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A REVIEW OF PROPHYLACTIC MEASURE AGAINST BRUCELLOSIS IN HUMAN WITH A LIVE ATTENUATED VACCINE §

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Introduction.

Brucellosis is an important Zoonosis which is World-Wide in distribution. This infection caused by bacteria genus Brucella which affects principally cattle, hogs, sheep and goats. Each group of animals is usually infected by its own type of organism, i.e., Br. Abortus in cattle, Br. Melitensis in sheep and goats, and Br. Suis in hogs. Man is susceptible to all three biotype of Brucella, but Br. melitensis seems to be more pathogenic for man in some regions.

Most incidence of human Brucellosis in area where goats and sheep flocks are developed is due to Br. Melitensis. The disease in man is a result of contamination by ingestion of non-pasteurized milk or other daily product derived from infected milk, mainly fresh cheese and cream, or by direct contact with infected materials.

The prevention of Brucellosis in man is dependent upon the elimination of disease in animals, which disseminate the brucella organism and constitute a serious of infection for healty animal and man.

Extensive investigation has determined that vaccination is essential and confer a significant degree of protection in animals. With this method there will be some delay before the incidence of the disease in animal is reduced so that the risk of infection for man is lessened. In the meantime there remains a need to protect human from infection. (Vershilova & Golubeva, 1953).

Human Vaccination.

In the U.S.S.R., a live brucella vaccine is being used in people who are in contact with infected animals. Vershilova (1961) has stated that almost 60% reduction in human cases has been obtained over the period 1952 to 1958 during which some 3 million people have been vaccinated. The vaccine consists of living organisms of derived from Br. Abortus Strain 19, a strain of reduced virulence, which has been extensively used throughout the world for immunizing cattle. One inoculation

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* Rev. 1 strain is non dependent mutant selected from a streptomycin-dependant culture of Br. melitensis strain 6015.

doses for subcutaneous injection of BA-19 vaccine contains 400 to 600 million of living brucella. No clinical signs of bruceliosis were observed in vaccinated persons although about 8% complained of general malaise, and headache, and 2% had a rise in temperature.

The safety trial of Russian BA-19 vaccine with comparison of living attenuated Rev. 1 vaccine* was carried out by Spink in Minnesota (Spink and al. 1962). Both vaccine has been inoculated subcutaneously in 32 healthy volunteers which was divided into two comparable groups. Detailled observation over a 6 month period of the clinical effect, and laboratory examinations revealed striking differences between the two groups. In group I, two of 16 persons developed acute brucellosis and 1 had a positive blood culture. In the Rev. 1 group, 11 of 16 persons developed acute disease, and blood culture were positive in 12 volunteers which subsided by following tetracycline therapy.

Production of agglutinines were revealed in all 32 persons. During the entire period, the agglutinine titers of group II tended to be higher than those given the BA-19 vaccine. Intradermo-reaction was positive in all person of the Rev. 1 group at the end of 6 months. In the BA-19 group only 7 were positive. This experience concluded that both vaccine particularly Rev. 1 could not be sufficiently safe in human for immunization porpose.

Elberg & Faunce (1964) have studies the relative immunogenicity of BA-19 strain and Br. melitensis strain Rev. 1 in Cynomolgus monkeys. As a result of this experience the BA-19 vaccine was considerably more effective when administered intracutaneously than subcutaneously, whereas, with Rev. 1 vaccine the difference was slight, but it conferred immunity in much lower doses.

In 1965, Pappagianis and Elberg described the effects of graded doses of viable Rev. 1 vaccine administered intradermally in human volunteers. The subject who received a dose of 1000 organisms did not show any elevation of temperature or symptom. The individual who has given 10,000 cells developed a lowgrade of febrile reaction. Of the others who were injected with 20,000 to 28,000 organisms developed fever and persistant symptoms and were treated with tetracycline. Other observation followed by blood culture, and serologic test were considered in this group. The authors conclude that the margin between a low dose of viable brucella and a dose of 1000 to 10,000 organisms is too small to allow the use of Rev. 1 in human being as a vaccine.

More recently the Russian have used the cutaneous method of vaccinating as they say this result in fewer serious reactions in sensitized person and can be used without preliminary skin testing (Smirnova 1961). It can be used for revaccination of persons. The intensity of the reaction to vaccination is dependent upon the degree of sensitization of the person prior to vaccination, those with negative skin tests having less reaction to vaccination than those with positive skin tests. Person who have active brucellosis in the past should not be vaccinated as it may lead to exacerbation of the disease. For this reactions it would seem preferable to perform a skin test perior to vaccination in preliminary studies.

According to the Russian report the cutaneous route of vaccination is preferable to subcutaneous route. However, a careful clinical study of the reactions to cutaneous vaccination is required before the method can be recommended for wide-scale use.

A Safety trial in human with the Russian strain BA-19 vaccine in Iran.

In 1963, a team from the Razi Institute with the assistance of WHO consulant and Co-operation of the public Health authorities in Iran carried out a safety test in human with the Russian strain BA-19 vaccine (Entessar 1964). The procedure for the safety test was that followed by Spink. Because of the variation in human being and the generalized symptoms associated with brucellosis, it was decided that half of the subjects would be given the living vaccine and the other half a placebo which consisted of heat-killed vaccine.

The Russian freez-dried vaccine prepared from strain BA-19 at the Gamelia Institute, Moscow, was used in this trial. This vaccine was divided in two parts. One lot (A) of the vaccine was reconstituted as direct and a viable count was perform on the day of vaccination. A second lot(B) of vaccine was killed by heating for 1 hour at 60°C. The calculation dose of living vaccine was 5.16×10^9 cells in two drops. The heat-killed vaccine contained a same dose. 34 persons were selected from 100 women by the clinician in charge of the study with collaboration of Brucella laboratory staff at the Razi Institute, on the basis of medical history, skin test with Castaneda's MPB antigen and serological examination.

17 persons were vaccinated with the living vaccine(A), and second group with heat-killed vaccine(B) by the skin scarification method. Following vaccination, the local reaction were observed by clinician and their temperature was taken twice a day for two weeks. Only three persons with a temperature above normal were recorded after vaccination. Slight local reaction caused by living vaccine were observed in 13 persons.

In group(B), one person had a temperature of 37,5°C, and a slight redness was observed on three persons in the area of scarification. Altogether, no severe local or systemic reactions were observed. Four weeks after vaccination, blood was collected for serological examination. The sera of 11 persons who had been vaccinated with the living vaccine contained 10 to 80 I.U. in the agglutination test and only two of these gave a 1/5 titer in the complement-fixation test, whereas only one person of the heat killed vaccine group had a titer of 10 units in the agglutination test and five them showed a lower titer. All the CF. tests in this group were negative.

Six months, after vaccination, 32 subjects were skin tested with the Castaneda's antigen and also serological examination. Eleven out of 15 person in group(A) showed a strong reaction with redness (1 -2cm) and induration without clinical symptoms. Eight sera in this group contained 10 to 40 I.U. and seven were negative in the agglutination, whereas only one of the positive sera in the agglutination test showed a titer of 1/5 in the CF. test.

In killed vaccine group, 16 were negatives on skin test and only one person showed a slight redness (1 cm) after 24 hours. Seventeen sera in both the agglutination and CF. test were all negatives.

The result of this experience has demonstrated that there were no obvious signs of undesirable reaction to the vaccination by cutaneous route. About 73% of subject following the living BA-19 vaccination, while in the group of killed-vaccine only one person developed a slight skin reaction and serological examination were all negatives.

Conclusion

It is well recognized that human infection will disappear when animal brucellosis is brought under control and eradicated. This is certainly not to be disputed. However, when one considers in realistic terms how long it will take in various countries to accomplish this, it is quickly clear that much human infection and illness will continue to occur. Because of this fact and in addition, in order to protect persons heavily exposed by occupation the U.S.S.R. has conducted a wide-spread campaign of vaccination in human against brucellosis.

The World Health Organization expert Committee on Brucellosis also belives that, it is necessary (1) to reconsider the traditional views concerning human prevention and (2) to study ways and means of providing occupationally exposed human a certain measure of protection until the infection incidence in animals is reduced to a level which take human disease less probable. For these reason the W.H.O. is supporting research on vaccine suitable for human use. At the present time the W.H.O. studies indicate that in the human trial too large a number of Rev. 1 cells were given, thereby causing brucellosis. The BA-19 strain from U.S.S.R. also produced some sever symptoms and both strains need much further study before they can be used in anything but very small safety trials. It is quite possible also to consider for this purpose very much smaller dose of Rev. 1 cells or even non viable cells mixed with some harmless adjuvant substance. But the conclusion seems clear that man is entitle to the same consideration as his domestic animals in being protected from his animals' disease.

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