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Issues in filariasis – a century of enquiry and a century of failure

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Summary

A great deal is known about the biology of the filarial parasites infecting man and of their transmission, their clinical manifestations, their treatment and their control but many more people are infected with Bancroftian filariasis and onchocerciasis today than more than 100 years ago when Manson discovered the first life cycle. There has been some success in the control of the *Simulium* vectors of onchocerciasis in parts of Africa and mass chemotherapy has helped to reduce Bancroftian filariasis in a few Pacific Islands but the main endemic areas have seen no benefit from all the advances in the techniques for controlling these diseases. There is an obvious need for more research to find better tools that are less hazardous to the environment and more acceptable to the affected communities. Fortunately the combined resources of the United Nations Development Programme, the World Bank for Development and the World Health Organization in the setting up of the Special Programme for Research and Training in Tropical Diseases has stimulated a renewed interest in these problems. An obvious area for further research is on the epidemiology of the diseases with special emphasis on transmission of the parasites to help with the development of predictive models which might assist in the design and evaluation of control programmes. There is a need for novel approaches to kill the vectors and for the development of more effective and less hazardous drugs. There is a need for immunologists to try to produce vaccines which will help to consolidate other methods of control but of more immediate value will be the production of more specific immunological diagnostic tests and methods for modifying the immunopathology processes caused by the disease and accentuated by treatment. But whatever new tools are produced it is still true to say that control measures will be effective only if there is active cooperation by the affected communities. It is therefore essential that laboratory research is supplemented with research on human behaviour in relation to the transmission of the diseases and also on the acceptability of control measures if we are to avoid the disappointments of many other antiparasitic control campaigns.

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Introduction

Patrick Manson first saw the development of *Wuchereria bancrofti* in the flight muscles of a mosquito in 1877 in Amoy in China. This was the origin of tropical medicine as a scientific discipline. It was the beginning of more than a century of international effort in studying filarial infections and in devising methods of control. But control has lagged behind enquiry and this is reflected in this special number of *Acta Tropica* with its emphasis on research. The filarial diseases have remained unconquered because the methods of control are inadequate. Further research is essential and it is good to see that this is a field of interest which continues to attract scientists from many parts of the world. This is a long tradition and the international interest in filarial infections can be seen from the milestones on the road to the discovery of the parasites and their life cycles and also in the development of control techniques. The microfilariae of *Wuchereria bancrofti* were first seen by the Frenchman, Demarquay in 1863. The adult worms were described by the Englishman, Cobbold in 1877 from material supplied by the Australian Bancroft and renamed *Wuchereria* by the Brazilian de Silva Araujo in honour of the German, Wucherer, who was working in Bahia. The microfilariae of *Onchocerca volvulus* were discovered by the Irishman, John O'Neil, who was employed as a ship's surgeon off the coast of Ghana in 1874 and the adult worms were described by the German Leuckart in 1893. It was a Guatemalan clinician, Robles, who in 1914 first described the severe ocular complication of onchocerciasis. Research was interrupted by the First World War and it was not until 1929 that the *Simulium* vector was discovered by the Scotsman, Blacklock, in Sierra Leone and it was not until 1947, after the Second World War, that the first effective drug, diethylcarbamazine, was discovered by an American team led by Hewitt. The greatest advance in terms of control was made in Switzerland in 1941 where the combined genius of P. Muller and his team at Geigy Ltd. gave to the world DDT, the insecticide which has saved millions of lives and relieved humanity of a vast burden of misery. It was DDT which was used by the Irishman, McMahon and his colleagues, to eradicate onchocerciasis and its vector from Kenya, an achievement which led to the present World Bank/WHO Onchocerciasis Control Programme in West Africa.

Unfortunately there are still many more people infected with filarial infections today than more than 100 years ago when Manson discovered the first vector. In spite of our knowledge and the availability of drugs and insecticides, the filarial diseases are still formidable problems. This is one reason for including them as part of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. We might ask why are the problems so formidable; if we know so much about how to control them why have we failed? Why is a special effort needed by WHO? What can we do to help relieve the great burden of misery affecting more than 300 million people ex-

posed to mosquito transmitted lymphatic filariasis and more than 30 million people affected by the dreadful skin and ocular lesions of onchocerciasis?

In general the magnitude of the problem is not because these diseases have extended their range or because they have become more severe in the individual patient, it is more because of the great increase in the number of people at risk, due to the population explosion in already affected areas. This is particularly true of Bancroftian filariasis because the parasite thrives on the hot humid tropical coastlands where conditions are not only ideal for mosquito breeding but also for agriculture. It is also in these areas where the well-intentioned efforts of sanitarians have increased the breeding of the mosquito vector by the provision of latrines and piped water supplies. The scarcity of fertile land and the need to cultivate in the *Simulium* infected valleys of Africa and Central America, has also resulted in increased exposure to onchocerciasis.

The control of lymphatic filariasis

There have been serious technical problems in relation to control strategies. In most of the areas where Bancroftian filariasis is endemic especially in India, the vector is *Culex quinquefasciatus (fatigans)*. This mosquito which is a mess-mate of man, breeds in drains, in domestic waste water and in latrines. Its close proximity to man and its constant exposure to insecticides has resulted in practically universal resistance to all the old and new residual insecticides. Alternative methods of mosquito control are available such as sanitary engineering and the use of larvicides, but the worst affected areas in the urban slums and the poverty stricken villages are also the poorest, so little is done to remove the vectors. Control of transmission by mass chemotherapy has also failed because the only available drug, diethylcarbamazine, is too difficult to administer. It is an inefficient anthelmintic requiring repeated doses and it produces serious side reactions in heavily infected patients. In some of the areas where lymphatic filariasis is caused by the nocturnal periodic *Brugia malayi* there is also the added problem of an animal reservoir resulting in reinfection following mass treatment.

However, not all is gloom, a great deal has been achieved in the control of filarial infection; more than is generally realised. These achievements have been discussed at some length in the Proceedings of the Medical Entomology Centenary Meeting which commemorated Manson's discovery of mosquito transmission. At that time I said: "The most important advances in control have come unobtrusively as a result of the efforts of a devoted but largely anonymous band of health officers, entomologists and entomological assistants, who have been responsible for the control of mosquitoes in all of the major cities, towns and even many small townships of the tropics. These measures were rarely aimed specifically against the vectors of filariasis but more against the vectors of malaria and arboviruses such as yellow fever and dengue. In many cities the

original purpose is forgotten and mosquito control remains an exercise in aesthetics which makes life more tolerable by removing 'nuisance' mosquitoes. All too often medical entomologists decry their failures. They forget the enormous advances that they have made in protecting the vast urban populations of the tropics from insect-transmitted diseases."

In some areas filariasis has completely disappeared as a result of improvements in housing standards and diminished exposure to mosquitoes due to environmental changes and there has been some control in areas where mass chemotherapy has been successfully supervised, as in some Pacific Islands. The disease has also disappeared from a few areas as an indirect benefit of malaria control campaigns where the vectors of both malaria and filariasis have been the same Anopheline mosquitoes, for example, in the Solomon Islands. But the main endemic area in India remains in spite of an enormous amount of effort to devise control programmes and very little has been done to control the disease in Africa.

The control of onchocerciasis

There are many reasons why onchocerciasis deserves special attention by WHO. It is one of the most dreadful of all parasitic diseases because it causes an unsightly irritating skin disease which results in social ostracism due to the premature aged appearance of the atrophic skin and also because of the high prevalence of severe ocular onchocerciasis which in many communities in the savanna regions of Africa affects more than 15% of the adult population. It is a greatly neglected disease because it is most severe at the "end of the road". It is a cryptic disease which is rarely diagnosed because medical practitioners in these remote areas mistake the skin and eye lesions for other diseases and, even if they think of the diagnosis, they are not equipped to look for the parasites in the skin or eyes. When deliberate surveys are carried out many "new" foci are discovered by the chance observations of affected individuals seen by ophthalmologists or pathologists. This accounts for recent discoveries of the disease in North Yemen, Saudi Arabia, Colombia, Brazil and Ecuador.

Onchocerciasis has been recognised as a disease of major economic importance because it causes the desertion of the affected areas and in the great savanna of Africa these are often the only fertile regions. The awareness of this economic and social problem by the international community has led to the Onchocerciasis Control Programme in the Volta Basin region of West Africa, financed by the World Bank for Development at the cost of \$ 250 million over a period of 20 years. It is a long term programme because the parasite lives for as long as 15 years and so far the only available method of control is to eliminate the vector. But even this project is dealing with only a small part of the great endemic area of Africa which includes almost the whole savanna and rain forest.

The methodology of onchocerciasis control has been developed from previous successful campaigns using DDT against the larval stages of the *Simulium* vectors in more limited foci in Kenya, Uganda, Zaire and Upper Volta. The vectors can be controlled by prolonged treatment of the rivers with DDT but this may involve some degree of damage to the environment and so this cheap and highly effective chemical is being replaced by the more biodegradable Abate. Unfortunately resistance to this insecticide has already developed in some parts of the Programme area in West Africa and here there is the added problem of re-invasion of *S. damnosum* from outside the treated area. Some of the West African vectors have been shown to have a wide dispersion pattern travelling more than 300 kilometres with no respect for international boundaries. In spite of the formidable problems which require the use of aircraft and helicopters to cover the immense distances involved in the control campaign, there is excellent international cooperation and support. Unfortunately there is no alternative to vector control because the filaricidal drugs which are available for onchocerciasis, namely diethylcarbamazine and suramin, produce unacceptably severe reactions. However there are good prospects for limiting transmission and the vector control campaign has already reduced transmission to negligible levels in the main endemic areas of the savanna in Upper Volta, Mali, Niger, Ivory Coast, Ghana, Togo and Dahomey, and a new generation is growing up in these countries without the threat of blindness.

What about the future?

There are worries about what to do when the present Onchocerciasis Control Programme comes to an end and what to do about the areas which are not included in the Programme. There is also increasing concern with the failure to relieve the suffering of those who are already affected with onchocerciasis and similar concern is felt at the failure to control Bancroftian filariasis. I believe that research to find new tools is of vital importance for the control of both diseases. We cannot, as is sometimes suggested, wait for the political and economic changes which result in an environment free from insect bites or for a primary health care system to deliver anthelmintics to the whole population. The pattern of transmission is so complex, with an enormous variety of vectors that each country and different regions of the same country, require entirely different techniques for control.

The control of filariasis and onchocerciasis is technically far too complex to be handed down to primary health care workers. Vector control is hazardous for the environment and treatment of the individuals with existing drugs is hazardous to the patient. The vectors are indifferent to national boundaries and the diseases are transported across frontiers by migrant labourers, nomads and refugees. The control of these diseases depends on international collaboration in research and international assistance in training of personnel. Fortunately

this is one of the aims of the UNDP/World Bank/WHO Special Programme and the Scientific Working Group on Filariasis has already stimulated a great deal of new research in this field. However, it is not easy to determine priorities and all too often it is the unexpected and at first seemingly irrelevant observations which lead to important breakthroughs. In the following discussion I have selected several areas of research which I personally believe require special encouragement if we are to accelerate control of these diseases.

Research priorities

The most neglected and yet essential requirements for the planning of any control campaign is reliable epidemiology. There is a need for much better parasitological and immunological diagnostic techniques and for better methods for determining transmission indices based on the correct identification of the parasites in the vectors. There is a need to create mathematical models for the analysis of the dynamics of transmission so that reliable predictions can be made of the relative significance of various control measures not only on transmission but also on the risk factors associated with the development of morbidity, especially elephantiasis and ocular onchocerciasis. The analysis of existing survey data for both Bancroftian filariasis and onchocerciasis suggests that repeated exposure is necessary before the parasites become established in the individual and the community, but these observations require confirmation. If it is true, then the "break point" in control campaigns might be reached long before the transmission indices reach zero. With these long lived parasites the best approach to reduce transmission would be by mass chemotherapy and a single shot treatment, such has now been found for many intestinal helminths and schistosomiasis, could totally transform the prospects for the control of filariasis and onchocerciasis. There is therefore an urgent need to find more effective and more easily administered drugs. It is likely that this will be achieved in the near future for the lymphatic parasites but with onchocerciasis there is always the fear that the more effective the drug the more severe the reactions. In this case, insect control may remain the main weapon of attack.

The disillusionment which has resulted from the development of insecticide resistance in mosquitoes has caused a great deal of pessimism amongst entomologists and as result mosquito control measures are no longer regarded as the main method of control of lymphatic filariasis. The pessimism is justified in relation to the use of residual insecticides against *Culex quinquefasciatus* but much can be done by concentrating the main effort against the mosquito larvae and by more involvement of the local community in eliminating breeding places and by encouraging more personal protection against mosquito bites. There is plenty of scope for research on novel methods of mosquito control. It is also important to encourage a combined approach to the control of filariasis and malaria in countries where both diseases are transmitted by the same mos-

quitoes. Of particular importance in this respect is research on *Anopheles gambiae* and *A. funestus* in Africa because it is here where they are the main vectors of both filariasis and malaria.

Research on the *Simulium* vectors of onchocerciasis is necessary to ensure that alternative methods of control will be available if insecticide resistance develops or if larval control becomes environmentally unacceptable. For this reason a high priority should be given to the establishment of the vectors in the laboratory. Recent developments with the breeding of North American simuliids suggests that this may soon be possible and this could open up a wide field of research.

Immunologists also have an important role in accelerating the control of these diseases. There are encouraging signs that immunodiagnostic techniques can be developed that are sensitive, species specific and capable of distinguishing active from past infections. Their introduction as reliable alternatives to parasitological methods will greatly accelerate preliminary surveys and the evaluation of control campaigns. All too often the development of promising new diagnostic techniques is seen as an academic exercise, as an ephemeral phenomenon, which brings temporary prestige to the research workers but is of no benefit to the community. A great deal of effort is wasted on the purification of heterologous antigens which inevitably lead to false positive reactions. Here one of the most important needs is a regular supply of the homologous parasites that infect man. These could be provided by cryopreservation techniques for microfilariae and by the production of infective larvae from vectors by membrane feeding or injection techniques. It will be necessary to establish supply centres in the endemic areas, possibly under the auspices of WHO as collaborating laboratories. The alternative is to develop laboratory models for *W. bancrofti* and *O. volvulus* or to establish in vitro culture systems. There is some promise of a monkey model for *W. bancrofti* but only the chimpanzee has been infected with *O. volvulus*. In vitro culture methods deserve encouragement as a possible source of material for immunological studies also for studying the physiology and metabolism of the parasites in relation to the development of better therapeutic agents. In this respect much more effort is required to study the stages of development from the mammalian rather than the insect host.

There is evidence to suggest that the main pathological lesions in lymphatic filariasis and onchocerciasis are immunologically mediated. This is an obvious field for research. But of more practical importance in relation to control is the problem of drug reactions and it is here where the immunologist and clinical pharmacologist may be of great assistance if they can devise methods for diminishing the severity of the reactions. There is also scope for closer collaboration with immunologists in the development of new drugs since it is known that diethylcarbamazine is only effective with the assistance of the immune system.

Protective immunity is the most neglected of all the areas of research related to human filarial infections, mainly because of the lack of suitable labo-

ratory models, but there are several promising leads. Much more emphasis should be given to this field of research especially at a time when molecular biologists are anxious to use their expertise to help solve the problems of the developing world. It is unlikely that vaccines will replace existing methods of control but they could be of great value in helping to consolidate successful control schemes.

Another neglected area of research in filariasis and onchocerciasis is in the area of human behaviour – human behaviour in relation to transmission of the disease and human behaviour in relation to the acceptability of control measures. Modifying human behaviour so as to avoid mosquito or *Simulium* bites is likely to be as effective in many areas as control measures based on insecticides or drugs. The wearing of long trousers to avoid the bites of *S. damnosum*, the use of mosquito nets and mosquito proofing of houses, the design of latrines and water supplies are examples where simple measures may have a major impact on transmission and morbidity. In the long run control measures are only likely to be effective if there is cooperation and participation by the affected communities. There is therefore a need to know a great deal more about the attitudes of the people to the diseases which afflict them and their reaction to control measures which we often prescribe without the consent of the people we are trying to help. New tools will be of little value if there is no desire on the part of the governments and communities in the endemic areas to get rid of the problem.