THE FUTURE OF MOSQUITO-BORNE DISEASES IN THE WORLD[1,2]

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ABSTRACT. The future of mosquito-borne diseases will depend on the improvements and implementation of chemotherapy and vaccination, as well as on biological and integrated control measures. *Bacillus thuringiensis* H-14, *B. sphaericus, Lagenidium giganteum* and other fungi are promising biological mosquito control agents. Other control measures include parasitoids, nematodes, larvivorous fish, *Toxorhynchites* mosquitoes, insect viruses, growth hormones, sex attractants, natural products, sanitation, and water management. Vector control should be combined with training of personnel and carried out on an international scale.

The future of mosquito-borne diseases in the world will depend on the success of three different approaches: treatment of the diseases by drugs, prevention of the diseases by vaccination and drugs, and interference with mosquito vectors by control measures, repellents, etc.

I shall mention briefly the first two approaches and discuss in more detail future disease prevention by mosquito control.

There are no antiviral antibiotics that could treat successfully diseases such as dengue, encephalitis or yellow fever, but there are drugs for the treatment of parasitic diseases, including malaria, the most important human disease today. The western world has been using quinine and drugs based on the structure of quinine for many decades. Unfortunately, malarial parasities are becoming resistant to these drugs. The sulfa drug Fansidar® was introduced a few years ago but resistance to it has also developed. Quinine, together with tetracycline, is still effective against strains of *Plasmodium falciparum.* In China a drug with a completely different chemical structure has been obtained from a weed, *Artemisia annua* (Anonymous 1981), effective against strains of *P. falciparum* that have become completely resistant to other antimalarial drugs. Apparently the Chinese have been using extracts from *A. annua* to treat malaria for nearly 2000 years, but the western world found out about it only a few years ago.

Prevention of malaria by vaccines has received great attention during the past decade and several laboratories are working on various aspects, but a vaccine against the blood stage or against the mosquito stage of plasmodia is not yet available. The development of a vaccine against the different strains of dengue is also encountering great difficulties. On the other hand, the yellow fever vaccine is one of the best known and it has proven its efficacy since its introduction by Max Theiler nearly 50 years ago. The World Health Organization recommends revaccination once every 10 years, but the antibody titer in American servicemen that were vaccinated in 1942 was found to be as high after 20 years, as it was a few weeks after vaccination (Max Theiler, personal communication, 1962). It is therefore likely that revaccination will be found sufficient to protect an individual for life.

Lasting immunity has been induced in individuals that contracted small pox, measles, chicken pox, yellow fever and several other virus diseases, but not in those who contracted common cold or influenza. Apparently efficient vaccines have been developed against diseases that confer lasting immunity, but not against diseases that can be contracted repeatedly. Unfortunately parasitic diseases caused by mosquito-borne plasmodia are characterized by lack of lasting immunity. Even in areas where malaria is endemic, people continue to contract the disease, despite repeated attacks of malaria. This does not imply that development of efficient vaccines against malaria is hopeless, but it underscores the necessity of different and novel approaches. New adjuvants will have to be developed and used in conjunction with the vaccines of the future.

Drugs and vaccines might solve many problems in the industrial world, but not in less developed countries. There, only efficient mosquito control can hold the promise for the future.

The struggle between man and mosquitoes began a long time ago and it will continue as long as the human race endures. In less developed countries mosquitoes have disputed every step of our invasion of their original domain persistently and successfully. We have never exterminated, and probably never will exterminate a single mosquito species. While we have been successful in preventing mosquitoes from

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spreading certain diseases in developed countries, our efforts to do so in the less developed countries have failed. Tropical countries in Asia, Africa, Central and South America are primarily affected, but there are areas that appear to be dry and yet are unsafe because of mosquito vectors. Mosquito-borne diseases are also of concern in industrialized countries, and the great discomfort caused by mosquito bites cannot be overlooked.

After the spectacular progress made in mosquito and malaria control by DDT, both the vectors and the disease are now increasing explosively. The comparatively small island of Ceylon, with some 18 million inhabitants, was practically free of malaria by 1963, when only 17 cases of the disease occurred there among 14 million people (Harrison 1978). At present, over 2 million cases occur in Sri Lanka every year. Similarly, only 50,000 malaria cases were reported in India in 1961, while over 35 million cases occur there annually today. In addition to *P. vivax*, the much more dangerous *P. falciparum* is on the increase there, as well as in other parts of Asia and Africa. Antimalarial drugs that were protecting against infection or used for treating those who became ill are rapidly losing their effectiveness. The control of mosquitoes remains the major approach to the control of several important diseases of mankind, including malaria, dengue, filariasis, encephalitis and others.

Governments in developed countries have the resources to provide adequate control measures, but those in the tropical developing world are hard hit and the prospects for future control of mosquitoes are not very bright at this time. What should be done and what can be done to change this situation so that in the years to come the mosquito populations can be significantly reduced?

Recently the World Health Organization of the United Nations listed the biological control agents against mosquitoes in order of priority (Anonymous 1984). The priority was based on the results obtained in the field as well as in the laboratory. The most promising of all agents is *Bacillus thuringiensis israelensis* (H-14). There is no doubt that it has the greatest potential in controlling mosquitoes, not only when used alone, but, perhaps even more so, in integrated control. *Bacillus sphaericus* is next in order of preference (Yousten 1984). The fungus, *Lagenidium giganteum* is also in the first group.

The second group comprises certain larvivorous fish as well as nematodes. The third contains *B. thuringiensis* strains other than H-14, as well as other larvivorous fish, *Toxorhynchites* mosquitoes, *Coelomomyces* fungi, snails, microsporidia, Entomopthorales, mass-produced *Culex*-infecting nematodes, and other nematodes. The fourth group is concerned with the control of tsetse flies, where the use of parasitoids and of reduvid bugs has been successful. Predacious cyclops, *Turbellaria* flatworms, and certain snail predators are also in this group.

WHO lists viruses and *Metarrhizium anisopliae* under "no priority—little potential." As far as *Metarrhizium* is concerned the field applications of this fungus have been disappointing. There has been very little work concerning the use of viruses against mosquitoes. No real effort has been made until now to find viral insecticides that could kill mosquitoes (Maramorosch and Sherman, 1985). This is an area where, especially in the tropics, an extensive search could be potentially very profitable.

Effective and economically acceptable control in the years to come will require intensive research as well as education and training. Three decades ago it was hoped that by using inexpensive DDT, mosquitoes and the pathogens carried by them would be completely eradicated. Unfortunately this hope has faded and we now realize that mosquitoes and mosquito-borne disease can only be curtailed, but hardly eradicated from the tropics. There are technical, financial, administrative and political problems that, for years to come, will interfere with effective mosquito control in most of the tropical developing countries. Insecticide resistance presents a serious technical problem which, we hope, will be overcome in part by proper application of integrated control programs (Laird and Miles 1983). Use of biological insecticides, including fungi, nematodes, bacteria, viruses, insect growth hormones, sex attractants, as well as inexpensive natural compounds (Schmutterer, et al., 1980), combined with small amounts of insecticides, will pose but little environmental hazards and will most likely be the future approach (Anonymous 1972, Bulla 1973, Burges 1981, Kurstak 1982, Rice 1983).

In order to provide economical and effective means of control, both the chemical and the biological insecticides will have to be improved considerably. This means that there will be a need for continuous basic and applied research, carried out not only in laboratories in developed countries, but also in the field in developing countries. The need for new, economic and effective methods to control mosquitoes will be the goal of entomologists during the next decade. At the same time, efforts will increase to provide suitable chemotherapeutic agents and effective vaccines against the mosquito-borne pathogens. But even if inexpensive prevention by vaccines and cure by drugs should become available and widespread, the battle against mosquitoes will have to continue to prevent the great discomfort they cause. New chemical pesticides, biological control methods, and sanitation and water management methods to prevent mosquito breeding will have to be combined.

The effort can only succeed if carried out on an international scale and with international collaboration. WHO has played a major role in developing countries where it established Collaborating Centers, where pesticides alone, and in combination with biocontrol agents, can be evaluated. Training of scientists and technical personnel will have to be increased. At present, academic research is often far removed from practical application.

There was a time, not long ago, when it was hoped that mosquitoes would be unable to develop resistance to biological control agents. Unfortunately, this hope has vanished. Resistance to biocontrol in laboratory experiments with the most promising *B. thuringiensis* showed that resistance to it, as well as to *thuringiensis* exotoxins developed in 50, or in 12 generations of mosquitoes, respectively. Resistance to mermithid nematodes developed in mosquitoes during 4–8 years, that is, during up to 300 generations of mosquitoes (Laird and Miles 1983). Resistance of mosquitoes to baculoviruses can also develop. It has been tested already with silkworm and the cytoplasmic polyhedrosis baculovirus that causes the flacherie disease. Resistance was observed in as little as 5 generations. Resistance to growth regulators, although less pronounced, also has been reported. Therefore, we cannot expect that a control method will be found to which no resistance would ever be developed. However, the development of resistance is not always undesirable. Such resistance was actually beneficial—when aldrin, dieldrin and heptachlor were used to control mosquitoes; the mosquito-eating fish, *Gambusia affinis,* soon became resistant to these insecticides and could continue its role in controlling mosquitoes.

Inexpensive natural products might become an important additional means of control. For centuries, crude extracts from the neem tree, *Azadirachta indica,* have been used in Asia and parts of Africa to control insect pests (Anonymous 1985, Schmutterer, et al., 1980). Among the insects affected by neem are also mosquitoes. The chemical industry did not become interested in this source of insecticides, because preliminary studies have indicated the very complex chemical structure of the active compounds. This structure indicated a prohibitively high cost for conventional chemical synthesis of analogs and recombinant technology has not been attempted as yet. The neem tree grows easily in arid tropics and India has a program to double the number of trees in less than a decade, by having one tree planted for every adult and child alive in India today—that is, an additional 750 million new neem trees. The leaves can be dried and crushed, mixed with water, and used as an insecticide. A 10 times more potent extract can be made using alcohol, but this may not be cost-efficient in developing countries. Neither kind of extract can be patented, of course and chemical firms cannot be blamed for turning away from neem tree compounds. However, developing nations in the tropics will most likely take advantage of this inexpensive source of insecticides.

Monomolecular films, covering larger bodies of water, will be used to interfere with mosquito breeding. The battle must go on. Even if complete victory in the war against mosquitoes cannot be expected, significant reduction of mosquito populations will, and must be, achieved.

In conclusion, future strategies to control mosquito-borne diseases will have to be international, because the range of mosquitoes is not limited by national boundaries. Realistic control of mosquito populations will depend on a thorough understanding of the goal to be achieved. We realize that extermination of a single, or several mosquito species will be impossible. Skills and energies of entomologists will have to be increased to combat and effectively reduce mosquito populations in order to maintain human health. We should keep alert to the mosquito problems we face today and anticipate the problems we are likely to face in the years to come when the world's population will be much greater than it is today.

Future integrated mosquito control strategies will require tests for possible biohazards (Miltenburger 1980). Precautions will have to be taken to make sure that humans and nontarget organisms are not adversely affected. No one can test for all possible effects nor guarantee absolute safety. Mistakes have occurred in the past and they may be expected to occur in the future. To keep such risks as low as possible, sufficient data on toxicity, pathogenicity, genetic risks, and environmental impact will be required. The potential effectiveness of integrated mosquito control appears promising.

I predict that selective and judicious use of insecticides, combined with biological insecticides and proper management practices will constitute an integral part of successful mosquito control programs in the future.

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