



IMMUNOLOGY

Antibody responses after natural infection and after vaccination

by

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Natural infection with yellow fever virus is followed by appearance of complement fixing (CF), haemagglutinin-inhibiting (HI) and neutralizing (N) antibody. There is a lack of information concerning the precise timing of appearance of such antibodies and the composition of such antibodies in the human host, but by inference from studies in animals it can be assumed that N and HI antibodies appear within a few days of infection followed shortly by appearance of CF antibodies. Neutralizing antibody is first demonstrable on the fourth or fifth day after onset of illness and the peak level may not be reached until the fourth week or later. Berry et al. (1931) in a study of laboratory acquired infections, mention a case in which both virus and N antibody were simultaneously present in the blood on the fourth and fifth day of disease. Downs et al. (1955) report a case where a virus was isolated on the eleventh day of illness, at which time, and also later, a low level of N antibody was present. The antibody level was so low that it prompted the statement "if virus had not been isolated, the diagnosis of yellow fever could not have been made on the basis of these neutralization tests".

The N (and HI) antibodies produced following infection persist for long periods of time, although there may be some drop in antibody levels over a period of years. The individual appears also to have a life-long immunity to YF virus. It has been postulated that the long persistence of antibodies may result from a persisting virus infection. This has not been proven.

Theiler and Casals (1954) present a detailed study of HI, CF and N test reactions in yellow fever cases (all diagnosed by virus isolation) originating in Trinidad and Brazil. In primary infections (i.e. in infections in individuals who had no detectable group B antibodies in the acute phase serum specimen), the HI response in all cases was higher for a YF antigen than for antigens of several other viruses of group B although crossing antibody was detectable in most of the cases studied. A similar situation obtained for the CF antibody, although there was considerably less cross-reactivity seen. In N test, the cross-reactivity with DI, D2 and Ilheus was either minimal or non-existent, whereas there was distinct YF neutralization in all serum specimens taken more than three days after onset of disease.

In secondary cases (i.e. cases in which group B antibody was present in the acute phase specimens) the serological response was distinctly different. A high level of HI and CF antibody was seen early, and crossing antibody to other group B viruses also appeared early, and attained levels to certain of the viruses at times surpassing the corresponding YF antibody level. In such cases, identification of the infection by HI or CF reaction, in absence of virus isolation, might be impossible. This is the familiar "anamnestic response" which has

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been frequently noted in various group B virus infections. A significant degree of development of cross-N antibody to D1 and D2 was observed. The position with respect to Ilheus virus was not so clear, possibly because most of the pre-existing group B experience was with Ilheus virus, precluding the possibility of a "conversion".

Spence et al. (1961) describe two yellow fever cases in prior group B immunes, both showing a marked development of group B crossing in HI and CF. In one case studied in NT, the convalescent serum specimen (40 days post-infection) neutralized 2.8 logs more of YF virus than did the acute (five day) specimen. However, the convalescent specimen also neutralized 1.3 logs more of SLE and 1.6 logs more of ILH. The individual was solidly immune to dengue in both specimens.

The antibody response following yellow fever immunization with both the French neurotropic (FN) strain of vaccine administered by scratch, and by the 17D vaccine administered by subcutaneous inoculation or by scratch has been studied by a series of laboratories over a number of years. The chapter by Smith in "Yellow Fever" (Strode, ed., 1951) summarizes the position as of that date. It was apparent that the antibody response following immunization with the FN vaccine was more pronounced than was the response following 17D immunization. The higher frequency of complications following the use of the FN vaccine has led to replacement almost entirely by the 17D vaccine.

A number of more recent studies have shown that with the newer HI tests, and with modifications of the N test, post-vaccinal immunity can be demonstrated in a proportion approaching 100%, of those who have received an adequate dose of viable vaccine. Lobo (1958) points out, in connexion with the use of the HI test, the importance of using a haemagglutinating antigen prepared from the 17D strain itself. A very significantly higher proportion of positive reactors were thus detected, as contrasted to the tests run in parallel using an antigen prepared from the JSS strain of yellow fever. This important observation has been repeatedly confirmed. Using the 17D haemagglutinin, a very close correspondence between HI and N test can be achieved. Theiler repeatedly observed, in a number of studies of immunized individuals, a prolongation of the average survival time of mice used in the conventional intracerebral inoculation of adult mice test, when results as judged by mouse mortality might be considered equivocal. He developed a test using as virus source the Asibi strain of yellow fever virus in monkey serum, and as test animal the infant mouse inoculated intraperitoneally. With this test conversion rates approaching 100% are achieved, with close correspondence also with HI tests. Incidentally, this test is a very sensitive one for detecting heterotypic group B antibody also.

The problem of the occasional individual in whom no detectable antibody response develops remains. With the impossibility of examination by a challenge with virulent virus, it is likely to remain unanswered. Whether pre-existing antibody to (certain) other viruses of group B is a factor which may block infection with and multiplication of the vaccine virus is conjectural.

Protection afforded by yellow fever immunization is certainly long-lasting, possibly effective for the life span of the individual. Groot et al. (1962) found N and HI antibodies in a high proportion of individuals living in a region in Brazil where naturally occurring disease has never been recognized, vaccinated 17 years earlier. In the HI tests, they also found the 17D haemagglutinin gave results more closely corresponding to N test results than did haemagglutinins prepared from two other YF strains.

It has been shown that vaccination with 17D vaccine can induce a serological response to a range of group B antigens, in individuals with pre-existing group B antibodies, whereas the response in group B negatives is much narrower in range, essentially limited to YF. Wisseman et al. (1962) studied the N response in Japanese who had had prior JE infection and showed a broadened response to several other group B viruses.

Pond et al. (1967) carried out similar studies in individuals with past history of SLE or dengue, history being supported by serological findings. These studies were limited to HI and CF, and they showed broad heterotypic HI responses in the prior group B immunes, with parallel findings with CF although at a lower level and more variable. They remark that "YF vaccination is a potent tool to recall past elevated HI titres of SLE and dengue antibodies for epidemiologic purposes in order to detect populations in which outbreaks of group B arbovirus infections have previously occurred and may recur".

Monath (1970) carried out detailed N test studies of the immunoglobulins appearing following 17D immunization. IgM antibodies were first detected on day eight or nine, rose to high titres between day 14 and 17 and tended to decline gradually thereafter. However, significant amounts were detectable as long as 82 days following primary immunization. IgG antibodies appeared between 10 and 17 days after immunization, tended to remain stable or to rise slightly thereafter, and did not surpass IgM titres. Both IgM and IgG antibodies had a high degree of specificity for certain strains of YF. Serum N titres were higher for FN or 17D than for Asibi or Dakar 1279. The antibodies were also highly specific when compared with several heterologous group B viruses. Monath remarks that the prolonged synthesis of IgM antibody suggests a persistence of antigenic stimulation.

Wheelock et al. (1969) have demonstrated that 17D virus infects and multiplies in unstimulated human monocyte cultures and in human lymphocyte cultures stimulated to blast development by phytohaemagglutinin. Unstimulated monocytes and lymphocytes exposed to 17D produced interferon. In further studies Wheelock et al. (1970) have demonstrated that in individuals vaccinated with 17D, their peripheral lymphocytes, stimulated by phytohaemagglutinin, lose their ability to support growth of 17D between seven and 14 days following vaccination but regain this capacity by the twenty-fifth day post-vaccination. In one donor, however, the refractory state persisted for 76 days, but had disappeared by the two hundred and forty-eighth day after vaccination. Wheelock et al. (1969) suggest that "following immunization, lymphocytes in the lymphoreticular tissues of immune individuals may contain 17D virus which remains in a slowly replicating or non-replicating latent state for prolonged periods of time".

REFERENCES

1. Berry, G.P. & Kitchen, S. F. (1931) Yellow fever accidentally contracted in the laboratory, Am. J. trop. Med., 11, 365-434
2. Downs, W. G., Anderson, C. R. & Spence, L. (1955) Isolation of yellow fever virus from a human patient on the twelfth day of illness, Trans. roy. Soc. Med. Hyg., 49, 557-579
3. Groot, H. & Ribiero, R. B. (1962) Neutralizing and hemagglutination-inhibiting antibodies to yellow fever 17 years after vaccination with 17D vaccine, Bull. Wld Hlth Org., 27, 699-707
4. Lobo, M. Bruno (1958) Avaliacao da imunidade pos-vacinal, Revista do Servico Especial de Saude Publica, 10, 167-175
5. Monath, T. P. C. Neutralizing antibody responses in the major immunoglobulin classes to yellow fever 17D vaccination of humans (In press)
6. Pond, W. L. et al. (1967) Heterotypic serologic responses after yellow fever vaccination: detecting of persons with past St. Louis encephalitis or dengue, J. Immunol., 98, 673-682
7. Spence, L. et al. (1961) Description of human yellow fever cases seen in Trinidad in 1959, W. Indian med. J., 10, 54-58
8. Strode, G. K. (ed.) (1951) Yellow fever, McGraw-Hill, pp. i-xv, 1-710
9. Theiler, M. & Casals, J. (1958) The serological reactions in yellow fever, Am. J. trop. Med. Hyg., 7, 585-594
10. Wheelock, E. F. & Edelman, R. (1969) Specific role of each human leukocyte type in viral infections. III. 17D yellow fever virus replication and interferon production in homogenous leukocyte cultures treated with phytohemagglutinin, J. Immunol., 103, 429-436
11. Wheelock, E. F., Toy, S. T. & Stjernholm, R. L. (1970) Lymphocytes and yellow fever. I. Transient virus refractory state following vaccination of man with the 17D strain, J. Immunol., 105, 1304-1306
12. Wisseman, C. L., jr. et al. (1962) Immunological studies with group B arthropod-borne viruses. I. Broadened neutralizing antibody spectrum induced by strain 17D yellow fever vaccine in human subjects previously infected with Japanese encephalitis virus, Am. J. trop. Med. Hyg., 11, 550-561