Moving from science to public health programs: lessons from vitamin A1,2

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ABSTRACT  The transition from research to the applications of its results is a difficult one. Several stages must be passed through before a discovery can be put to practical use. The development of the current standards for vitamin A is a good example of both a successful and a difficult transition. The importance of the public media and of international organizations, especially the World Health Organization, in any transition is noted. Movement from research to practical applications requires that scientists take an active, sensible leadership role, that mechanisms for disseminating information and for bringing about scientific consensus are used effectively, and that international funding and support agencies take a role. Am J Clin Nutr 1998;68(suppl):513S–6S.

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INTRODUCTION  Moving from research to its mainstream application for the benefit of society can prove as difficult and elusive as making the discovery in the first place. More than a century passed before Edward Jenner’s discovery of successful vaccination resulted in the eradication of smallpox; over 40 y after the development of a successful polio vaccine, the disease was finally eradicated from the Western Hemisphere, but not yet from the rest of the world. A physician who noted that children receiving aspirin after tonsillectomies bled more than those not receiving aspirin began prescribing aspirin to prevent myocardial infarction 40 y before we recently rediscovered and adopted this therapy.

Often, the problem lies with the scientist that makes the original discovery. Having created and published the data, he or she commonly moves to a new phase of their research without concern for the relevant application of the knowledge produced. Thus, the persons most deeply involved in the discovery and most passionately convinced of its validity all too often abandon their own work before it has influenced clinical practice or national health policy. Multiple steps stand between a research discovery and a change in policy. These include, but are not limited to: 1) making the discovery; 2) proving, to one’s own satisfaction, that the discovery is indeed real; 3) documenting variability of the results in different populations, environments, and cultures; 4) overcoming the traditional reticence of other scientists in the field and convincing them of the discovery’s validity; 5) educating policymakers about the discovery and its policy implications; and 6) devising and establishing programs that actively put the discovery to work.

Several examples epitomize critical stages of success, and others, of failure. One example we’ll return to is nutrition in general and vitamin A in particular. EV McCollum, the founding chair of biochemistry at The Johns Hopkins School of Public Health, was a true public health scientist. He not only discovered vitamins A and D (1) and revolutionized nutritional science in the process (2), he worked equally hard at teaching homemakers to feed their families more nutritious diets. To spread the word, he published over 100 articles in McCall’s magazine, served on presidential commissions, and traveled widely, lecturing to home economics teachers. He worked closely with pediatricians, educating them about the relation between rickets (until then a disease of mysterious origin) and the preventive and curative powers of vitamin D. McCollum suffered no loss of scientific standing or credibility for these efforts, a concern repeatedly raised by researchers who fear that promotion of the practical value of their discovery for people’s health will detract from their standing as scholars.

VITAMIN A

The development of oral rehydration therapy provides another lesson. Soon after it was clear that a safe oral solution for rehydration of cholera victims was at hand and effective even in remote field settings (3), Alex Langmuir, who had followed its development closely, arrived at the Cholera Research Laboratory in Dhaka on one of his periodic visits. Langmuir asked what the investigators planned to do next. They excitedly discussed a series of studies to explore the physiologic basis of their success, refining and improving the solution. He cut them off. “No,” Langmuir declared, “you are going to repeat the practical field demonstration in Bengali adults, Nepalese children, Nepalese adults, Filipino children, etc, and you are going to publish each study in a different journal.” They did. His purpose, and the result, was to saturate the medical establishment with this new

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discovery, ensuring that everyone had heard of it (A Langmuir, personal communication, 1987). He helped ensure that they took notice and provided them with evidence that it worked in different cultures and environments and could not be easily dismissed as something that is good for Bengali but not Filipino children.

My own experience with vitamin A deficiency and childhood mortality is consonant with these patterns of response to new discoveries and provides clues about ways to overcome predictable obstacles to practice. Despite McCollum’s one-man educational crusade, scientific insights from the first 2 or 3 decades of this century had relatively little effect on the public’s health (4). Animal experiments and a smattering of clinical studies strongly suggested that vitamin A deficiency was not only responsible for an important form of pediatric blindness, but for morbidity and mortality as well. Indeed, Stephenson and Clark (5) showed that vitamin A–deficient animals died at excessive rates and suffered severe systematic infections long before their deficiency was severe enough to cause xerophthalmia. Ellison (6) proved, in a classic randomized clinical trial in children hospitalized in London for moderate-to-severe measles, that vitamin A supplementation (as cod liver oil) reduced case fatality rates by 50%. Yet none of this changed health policy, accepted scientific paradigms, or the clinical management of measles.

Many years later, in 1983, we observed that vitamin A status seemed closely linked, in a dose-responsive way, with preschool-age mortality (7). Our publication of these findings was essentially ignored, with the exception of a single inquisitive letter to the editor: no one challenged our observation, publicly agreed with it, or, as far as I know, planned to confirm or refute it. We then launched a randomized trial of periodic large-dose vitamin A supplementation every 6 mo. The conservative intention-to-treat analysis indicated that supplementation reduced preschool-age mortality by >30% (8). The response from those in the nutritional science community was bimodal: some were interested and enthusiastic; most were either nonbelieving or openly hostile. One researcher was quoted in a news article as saying, “If Sommer claimed a 10% impact we might have believed it; but not 30%.” We may have convinced ourselves that we were onto something, but we clearly had not convinced the scientific community at large; without at least general agreement among interested scientists, there was little hope of convincing policymakers. Note that the one telling exception was in Indonesia; having been a party to the research, workers there believed and accepted the result and began to address its programmatic implications. Policymakers immediately drew up plans for a nationwide vitamin A intervention program, and included it in their 5-y national plan. Indonesia has continued with an active and productive research program ever since.

Martin Forman, then director of the US Agency for International Development (USAID) Office of Nutrition, instantly recognized the need for replicative randomized trials conducted by different qualified teams in different countries. Only then, he reasoned, would there be a critical mass of evidence from widely scattered populations and environments that would, if valid, capture a group of international and local scientists. After several organizational meetings and half a decade of additional field work, the results (4) and opinions largely coalesced (9; 10; GH Beaton, R Martorell, KA L’Abbe, unpublished observations, 1992). Importantly, policymakers were involved in the research projects in their own countries, even if at an advisory level, thereby setting the stage for their interest and commitment and subsequent action on the results.

As evidence grew, so did international political support. A consensus meeting held at the Rockefeller Study Center in Bellagio, Italy, in 1992 issued a concise series of recommendations and supporting data that was reprinted in mainline medical journals (11) as a means of bringing the debate to closure. The United Nations Activities Coordinating Committee/Subcommittee on Nutrition issued its own analysis. As a result of these published and widely circulated conclusions, scientists and policymakers followed and participated in the worldwide endeavor through involvement in the meetings of the International Vitamin A Consultative Group (IVACG) every 18 mo and actively shared information. Furthermore, the personal commitment of a few highly respected international leaders, including the late James Grant, then director of the United Nations Children’s Fund (UNICEF); Hiroshi Nakajima, Director General of the World Health Organization (WHO); and V Ramalingaswami, chair of the International Conference on Nutrition, made control of vitamin A deficiency by the year 2000 an integral goal of the World Summit on the Rights of Children, the International Conference on Nutrition, the World Health Assembly, the Food and Agriculture Organization (FAO), and UNICEF.

Fifteen years ago, few countries were concerned about vitamin A deficiency as a significant public health problem; even fewer were attempting to do anything about it. Although vitamin A deficiency will certainly not be controlled worldwide by the year 2000, more than 60 countries now recognize its importance and are actively engaged in developing or implementing intervention activities.

There is some telling irony to this tale. Soon after proving to our own team’s satisfaction that vitamin A prophylaxis could reduce overall preschool mortality by at least 30%, we wondered whether it might not play a major role in the high case-fatality rates associated with measles in African countries, where vitamin A deficiency was not considered a serious or prevalent problem. A small hospital-based randomized study in central Tanzania showed that large-dose vitamin A supplementation resulted in a 50% reduction in the rate of severe measles complications and in measles case fatalities (12). The article was published by the British Medical Journal in the section “Research from the South,” suggesting to many readers that, whereas the results were too impressive to ignore entirely, the study was at least faintly tainted. Ironically, this was the same journal that had published the identical London study almost half a century earlier (6).

Despite this single study of relatively small size, UNICEF and the WHO officially recommended large-dose vitamin A supplementation for the routine treatment of measles under conditions existing in most developing countries (13). No doubt, the impetus for this response was the growing evidence of the role of vitamin A in preschool mortality as a whole, and particularly in measles-specific mortality. With community-based prophylactic studies now capped by a randomized therapeutic trial, it must have seemed the prudent thing to do even in the absence of replicative data. Subsequent studies proved that the decision was a wise one (4). With a resurgence of measles and measles deaths in the United States, particularly in children with low vitamin A concentrations, the same recommendation has been adopted by the American Academy of Pediatrics.

An entirely fortuitous event that affected the widespread acceptance of our research shows the importance of the public media. A colleague, while in flight to a refugee relief camp dur-
ing the Ethiopian famine of the mid-1980s, was seated next to the then UNICEF director James Grant and told him of the importance of vitamin A supplementation during refeeding to prevent blindness and reduce childhood mortality. On returning to the United States, Grant asked that I brief him and his colleagues on these developments, an event that initiated his and UNICEF’S continuing interest and support for the control of vitamin A deficiency. As research moved forward and the data solidified, UNICEF officers around the world were instructed to inform country counterparts of important developments and to encourage the organization of vitamin A programs. Later, a Time magazine article about the Ethiopian famine included a sidebar article about the lifesaving properties of a new “golden bullet,” the gelatin capsule used to distribute vitamin A. We have never lived down this sobriquet among our research colleagues, but it served as a powerful marketing tool among policymakers and the public.

Finally, one cannot overestimate the value of WHO publications. Because those at USAID who supported our research and created IVACG recognized early on the importance of having senior leadership of IVACG come from within the UN system in general and WHO in particular, IVACG’s first chair, Edward DeMayer, the distinguished WHO nutritionist, arranged to have the recommendations and conclusions of the first major international meeting held in Indonesia in 1974 published in the WHO’s Technical Report Series (14). These conclusions included the criteria by which vitamin A deficiency could be classified as constituting a public health problem (thereby declaring that vitamin A deficiency could pose an important health problem) and recommended dosages of vitamin A for preventing such a problem and for treating active xerophthalmia. By the second such conference, held 8 y later, the original recommendations could be refined on the basis of data generated during the intervening decade. These, too, were published by the WHO (15), and although the recommendations were never official (which would require the work of expert committees constituted specifically for that purpose), their publication in the Technical Report Series provided the appearance of the WHO’s imprimatur, which gave the recommendations validity in the eyes of policymakers worldwide that would never have been achieved otherwise.

In summary, moving from science to public health programs requires a group of individuals, including scientists originally involved in the discovery, to take an active, balanced, objective leadership role. It requires a clearly defined series of steps that include ensuring that the conclusions are valid, that the environments in which they are relevant are defined, and that the local scientists and policymakers are involved in the process. Especially important are mechanisms such as IVACG for sharing information and disseminating results (including lessons learned in overcoming programmatic obstacles), bringing the scientific discussion to closure, and widening the network of involved organizations, particularly credible entities like UNICEF and the WHO. Nothing can substitute for a dedicated funding agency (USAID in the case of vitamin A), regardless of the support that others might bring to the table. When the time is right, all appropriate means must be employed to get the word out. Major reports about vitamin A appeared in AsiaWeek, Time, The New York Times, and the mass media around the world; these in turn stimulated other media outlets that drew further political and financial support: in the United States, a television story (on 20/20, moderated by Hugh Downs, who worked closely with UNICEF) captured the attention of members of Congress who increased their support for USAID’s vitamin A and child survival accounts.

CONCLUSIONS

The success of any efforts to translate research into public health programs depends on continuing research that overcomes unanticipated obstacles or simplifies implementation. The smallpox eradication program would have failed in the absence of such research (16). Its original approach, to vaccinate the entire population, proved impractical and was replaced by “surveillance and containment,” concentrating resources on vaccinating all those known to have been in contact with an active case. The vaccine, originally heat labile, was lyophilized, thereby simplifying storage and transport. And just as vaccine supplies were running low, along came the simple but brilliantly designed bifurcated needle, which required so little vaccine per application that it effectively quadrupled the world’s supply overnight.

Convincing policymakers to implement programs is always difficult. They are constantly dealing, within a politically charged environment, with requests that exceed resources. In the case of vitamin A deficiency, xerophthalmia and blindness were perceived by medical and public health personnel, but by very few policymakers, to have sufficient claim on limited resources. It was only after the relation of vitamin A deficiency to morbidity and mortality became apparent that policymakers became interested. Cost-benefit analyses are useful only to a point; every society interprets these through their own culture (what economists call externalities) in determining what they are and are not most concerned about.

It is clear from the articles in this supplement that our knowledge concerning the role zinc plays in health and disease is rapidly approaching a critical mass. Scientific leaders should set timely targets for follow-up meetings at which additional data can be considered, discussed, and assimilated. Even before then, once consensus is reached on the value of targeted zinc supplementation, meetings should be held with policymakers appropriately experienced with micronutrient issues to consider and compile alternative programmatic strategies. These will begin to stimulate international interest, provoke suggestions and locally appropriate refinements, and serve as a basis for advocacy and commitment.

REFERENCES

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