A New Assay: Specific Interferon-γ Detection for the Diagnosis of Previous Q Fever

Stephen R. Graves

Microbiology, Pathology North–Hunter, New South Wales Health Pathology and Australian Rickettsial Reference Laboratory, Geelong, Victoria, Australia

(See the Major Article by Schoffelen et al on pages 1742–51.)

Exposure to a microbe may be either clinically apparent (ie, the patient is sick) or not (ie, latent infection). In either case, antibodies are usually synthesized by the B-cell arm (humoral immunity) of the patient's adaptive immune response. This is the marker of exposure detected by most serological tests carried out in diagnostic laboratories. However, the other component of the adaptive immune system, the T-cell (or cell-mediated) immune response, is equally important to the patient's recovery and survival. However, this aspect of the immune response is rarely used to diagnose infection as T lymphocytes are involved, rather than antibodies, and they are more difficult to use in routine laboratory testing. Nevertheless, cell-mediated immunity (CMI) is both sensitive and specific, both features being the hallmarks of a good diagnostic test.

The article by Schoffelen et al [1] in this issue of *Clinical Infectious Diseases* uses the CMI arm of the patient's adaptive immune response to diagnose Q fever, or more correctly, to diagnose previous exposure to *Coxiella burnetii*, the causative bacterium.

When T lymphocytes in the patient blood are exposed in vivo to antigen deposited in the skin, they are attracted to the site and undergo antigen-stimulated proliferation while in the process of "attacking" the invading microbe (antigen). This produces an induration (lump) in the skin. One of the key cytokines involved in this process is interferon gamma (IFN-γ).

If the patient's T lymphocytes are exposed to antigen in vitro, IFN-γ is produced and can be measured. This is the basis of the assay developed by the authors. It is a good assay (sensitive and specific) but will probably never take over from the current serological assays for the simple reason that T lymphocytes in blood are more difficult to work with in the diagnostic laboratory than are antibodies in serum. Nevertheless, it is an additional diagnostic test and could be very useful in certain patients with difficult-to-interpret serology results.

It would be well worth developing as a routine assay in diagnostic reference laboratories in countries where Q fever is a problem—and this is probably every country in the world, except New Zealand (where no cases have ever been diagnosed). Countries that have periodic outbreaks, such as the Netherlands and Germany, may find such an assay to be a very valuable additional tool in controlling Q fever. Countries with high levels of background Q fever (but rarely large outbreaks because of different local animal husbandry practices), such as Australia, may also find it useful. Unfortunately, where large distances are involved in transporting patient samples to the diagnostic laboratory, the assay may not be useful, as the patient's T lymphocytes (as distinct from their antibodies) may not survive the long trip to the laboratory. For this new assay, it would be important to know the maximum time available to get blood from the patient to the laboratory. In a related diagnostic test for tuberculosis, it is 12 hours, greatly limiting the usefulness of the assay in Australia.

Interestingly, a similar assay was used many years ago in Australia when the human Q fever vaccine (QVAX) was being developed and tested, to show that vaccinees developed a CMI response [2–6].

Schoffelen et al's results show that skin testing, serological testing, and their new T-cell in vitro assay give essentially the same diagnostic results, which is very pleasing. One area of diagnostic difficulty in Q fever is the accurate diagnosis of the post–Q fever "fatigue syndrome." There appears to be no serological pattern that correlates with it. It would be interesting to know if there were an INF-γ release assay that could diagnose it. That would be of great practical benefit to the practicing medical microbiologist. Would Australian doctors and laboratories use

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Correspondence: Stephen R. Graves, Microbiology, Pathology North–Hunter, New South Wales Health Pathology, Locked Bag 1, Hunter Region Mail Centre, 2310, Australia (stephen.graves@hnehealth.nsw.gov.au).

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this new assay in prevaccination testing? Yes, because the current skin test and serological tests may both give false-negative results, with the result that the patient is immunized and may develop an adverse reaction to QVAX. But would the greater "sensitivity" of the new assay result in some normal person not being vaccinated (due to a false-positive reaction) and then being susceptible to Q fever in their workplace? Possibly. I have seen several cases in which Q fever has occurred in patients who were refused vaccination on the basis of faulty (false-positive) pretesting. The answer to this conundrum is to develop a better Q fever vaccine that does not require the patient to be pretested.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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