

Immunodiagnosics – Unfulfilled promises and needs

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The health of a population is not only one of the key indicators of its development but also its determinant. The developments in the field of biotechnology provide unparalleled opportunities to explore newer strategies for prevention, early diagnosis and specific therapy for a large number of diseases afflicting our people. Fortunately, the country recognized the importance of biotechnology and promptly instituted programmes in this field. There are several areas in the field of human health which could benefit a great deal from the developments in biotechnology. These include vaccines, antibiotics, recombinant hormones, etc. However, I have chosen to discuss immunodiagnosics. Unlike other areas, such as the development of vaccines and new drugs, which take a long time, immunodiagnosics can provide a quick indicator of the overall activity.

There are more than 50 research laboratories in the country currently claiming to be competent enough to develop immunodiagnostic kits. Many have already developed some and several have passed them on to the industry for marketing. Public money has been spent to support these efforts, yet public has hardly got any worthwhile products in return. The country is still importing a number of these kits at high prices, not always suitable to meet the needs of the country. Being one involved in supporting indigenous efforts in this direction for the last several years through various grant-giving agencies, I find myself dismayed at the current scenario. It is obvious that with the generous support from the Departments of Science & Technology and Biotechnology in the field of molecular biology, the country has developed infrastructure and individual expertise, but there are enough missing links in the innovative chain which are necessary to convert the bench science to a product. I am, therefore, tempted to share my perceptions on this issue, not to find fault with those who have striven and failed, but to initiate more critical thinking necessary to evolve a comprehensive fail-proof system to prevent the current waste of our resources and efforts.

Is there a need for investment in the field of immunodiagnostic?

The availability of specific therapy for a large number of infectious diseases still rampant in the country dictates the necessity for sensitive and specific diagnostic tests. Malaria, filaria, diarrhoeal diseases, typhoid, tuberculosis, leprosy, leishmaniasis and a host of viral diseases are responsible for the distressingly high morbidity and mortality prevalent in the country. In a country like the United States, where the incidence of most of these diseases is very low, the annual market for diagnostic kits and DNA probes has been estimated to be 200–300 million dollars. The need for these products will no doubt be several times greater in India. It has been estimated that in 1994 the market for immunodiagnosics was approximately Rs 90 crores. This is expected to increase several fold by 2000 AD (personal communication with P. K. Ghosh, Director DBT). Diagnostics no doubt constitute only a part of the overall requirement of biotechnological products for human and animal health, which nonetheless is not insignificant. There are nearly 90 industrial units currently engaged in producing biotechnological products in the area of animal and human health. Before this market is captured by multinationals, it should be possible to exploit indigenous competence and infrastructure already developed for this purpose. This requires an urgent in-depth study of the prevailing bottlenecks and shortcomings at every level and establishing a mechanism to weave together the current efforts into a coherent goal-directed activity.

In this era of free market economy it could be argued that, since many of the diagnostic kits can be imported, why invest our resources to develop these. There are several reasons, not just national honour, which necessitate such investments:

(i) There are many diseases prevalent in the country for which no diagnostic kits are available, nor is there any interest in the industry abroad to develop these

(ii) The organisms responsible for the disease in India are not always identical to those prevalent abroad. Hence, a test developed elsewhere may not have the requisite sensitivity. This has already been demonstrated for imported kits for hepatitis C, HIV, etc. Besides clinical diagnosis, this is even more important for molecular epidemiology.

(iii) In the absence of locally developed kits, a number of imported ones are currently being used at high cost even though their sensitivity is far from satisfactory. This is true for the imported ELISA tests for tuberculosis and cysticercosis used by most of the private diagnostic laboratories today.

(iv) The cost of imported kits is not affordable by the common man. An ELISA test for tuberculosis costs the patient Rs. 1000.

The current status of indigenously developed kits

As mentioned earlier, a number of individual scientists and national laboratories have, during the last 5–6 years, developed several immunodiagnostic kits. These include tests for pregnancy, malaria, filaria, tuberculosis, typhoid, leishmaniasis, cysticercosis, amoebiasis, as also kits for determining blood groups and a variety of hormones. Development of diagnostic kits based on monoclonal antibodies, DNA probes, PCR and peptide sequences for diagnosis of HIV, tuberculosis and hepatitis has been reported from various labs. A number of these have been independently developed by several investigators. To the best of my knowledge, except for the pregnancy diagnostic kit and leishmania antigen detection kit, none other is being marketed. At least a couple (filaria, typhoid) had to be withdrawn from the market after introduction. Some of the problems in these kits were:

(i) Initial claim based on a limited number of samples could not be confirmed on field trials

(ii) Lack of independent validation prior to transfer to the industry

- (iii) Inadequate evaluation of the shelf-life.
- (iv) Problems related to upscaling and large-scale production of the test developed in the laboratory.
- (v) Absence of mechanism for strict quality control.
- (vi) Unreliability of locally available component and back-up materials.

To this may be added the following:

- (i) Inadequate information on epidemiological characteristics prior to developing the test.
- (ii) Inadequate interaction between the laboratory scientists and clinicians on the one hand and scientists and industry on the other.
- (iii) Lack of appreciation of field conditions and market forces on the part of the scientific community.
- (iv) Lack of incentives for the industry to invest in indigenous kits.

It would be extremely rewarding to evaluate critically the factors responsible for these scientific successes which failed in the market place.

As a result of these problems, it is not uncommon to hear that a particular scientist/laboratory has generated antibodies sufficient for thousands of kits for diagnosis of one or the other disease. Yet there is no one coming forward to convert it into a commercial product. On the other hand, the representatives of the industry point out that at least some of the tests they introduced in the market failed to live up to the claims. Regrettably, in at least two such cases known to the author, no follow-up action seems to have been taken to remedy the shortcomings. In at least three instances involving several groups, when independent validation was carried out prior to transfer of the test to industry, the investigator's claims were not found to be fully justified even though at least a couple of tests were found to be very promising. This has led to an unfortunate credibility gap about such products. In this connection let me quote Dr Heinrich Rohrer¹, Nobel Laureate, who warned against exaggerated promises – 'Promises and exaggerations invariably beget new promises and greater

exaggerations: the gap between reality and wishful thinking widens exponentially, and more and more efforts become tied up in maintaining the pretense instead of pursuing solid scientific work. Even if we become expert pretenders and manage to uphold this posture until retirement – or even longer – this has a damaging influence on the image of science in society as well as in economic and political circles'. Those familiar with the current status of development of immuno-diagnostics and immunoprophylactics in the country will appreciate the validity of this statement. In some other cases the industry did not find the commercial viability of the test even if the product was satisfactory.

Is there a hope for future?

There is little doubt that with the existing infrastructure and expertise available in our scientific institutions, and the growing awareness in the indigenous industry of the possibilities of exploiting these for commercial purposes, there are a number of tests already developed which could be upgraded to achieve the required specificity and sensitivity. It should be possible to fulfill the projected requirements for such products profitably for all concerned. It is hoped that the lessons learnt from the ongoing experience would help to overcome the existing deficiencies in near future.

Suggestions for future actions

The following suggestions are made in the light of the experience gained so far:

1. A better interaction between the laboratory investigator and a clinician is necessary to understand the aetio-pathological and epidemiological aspects of the disease for which a test is being developed.
2. It is not enough to demonstrate the sensitivity of a test using pure cultures of an organism but to establish the same in appropriate clinical specimens.
3. The test should be validated using a large number of well-characterized speci-

mens obtained from different sources

4. The test should then be confirmed using coded specimens.

5. It is desirable to have an independent investigator, not involved in developing the test, to verify the results.

6. The stability of the reagents and their shelf-life under field conditions should be established.

7. The availability of facilities necessary to perform the test where it will be required – doctor's clinic, primary health centre, district or state hospital – should be taken into account while developing a test. A test based on radioimmunoassay (RIA) or PCR is of no use for district hospitals and private practitioners. However, there may be enough demand for these by major hospitals and diagnostic laboratories.

8. Involvement of industry is necessary to assess the market potentials of a test

9. It is necessary to create a national facility to validate the claims and provide for quality control of such products.

10. Among other things, to fulfill this requirement we need to create an accredited facility to serve as a repository of well-characterized microorganisms collected by investigators from all over India.

A survey of the recent developments, current status and the emerging scenario convinces me that there are unparalleled opportunities for Indian biomedical scientists to accelerate their efforts in a concerted and coordinated manner to convert their bench work to a usable and marketable product. It will not only restore the credibility of our science but will be a great service to the millions of our people. Provided the quality of the product is assured, the national market alone should provide rich dividends to any entrepreneur or industry. For some of these products there is a potential export market.

1. Rohrer, H *Interdiscipl Sci Rev.*, 1994, **19**, 193-199

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