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New answers to malaria problems through vector control?

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Like so many other of science's latest concepts, integrated anopheline control methodologies were being advocated long before their present name was conceived. Thus almost a century ago, Mrs Carrie B. Aaron of Philadelphia provided a preview[1] of what such an approach to vector suppression would one day comprise. First prizewinner in an essay competition designed to promote mosquito and housefly control via the use of predaceous Odonata, she began by outlining the morphology, life histories and ecology of these pests and their suggested biocontrol agent. Then, proceeding to a consideration of the medical problems posed by Culicidae and Muscidae, she touched (nearly a decade before the *Plasmodium* cycle was elucidated) upon the possibility of the

former transmitting malaria; and nicely presented the alternatives facing all practical insect control. Anticipating the late Dr Rachel Carson, she declared that while 'A large and eminent school of scientists believe it unsafe to overthrow the equipoise of nature, ... an equally numerous school take the ground that it is incumbent upon man to first ascertain the exact nature of any creature, and utilize or destroy as in his judgement may seem best ... gladly risking the effects of the outrage thus offered (to Nature, M.L.), that the great evils worked by the species may be prevented'. Mrs Aaron then furnished a plan for mosquito suppression combining chemical (sprayed petroleum), biological (fish, mass-produced dragonflies) and source reduction (flushing, circulating, grading) measures against the immatures; with repellents (oil of pennyroyal) and predators (insectivorous birds, adult Odonata) against the adults. Her suggested avian predators were both species that might be expected to capture their share of crepuscular anophelines the habits and vectorial role of which had still to be elucidated – one the Common Nighthawk *(Chordeiles minor)* being partly nocturnal, and the other, the Whip-poor-will *(Caprimulgus vociferus)*, strictly so. Among the 187 references in her bibliography was an 1880 one reporting 600 mosquitoes from the crop of a nighthawk. As a commentary on relevant research progress, a current field guide to birds of eastern North America[7] states that *C. minor* stomach content analysis 'has shown that in a single day one bird captured over 500 mosquitoes'. But although she included dragonflies in her proposed control plan, Mrs Aaron[1] did so only 'with a view to the possibility that others may not look upon this problem as we do', her own field observations having convinced her that the habits of these insects and mosquitoes overlap insufficiently for significant control to be expected; she also foresaw major mass production and field application difficulties. In her view, larvicidal 'common illuminating oil' carefully sprayed so as not to prejudice already-present natural factors limiting culicid populations (fish, odonate larvae) was both far more effective than adult dragonflies and sufficiently cheap for widespread use. She even conducted small-scale tests the projected results of which enabled her to claim 'that three dollars' worth of the crude oil will suffice, according to our estimate, to cover an area of one hundred acres of water surface five times in one season' for excellent mosquito control, thereby (as her tests were undertaken in 1889) gaining three years' priority over Howard[17] whose similarly small-scale experiment in the Catskills in 1892 was later recognized by Ross[38] as the first significant field trial of larval oiling (as early as 1867 Howard[17] had, however, demonstrated the killing of mosquito larvae by adding kerosene to an Ithaca, New York, watering trough, and he himself mentioned still-earlier precedents for such non-quantitative demonstrations). Finally Mrs Aaron[1] even anticipated the application of invertebrate pathology to vector control by proposing the culture and use of entomophthoraceous fungi against adult houseflies, urging that these entomopathogens 'are undoubtedly a potential class of insecticides, with great recuperative and reproductive capacities...'.

Thus a basis for rational control of Culicidae of public health importance was being laid in the Americas 'before the malaria discoveries directed the attention of European observers especially to the question of mosquito control'[17]. Howard[17], while reviewing the few other chemicals then available for the purpose, concluded that until the possible discovery of something better 'the kerosene known as fuel oil will be found to be the most satisfactory'. Ironically, such a 'something better' had already been synthesized a quarter of a century earlier. Howard's book had only just appeared, and four more decades were to pass before recognition of the insecticidal qualities of DDT, when Ross[37] made the startlingly perceptive statement that 'I have long wished to find an ideal poison for mosquito larvae. It should be some solid substance or powder which is cheap, which dissolves very slowly, and which, in weak solution, destroys larvae without being capable of injuring higher animals. What a boon it would be if we could keep the surface of a whole town free from larvae simply by scattering a cheap powder over it, once in six months or so. It is very possible that such a substance exists, but unfortunately we have not yet discovered it.' Almost as unfortunately, when we finally did, DDT's unprecedented initial successes against insect pests and vectors caused many to regard it as a panacea. This was especially so in mosquito control, so that for a number of critical years, during which resistance and nonselectivity problems (the latter especially arising from biomagnification following massive area applications in economic entomology) were developing, it was generally forgotten that Mrs Aaron's professional successors, Howard[17] and Ross[37] had advocated the purposeful use of not just larvicidal chemicals but also of all other means of control known to them. Thus Howard[17] stressed the value of source reduction through the elimination of 'accidental receptacles', the covering of cisterns and rain barrels, and draining, dyking and filling; recommended deliberate salination to eliminate freshwater mosquitoes from coastal ponds; and, in cases where the owners refused to permit oiling, urged the introduction of larvivorous fish into water bodies too productive to drain (e.g. the dams for contemporary mills and iceworks, stock watering ponds). He also advocated the application of repellents to the skin, besides anti-imago measures including the screening of houses, the whitening of inner walls for easier recognition of mosquitoes for hand capture, and the indoor use of fumigants via the burning of pyrethrum powder and a contemporary Chinese version of the (still) cheap and invaluable mosquito coil. The dawning realization that vector suppression was destined to be fundamental to the fight against malaria and other vector-borne diseases, thus provided further occasion for a pioneering statement on the chemical, biological and environmental components of integrated control.

Importantly, all were to be used in disciplined fashion and in expectation of the collaboration of each population being protected. In connection with what Ross[37] advocated as 'sanitary anarchy', Howard[17] reported how well the contemporary US Army *Aedes aegypti* and *Anopheles* suppression campaign was proceeding – under military regulation – during what proved to be a remarkably successful campaign against yellow fever and malaria in Cuba. Howard[17] also cited then-recent ordinances of the City Council of Winchester, Virginia; which was furnishing valid public information on mosquitoes and

their control, stressing the need for *protracted control* 'perhaps several seasons through' – and providing a fine for non-compliance.

Acknowledging the excellence of Howard's book, Ross[37] went on to observe that 'of course, campaigns against mosquitoes in civilized countries will always be much easier than campaigns in the tropics'. Nothing if not blunt, he included the following in his section 20, 'Where not to start Mosquito Brigades'. – '... *Native Towns and Villages.* – Unless Europeans are present in towns and villages, mosquito gangs will scarcely be possible; because in the first place there will be no one to direct them, and in the second place there will be no one to pay for them. I fear that we shall generally have to leave small native towns and villages to their fate for the present, unless there is a much more marked advance of civilization than we can observe at present, or unless some one comes forward to provide the money required.' While his precursors had pointed the way to integrated mosquito control, it remained for Ross to spell out the details of the manner in which all then-available chemical, biological and environmental measures were to be organized in long-term anopheline control programmes for the prevention of malaria transmission, and precisely how these programmes were to be administered, supervised and paid for. Ross' recommendations having been summarized elsewhere very recently[21] I shall not repeat them here. For present purposes I simply want to emphasize this conviction that without the assurance of adequate funding, discipline and continuing leadership based in the target area, there's no point in starting a mosquito control operation.

Whenever such an approach has been adopted under conditions where 'sanitary anarchy' could prevail, though, positive results have been achieved. The Pacific Campaign in World War II offers excellent examples. Thus after the initial savage fighting, malaria control operations were adequately funded, well conducted and immensely successful. Anyone who served at that time in the allied forces on Guadalcanal, Solomon Islands, will remember the American basecamp public-address systems thundering out Harry James' version of 'The Flight of the Bumblebee' every day at dusk. On an island where four months after their initial assault the US 1st Marine Division had suffered 5749 malaria cases (by 10 December 1942[8]) fully effective malaria control was now being maintained. That attention-rivetting evening tune, by recalling mosquitoes rather than bumblebees to every hearer, was the final reminder to roll down shirtsleeves and tuck trousers into boot tops. The regulation was well policed, and failure to comply was drastically dealt with. However nobody could honestly plead ignorance by way of excuse, for the musical warning was merely one part of a comprehensive information programme which saw the military camps plastered with anti-malaria posters and strewn with relevant eye-catching pamphlets.

Such an approach reflected official recognition of the fact 'that the new methods of Anopheles mosquito control developed during World War II will not, alone, in the future prevent malaria among troops exposed in highly endemic areas'[8]. Prominent among these 'new methods' was the liberal use of DDT, ushering in the brief but heady period during which there was widespread conviction that anopheline control now indeed had its panacea. This kind of thinking reflected the success of the then-recent malaria suppression landmark, the Rockefeller Foundation's 1930–1940 campaign in Brazil, which eradicated the *introduced* African *Anopheles gambiae* in a costly, sustained and highly disciplined effort relying upon Paris green as 'the only antilarval measure employed throughout the infested area' and weekly adulticiding, based upon contemporary South African experience and involving the use of a pyrethrum concentrate with carbon tetrachloride in kerosene or diesel oil[43]. Soon after World War II – and overlooking the fact that 'by diligent search for mosquito breeding areas, extensive drainage, and thorough oil larviciding' (shades of those pioneer, turn-of-the century, generalists!), a great reduction in malaria incidence had already been achieved in South Pacific battle areas *before* the advent of DDT[8] – the Rockefeller Foundation attempted to eradicate the *indigenous* malaria vector, *Anopheles labranchiae,* from Sardinia by a combination of larviciding and residual adulticiding with DDT. By the programme's third year costly and increasingly large-scale drainage and clearing operations were added. Although these soon expanded until they employed $^4/_5$ of the overall work force of 30,000 + (six times the number originally envisaged), *A. labranchiae* was not eradicated[29]. Nevertheless, over the five-year (1946–1950) operation, malaria transmission fell to vanishing point. By the end of 1949, too, three years of residual household spraying with DDT had interrupted transmission in much of Greece; where, two years later, shortage of the pesticide caused the suspension of spraying in Crete, despite which autochthonous malaria failed to recur on this large island[28]. Out of all this, the then-young World Health Organization (WHO) developed its Malaria Eradication Programme (MEP) in the mid-1950s.

An activity that never achieved 'a consensus among malariologists'[40] WHO/MEP comprised a virtually worldwide effort (the populations not benefiting from which, were largely those of tropical Africa – left out because of the general lack of the necessary health infrastructure). Its goal was the ending of malaria transmission and the elimination of the reservoir of infective cases in time-limited campaigns via three to five years' residual adulticiding (initially with DDT, and then as resistance problems burgeoned, other chlorinated hydrocarbons and eventually other synthetic organic pesticides) throughout very extensive MEP areas, relatively short-term vector suppression being succeeded by anophelism without malaria in formerly malarious zones[34]. By 1967 rather more than one billion people 'were living in areas from which malaria had been eradicated, or where the eradication programme had reached the phase of consolidation'[34]. Four years later it could be claimed[5] that DDT, as used against anophelines alone, had already saved some 15 million human lives that would otherwise have been lost to malaria. Well before then, though, pesticide resistance, refractory behavior of some anophelines towards residual deposits and the inactivation of the latter were recognized as major technical factors leading to dangerously high levels of vector survival[34]. At its 22nd Session in 1969 the World Health Assembly thus recommended the abandonment of MEP in favor of individual states

reverting 'to containing the disease at levels that their own general health services, rudimentary though many of them were, could cope with'[20]. Meanwhile, the mass communications media (if only vector-borne disease control enjoyed their resources!) were aiding and abetting a new group clearly in need of help, the environmentalists, to paint a highly saleable but commonly grossly exaggerated picture of the health and ecological hazards posed by pesticides in general and DDT in particular[36]. As Davidson[10] so nicely expressed it, 'the extremely influential "environmentalists" are inhibiting the control of malaria. They seem deaf to any plea that most of the things designed to improve the quality of life involve an element of risk'. In the face of there being 'no conclusive evidence from anywhere that DDT has ever killed anybody'[10] and that WHO/MEP was based upon indoor applications of residual sprays scarcely likely to cause environmental harm anyway, one can only wonder how these activists can live with such results of their campaigning as those that followed the premature withdrawal of WHO/MEP from the Indian subcontinent and Sri Lanka. Thus the latter island, notoriously malarious until MEP had reduced its annual case incidence to 17 in the mid-1960s, suffered so massive a resurgence of the disease through abandonment of DDT household spraying for primarily political considerations, that by the end of the decade one million of its total population of 12 million were again infected. In India, where a half-billion were exhibiting only 40,000 malaria infections annually by the mid-1960s, the incidence was back to about six million a decade afterwards.

For following the reversion to a control philosophy, with renewed attention to chemical larviciding which is potentially far more hazardous to 'the environment' than residual adulticiding, anopheline suppression continued to be plagued by snowballing problems. These included the increase and diversification of pesticide resistance[4], the decreasing availability and spiralling cost of chemical insecticides, and what Pampana[34] termed 'operational and administrative factors'. Prominent among the latter were growing preoccupations with personal 'rights', and 'safety'[10], and the growing awareness among Third World politicians that strict enforcement of urban source reduction and sanitation, tends to lose votes. There are refreshing exceptions to this generalization, such as Singapore's, but we are too often assured that 'it just can't be done these days', or 'our people simply would not tolerate it'. The sort of issues advanced in support of so negative a viewpoint include the alleged impossibility of implementing official orders to dispose of e.g. backyard heaps of discarded automobile tyres (these being both a source of myriads of *Aedes aegypti* and the raw materials for a 'cottage industry' producing cheap footwear). Unhappily, therefore, the vast and expanding urban connurbations of the Indian subcontinent, tropical Africa, Latin America and the Eastern Mediterranean, continue to feature all too prominently in the registers of vector-borne disease.

'Operational and administrative factors'[34] also, however, included some that were not to be spoken of. Thus MEP was held to have been successfully concluded in 13 countries by 1968. All (and certainly the European contingent of Bulgaria, Hungary, Poland, Romania and Spain) might well have satisfied a reincarnated Ross as to their prevailing level of civilization, and although several would have failed to meet his 'European leadership' criterion these admittedly still included well-qualified Europeans in their native towns and villages. But what really brings home the unachievability of MEP is that among those 13 countries the only Third World or 'developing' ones were five tiny island states of the Caribbean and Eastern Mediterranean[34]. Among the few others then still to be declared freed from malaria was the little Indian Ocean island of Mauritius, which is believed to have first become malarious (in 1867) a few years after the accidental importation of *Anopheles gambiae* and *A. funestus*[34]. Mauritius, designated as malaria-free in 1973, enjoyed the resumption of such a state after 106 years for a lamentably short time. For in 1975, by a combination of increased air and sea traffic, consequent quarantine carelessness and Cyclone Gervaise, the disease returned to the island where, by 1982, its incidence had risen 11-fold to over 650[3]. Just as reintroduction of *Aedes aegypti* by sea and/or air into tropical American countries that had been declared free from this vector during an earlier WHO venture were blamed for an eradication programme's failure (although my own visits to Central American countries as a WHO Secretariat member in the early 1960s caused me to doubt greatly that actual eradication *had* been even briefly achieved), much now began to be heard of the risk of malaria reintroductions. The gravity of this problem, particularly as it relates to *parasite* reintroductions through the steady increase in human mobility (probably over 900 million airline passengers in 1980 alone!) has been ably presented by Bruce-Chwatt[6]. Turning to vector importations, Takahashi[45] and Russell et al.[39] have reported interceptions of potentially dangerous anophelines aboard aircraft reaching Tokyo, Japan (especially from Manila, Philippines) and Darwin, Australia (especially from Den Pasar, Indonesia) respectively, while Ward[48] has indicated that Guam, Marianas, which remained altogether free from *Anopheles* until World War II, now has no less than five established species of this genus! Since 1966, too, a few cases of malaria (*Plasmodium falciparum*) thought to have been contracted on Guam, have been recorded.

Bearing in mind the prevailing widespread neglect of aircraft disinsection on many routes and of airport insect control in many countries[22], we must indeed recognize the hazard of airborne importation of vectors (on occasion already infective for *Plasmodium* as in the case of recent Belgian, Dutch, French and Swiss instances discussed by Smith and Carter[42]) into countries no longer malarious or until now malaria-free because of the absence of anophelines. It is clearly vital that permanent measures for appropriate airport vector control and aircraft disinsection – seen as 'bad for tourism' by the authorities of many tropical Third World countries[22] – be included in future integrated methodologies for the control of *Anopheles* and malaria.

Whatever our achievement has been in actively suppressing malaria – and it is certain that the classical 'disappearance of malaria before the plough' has been proceeding apace, leading to some inflation of the credit claimed for malaria eradication and control programmes – it is clearly far from adequate. Noguer et al.[33] cautioned that

current malaria incidence figures had to be taken as underestimates for reasons ranging from diminishing case detection activity to the total absence of up-to-date figures for some countries, an alarming thought when in that same year (1978) the number of cases of the disease actually reported to WHO's six Regional Offices stood at ca 13.7 million[6]. Bruce-Chwatt[6] further points out that according to the latest WHO estimates 'some 1620 million people inhabit areas of the world where the exposure to malaria infection is moderate to high, depending on the degree of endemicity'. Even allowing for the increasing global population this suggests a situation if anything worse than that of a decade and a half earlier, for Pampana[34] had estimated that 1692 million were then inhabiting areas still malarious or which had recently been so. In 1983 Schliessmann[40] somewhat gloomily commented that the accomplishments of the past 25 years of research 'toward developing a malaria vaccine and/or methods for biological or genetic control of vectors' do not suggest the likelihood of radically improved control developments by the end of the century. He appeared unaware of the commercial availability of *'B.t.i'* (*Bacillus thuringiensis* subsp. *israelensis*), the first really practical 'microbial pesticide', key information about which had already appeared in *Mosquito News*. In fact, progress towards at least malaria vaccines and practical biocontrol over the preceding quarter of a century had actually been such as to render the radical improvements to which Schliessmann referred, very likely indeed – were it not for the bureaucratic and political expediency that favor the small wars, international terrorism and factional disturbances currently compromising health programmes in malarious areas from tropical Africa through the eastern Mediterranean and S/SE Asia to the American tropics. Thus in the last-mentioned area, the 33rd World Health Assembly (May 1980) recognized a 'moderate' increase in the number of malaria cases reported from the New World, 'mainly because of the deteriorating situation in Central America'[6]. With an additional year's data, though, Schliessmann[40] could declare that the known number of cases of this disease, having virtually doubled (from 177,100 to 338,400) over the period 1962/1971, had done so again over the following decade – reaching 638,000 in 1981; since when, revolutionary activity in Central America has been stepped up to a point where any attempt to monitor further deterioration in the malaria situation (certainly reflecting the disruption of anopheline control at least as much as any other factor) could only be conjectural.

By the end of the next decade and a half, too, the close of the twentieth century will be at hand. So will the moment of truth for WHO's present slogan, 'Health for All by the Year 2000', concerning which relevant rhetoric is reported in each fresh issue of the *WHO Chronicle*[30] and *World Health*[31]. It seems to have been forgotten in Geneva that WHO's Constitution of the late-1940s defines 'health' as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. Noting as the clock ticks on that 'merely the absence' of but one major killer of mankind, malaria, by 2000 A.D. is quite out of the question, one can only conclude that WHO would do well to have a moratorium on such slogans. Actually, soon after WHO irrevocably committed itself to the goal of 'Health for All by the Year 2000', defined in political rather than scientific terms by its African Deputy Director-General[27] as 'An irresistible logical process and a passionate protest against the doctrine of inequality and want', another of the Organization's senior Secretariat members[16] expressed misgivings about the continuing feasibility of obtaining the pesticides that would be needed in this context; arguing that the success of campaigns by environmentalists having led to stricter regulations 'concerning the production, marketing and use of chemical insecticides which in turn dramatically reduced the development of new compounds that could be used in public health', this fact, resistance and the deteriorating world economic situation were pricing control agents beyond the reach of many of the countries standing most in need of them. A year later (i.e. 1982) Simuchoba[41] reported that Dr Dan Kaseje of Kenya had dismissed WHO's end-of-century goal as unrealistic, declaring that a 12-year effort in his country had failed to raise the availability of health services beyond about 20% in the rural areas where ca 90% of Kenya's 17.5 millions are located; and that 'All that has happened in rural health is talk'. This seems a fair statement in the midst of much rhetoric. It is probably at least equally applicable to most if not all of the many lands of Black Africa, down to South Africa's northern border. With the United Nations Educational, Scientific and Cultural Organization (UNESCO) currently at risk[47] because of the increasing domination of its activities by the politics of protest and inexperience, we can only hope that such erosion of the mandate of UN Specialized Agencies is not destined to threaten the health of the whole complex of our family of nations by 2000 A.D.?

Less preoccupation with the political attractions of consensus, and an international health policy embodying Ross' 'sanitary anarchy' (whereby no vector control operation would be commenced without the best possible prior advice from outside as well as within the Region in question, nor without absolute assurance of total and continuing support from the administration of the country being aided), would ensure less 'talk'[41] and more effective action in the field of vector control. It would be encouraging, too, to see some sign that the term 'integrated control' is really being understood by all concerned in WHO, currently administering interagency support to a People's Republic of China project to control anophelines in rice fields. Billed as an integrated vector control effort[35] and conducted under circumstances where such an approach could be highly productive[20], this describes 'the environmental management of the rice fields and biocontrol of the larvae as the major control approaches'. Therefore, by omitting the conjoint use of adulticidal chemical pesticides to supplement these other approaches as necessary, the project would appear to fall short of complete integration. This has already been the case with some other allegedly 'integrated' vector control undertakings elsewhere. WHO's research activities were decentralized to the Organization's six Regions in the mid-1970s, with inevitable dilution of the talent that could thereafter be assembled to consider specific health problems and make recommendations for their solution. That decentralization was soon followed (in 1977) by the establishment of a Special Programme

for Research and Training in Tropical Diseases (TDR), an activity implemented by WHO in co-sponsorship with the United Nations Development Programme (UNDP) and the World Bank, with the interdependent objectives of securing new and improved tools to control malaria and five other major diseases still rife in the developing countries, and of strengthening these countries' national institutions to enhance their relevant research capabilities[15]. Under the first objective there is provision for redressing the imbalance between biocontrol of vectors and conventional chemical control, which has dominated vector suppression since first DDT became available. While the concept is timely, my point about adverse consequences of the regionalization of WHO research is made by two of the recommendations of the November 1979 session of the TDR Scientific Working Group on Biological Control of Vectors (WHO/BCV/SWG). Firstly, this meeting named certain freshwater fish as high priority candidates for research prerequisite to their practical use as mosquito larvivores in South Korea – a use totally inappropriate to their importance as intermediate hosts of *Clonorchis sinensis*, of which the 20 or more participants, including Secretariat staff, appeared unaware. Secondly, the SWG advised against any further WHO support of the most valuable of all anopheline larvivores, *Gambusia affinis*.

The grounds for the latter action were that the mosquitofish poses hazards to some fish of economic importance, as well as rare and little-known ones. Of course it does! But what larvivore mass-cultured for field use could fail to do so? Any such use, however carefully conceived, inevitably constitutes interference with a natural food web (which even in the smaller aquatic sites can be of daunting complexity), providing ammunition for future protagonists of some unintentionally prejudiced creature (perhaps a great rarity on the brink of extinction for purely natural reasons) which may suddenly become the centre of a controversy orchestrated by academics knowing little and caring less about human health problems prejudiced thereby. We thus come back to Mrs Aaron's[1] alternative to inaction, the reasoned risking of a measure of harm to what are now termed 'non-target organisms', so 'that the great evils worked by the (target... M. L.) species may be prevented'. It is good to be able to record that in 1980 WHO/BCV/SWG reversed itself on the two 1979 recommendations discussed above. Neither, though, should ever have been made; nor would they have been, in a day when expertise, not geographical location, was the prime basis for selecting WHO's research advisers.

TDR training activities are aimed at the laudable end of furnishing Third World countries with adequate cadres of their own professional and technical manpower for contemporary vector research and control. Whether such an end can be achieved to order is, of course, speculative. Surely research excellence, geared to practical application, is something that *evolves*? Such evolution took place over many years at one Africa's oldest, and still probably the best, laboratories in our field – the South African Institute for Medical Research, Johannesburg. Being sceptical about TDR's ability to *create* equivalent research excellence in tropical Africa in the short term, I seriously question whether the Special Programme's training objectives are attainable this side of 2000 A.D. My reasons for such doubt are fourfold. First, the lack of potential (already basically trained) manpower in the Third World countries concerned; second, a likely lack of objectivity (for both tribal and external political reasons) in selecting candidates for further training abroad; third, the improbability of acceptable employment awaiting successful such candidates on their return; and fourth, the difficulty of enticing them back home anyway.

Our preoccupation with safety-related issues since the early 1970s[36] of course has a thoroughly rational basis. Unarguably, it is just as important that integrated mosquito control methodologies should have minimal adverse impact on non-target organisms as that they should be maximally effective against the target species. It is also important, though, that such issues do not become an obsession. When this happens, it is only too easy for present-day expert advisory groups to concentrate on highlighting 'gaps in knowledge' in their reports, rather than recommending forthright control action (such as the theoretically – and since the Tuvalu project (shortly to be discussed), demonstrably – safe introduction of new commercial microbial control and insect growth regulator products into the drinking water supply of an entire Pacific atoll community[26] against *Aedes aegypti*). International bodies convening such advisory groups, e.g. WHO, always welcome calls for them to support so blameless an object as additional safety research; never, of course, destined to answer any more than a philosopher might, the question, 'How safe is safe?' In this context, and with specific application to the meaning of 'safe' with respect to food additivies, it is interesting to note that the legislative history of the current American federal Food, Drug, and Cosmetic Act has required the US Food and Drug Administration (FDA) to equate safety with proof of 'a reasonable certainty of no harm'[18]. Such a commonsense solution of the ecological acceptability dilemma concerning candidate innovative control agents could accelerate the commercialization of badly needed biocontrol products based on naturally occurring biological agents (and eventually, genetically engineered ones too) and answer in the negative the question posed by Klausner[19], 'will regulation be the biggest pest?'.

One of the four regional sub-targets of item 13.2, 'Disease Vector Control'[52] of WHO's next (1984–1989) Five-Year Plan, is 'To reduce by 1989 *Aedes aegypti* populations to a level where transmission of dengue and urban yellow fever would be improbable in as many countries as possible in the Americas'. Specified sub-target research to be conducted includes, broadly based investigations of 'the distribution, population dynamics, ecology' *of the world's best-known mosquito;* the predeliction of which for artificial containers as larval habitats, outside of the original African homeland propensity of 'wild' *A. aegypti* subsp. *formosus* for tree-hole breeding, makes the globally tropical vector of today's dengue hemorrhagic fever and – in a few residual areas – yellow fever, the most susceptible of all mosquito vectors of disease to a determined and sustained control assault based upon known facts[26].

Provided that adequate funds are furnished, something new will of course always be found out about anything, if sufficient time and talent are devoted to the task. Surely better by far, though – once sufficient (and not neces-

sarily exhaustive) background information on the target vector has accumulated, and when adequate source reduction, larvicidal and adulticidal control measures have been identified as constituents of an appropriate integrated control methodology – would be the welding together of these components for immediate practical application! In the case of *Aedes aegypti* there are good historical precedents for this vector's suppression under Ross' 'sanitary anarchy'. Moreover, and as is not yet the case for any species of malaria vector, a fully integrated control methodology combining conventional approaches with the latest innovative technology, has been developed in the South Pacific atoll group of Tuvalu and applied, with demonstrated efficacy, on the chief island, Funafuti[26]. This methodology was founded upon disciplined source reduction with full community participation, fostered by a preliminary public relations effort including the preparation of adequate informative and instructional material in the local dialect of the Polynesian language. It combined non-chemical action against the immature stages of *Aedes aegypti,* using the Teknar® liquid formulation of the first anti-mosquito 'microbial pesticide', *Bacillus thuringiensis* subsp. *israeliensis,* and Altosid® briquets and tablets (i.e. the juvenile hormone mimic methoprene, an insect growth regulator), together with adulticidal residual spraying of the interiors of all houses and other buildings on the atoll using Ficam® W (i.e. the carbamate, bendiocarb). The more academically minded might, incidentally, care to ponder the prospects for basic additions to the sum of knowledge resulting from the *operational* research pre-requisite to any goal-oriented project of this nature, for in the initial larval habitat survey on Funafuti a previously overlooked *A.aegypti* site of potential epidemiological significance there and elsewhere was discovered – the water-retaining central cavity of peridomestic papaya trees[25].

Bacillus thuringiensis subsp. *israelensis* – *'B.t.i.'* for short, and sometimes referred to as serotype H-14 – was discovered in Israel's Negev Desert as recently as 1976[32]. Thanks to the pre-existing quarter of a century of experience with other subspecies and serotypes of *B.t.* in agricultural and forestry entomology, and particularly to the accelerated attention devoted to the organism through its being fed into the fine WHO system of Collaborating Centres concerning biocontrol, it rapidly gained universal recognition as the first really promising 'microbial pesticide' for use against mosquitoes, and blackflies too. Several safety-assured *B.t.i.* products have already been commercialized. Notable among other as-yet unmarketed candidate biocontrol agents of mosquitoes are three for which WHO/BCV/SWG has provided important research support. – *Bacillus sphaericus*[9], the fungus *Culicinomyces clavisporus*[44] and the nematode *Romanomermis culicivorax*[11]. Unlike *B.t.i.,* which is not marketed in viable state, all three of these potential biocontrols offer the prospect of self-replication in the field, although experience to date suggests that intermittent inundative applications (but at longer intervals than in the case of *B.t.i.*) rather than single inoculative ones will probably still be necessary.

The prognosis for biological components of future integrated mosquito control methodologies is thus promising, although a due sense of proportion must be maintained. Thus the overall message that continues to be heard from most of the groups and individuals engaged in studying and promoting the organisms just mentioned, is the one recently put into words by Gregory[15], who declared the goal of WHO in this connection to be 'control of the disease vectors of ... malaria, through biological rather than chemical means'. Such a goal is illusory. Conveying the discredited implication of an either/or situation, it flies in the face of all vector control experience since this century began. While the prospect of a biocontrol panacea is commonly held out by writers of research grant applications hoping to gain sympathetic attention from the anti-chemical lobby, all the evidence demands its repudiation; for the very best of the agents still, or likely to become, available for practical use against anophelines and other mosquitoes – be they biological, chemical or environmental – cannot of themselves alone bring about the required levels of vector suppression. A selection of approaches from all of these sectors will be essential for the proper design of each future integrated control methodology tailored to the specific requirements of each uniquely individual control problem.

In this context it is worth keeping in mind that pre-*B.t.i.* biocontrol agents employed against mosquitoes were overwhelmingly the two widely exported New World larvivorous fish, *Gambusia affinis* and *Poecilia reticulata*[13], and that these, like various more localized approaches to naturalistic control[49], performed best when being applied and maintained by some dedicated individual of broad biological background; K.B. Williamson, who was widely active in tropical Africa and Asia in the 1920s and 1930s, is perhaps the outstanding example. His kind of vector control scientist became something of an endangered species during the quarter-century ascendancy of the synthetic chemical pesticides between the advent of DDT during World War II, and the upsurge of environmentalist activism from the end of the 1960s. One good consequence of the latter phenomenon was that its pressures helped to make room for biologists in vector control once again. However, many of these followed the example of their chemically oriented predecessors by specializing narrowly. Tschirley[46] has remarked on this trend as it pertains to economic entomology's Integrated Pest Management (IPM); attainment of which it is preventing because 'It is far easier to scale the professional heights in a narrow field of specialization than in a broad, complex area such as systems of crop protection' – or in medical entomology, integrated mosquito control methodologies! Unlike the often mud-bespattered vector control leaders of Williamson's stamp and generation, these contemporary workers in the field of biocontrol have tended to reject the environment of the field in favor of that of the laboratory. Into the latter, it should be appreciated too, the discipline of mosquito genetics has largely retreated; after enjoying (since the early 1960s) lengthy support from WHO. While valuable fundamental results of lasting importance were achieved, this line of investigation has failed to lead to any practical application to present or contemplated mosquito control by way of autocidal techniques as originally envisaged by enthusiasts for genetic control.

Fortunately, therefore, the remaining chemical pesticides

upon which (although at considerable and ever-increasing cost) we can still depend, have lately been joined in our mosquito control armoury by those first commercialized products based upon a biocontrol agent *(B.t.i.)* and a synthetic juvenile hormone mimic, the insect growth regulator, methoprene. Examples of the growing range of these products are increasingly advertised in current issues of *Mosquito News*. Both groups of innovative agents are only effective against the immature stages of Culicidae (and a few other aquatic insects too). Meanwhile, for reasons of developed resistance and environmental unacceptibility, one whole group of synthetic organic compounds, the chlorinated hydrocarbons, are no longer usable for larviciding in the anopheline control programmes that have replaced former MEP projects based on residual adulticiding; and as a group, the carbamates are 'insufficiently potent as larvicides'[4]. Among the organophosphates, though, malathion is still widely used against larval anophelines, as are other more toxic OPs. While as a residual adulticide malathion is still 'the principal replacement for DDT in areas of mosquito resistance'[12], seven species of *Anopheles* are now resistant to it. This leaves us facing residual spraying with still more toxic and costlier OPs or carbamates[4,50]. Also (shades of Aaron, Howard and Ross!) a refined oil (Flit MLO®) is being recommended in this context. While in the words of A.W.A. Brown, certain synthetic pyrethroids are proving 'highly potent larvicides for culicines' as well as 'effective residual adulticides against anophelines'[4].

The ingredients for integrated control methodologies targeted to specific anophelines are thus ready to hand (indeed, there are considerably more candidate biocontrols – pathogens, parasites, competitors and predators – for such predominately surface-water breeders than in the case of container breeders like *Aedes aegypti*, against which source reduction is clearly more practical anyway). We thus have the means of buying time 'by maximizing the opportunities for each first-rate larvicide or adulticide to remain effective for as many years as possible' so that 'what is known as integrated control may relegate chemical control to its strong suit, namely a precision which can obtain immediate and thorough control in definite areas at planned times'[4]. R.E. Fontaine has also lately gone on record[12] with the telling statement that 'The technical limitations of residual spraying with a single insecticide demand that it should be supplemented by other methods of control whenever feasible'. Brown and Fontaine, both from a base of very considerable international experience, wrote as academics. Not so J. Goose[14], who from the industrial standpoint submitted that 'it is to be hoped that malaria control campaigns will use residual insecticides in integrated programmes involving mosquito source reduction by the time-honored (but now, unfortunately, it seems sometimes forgotten) methods of sanitation and water management as well as, mosquito larvicides and the use of chemotherapy. It is also to be hoped that, in the not too distant future, biocontrol agents and malaria vaccines will take their place in those integrated programmes.' Among those biocontrol agents, in the case of anophelines, are such South American and African transient-pool fish as *Cynolebias* spp. and *Notobranchius* spp. respectively, both of which could help to fill presently unutilized ecological niches in tropical South Pacific habitats of such malaria vectors as the *Anopheles farauti* complex, major vectors in Melanesia and the only ones present in Vanuatu (formerly known as the New Hebrides). Aquatic faunal manipulation in such regions which for reasons of geographical isolation have sharply limited natural predator complexes to regulate anopheline populations, could contribute significantly to future integrated control of the latter.

Why, then, must actual integrated anopheline control methodologies – seen so clearly as urgently necessary by practical people with collective experience spanning the governmental/university/industrial spectrum – be awaited any longer? And I am not (and neither were those just quoted) referring to basically conventional chemical methods with a sop to the principle of integration by e.g. some relatively minor use of larvivorous fish too, or to the e.g. inoculative application of field-collected mosquito pathogens without provision for mass cultivation and successive inundative applications unaccompanied by selectively designed adulticidal chemical control measures appropriate to each particular problem. One reason for the continuing inertia is failure by some of those responsible for major vector control projects to appreciate that safe, effective, quality-controlled products based upon *B.t.i.* (not to mention such 'third generation pesticides' as methoprene) are now available in substantial quantities from North American and European manufacturers. Instead, efforts continue to be made to convey the message that salvation is at hand for Third World countries with fermentation capacity (i.e. a beer industry), but lacking hard currency reserves, via production of their own biocontrol agents cheaply instead of depending upon conventional chemical pesticides produced in a few affluent countries. This idea arises from the groundless generalization that 'the production of biological agents does not require the costly infrastructure associated with the synthesis and formulation of conventional insecticides'[16]. As pointed out elsewhere[20], 'Even with the best resources of the industrialized world, it takes much skilled effort and time to achieve a standardized product meeting relevant governmental regulatory criteria prior to marketing', a sufficiently costly endeavour to which must be added the expertise and outlay required to ensure the safety of plant workers and any closely adjacent residents (not to mention people and ecosystems subsequently exposed to the product) and achieve and maintain proper formulation, standardization and quality control[53]. While all this just *might* be practical now or in the near future in a select few of the more advanced and stable Third World countries*, it is quite out of the question for most of those states (many of them subject to severe political instability) standing in greatest need of vector control supplies and programmes. Another compelling reason for the continuing failure to translate theory into practical action in the matter of integrated anopheline control methodologies, is the lack of vector control leaders with the requisite breadth of training and experience; or at any rate, their lack in those

*And since these words were written India's December 1984 disaster at the Bhopal pesticide plant has introduced fresh doubts.

Third World countries with the worst malaria problems, particularly those of WHO's African, Southeast Asia and Western Pacific Regions, which as stated by Bruce-Chwatt[6] respectively accounted for 39%, 31% and 25% of the ca 13.7 million cases of the disease actually reported to WHO in 1978.

The year 2000 A.D. will have come and gone before ambitious programmes for the strengthening of education, training and research in such countries have finally resulted in the presence there of sufficient numbers of their own nationals to form, without reinforcement from elsewhere, 'mosquito brigades' of the sophistication now required. It will therefore be necessary to make good the deficit from other parts of the world, just as it was when this century dawned. And just as was the case then, the costs are going to have to be borne by the wealthier countries. One can but hope that these will not only be the industrialized ones which have carried the torch to date, but also those singularly fortunate small states which, at remarkably little cost to themselves, have acquired enormous assets in hard currency from the happy geographical accident of their location in relation to major oil reserves.

Much of the manpower for the required integrated anopheline control cadres to be paid for from such external sources, will inevitably also have to be imported. Most will come from industrialized countries having strong research groups (in all three relevant sectors, university, government and industrial) in every aspect of conventional and innovative mosquito control, besides a history of the successful domestic operation of mosquito control agencies. No less that 533 of the latter had operational programmes in the USA and Canada alone in the fiscal year 1975–1976, the total areas larvicided and adulticided respectively being 4,713,845 acres (1,907,667 hectares) and 30,488,988 acres (12, 338,619 hectares)[2]. Incidentally, for countries long free from malaria except for intermittent imported cases, so impressive an organization of continuing pest and vector control is an eloquent commentary on the heightened demands of healthier, better educated and more prosperous populations for relief from biting fly attack on a permanent basis, even after the risk of vector-borne disease has been reduced to a very low level.

There is little doubt but that at a time when the western world's economic recession is causing severe shortages of employment for public health entomologists, like other scientists (recent graduates in particular), the challenge of recruitment to foreign service 'mosquito brigades' would meet with a ready response from the USA, Canada and European countries where, as in the USA, safety-assured innovative products for vector control are already being marketed.

The modern equivalent of Ross' 'mosquito brigades' that I have in mind would always be composed of equal numbers of foreign and indigenous staff. Such an arrangement worked harmoniously in Tuvalu during the *Aedes aegypti* project recently completed there[26]. I have confidence in its timeliness, and applicability elsewhere to vastly more ambitious undertakings, especially malaria control ones. These will, however, be costly, many of them extremely so. But the guarantee of support to see each project through to completion would not be the only prerequisite. There would have to be the most binding agreement (as distinct from glib assurance) on the part of each government concerned, not only to provide the project with its fullest possible support at all times (this obligation covering such things as the utmost facilitation of delivery of incoming equipment and supplies to operational sites, without, for example, the endless bureaucratic Customs delays that have plagued international health projects in even the most stable of tropical African countries), but also to assure that on completion the project will be succeeded by the establishment of permanent mosquito control agencies, staffed by the local counterparts whose service on the integrated control teams would by then have fitted them for their new responsibility.

So practical an approach could solve the problem enunciated by Ross[37] in a fashion strongly supportive of TDR hopes to see Third World countries furnished with resident cadres of their own professional and technical manpower for vector control and relevant research, by the end of this century. Meanwhile, it could not but further the prospects for notable advances towards health betterment there, via *Anopheles* suppression. However, without adequate financial support for salaries, purchase of equipment and supplies including control agents, and administrative, laboratory and field running costs, we shall be back to Ross[37] conclusion about 'generally [having] to leave small native towns and villages to their fate for the present'.

To conclude, more, much more, research relating to *Anopheles* remains to be done as each new advance in knowledge leads to another. For example, our lately acquired understanding of cytogenetics and linkage groups in these and other vectors, is now leading to the elucidation of species complexes that will stand until the next advance in sophisticated taxonomy. But we must get our priorities in order, unless we propose, indeed, to literally research these vectors to death! For a very substantial proportion of current studies in this and related fields is not going to make the slightest difference to our already-existing capacity to control anophelines and malaria. Such essentially scholarly work should not be competing for funds with operational control programmes, which in their turn should not (so close, after all, to the end of our millenium!) be awaiting the results of further investigations other than the purely operational research prerequisite to the design and implementation of an appropriate control methodology. Upwards of 90 years of unremitting research have already handed us the key to the solution of the world's remaining anopheline control problems which – granted clear-headed organization, discipline, scientific capacity and dedication and above all, massive financial support – *can* be solved via the 'new answers through vector control' that stand ready and waiting; I cannot envisage any malaria situation, anywhere, that could not be resolved *now* through an integrated vector control methodology based on source reduction with full community involvement and the sustained use of appropriate combinations of selected adulticidal chemicals as residuals and space sprays, the equally commercially available microbial products and insect growth regulators for application against the aquatic stages, and (particularly as a long-term aid to

anopheline population suppression) the building up of self-replicating parasite/predator/competitor complexes designed to augment pre-existing natural population limiting factors in each particular problem area. Costly? Of course it will be, tremendously so; but in the light of recent global economic experience, still costlier, the longer that forthright action is delayed.

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Short Communications

Muscle fluorometry: a determination of the depth of penetration

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Summary. Fluorometric recordings of NADH (nicotinamide adenine dinucleotide) were made on rabbit papillary muscles. The specimens were placed between the UV light source and a small window of the detection stage. As the muscle was moved over the window in a transverse direction, simultaneous measurements could be taken of transmitted UV light and fluorescent light for various thicknesses of tissue. It is concluded that a muscle thickness of 0.65 mm is optimal before absorption of the incident light decreases the fluorescence signal.
Key words. Rabbit papillary muscle; muscle fluorometry; penetration depth.

Following the first investigations of muscular energetics, the need arose for a suitable monitor that could relate the growing pool of myothermic data to specific biochemical reactions. The technique of tissue fluorometry was subsequently developed[1], allowing intracellular oxidation-reduction levels to be monitored continuously in whole muscle preparations.

For most investigations, the experimental method involved focussing a beam of 365 nm light onto the surface of an intact muscle while continuously recording the fluorescent light originating from the same plane[2–4]. As some of the excitation light will be absorbed by the muscle, the depth of penetration from which it is possible to record fluorescence may be limited. While this might not be undesirable for studies involving localized functional regions such as the cortex of the brain and kidney[5], the interpretation of data obtained from whole muscle preparations (particularly those with heterogeneous fibre distributions) might prove difficult if tissue fluorescence were being recorded only from the most superficial cells.

This problem has been approached in two ways. The first was to measure as accurately as possible tissue fluorescence while varying the effective muscle thickness. A fluorometer system was constructed such that the tissue fluorescence was recorded from the opposite side (or 180 degrees to) the beam of incident light. This has the advantage that, by narrowing the field of view to a fraction of a millimetre and moving muscles with a circular cross section horizontally across the field, an indication of the amount of light absorption taking place can be obtained. To verify the experimental results and to simulate other recording conditions, a model of the generation and absorption of fluorescent light was prepared and run on a VAX-11/780 computer.

Right ventricular papillary muscles were removed from adult (1.8 kg) rabbits and placed in modified Krebs-Henseleit solution containing (in mM); NaCl 118.0, KCl 4.75, $CaCl_2$ 2.54, KH_2PO_4 1.18 $MgSO_4$ 1.8, $NaHCO_3$ 28.4 and glucose 10.0. The muscles were kept under light tension and equilibrated with 95% oxygen 5% carbon dioxide mixture. Fluorometric measurements were made using a microfluorometer essentially the same as that developed by Jöbsis and Stainsby[6].

For experimentation a suitable muscle was selected and placed in a perspex clamp that held the muscle vertically while allowing it to be moved horizontally across the field of view by a micrometer. The fluorometer field was reduced to 0.3 mm diameter by an aperture in a piece of silver coated with nonfluorescent paint placed as close as possible to the muscle surface. Measurements were performed using two right ventricular papillary muscles approximately circular in cross section and having diameters of 1.4 ± 0.1 mm. Each muscle was placed in the clamp and moved through the field of view until a maximum fluorescence reading was obtained. This was standardized to 100% for both tissue fluorescence and excitation light. The muscles were then repositioned at the edge of the aperture and moved horizontally across the fluorometer field in increments of 0.05 mm. A sample of chart recording for one complete scan showing the outputs of tissue fluorescence and excitation light is presented in figure 1. Four scans were made on each muscle and the data are presented in figure 2. The fluorescence obtained at both zero and maximal horizontal muscle movements originated solely from the fluorometer optics, as the muscles were outside the field of view. The fluorescence output increased rapidly as thicker portions of muscle were brought into the fluorometer field until a plateau was reached. This corresponded to the maximum thickness of the muscle at which point absorption of both incident and fluorescent light became limiting. Presumably, had the diameter of the muscles been larger, a greater reduction of fluorescence would have been evident.

In theory, the absorption of light in a homogenous medium should be described by an exponential function of the type

$$I = I_0 e^{-ax}, \quad (1)$$

where I_0 and I are the incident and tranmitted light respectively, x is the thickness of a particular medium and a is a constant for the absorption of the light through that medium. Thus, it is possible to describe mathematically the present arrangement whereby incident UV light of 365 nm is producing