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The evaluation of Pasteurella pestis vaccines in Praomys (Mastomys) natalensis

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of the vaccine, there was a vigorous serological response in these animals. Virulent challenge with 131,000 P. pestis 195/P resulted in protection of 66% of the vaccinated langurs. Resistance to plague was indirectly reflected by the mouse protection indices, which were below 10. None of the langurs with a MPI above 10 survived.

A clinical trial of the USP plague vaccine in 25 human volunteers confirmed that this vaccine causes mild local and systemic reactions (Meyer, 1970). Single booster inoculations of 0.2 ml of the vaccine resulted in a MPI below 10 in 65% of the vaccinated. Meyer (1970) then concluded that killed vaccines of the USP type sensitise humans to the extent that small, repeated booster inoculations activate the immune mechanism.

Inoculation of the USP vaccine in Praomys proved to be non-toxic by the intraperitoneal route in doses of 2,000 million organisms. This rodent species was also protected against virulent challenge both by subcutaneous and intraperitoneal inoculation of the vaccine. A lower protection rate was however obtained in Praomys, using the USP killed vaccine, than by the live attenuated P. pestis strains.

In Praomys differences in immunogenicity of live and killed plague vaccines can be demonstrated. Unlike the guinea pig, which shows a poor response to killed plague vaccines, Praomys, like the white mouse, responds to both live and killed vaccines. The ability of live vaccines to confer greater protection is probably attributable to the synthesis of protective antigens in vivo during multiplication and invasion of the organisms.

Pathological changes following inoculation of live attenuated P. pestis.

The pathological changes observed in animals which died after vaccination with attenuated P. pestis were mainly characteristic of a virulent plague infection. In Cercopithecus there was a marked lung involvement with bloodstained fluid in the pleural cavities. The spleens were flabby and congested, with a monocyte proliferation. These changes were also present in the livers and kidneys and there were generally masses of P. pestis in all the tissues.

These changes were also seen in Praomys. Investigation of the development of these changes showed that at an early stage there is a proliferation of mononuclear leucocytes in the spleen and lungs, which after 24 hours becomes abundant in these and other tissues. In comparison, the early changes in Praomys, after infection with a virulent strain, were less marked but polymorphonuclear leucocytes become aburdant after 48 hours in the liver and splenic sinuses and the alveolar walls of the lungs.

Despite severe pathological changes in the lungs of Praomys after vaccination with attenuated P. pestis, isolation of the bacilli was infrequent. In these animals the spleen and liver often appeared normal. Similar findings have been reported by Meyer (1950) who regularly found marked lung involvement in the absence of spleen and liver lesions in partially immune animals, dying from a challenge dose after a prolonged illness.

Sprunt and Camalier (1942) had previously demonstrated that intravenous injection of rabbits with staphylococcus toxin damages the parenchyma of the lungs, bronchi and bronchioles. They then concluded that pulmonary damage may occur as a result of toxaemia from a distant focus

even in the absence of actual bacteraemia. Meyer (1950) suggested that animals partially immune to plague are able to withstand the initial onslaught of the challenge infection for a few days, but multiplication at the site and in the regional lymph nodes creates a focus of bacilli which is capable of liberating increasing amounts of toxin from the disintegrated organisms. The toxin then enters the blood stream and selectively affects pulmonary tissue and a few initial pulmonary foci of infection are established. These lesions then progress, because of local toxic action, to confluent bronchopneumonic necrosis. Meyer (personal communication) has found that partially immune animals dying from a large challenge dose after a protracted illness are apt to show secondary embolic pneumonic plague in the absence of spleen or liver lesions, as a result of fibrin formation in the capillaries damaged by the toxins. If the pathological changes in the lungs of Praomys can be attributable to the action of circulating toxins it is likely that these are liberated from foci of multiplication such as the regional lymph nodes, rather than by the formation of secondary emboli, as death usually occurred within 3 - 6 days after inoculation with the attenuated strain and P. pestis was not isolated from the lungs of all cases with pulmonary pathology. The endotoxin described by Altizo and Surgalla (1970) may be the most important.

The use of Praomys (Mastomys) natalensis as a test animal for plague vaccines.

Standardised procedures have been adopted for the evaluation of the USP killed vaccine (Meyer, 1970) and the Haffkine vaccine (Kabbu, Kimbkar and Dhala, 1968). Similar standardised methods are now required for live attenuated vaccines and suggestions have been put forward by Meyer (personal communication) and Brygoo and Courdurier (1956). These

workers agree that the immunogenic efficacy should be tested in white mice, but Meyer also suggests the use of guinea pigs for a test of harmlessness and immunogenic efficacy. He also states that before the vaccine is used for human inoculation, detailed studies should be conducted on at least one species of subhuman primate highly susceptible to plague. Recent findings by Burrows and Gillett (1971) have shown that a number of [illegible] isolates from Brazil had attenuated virulence in guinea pigs but not white mice. The host-specificity of these isolates was found to be determined by a nutritional requirement, namely glycine. These authors then stressed that a demonstration of non-pathogenicity of a bacterial strain towards a presumed sensitive animal species does not assure its safety for man.

The experimental work outlined in this thesis reveals the value of using the multimammate mouse Praomys (Mastomys) natalensis as a test animal for comparing live attenuated plague vaccines. Both the immunogenicity and pathogenicity of the vaccine strain can be determined in this animal species. Breeding colonies of Mastomys have been established in many parts of the world, including countries where plague vaccines are made such as the eastern United States of America, Britain and France.

However, the very high susceptibility to plague and semidomestic habits of this rodent prohibit its importation to hyperenzootic plague areas for experimental use. Even in well controlled laboratories there is always the possibility of animals escaping. If they should become established in the wild, they would provide another link between wild and domestic plague and thus increase the danger to man. The search for other experimental animals which would be of value in investigating live plague vaccines should therefore be extended in countries where plague vaccines are produced. Other endemic rodents which are highly

susceptible to plague and adaptable to the laboratory may react similarly to [illegible]. Standard procedures may then be adopted using these animals for testing the immunogenic efficacy and harmlessness of the vaccines and using white mice and guinea pigs as controls.

CHAPTER 12.

Summary and Conclusions.

The search for improved plague vaccines and more suitable experimental animals than in use at present, warranted the investigation of live and killed vaccines in a laboratory adapted wild rodent species (Praomys (Mastomys) natalensis) found suitable for plague investigations in South Africa.

An attenuated EV76 Pasteurella pestis strain from Madagascar had been passaged through iron treated guinea pigs and designated EV51f. Following subcutaneous inoculation into vervet monkeys (Cercopithecus aethiops) in doses betwe . 100 million and 101 viable bacilli, this attenuated EV51f P. pestis strain invades the body and causes death in 26% of the inoculated animals. The strain had also been found to be pathogenic in langur monkeys and to cause local reactions in man. It stimulated haemagglutinating and mouse protecting antibodies in vervets and protected 70% against a subcutaneous challenge inoculation of 8,770 virulent P. pestis 170 days after vaccination.

The EV51f strain is not pathogenic in guinea pigs and confers a high rate of protection on these animals.

In Praomys (Mastomys) natalensis the EV51f strain was pathogenic in high doses following subcutaneous inoculation. Doses over 10,000 viable bacilli stimulated haemagglutinating antibodies and protected a high percentage of these animals against a subcutaneous challenge inoculation of virulent P. pestis. This vaccine strain was not pathogenic in white mice by subcutaneous inoculation, but the protection rate was similar to that of Praomys.

As the passage of the EV76 strain through iron treated guinea pigs would select those bacilli which are only F-, the character for which iron compensates, the pathogenicity of the attenuated P. pestis strain EV51f in laboratory animals is likely to be a reflection of the availability of iron in vivo. Judging from the pathogenicity of the strain, the availability of iron is probably high in vervet monkeys, in which even low doses of the vaccine multiply and cause mortality. In Praomys the availability of iron is probably low, as only high doses of the vaccine cause mortality and low doses are non-immunogenic. Guinea pigs are intermediate as even very low doses of the vaccine confer good protection against virulent challenge. The response of man to the EV51f strain appears to resemble Praomys more closely than vervets or guinea pigs, as in man high doses of the vaccine cause reactions and low doses do not stimulate serological antibodies.

Lyophilisation has an adverse effect on the attenuated EV51f strain as an agar-grown culture caused higher mortality in Praomys and conferred greater protection against a virulent challenge inoculation than the lyophilised preparation.

Subcutaneous inoculation of Praomys with the EV51f strain was shown by bacteriological culture techniques to result in rapid extensive invasion of the tissues and this was followed by a rapid clearing of organisms from the body. The extent of invasion by the strain therefore appears to be more important in establishing immunity in Praomys than the duration of persistence in the tissues, as the latter was very short. Invasion of the tissues by virulent plague bacilli introduced subcutaneously in Praomys was delayed initially but later appeared to follow the same route as in white mice. In actively immunized Praomys inocu-

lated with virulent P. pestis, the distribution of bacilli resembled an attenuated strain in normal animals, but differed quantitatively and the rate of spread throughout the body was more gradual. The duration of survival of virulent P. pestis in the tissues of immune Praomys was also longer. This could be of epidemiological importance, as it is a possible method of persistence of plague in nature.

Single intracutaneous inoculations of the EV51f strain in Praomys resulted in the administration of only low doses of the vaccine. These were nonpathogenic and resulted in similar rates of protection against a virulent challenge dose as subcutaneous inoculations of the vaccine. Intracutaneous inoculation of Praomys therefore did not result in localisation of the vaccine strain to the site and thus prevent exposure of antigen to cells responsible for the production of immunity, as has been suggested in man.

Investigation of the original EV76 vaccine strain maintained at the Institut Pasteur, Paris, showed that this strain is also pathogenic in Praomys by subcutaneous inoculation of high doses, but not in white mice. The highest dose conferred better protection against virulent challenge inoculation than the EV51f strain, but the protection of the lower doses was similar. The EV76 (Paris) strain was also shown to have deteriorated during lyophilisation. It is suggested that the method of Stamp (1947) of preserving bacteria in dried gelatin pellets is a better method than lyophilisation for the preservation of the antigenic structure and viability of live attenuated P. pestis vaccines.

The gross and microscopic pathological changes following inoculation of these live attenuated strains and the changes after virulent chal-

lenge inoculation are described.

The immunity of Praomys against a virulent challenge inoculation was boosted by two sub-lethal doses of lyophilised EV76 (Paris) vaccine, but not by small or intermediate doses. This agrees with the findings in human volunteers, in which small doses of this vaccine did not booster the serological response in men previously immunised with the USP killed vaccine. The mass of antigen inoculated is therefore important as only large doses of live attenuated vaccine are capable of sufficiently stimulating the immunologically competent cells responsible for the production of a high level of protection against virulent challenge.

The EV51f strain was shown to be invasive and pathogenic in Praomys, not only by subcutaneous inoculation, but also when administered via the oral route. It is unlikely therefore that this route of administration of live attenuated plague vaccines will be used in humans. The pathological changes and probably route of invasion following the oral administration in Praomys are described and discussed. A high rate of protection against a subcutaneous challenge inoculation of virulent P. pestis was obtained by oral administration of the vaccine. This protection was boosted by a subcutaneous inoculation of the vaccine given simultaneously to the oral dose.

In Praomys the attenuated P. pestis strain Tjiwidej was nonpathogenic by subcutaneous inoculation. It stimulated haemagglutinating antibodies and conferred a high level of immunity against a subcutaneous challenge of virulent P. pestis, in proportion to the size of the vaccine dose. Slightly better immunity was achieved with a combination of the Tjiwidej and EV76 (Paris) strains than by two inoculations

of the same strain. The two strains lack different single virulence factors and together provide the three important determinants in immunity to plague. The antigenic make-up of the vaccine strain is therefore of importance in immunity to plague. Further investigation of the combined use of these two vaccines together or sequentially may lead to trials in human volunteers.

The important role of the antigenic structure of vaccine strains and the F1 antigen in particular, in immunity to plague was also shown by investigation of the non-pigmented M23 attenuated P. pestis strain in Praomys. This strain was pathogenic in high doses, but did not protect against a virulent P. pestis inoculation. The absence of oedema in the lungs and subcutaneous tissues in vaccination deaths in fatal non-pigmented M23 infections, in contrast to the EV51f and EV76 (Paris) infections, is suggested to be attributable to the absence of F1 antigen, but the role of F1 in oedema formation is obscure.

High doses of the USP killed plague vaccine have no apparent adverse effects on Praomys and immunity is established in this rodent by subcutaneous and intraperitoneal inoculation of the vaccine. The immunity established against virulent P. pestis challenge inoculation was lower than that achieved by the live attenuated vaccines and even repeated inoculation of high doses of killed vaccine could not protect all animals against the challenge inoculation.

The multimammate mouse Praomys (Mastomys) natalensis was shown to be of value in investigating the pathogenicity and immunogenicity of live attenuated plague vaccines and this may lead to more extensive use of this or other laboratory adapted susceptible wild rodents for evaluating plague vaccines.

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