Am. J. Trop. Med. Hyg., 88(3), 2013, pp. 409–410
doi:10.4269/ajtmh.12-0741

Editorial
Good Things Are Worth Waiting For

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The diagnosis of intestinal schistosomiasis has historically relied, and continues to rely, upon stool examination using the modified Kato technique.[1] Efforts to replace the Kato-Katz method by determination of circulating antigens go back half a century,[2] but success has been elusive despite Gold and others[3] showing (in experimental animals) that antigen concentrations and worm burdens are indeed correlated. The antigen they worked on is found in both blood and urine, just as the one targeted by the point-of-care circulating cathodic antigen (POC-CCA) assay for the diagnosis of *Schistosoma mansoni* infection. This commercial detection system, already successfully investigated in the field by several research groups, has now been evaluated in a large-scale trial covering five African countries.[4] Interestingly, long before monoclonal antibodies and the polymerase chain reaction (PCR) had made diagnosis sufficiently sensitive *BMJ* (Editorial)[5] supported the use of measuring antigens secreted in the urine. Although, at first it was only possible to detect blood-borne antigens in massively infected animals, Phillips and Draper[6] showed the presence of circulating antigens also in human sera by the addition of citric acid followed by double counter-current immunoelectrophoresis in a hypertonic buffered gel to ensure breakup of any antigen-antibody complexes. Nonetheless, in one of the quirks of science, and contrary to the suggestion by the *BMJ* editorial, a wild goose chase seeking new and different circulating antigens ensued, eventually veering off toward immunopathology rather than staying the course. This "swerve" in scientific focus guaranteed continuation of the Kato-Katz approach, which still reigns supreme in spite of missing many light infections. It should, however, be pointed out that this test is useful in areas deemed moderately and highly endemic according to current World Health Organization (WHO) guidelines,[7] its limits only becoming apparent when the intensity of disease is low, e.g., in well-controlled areas.[8] Although schistosomiasis control has come to rely almost exclusively on mass drug administration (MDA) with the drug used (praziquantel) being comparatively cheap, a tool to maximize cost effectiveness and health impact would still be useful.

Unperturbed by the waning interest in the diagnostic aspects of circulating antigens, Professor André Deelder in Leiden, the Netherlands, and his co-workers did not leave the diagnostic trail. They continued the line of research on the anodic (CAA) and the cathodic antigen (CCA) as markers for infection,[9] that began where Gold and others[3] left off. After many years of false starts, a promising assay based on nitrocellulose strips was advanced for the testing of urine samples mixed with monoclonal antibodies specific for CCA and tagged with colloidal carbon.[10] This approach, commercialized as the POC-CCA assay, is not only significantly more sensitive than Kato-Katz, but also rapid, specific, standardized, and easy to read.

The sensitivity of POC-CCA and other tests in use (Kato-Katz as well as DNA-based diagnostics such as PCR) cannot be directly compared, as the former assay is not limited to the sample provided but reflects the worm load in the subject as a whole. It also follows that the POC-CCA provides the better measure of infection. Still, there is room for improvement such as, for example, a return to the Phillips and Draper[6] immunocomplex breakup experiments that could ratchet up sensitivity one more notch. This is not just of academic interest as the detection of even extremely light infections, perhaps just one worm pair, will be needed for certification of eradication, something that WHO might be asked to provide for the People's Republic of China (PR China) within this decade. Rather than purely supersensitive antigen detection, however, realistic accreditation will probably rest more upon a combination of antigen and antibody detection in subjects in former endemic areas, coupled with snail diagnostics in diverse testing ranges based on spatial statistics. Moreover, the POC-CCA assay has the sensitivity and the standardized approach needed for realignment of the three WHO levels of prevalence to be founded on more reliable cut-off values than they are at present. This can be done already today and represents no small advance.

Sensitive detection is needed to progress from schistosomiasis control to elimination. PR China has been unusually successful in controlling schistosomiasis and contemplates elimination of the disease by 2020.[11] However, compliance is becoming a major problem as people are becoming increasingly less inclined to provide fecal samples[12]; this could be counteracted by changing from fecal to urine sampling as the latter would be more acceptable than both blood samples and fecal sampling. The success of the Chinese control program owes much to its reliance on snail control together with MDA, whereas the approach in sub-Saharan Africa is open-ended as transmission control is not part of the present strategy and therefore runs an even greater risk of compliance failure.

Although time and money do not constitute scientific variables, they naturally play an important role. According to Speich and others,[13] a single Kato-Katz thick smear requires about 20 min per sample and the cost, including salaries, estimated at USD 1.73 is almost identical to that given for the POC-CCA assay.[4] Published assessments of this kind are rare but the costs cited are backed up by those involved in field surveys, which removes the argument that a commercial test cannot cost more than 1 USD.

There is much to be gained by switching from Kato-Katz to POC-CCA; however, this would also mean complete transformation of control activities. Advocacy explaining why control programs should change will be needed: WHO has an

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important role to play here as well as in directing additional studies to ensure sufficient evidence is collected before changes are instituted. To make the conversion complete, the POC-CCA assay should be adapted also for *S. haematobium* and *S. japonicum*, the former because mixed infections are commonplace in Africa, the latter because of the prerequisite for improved diagnostics in PR China when the elimination phase is embarked on.

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