably now be regarded as the single most useful tool for both the diagnosis, follow up of treated cases and for surveys and control programmes in Kenya. It is reliable, simple, non-invasive and relatively cheap for a poor country. Its only limitation is that it cannot be used for the chest.

6.4 The Immunoelectrophoresis (IEP) test was found to have a sensitivity of 62% in this country and this together with the fact that it requires special facilities not easily available in a district hospital, makes it unsuitable for routine clinical application in the more peripheral centers. However, it would be useful in a few specialist centers for the diagnosis assessment of the

effectiveness of a control programme by examination in children and young adults in a given population.

6.5 The immunological issues raised by this test (IEP test) in Kenya need further elucidation. More work is needed on the role of circulating antigens especially in those cases of surgically confirmed hydatidosis in whom the IEP test is negative. As a result of this and other studies in Kenya, work is now going on, on circulating antigens in both the seronegative and seropositive cases on human hydatidosis.

6.6 There was no cross-reactivity between E.granulosus and other parasites in Kenya in this study. Therefore the IEP is specific enough in Kenya.

6.7 The mebendazole pharmacokinetics study in Kenya confirmed the known fact that fat enhances the absorption of this drug. This factor should now be applied in all future therapeutic endeavours using mebendazole in huma hydatidosis in Kenya.

6.8 The pharmacokinetis study also confirmed that mebendazole enters hydatid cysts in Kenya patients.

6.9 The recommended mebendazole optimal therapeutic level (90) of 100 ng/ml was achieved in this study in all the patients at one time or another. This resulted in the killing of the protoscoleces in all the patients. This finding is of great use clinically and in control programmes.

6.10 As a result of this study the Radioimmunoassay test can now be done in the department of Medicine for routine assay of serum drug levels.

6.11 In this study the examination of protoscoleces by motility, evagination, eosin exclusion test and morphology were all found to be very useful and these are simple side-laboratory of field laboratory techniques and can be regularly applied in diagnosis, after treatment and in field work as tests of viability of the protoscoleces.

6.12 In this study no serious toxic effects were noted from mebendazole since all functions of bone marrow, kidney and liver remained normal. Previous reports of glomenulonephritis (96) are likely to have resulted from the deposition into the kidneys of very large amounts of antigen released from the cysts during drug therapy.

6.13 The results of this work suggest that mebendazole can actually work in hydatid disease and it would probably be justified to use it in the absence of a better alternative.

6.14 Albendazole is more soluble and easier to administer to patients and in view of an initial encouraging response in the study, further work is going on to assess its value in cases with inoperable hydatid disease. It may eventually reduce the number of cases requiring surgery, as well as the number of recurrences as it could in future be used in conjunction with surgery to deal with problems arising from spillage.

RECOMMENDATIONS

1. With the information now available, control programmes and improved therapy are possible in Kenya and it is hoped that this will now be applied.

2. Chemotherapy should now be routinely undertaken using Albendazole as this may help reduce the number of inoperable cases of hydatid diseases in Kenya.

3. A countrywide survey should be undertaken to determine the incidence of human hydatid disease in all the Districts of Kenya. A combination of the immunoelectrophoresis test and ultrasonography would be suitable for this purpose.

4. Circulating Echinococcus granulosus antigens should be studied in known cases who have negative for arc 5 as this test may be useful for surveys and for follow up of treated cases.

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