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EDITORIAL

Serodiagnosis of tuberculosis

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In the developing countries, which have the majority of the world's population, tuberculosis is one of the most important infectious diseases, causing illness and death on a very large scale. In these countries there has been little or no decline of this disease during recent years and improved control programmes and case identification are therefore imperative. In the developed countries tuberculosis is no longer among the most common diseases but it often causes diagnostic problems. More rapid methods for diagnosis would be a great advantage. Thus, a serodiagnostic test for tuberculosis would be extremely useful throughout the world. It would speed up diagnosis, and would be valuable when bacteriological proof is difficult to obtain, or when tuberculosis is part of a differential diagnosis.

Attempts to develop serodiagnostic tests for tuberculosis have been made for more than ninety years. In 1898 ARLOING and COURMENT published studies on agglutination of *Mycobacterium tuberculosis* cells using sera from patients with tuberculosis [1, 2]. Since that time a large number of publications have been made in this field (see review articles [3, 4]) and most serological techniques have been utilized. Most of the studies demonstrate similar results. They show that sera from patients with tuberculosis contain antibodies against the tubercle bacillus. As a group the tuberculosis patients have much higher antibody titres than healthy controls or patients with other diseases. The variations within the groups are large, however, and the groups do overlap. False positives and false negatives occur frequently. The tests therefore have comparatively little diagnostic value and serodiagnostic tests for routine diagnosis are not in general use.

There are several reasons for the failure to produce a serodiagnostic test which is both specific and sensitive enough. Most tests developed so far have been based on antigen preparations such as culture filtrates, purified protein derivatives (PPD) or whole cells, and such preparations always contain many epitopes. Mycobacteria are rich in cross-reacting antigens and *M. tuberculosis* is known to share antigens with other species of Mycobacterium as well as with nocardiae, corynebacteria, rhodococci etc. [5]. This may be the cause of the false positive tests amongst the controls, since these organisms abound in the enviroment and/or the normal human flora. A special problem in this respect is BCG vaccination, since *M. tuberculosis* and *M. bovis* BCG are immunologically very similar. A recent study by TURNEER *et al.* [6] demonstrated the interference of BCG vaccination with the IgM and IgG response.

A comparatively large number of false negatives have been shown in several studies, and may be explained by the presence of immune complexes. Several authors have shown that patients with tuberculosis not only have antibodies but also mycobacterial antigens circulating, which might therefore, result in the production of immune complex. CARR *et al.* [7] showed, for example, that most of the patients studied had immune complex. KRAMBOVITIS [8] reported that low antibody activity was assocated with heavy infection, suggesting that a release of mycobacterial antigens results in reduction of antibodies. Other investigators have not, however, found such a correlation [9].

During the last ten years, some investigators have used purified antigens for serodiagnosis of tuberculosis. Thus, DANIEL and DEBANNE [4] used purified cytoplasmic proteins from unheated culture filtrates of *M. tuberculosis*. One antigen, designated antigen 5, was found to be more satisfactory in enzyme-linked immunosorbent assay (ELISA) serodiagnosis than other antigens [10]. In a more recent ELISA study MA *et al.* [11] used antigen 5 for diagnosis of tuberculosis in China. Serum specimens were positive in 73 of 84 patients and in none of the healthy control subjects. REGGIARDO *et al.* [12] used three purified glycolipids from *M. bovis* BCG as antigen in a haemagglutination test. They tested tuberculous patients and healthy contacts and found that 82% of the patients and 21% of the contacts gave positive responses. Two of the lipids used were phosphatidylinnasitol mannosides which are common to a wide range of actinomycetes [13], thus explaining the many false positives. It may be mentioned that REGGIARDO *et al.* [12] found widely variable patterns of response to the three antigens and emphasized the importance of using a battery of tests, each with a separate antigen. Furthermore, antibody classes have been investigated demonstrating that IgG antibodies are more discriminative than IgA and IgM [14]. GIBSON *et al.* [15] also showed that the discrimination between patients was greatly improved by assay of IgG in its four subclasses. Even if the studies mentioned have both false negatives and false positives,

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the results are more promising than in many of the earlier studies, and may thus lead to the development of a suitable serodiagnostic test for routine laboratory practice.

Methods for the detection of mycobacterial antigens in body fluids have also been developed. Most of these studies have concerned tuberculous meningitis. Various methods, such as latex agglutination [16], passive haemagglutination [17], ELISA [18] and radioimmunoassay [19], have been used and in some studies monoclonal antibodies have been employed [17]. In these studies both false positives and false negatives also occur but the numbers are comparatively small. They may thus lead to new methods for rapid diagnosis of tuberculous meningitis.

Despite the fact that attempts have been made for over ninety years, serological tests for tuberculosis are not in general use at routine diagnostic laboratories. It is tempting to conclude that such a test cannot be developed. However, the author remains convinced that such a pessimistic notion is false. During recent years several studies have yielded promising results with a substantial increase in both specificity and sensitivity. Tests, which include the demonstration of antibodies against several antigens specific for *M. tuberculosis* or the demonstration of several specific antigens, would probably result in even better results. The problem of the immune complex must also be solved in order to decrease the false negatives. It is likely that future tests will include assays for both antigens from and antibodies against the tuberculous organism [20]. Monoclonal antibodies will remain important in many respects: for the purification of specific antigens, for competitive inhibition tests, or for antigen capturing assays. Further research in these areasis essential and should lead to a useful serodiagnostic test.

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