The Journal of Experimental Biology 206, 3727-3734

doi:10.1242/jeb.00677

Editorial

Research approaches in the development of interventions against vector-borne infection

Andrew Spielman

School of Public Health and Center for International Development, Harvard University, 665 Huntington Avenue, Boston, MA 02115, USA

(e-mail: aspielma@hsph.harvard.edu)

Accepted 18 August 2003

Summary

The conceptual basis of public health entomology developed at the turn of the twentieth century with the seminal experiments that guided the first vector-directed interventions. Within 50 years, technological advances built confidence in the power of research to resolve threats posed by vector-borne pathogens. Hope that the resulting diseases might be eliminated by time-limited interventions, however, soon became remote, thereby intensifying research efforts in vector biology. Beginning in the 1960s, US investigator-initiated grant proposals in vector biology were reviewed by a panel of the National Institutes of Health (NIH) that considered all proposals relating to 'Tropical Medicine and Parasitology' (TMP). Following the recommendation of a conference held in 1978, proposals relating to insect physiology came to be reviewed by TMP. A standing '*ad hoc* entomology' study section was formed in 1982 to deal with this influx of proposals. Another conference, held in 1993, encouraged consideration of proposals relating to vector transgenics by that study section. By 1994, this diversion caused the community of US public health entomologists to petition, in vain, for a return to the original concept of vector biology. By 2003, so many molecular proposals were submitted that entomological studies containing a field component were removed to an epidemiological study section distinct from TMP. In 2002, only half as many vector biology training programs could be identified in the US as in 1982, with a proportionate loss of associated faculty. A conference convened by the Institute of Medicine in 2003 concluded that the 'human resource capacity' in the US suitable for dealing with vector-related issues in health should be rebuilt. Although the development of such a discipline would depend largely on the system of investigator-initiated research proposals awarded by NIH, private donors and foundations seem likely to play an important role in this dynamic. The meld of vector biology, insect physiology and vector transgenics that will characterize the faculty that produces this new generation of public health entomologists remains to be defined.

Key words: public health entomology, vector biology, insect physiology, vector transgenics, research.

Introduction

Vector-associated human disease directly causes much misery while creating massive obstacles to economic development. Malaria is said to claim the lives of a million or more tropical residents each year and dengue several tens of thousands (Carter and Mendis, 2002; World Health Organization, 1997). In more temperate parts of the world, the risk of Lyme disease and its co-transmitted infections continues to rise. West Nile virus, too, increasingly afflicts the residents of certain of these more affluent regions. On a more mundane level, head lice infest the scalps of children virtually everywhere; their otherwise largely harmless attentions result in much school absenteeism. In spite of notable progress against many other diseases, these and other arthropod-associated infections continue to burden human affairs.

The armamentarium available for implementing interventions against vector-borne infection relies largely on insecticides. Residual and aerosol applications of adulticides have recently been supplemented by the use of various kinds of impregnated materials. Larvicidal applications, too, take many forms. Although environmental modification provides the basic level of protection against infections throughout much of the world, such measures tend to be expensive and may threaten biodiversity. Draining and filling of the breeding sites of mosquitoes, for example, permanently eliminate natural habits. The force of transmission of the various vector-borne anthroponotic infections may be modifiable by the application of vaccines or drugs. These measures have so far been applied against zoonotic infections, however, solely for prophylaxis or case management. Improved housing, on the other hand, may provide a strong element of sustainable protection against vector-borne infection while only minimally affecting the environment. Although our 'quiver of arrows' is extensive, we lack sustainable strategies for relieving the burden imposed on us by vector-arthropods.

The technology required for intervening effectively against vector-borne infection is based on systematic experimental research, activities that derive ultimately from the university system. Research scientists, of course, are educated in such institutions, and many continue to be employed there throughout their careers. Although others participate in research activities in federal or local agencies or in industry, the research interests of their university colleagues inevitably constitutes their own starting points. The forces that determine the composition and research orientation of a university faculty, therefore, largely shape the activities of the research establishment. A large share of the world's research activities is conducted in the USA. Accordingly, the following discussion describes the origins of the research traditions that pertain to vector-associated disease and will examine the forces that determine the dimensions of this research base in the US university system.

Discussion

Early research activities

Concepts concerning the contribution of hematophagous arthropods to human disease trace back to the 1880s when Patrick Manson experimented with his filarial-infected Taiwanese gardener (Chernin, 1977). He fed mosquitoes on the man and discovered that the microfilariae that he observed in the gardener's blood metamorphosed in the bodies of these insects. Not realizing that mosquitoes can feed more than once, he suggested that the worms infected new human hosts when ingested in drinking water. His protégé, Ronald Ross, subsequently observed 'black bodies' that developed from degenerating oocysts in culicine mosquitoes that had ingested avian malaria parasites and conducted a series of insightful experiments during the late 1890s. The role of mosquitoes in the transmission of human as well as avian malaria was, thereby, established. Ross understood that mosquitoes ingested vertebrate blood repeatedly over a period of many days. Similar accomplishments were recorded at about the same time in Italy. The first demonstration of transmission of a pathogen *via* the bite of a hematophagous arthropod was registered by Theobald Smith in an unusually influential study conducted during the early 1890s, demonstrating that Texas cattle fever is tick-transmitted (Smith and Kilbourne, 1893). This research analysis of babesiosis recommended pasture rotation for interrupting transmission of this tick-borne infection, an effort that was implemented successfully. These observations, conducted by scientists working largely in isolation, proved to be seminal.

The first major research effort that provided a basis for anti-vector interventions against a human disease was conducted by a team of sophisticated investigators in Havana in 1902. This four-member United States Army Yellow Fever Commission conducted a model investigation on the cause of yellow fever. Although the Cuban physician Carlos Finlay had previously associated *Aedes aegypti* with this disease (Finlay, 1886), he failed to convince his colleagues of this relationship. They noted that Finley's human subjects were not kept under close observation and suspected that they acquired infection by some other route. The key experiment that led to the ultimate demonstration of the transmission of this infection in 1902 is instructive in light of our current 'human subjects' practices (Agramonte, 1915):

> *'As the idea, that Carroll's fever must have been caused by the mosquito that was applied to him four days before, became fixed upon our minds, we decided to test it upon the first non-immune person who should offer himself to be bitten; this was of common occurrence and taken much as a joke among the soldiers about the military hospital. Barely fifteen minutes may have elapsed since we had come to this decision when, as Lazear stood at the door of the laboratory trying to "coax" a mosquito to pass from one test-tube into another, a soldier came walking by, towards the hospital buildings; he saluted, as it is customary in the army upon meeting an officer, but, as Lazear had both hands engaged, he answered with a rather pleasant "Good Morning." The man stopped upon coming abreast, curious no doubt to see the performance with the tubes, and after gazing for a minute or two at the insects he said: "You still fooling with mosquitoes, Doctor?" "Yes," returned Lazear, "will you take a bite?" "Sure, I ain't scared of 'em," responded the man. When I heard this, I left the microscope and stepped to the door, where the short conversation had taken place: Lazear looked at me as though in consultation; I nodded assent, then turned to the soldier and asked him to come inside and bare his forearm. Upon a slip of paper I wrote his name while several mosquitoes took their fill; William H. Dean, American by birth, belonging to Troop B, Seventh Cavalry; he said that he had never been in the tropics before and had not left the military reservation for nearly two months. The conditions for a test case were quite ideal.*
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> *I must say we were in great trepidation at the time; and well might we have been, for Dean's was the first indubitable case of yellow fever about to be produced experimentally by the bite of purposely infected mosquitoes. Five days afterwards, when he came down with yellow fever and the diagnosis of his case was corroborated by Dr Roger P. Ames, U.S. Army, then on duty at the hospital, we sent a cablegram to Major Walter Reed, chairman of the board, who a month before had been called to Washington upon another duty, apprising him of the fact that the theory of the transmission of yellow fever by mosquitoes, which at first was doubted so much and the transcendental importance of which we could then barely appreciate, had indeed been confirmed.'*

Although Lazear's accidentally acquired and fatal laboratory infection of yellow fever is described, the reader is left to wonder whether Dean survived his experimentally induced episode. This team of US Army scientists subsequently devised and conducted a series of well-controlled experiments that convincingly implicated *A. aegypti* in the transmission of yellow fever and that finally justified the intensive and extensive sanitary measures that freed Cuba of yellow fever, thus permitting the opening of the Panama Canal. The health relevance of research in public health entomology thereby became axiomatic.

Yellow fever disappeared from temperate-zone cities during the pre-war years, initially due to sanitary measures that largely eliminated the breeding sources of *A. aegypti* and later by complementary vaccination campaigns. Interestingly, dengue now proliferates in sites from which yellow fever receded into its forest reservoir nidi, in spite of a similar mode of transmission. Yellow fever once ravaged cities as far north as Philadelphia. The 1780 Continental Congress of the newly independent USA, for example, was nearly disrupted by such an outbreak during the preparation of its Constitution (Wills, 1996), perhaps due to the indoor storage of drinkable water. The development of municipal water supplies, of course, helped eliminate that threat to human health.

Before residual insecticides became available, malaria was mainly countered by means of source reduction and case management. The notorious drought-induced Sri Lankan outbreak of malaria of 1934, for example, claimed the lives of 80 000 people and sickened a third of the population before it ran its course (Jones, 2000). The subsequent liberal distribution of quinine may have helped terminate the outbreak. At about the same time, Fred Soper led a successful campaign against a monumentally destructive outbreak of malaria in Brazil (Soper, 1975). *Anopheles gambiae* had recently been introduced into the Natal region of that country and proliferated there. His teams identified the characteristic breeding sites of these insects, which were then systematically destroyed in parallel with efforts to place pyrethrum residues on the inside walls of houses. That measure was excessively costly because these extracts of chrysanthemum flowers lose insecticidal activity within about a week. In spite of enormous obstacles, this introduced species was eliminated from Brazil before it could become well adapted to its new habitat and was later eliminated from a newly established infestation in the vicinity of Aswan, upper Egypt. The 'bonification' (environmental improvement) efforts of Italy together with the depression era anti-malaria campaigns in the USA successfully reduced human–vector contact to the point that transmission was interrupted there (Kitron and Spielman, 1989). These interventions included a novel system of 'water-level management' that stranded the larvae of the vector mosquitoes at the margins of the reservoirs that had recently been installed. Classical environmental management programs effectively reduce the force of malaria transmission in particular endemic environments.

Research leading towards malaria eradication

Unprecedented governmental and foundation support was devoted towards public health research during the second half of the twentieth century. The Rockefeller Foundation, in particular, invested heavily in malariological and arboviral research. Fred Soper, Paul Russell, Thomas Aitken and Wilbur Downs drew their salaries from this source. The French, Italian, British and United States governments supported large-scale research efforts that transformed this nascent science.

Initially, this explosion in research activity was staffed largely by the participants in the Malaria in War Areas program of World War II. In the USA, these demobilized veterans staffed the newly formed agencies now designated as the Centers for Disease Control and Prevention (CDC) and the Agency for International Development (AID) and comprised the faculties of the burgeoning university system. Similar transformations characterized employment in other countries. Others served on the research staffs of the World Health Organization (WHO) or the Pan American Health Organization. Their wartime experiences imbued these people with faith in the research enterprise, with goals that focused on defined technological solutions: a novel drug, a vaccine, an insecticide. They largely staffed the university faculties during the post-war years and gave rise to the following generations of workers in public health entomology.

Current strategies for intervening against vector-borne infections began to assume their present form at about the time of World War II. The first persistent organic pesticide, which was discovered in 1939 by the Swiss scientist Rudolf Geigy, emerged from its veil of secrecy with the end of hostilities. American and British troops enjoyed the benefit of this discovery during the war, most visibly in Italy, when numerous civilians were liberally powdered with a DDT formulation in a successful effort to eliminate an outbreak of epidemic typhus. Soon thereafter, the cyclodienes, the organophosphorous compounds and the carbamates emerged as byproducts of intensive efforts of the various combatants in that conflict to synthesize neurotoxic moieties. The pyrethroids, microbial insecticides and growth regulators were developed somewhat later.

The experience of the Allied troops who participated in the Malaria in War Areas program during World War II was formative. The availability of DDT and of atabrine, the first synthetic aminoquinoline, revolutionized antimalaria measures, and concurrent development of the first generation of antibiotics opened the way for the treatment of such vector-borne infection as scrub typhus, epidemic typhus and various other rickettsial diseases. The '17d' yellow fever vaccine was an essential military prophylactic, and penicillin provided a case management panacea. These extraordinarily effective technological solutions built confidence in the power of research to provide readily applied answers to the threats posed by vector-borne infections.

The conceptual basis for intervening against vector-borne pathogens was laid down in 1957 with the publication of

George Macdonald's malariometric model (Macdonald, 1957). This culminating publication ranked the entomological components of vectorial capacity (Garrett-Jones and Shidrawi, 1969) and created the theoretical rationale for the massive worldwide effort to eradicate malaria (Spielman et al., 1993). Vector longevity, Macdonald argued, is the weak point in the life cycle of malaria, operating to the power of 12, the mean duration of the extrinsic incubation period of *Plasmodium falciparum*. In his International Development Advisory Board (IDAB) report of 1957, Paul Russell noted that DDT provided the ideal avenue for exploiting this discovery (Anonymous, 1956). Mosquitoes undergo at least an hour of diuresis after imbibing a meal of blood and they do so mainly while resting on a wall close to sleeping people. He reasoned that a residue of insecticide deposited there in a concentration that would be lethal in less than an hour of contact would reduce the force of transmission of this infection with unprecedented power. The report argued that agricultural applications of these chemicals would soon compromise the anti-vector usefulness of these insecticides and that the then-current window of opportunity would close. Three years, the report declared, would suffice. Rachel Carson's *Silent Spring* (Carson, 1962) had not yet been published, and the environmental movement was, itself, silent. The United States Congress incorporated eradication into its highest priority Mutual Security Act, and the President of the United States, Dwight Eisenhower, demanded 'unconditional surrender'. Dedicated funding, which would continue for five years, until 1963, relied entirely on this one mode of entomological intervention. The logic of the IDAB report seemed irrefutable. A half-century of experimental and computational research had come to fruition. In spite of the initial promise of this 'era of DDT', the failure of the eradication effort dashed hope that vector-borne pathogens might be eliminated by time-limited interventions.

Research in the post-eradication years

Huge health gains against malaria were registered during 1958–1963, including notable advances in parts of Africa. India was rendered almost malaria-free. But, '0% prevalence' was achieved only on the islands of Jamaica and Taiwan. Agency and faculty interests then shifted, and entomological interventions were de-emphasized. It was said that '*The entomologists have tried and failed; now let's let real scientists do the job*.' The WHO formally abandoned eradication as a goal in 1969, when, with several 'partner' organizations, the Tropical Disease Research unit (TDR) was formed. The first indication of promise for a vaccine against malaria was registered at about that time (Nussenzweig et al., 1967), and the search for a malaria vaccine came to dominate the research agenda of many institutions. Vaccinology was a central activity of TDR. This granting agency, however, is peculiarly irrelevant to the research needs of the US university system because its budgetary regulations permit no salary distributions to principal investigators. Such grants are better suited to institutions located where faculty salaries derive mainly from federal sources.

In teaching institutions in the USA, health-related positions for junior faculty are allocated largely on the basis of external funding. Such 'soft' funding less critically defines faculty profiles in universities whose appointees receive their salaries from the various states. During the second half of the twentieth century, the administrations of schools of public health and of medicine increasingly designed their faculties around the 'investigator-initiated' system of research grants awarded by the National Institutes of Health (NIH), and the 'RO1' system of grants has served largely as the engine of faculty growth. Job descriptions are composed around this perception. Before 1982, proposals relating to vector-associated disease were reviewed by the members of the 'Tropical Medicine and Parasitology' (TMP) study section of the National Institute of Allergy and Infectious Disease (NIAID). The entire gamut of relevant disciplines was considered by this group of experts in entomology, microbiology, vaccinology and other disciplines. The result was salutary.

Developments following the Woods Hole Conference of 1978

Entomological review was separated from the regular TMP study section in 1982 in the wake of the development of the first hormonomimetic insecticides and the landmark meeting of this committee in 1978 in Woods Hole, MA, USA. The meeting was inspired by the research accomplishments of the noted insect physiologist Carroll Williams, who spoke of the 'third generation of insecticides' that was then being developed. His 'golden oil', which effectively inhibited the metamorphosis of mosquitoes (Spielman and Williams, 1966), became the progenitor of methoprene and the various related chemicals that have increasingly been employed in public health programs. Although funding for insect physiology had then derived largely from the National Science Foundation (NSF), the sense of this meeting held that any research effort pertaining to the physiology of insects would be relevant to tropical medicine or parasitology. The NIAID accepted this recommendation and agreed to consider such proposals. Many were subsequently submitted and were reviewed by the TMP study section, meeting as a whole. Of these, some proposals in insect physiology were funded, and this encouraged additional submissions, which, in turn, required the assignment of reviewers who specialized in insect physiology. Within four years, so many basic physiological proposals were submitted that a new *ad hoc* committee was formed to evaluate all proposals requiring entomological attention. The members were to serve without limit of time. Epidemiological and parasitological applications of entomology as well as certain arbovirological proposals were thereupon separated from the health-related sciences and placed in a context that included basic insect physiology. The composition of this standing committee thereafter evolved to match the proposals that were submitted, which would necessarily tend to favor subjects familiar to the members of the committee.

By 1994, the effect of this separation of entomology from health was such that the community of public health entomologists in the USA became alarmed. Led by George

Craig, the various North American societies that were most directly concerned with tropical health – including the American Society of Tropical Medicine and Hygiene, Entomological Society of America, Society of Vector Ecology and American Mosquito Control Association – addressed resolutions to Howard Varmus, Director of the NIH, requesting corrective action. Craig's cover letter pointed out that 93% of the 56 grants in vector biology that were funded in 1993 dealt with fundamental insect physiology or molecular genetics and that their principal investigators were mainly associated with experimental research rather than tropical medicine or medical entomology. Within a decade of the *ad hoc* study section becoming a separate unit, virtually all NIAID-funded work on vector-associated disease was being conducted entirely at the bench. No analysis of previous funding patterns was provided.

Developments following the Keystone Conference of 1998

American scientists concerned with vector-associated infections began to employ molecular techniques during the late 1980s; the first symposium on this subject was held at the annual meeting of the American Society of Tropical Medicine and Hygiene in 1986. It examined the idea that the pathogen-competence of a vector population might be reduced by releasing transposon-favored, transgenically incompetent mosquitoes. None of the speakers were, themselves, engaged in work on vector arthropods. This situation soon changed. Numerous vector-related projects soon focused largely on molecular genetics. Indeed, 22 of the 53 titles that comprised the 1998 Keystone Symposium on transgenesis, entitled 'Toward the Genetic Manipulation of Insects', dealt with mosquitoes or kissing bugs. The expertise of three of the five conference organizers derived largely from their research accomplishments with mosquitoes. This influential symposium was the second in a continuing series of such events that were funded by the MacArthur Foundation and were attended by members of various granting agencies. The sequencing of the genome of *P. falciparum* (Gardner et al., 2002) and *A. gambiae* (Holt et al., 2002) and the ongoing NIAID-funded effort to sequence that of *A. aegypti* (designated as U01-AI050936) greatly facilitated such work. The creation of an insect that might be released in nature and that would transmit particular useful genes to a disproportionate fraction of its offspring became the goal of many research efforts.

The self-generating dynamic that followed the acceptance of insect physiology by the TMP study section in 1978 operated once again in 1998. The many proposals relating to molecular genetics that were submitted to the *ad hoc* medical entomology panel, now designated as an '*Ad Hoc* Special Emphasis Panel', required appropriate reviewer's expertise. Members of a review panel would naturally tend to favor proposals in their own discipline. Such a shift in membership encouraged the submission of more proposals of this nature, and the more molecular proposals that were submitted and funded, the more the membership shifted. In a session held in 2002, for example, 17 of the 20 members were themselves engaged exclusively in experimental research performed in the laboratory. This process accelerated into 2003 when the *Ad Hoc* Special Emphasis Panel was divided, much as the original TMP study section was divided in 1982. All entomological proposals that included a field component were thereupon removed to one of the epidemiological study sections then operating within the NIAID.

Sources of research funding

The NIAID program of investigator-initiated grants in TMP was augmented in 1980 by a system of Tropical Disease Research Units (TDRUs) that originally was designed to support overseas work on the five parasitoses selected by the WHO. The effort was expanded in 1995 to encompass the entire gamut of tropical infections. The International Center for Infectious Disease Research (ICIDR) provides similar overseas support. ICIDR and TDRU awards are 'program grants', each of which comprises several discrete 'projects', and they are generally based in a tropical site. Although few in number, these university-based programs continue to provide first-rate employment and training opportunities for people engaged in research on vector-borne infections.

The NIH's system of training grants has long provided crucial support to many generations of students interested in vector-associated disease. The NIAID program is designated for US nationals and that of the Fogarty International Institute for foreign students. Although both programs support students, neither provides faculty salaries. The CDC recently initiated a system of training grant awards in public health entomology and awards research contracts in response to particular emerging infections. These training programs and occasional research efforts do little to stimulate faculty hiring.

The United States military was an important source of extramural funding for research in vector-associated disease during the 1970s. This program funded investigator-initiated proposals, much as those considered under the NIH RO1 system, and awarded funds according to the opinions of an *Ad Hoc* Study Group on Medical Entomology of the Walter Reed Army Institute of Research. The panel operated in the pattern of an NIH study section. The program, however, was too small to influence staffing patterns in the American university system and it ended during the mid-1980s. Particular projects on such vector-borne 'select agents' as those responsible for tularemia and eastern equine encephalitis have been funded by the Defense Advanced Research Projects Agency (DARPA). But this source of funding, too, is small and short-lived and may not influence university hiring practices. The various Naval and Medical Research Units (NAMRUs) also maintain overseas laboratories that conduct research projects devoted to vector-borne infection. Grants from the National Oceanic and Atmospheric Administration support faculty engaged in research on the distribution of these infections.

The AID became a major granting agency in 1963, in the wake of the failure of the worldwide effort to eradicate malaria. Although malariological research was discouraged during the eradication effort, 5% of all operational funds were designated for research after the effort was abandoned. An audit of the program, conducted in 1983, described a $125 million general research fund that had been awarded since 1963 (General Accounting Office, 1982). Of this, the $26.5 million that had been spent was devoted mainly to academic research on drug and vaccine development. Robert Desowitz's *Malaria Capers: Tales of Parasites and People* (Desowitz, 1993), however, described the sadly disappointing nature of this research effort. AID's subsequent program of 'environmental impact evaluation' provided opportunity for numerous university faculty to gain important experience in the epidemiology of infectious disease but provided little salary support. Such 'non-academic' units as Harvard University's Institute for International Development (HIID) once devoted important resources to the central administration of that institution but generated few new teaching faculty. HIID was recently transferred to another university. The NSF also awards relevant funds. Although various of the non-health-related US governmental agencies provide some support for university faculty, their impact on university hiring practices seems slight.

Funds from the US Department of Agriculture (USDA) largely shape the faculties of the various American land-grant institutions. Faculty at these state universities draw their salaries as a line item in each state's budget, and many also acquire research funding from federal 'Hatch' funds. Until recently, these universities produced many of the medical entomologists employed by public health agencies and in the university system. The entomological orientation of the land-grant programs is uniquely strong, and the departments of entomology in the US tend to be located in such institutions. This element of financial permanence largely insulates the faculties of land-grant colleges in the US from peer-generated pressures on their faculty profiles. Although NIAID funding supplements their basic agriculture-oriented sources, the faculty profiles of the land-grant schools tend to respond less directly to public health requirements than do those of schools of medicine and of public health.

Various foundations have long played an important part in funding research efforts relevant to vector-borne infection. The Rockefeller Foundation, of course, contributed much fundamental knowledge during the early part of the twentieth century. The MacArthur Foundation's program has focused narrowly on vector transgenics, as has the Burrough's Wellcome Foundation. The Gates Foundation has entered this field of endeavor with a system of unusually large donations. A multi-million dollar gift to the London School of Tropical Medicine has permitted that institution to transform its malaria activities with a multi-faceted program of research. An even larger, but anonymous, gift permitted the malaria program of the Johns Hopkins Bloomberg School of Public Health to expand. New faculty appear to have been recruited in response to both of these gifts. The Gates Foundation has recently requested suggestions for a 'grand challenge', and we await the result. This effort, too, seems likely to increase the number of scientists engaged in research on vector-borne infection. Although foundation support tends to be directed towards narrow, 'cutting edge' goals, such funds have been sufficiently generous and sustained since the early 1990s to influence faculty hiring patterns.

Anti-malaria interventions recommended by multilateral agencies at the beginning of the present millennium can be encapsulated mainly by two acronyms, ITM and CT, representing 'insecticide-treated materials' and 'combination therapy'. The Roll Back Malaria (RBM) program of the WHO and its partner agencies seeks to halve the burden of malaria during the first decade of the millennium and to halve it once again by 2015 by 'scaling up' the application of these techniques (Nabarro and Mendis, 2002). Only limited operational research is conducted, and progress has not yet been reported. The United Nations recently launched a Millennium Development Goals program that is to formulate a poverty reduction program for the developing world. One component of that program is concerned with anti-malaria strategies. The role of research in this developing strategic formulation is yet to be defined.

Changes in vector-related activities in US universities

A comprehensive review of the status of training and research in public health entomology was conducted in 1982 (National Research Council, 1983). This 'Coolfont Symposium' was organized by the National Research Council and included participants from various universities, diverse laboratories, the military, federal and multilateral granting agencies and various foundations. Questionnaires were submitted to 28 schools of medicine, public health, departments of biology and departments of entomology that were identified as potential sources of training in disciplines that pertained to the transmission of vector-associated disease. The 24 responding institutions listed 63 relevant faculty, and about half had only one faculty member. Of those responding, 17 had teaching programs that included some field-related component; but only seven had overseas components.

Characteristics of the different programs, identified at the Coolfont Symposium, are instructive. Because faculty in the seven land-grant institutions draw their salaries from their state coffers, they tend to design their research and teaching programs around local needs. The training programs of these institutions focused on the biology of the vectors themselves, and none included coursework in epidemiology or pathogenesis. A few included virological components. The seven health-oriented institutions, conversely, emphasized coursework pertinent to the burden of human disease while downplaying entomological subjects. The salaries of these health-related faculty were then, as now, notoriously 'soft', deriving mainly from external sources, which induces them to cast a broad net in their search for grant support. Overseas activities play a large part in their endeavors. The three responding departments of biology were housed in private institutions. Their programs and research orientation differed. One, at the University of Notre Dame, trained a large fraction of the medical entomologists of the time and focused on the biology and genetics of mosquitoes. Some seven doctoral-level vector biologists had been graduating from these diverse US institutions each year. In general, the respondents suggested that the growth of their programs was less dynamic than in the recent past.

A smaller, but comparable, survey of US training opportunities in public health entomology was conducted in 2002 by Walter Tabachnik at the request of the American Mosquito Control Association (personal communication). He found that 12 universities had active doctoral-level programs in the subject and that they employed 33 relevant faculty. These instructors had been producing some nine doctoral graduates in vector biology per year since 1998. A simple comparison of the Coolfont and Tabachnik surveys suggests that nearly half of the relevant programs may have been discontinued during the past two decades and that the extant programs employed only half as many faculty as in 1982. Surprisingly, no diminution in doctoral graduates was evident.

Transgenesis came to dominate vector-oriented studies beginning in 1993, when a series of notable research findings was published (Aldhous, 1993). As practiced, these research efforts generally include no field component. TDR, the MacArthur Foundation and the Wellcome Foundation modified their funding policies in 1993 such that future grants in this discipline would be devoted to attempts to create transgenic vector insects. Although the public health usefulness of such a mosquito was then controversial (Spielman, 1994a,b,c) and still remains in doubt, an aura of excitement has increasingly come to surround vector transgenesis. The proportion of the faculty that Tabachnik surveyed who were engaged in this narrowly focused aspect of the study of vector-associated disease may be quite large. In general then, fewer university faculty in the US appear to be prepared to investigate the transmission of vector-borne pathogens than in the recent past. The magnitude of the investment in research in vector transgenics will affect this trend.

Conclusions

A panel recently convened by the Institute of Medicine (IOM) recognized that the US now lacks the capacity to confront the health threats posed by vector-borne pathogens (National Research Council, 2003). The panel concluded that:

> '*CDC, DOD, NIH, and USDA should work with academia, private organizations, and foundations to support efforts at rebuilding the human resource capacity at both academic centers and public health agencies in the relevant sciences – such as medical entomology, vector and reservoir biology, vector and reservoir ecology, and zoonoses – necessary to control vector-borne and zoonotic diseases.*'

These diverse federal agencies differ in their faculty-enhancing policies. In the past, only the NIH had sufficient resources and a commitment to investigator-initiated research to affect staffing decisions at health-related and private US institutions. The influence of the USDA mainly affects land-grant institutions, and staffing decisions there respond largely to the interests of their respective state legislatures. The departments of entomology in these institutions, therefore, tend to be shaped by local interests. Funding patterns of the CDC and the Department of Defense (DOD) have been much smaller than that of the NIH, and they have been directed towards narrowly defined goals that have changed as the perceived need has changed. The NSF, which was not included in the IOM recommendation, at least until recently, has tended to fund basic, rather than health-related, research. CDC, DOD and USDA employ vector-related health scientists but without stimulating the faculty appointments that result in their production. The 'human resource capacity' at US universities that might be capable of dealing with vector-related issues in health, therefore, would depend largely on the system of generous investigator-initiated research that resides at the NIH.

The IOM recommendation cited above omits reference to the contribution of private foundations to the human resource capacity of US academe. The Gates Foundation and the Burroughs Wellcome Foundation seem likely to play an important role in this dynamic. The funding policies that they pursue in the immediate future may encourage faculty to engage in insect transgenesis, insect physiology or research relating to transmission of pathogens.

Changes in the NIH system of proposal review may impose novel constraints on health-related research on vectors conducted by the faculty of US universities in the immediate future. Investigator-initiated proposals might be evaluated at the NIH in an epidemiological context in place of the biological milieu that pertained in the recent past, and the research tradition of at least some of the authors of these proposals will differ fundamentally from that of their reviewers. Faculty working in land-grant institutions, in particular, may not readily be able to address reviewers whose research tradition focuses on numerical rather than experimental applications. In addition, many of the reviewers of proposals dealing with vector transgenics will, themselves, be practitioners of that discipline. Authors of research proposals that pursue aspects of insect physiology may also find themselves at a disadvantage. These developments seem likely to increase the numbers of funded research proposals that approach vector biology from the tradition of vector transgenics. The administrators of US schools of public health and of medicine, therefore, would feel constrained to plan their staffing policies accordingly.

Required is a cohort of scientists who can usefully produce the next generation of public health entomologists and whose research activities will promote that goal. Their programs will strike some balance between the three entomological interests that have vied for support during the past half century – vector biology, insect physiology and vector transgenics – and the work should incorporate strong epidemiological features. Our ability to '*control vector-borne and zoonotic diseases*' depends on the research activities of a strong cohort of vector biologists who are capable of using techniques developed by insect physiologists and molecular biologists. Over-investment in any particular, speculative intervention modality, of course, is to be avoided. Because faculty-hiring priorities are determined so strongly by the NIH system of investigator-initiated grants, a major responsibility in this regard falls on that federal agency. Participation by foundations and private donors may contribute powerfully to the outcome of this process. The characteristics of the evolving discipline of public health entomology remain to be defined.

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