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.

REFERENCES.

Albizo, J.M. and Surgalla, M.J. (1970). Isolation and biological characterization of Pasteurella pestis endotoxin. Infect. Immun., 2, 229-236.

Amies, C.R. (1951). The envelope substance of Pasteurella pestis. Br.J.exp.Path., 32, 259-273.

Bablet, J., Girard, G. and Robic, J. (1937). Reaction spleniques observées chez le cobaye après inoculation intrapéritonéale d'une souche de peste de virulence affaiblie. C. r. Séanc.Soc.Biol., 124, 1055-57.

Baker, E.E., Sommer, H., Foster, L.E., Meyer, E. and Meyer, K.F. (1947). Antigenic structure of Pasteurella pestis and the isolation of a crystalline antigen. Proc.Soc.exp.Biol.Med., 64, 139-141.

Baker, E.E., Sommer, H., Foster, L.E., Meyer, E. and Meyer, K.F. (1952). Studies on immunization against plague I. The isolation and characterization of the soluble antigen of Pasteurella pestis. J.Immun., 68, 131-145.

Berman, S., Altieri, P.L., Groffinger, A. and Lowenthal, J.P. (1970). Freeze-drying various attenuated strains of Pasteurella pestis. Cryobiology, 7, 40-43.

Brygoo, E.R. and Courdurier, J. (1956). Test sur souris de l'efficacité du vaccin EV. Ann.Inst.Pasteur, 91, 939-943.

Brygoo, E.R. and Rajemison, S. (1969). Essai de sensibilisation de la souris, pour le diagnostic de la peste, par un immuno-depresseur. Archs Inst.Pasteur Tananarive, 38, 21-25.

Burgess, A.S. (1927). The selection of a strain of Bacillus pestis for the preparation of vaccine, with special reference to the effect of animal passage on virulence. J.Hyg., Camb., 26, 152-162.

Burgess, A.S. (1930). Virulence, immunity and bacteriological variation in relation to plague. J.Hyg., Camb., 30, 165-179.

Burrows, T.W. (1957). Virulence of Pasteurella pestis. Nature, Lond., 179, 1246-1247.

Burrows, T.W. (1963). Virulence of Pasteurella pestis and immunity to plague. Ergebn.Mikrobiol.ImmunForsch.exp.Ther., 37, 59-113.

Burrows, T.W. and Bacon, G.A. (1956a). The basis of virulence in Pasteurella pestis: attempts to induce mutation from avirulence to virulence. Br.J.exp.Path., 35, 129-133.

Burrows, T.W. and Bacon, G.A. (1956b). The basis of virulence in Pasteurella pestis: comparative behaviour of virulent and avirulent strains in vivo. Br.J.exp.Path., 35, 134-143.

Burrows, T.W. and Bacon, G.A. (1956a). The basis of virulence in Pasteurella pestis: an antigen determining virulence. Br.J.exp. Path., 37, 481-493.

Burrows, T.W. and Bacon, G.A. (1956b). The basis of virulence in Pasteurella pestis: the development of resistance to phagocytosis in vitro. Br.J.exp.Path., 37, 286-299.

Burrows, T.W. and Bacon, G.A. (1958). The effects of loss of different virulence determinants on the virulence and immunogenicity of strains of Pasteurella pestis. Br.J.exp.Path., 39, 278-291.

Burrows, T.W. and Gillett, W.A. (1971). Host specificity of Brazilian strains of Pasteurella pestis. Nature, Lond., 229, 51-52.

Cavanaugh, D.C., Thorpe, B.D., Bushman, J.B., Nicholes, P.S. and Rust, J.H. (1965). Detection of an enzootic plague focus by serological methods. Bull.Wld Hlth Org., 32, 197-203.

Cavanaugh, D.C., Dangerfield, H.G., Hunter, H., Joy, J.T., Marshall, J.D., Guy, D.V., Vivona, S. and Winter, P.E. (1968). Some observations on the current plague outbreak in the Republic of Vietnam. Am.J.publ.Hlth, 58, 742-752.

Chen, T.H. (1952). Studies on immunization against plague. IV The method of the hemagglutination test and some observations on the antigen. J.Immun., 69, 587-596.

Chen, T.H., Foster, L.E. and Meyer, K.F. (1961). Experimental comparison of the immunogenicity of antigens in the residue of ultrasonated avirulent Pasteurella pestis with a vaccine prepared with killed virulent whole organisms. J.Immun., 87, 64-71.

Chen, T.H. and Meyer, K.F. (1955). Studies on immunization against plague. XI A study of immunogenicity and toxicity of eleven avirulent variants of virulent strains of Pasteurella pestis. J.infect. Dis., 96, 145-151.

Chen, T.H. and Meyer, K.F. (1965). Susceptibility of the langur monkey (Semnopithecus entellus) to experimental plague: Pathology and immunity. J.infect.Dis., 115, 456-464.

Chen, T.H. and Meyer, K.F. (1966). An evaluation of Pasteurella pestis Fraction-1-specific antibody for the confirmation of plague infections. Bull.Wld Hlth Org., 34, 911-918.

Cooking, E.G, Keppie, J., Witt, K. and Smith, H. (1960). The chemical basis of the virulence of Pasteurella pestis II. The toxicity for guinea pigs and mice of products of Past. pestis. Br.J.exp.Path., 41, 460-471.

Compton, A. (1928). Sensitization and immunization with bacteriophage in experimental plague. J.infect.Dis., 43, 448-457.

Compton, A. (1930). Immunization in experimental plague by subcutaneous inoculation with bacteriophage. Comparison of plain and formaldehyde-treated phage-lysed plague vaccine. J.infect.Dis., 46, 152-160.

Crumpton, M.J. and Davies, D.A.L. (1956). An antigenic analysis of Pasteurella pestis by diffusion of antigens and antibodies in agar. Proc.R.Soc.(B), 145, 109-133.

Davis, D.H.S. (1963). Wild rodents as laboratory animals and their contribution to medical research in South Africa. S.Afr.J.med.Sci., 28, 53-69.

Davis, D.H.S., Heisch, R.B., McNeill, D. and Keyer, K.F. (1968a). Serological survey of plague in rodents and other small mammals in Kenya. Trans.R.Soc.trop.Med.Hyg., 62, 838-861.

Davis, D.H.S. and Murray, J.F. (1968b). The multimammate mouse Praomys (Mastomys) natalensis as an experimental animal for investigations of plague. Unpublished report.

Devignat, R. (1949). La prophylaxie de la peste au Lac Albert par l'association de la dératisation et de la vaccination (virus-vaccin E.V. de Girard et Robic). Bull.Soc.Path.exot., 42, 43-52.

Englesberg, E. and Levy, J.B. (1954). Studies on immunization against plague. VI. Growth of Pasteurella pestis and production of the envelope and other soluble antigens in a casein hydrolysate mineral glucose medium. J.Bact. 67, 438-449.

Falbitch, M.M. (1964). Invasion capacity of avirulent plague [illegible]. Zh. Mikrobiol.Epidem.Immunobiol., 41, 36-41.

Flu, P.C. (1929). Immunisation des rats blancs contre la peste expérimentale au moyen des bacilles pestoux virulents lysés, en suspension concentrée, par des bactériophages antipesteux. C.r.Séanc. Soc.Biol., I, 837-838.

Gale, G.W. (1941). An outbreak of pneumonic plague in the Kalahari. S.Afr.med.J., 15, 369-373.

Girard, G. (1936). The plague in Madagascar and the new knowledge gained from research during the last three years. Q.Bull.Hlth Org., 5, 103-107.

Girard, G. (1955). Plague. A.Rev.Microbiol., 9, 253-276.

Girard, G. (1963). L'immunité dans l'infection pesteuse. Biol.méd. (Paris), 52, 631-731.

Girard, G. and Radaody-Ralarosy, P. (1940). Sort de deux souches de bacilles pesteux atténués inoculées au cobaye par voie sous-cutanée. C.r.Séanc.Soc.Biol., 133, 580-582.

Girard, G. and Robic, J. (1942). L'état actuel de la peste à Madagascar et la prophylaxie vaccinale par le virus-vaccin EV. Bull.Soc.Path. exot., 35, 42-49.

Goldenberg, M.I., Quan, S.F. and Hudson, B.W. (1964). The detection of inapparent infections with Pasteurella pestis in a Microtus californicus population in the San Francisco bay area. Zoonoses Rec., 3, 1-13.

Grasset, E. (1941). Live plague vaccine as a prophylactic against plague. S.Afr.med.J., 15, 373-375.

Grasset, E. (1942). Plague immunization with live vaccine in South Africa. Trans.R.Soc.trop.Med.Hyg., 35, 203-211.

Grasset, E. (1946). Control of plague by means of live avirulent plague vaccine in South Africa. Trans.R.Soc.trop.Med.Hyg., 40, 275-294.

Habbu, M.K., Nimbkar, Y.S. and Jhala, H.I. (1968). Selection of a suitable batch of plague vaccine for use as a standard. Indian J. Path.Bact., 11, 252-259.

Haffkine, W.M. (1906). Les inoculations antipestueses. Bull.Inst. Pasteur, 4, 825-840.

Hallett, A.F. (1965). Plague reservoir survey in Southern Africa: Collection of sera for haemagglutination tests. S.Afr.J.med.lab. Technol., 11, 55-59.

Hallett, A.F., McNeill, D. and Meyer, K.F. (1970). A serological survey of the small mammals for plague in southern Africa. S.Afr. med.J., 44, 831-837.

Heckly, R.J., Anderson, A.W. and Hockenmacher, M. (1956). Lyophilization of Pasteurella pestis. Appl.Microbiol., 6, 255-261.

Irwin, J.O. and Cheeseman, E.A. (1939). On an approximate method of determining the median effective dose and its error, in the case of a quantal response. J.Hyg., Camb., 39, 574-580.

Jackson, S. and Burrows, T.W. (1956a). The pigmentation of Pasteurella pestis on a defined medium containing haemin. Br.J.exp.Path., 37, 570-576.

Jackson, S. and Burrows, T.W. (1956b). The virulence-enhancing effect of iron on non-pigmented mutants of virulent strains of Pasteurella pestis. Br.J.exp.Path., 37, 577-583.

Janssen, W.A. and Surgalla, M.J. (1969). Studies on the infectivity and immunogenicity of a noncapsulated strain of Pasteurella pestis. Bact.Proc., 75.

Jawetz, E. and Meyer, K.F. (1943). Avirulent strains of Pasteurella pestis. J.infect.Dis., 73, 124-143.

Jawetz, E. and Meyer, K.F. (1944a). The behaviour of virulent and avirulent Pasteurella pestis in normal and immune experimental animals. J.infect.Dis., 74, 1-13.

Jawetz, E. and Meyer, K.F. (1944b). Studies on plague immunity in experimental animals: I Protective and antitoxic antibodies in the serum of actively immunized animals. J.Immun., 49, 1-14.

Jawetz, E. and Meyer, K.F. (1944c). Studies on plague immunity in experimental animals: II Some factors of the immunity mechanism in bubonic plague. J.Immun., 49, 15-30.

Keppie, J., Cocking, E.C. and Smith, H. (1958). A non-toxic complex from Pasteurella pestis which immunises both guinea pigs and mice. Lancet, I, 246-247.

Kolle, W. and Otto, R. (1903). Untersuchungen über die Pest-Immunität. Z.Hyg.Infektkrankh., 45, 507-544.

Kolle, W. and Otto, R. (1904). Weitere Untersuchungen über die Pestimmunität. Z.Hyg.Infektkrankh., 48, 399-430.

Korobkova, E.I. (1955). Methods of increasing the efficacy of live anti-plague vaccine. Zh.Mikrobiol., 11, 15-21.

Korobkova, E.I., Liskina, I.V. and Filipov, F. (1970). The effectiveness of live plague vaccine in relation to the method of its application. In: Problems of particularly dangerous infections No.2, 115-118, Saratov.

Korobkova, E.I., Lobanov, V.N. and Kuznetsova, O.R. (1964). Stabilization of immunogenic properties of the Girard and Robic EV strain. III. The effect of passage through the animal body and the significance of individual colonies selection in the immunogenicity of the EV strain. Zh.Mikrobiol.Epidem.Immunobiol., 41, 16-21.

Korobkova, E.I. and Samoilova, L.V. (1962). On the nature of immunity against plague. Zh.Mikrobiol., 11, 76-82.

Lawton, W.D., Fukui, G.M. and Surgalla, M.J. (1960). Studies on the antigens of Pasteurella pestis and Pasteurella pseudotuberculosis. J.Immun., 84, 475-479.

Levi, M.I., Suchkov, Y.G., Orlova, G.M., Gerasyuk, L.G., Shkoda, A.M., Peysakhis, L.A., Stogova, A.N., Lopatina, N.F., Sukharnikova, N.A., Pak, G.Y., Muminov, K.M., Donkaya, T.N., Nassonov, L.G., Weinblat, V.I., Murtazanova, E.S., Sthelman, A.I., Lavrentev, A.F., Basova, N.N., Kulov, G.I., Golkovsky, G.M., Salomov, N.I. and Zalygina, N.I. (1964). Significance of serological methods in the epizootological study of plague in wild rodents. J.Hyg.Epidem. (Praha), 8, 422-427.

Markenson, J. and Ben-Efraim, S. (1969). Comportement in vivo des souches de Pasteurella pestis en relation avec leur efficacité comme vaccins vivants. Ann.Inst.Pasteur, 117, 196-212.

McCrumb, F.R., Mercier, S., Chen, T.H., Meyer, K.F. and Goodner, K. (1955). Studies on the antibody patterns in pneumonic plague patients. J.infect.Dis., 96, 88-94.

Meyer, K.F. (1950). Immunity in plague: A critical consideration of some recent studies. J.Immun., 64, 139-163.

Meyer, K.F. (1953). Recent studies on the immunity response to administration of different plague vaccines. Bull.Wld Hlth Org., 9, 619-636.

Meyer, K.F. (1970). Effectiveness of live or killed plague vaccines in man. Bull.Wld Hlth Org., 42, 653-666.

Meyer, K.F. and Foster, L.E. (1948). Measurement of protective serum antibodies in human volunteers inoculated with plague prophylactics. Stanford med.Bull., 6, 75-79.

Meyer, K.F., Holdenried, R., Burroughs, A.L. and Jawetz, E. (1943). Sylvatic plague studies IV. Inapparent, latent sylvatic plague in ground squirrels in Central California. J.infect.Dis., 73, 144-157.

Meyer, K.F. and Larson, A. (1960). The pathogenesis of cervical septicaemic plague developing after exposure to pneumonic plague produced by intratracheal infection in primates. Haffkine Institute. Proceedings of the Symposia held during the Diamond Jubilee, Jan 10 to 14, 1959. I. Symposium on plague, Bombay.

Meynell, G.G. and Meynell, E. (1965). Theory and practice in experimental bacteriology. University Press, Cambridge.

Morison, J., Naidu, B.P.B. and Avari, C.R. (1924). The production of immunity against plague by vaccine. I. Haffkine's plague prophylactic. Indian J.med.Res., 12, 313-320.

Naidu, B.P.B. and Jung, [illegible].S. (1929). The relative toxicity and immunizing value of Haffkine's plague prophylactic and other anti-plague vaccines compared. Indian J.med.Res., 17, 199-213.

Naidu, B.P.B., Malone, R.H. and Avari, C.R. (1926). Notes on the potency of Haffkine's plague prophylactic. Indian J.med.Res., 13, 823-834.

Otten, L. (1933). Experimental vaccination in plague. I. Dead vaccine. Meded.Dienst Volksgezondh.Ned.-Indië, 22, 131-149.

Otten, L. (1936). Immunisation against plague with live vaccine. Indian J.med.Res., 24, 73-101.

Payne, F.E., Larson, A., Walker, D.L., Foster, L. and Meyer, K.F. (1955). Studies on immunization against plague. IX. The effect of cortisone on mouse resistance to attenuated strains of Pasteurella pestis. J.infect. Dis., 96, 168-173.

Payne, F.E., Smadel, J.E. and Courdurier, J. (1956). Immunologic studies in persons residing in a plague endemic area. J.Immun., 77, 24-33.

Pirie, J.H.H. (1927). Experiments with vaccines, sera, etc., in the prophylaxis and treatment of plague. In: The plague problem in South Africa: historical, bacteriological and entomological studies. Publs S.Afr.Inst.med.Res., 3, 187-206.

Pirie, J.H.H. (1929). Plague studies. I. Bacteriophage in the prophylaxis and treatment of experimental plague. Publs S.Afr.Inst. med.Res., 4, 195-202.

Pirie, J.H.H. and Grasset, E. (1938). Plague. Killed versus live organisms for protective immunization and for the preparation of curative serum. S.Afr.med.J., 12, 294-296.

Pollitzer, R. (1954). Plague. Monograph Ser. W.H.O., No.22.

Pollitzer, R. (1960). A review of recent literature on plague. Bull.Wld Hlth Org., 23, 313-400.

Quan, S.F., Chen, T.H. and Meyer, K.F. (1956). Preserved living avirulent plague vaccine. Bact.Proc., 78.

Reed, L.J. and Muench, H. (1938). A simple method of estimating fifty per cent endpoints. Am.J.Hyg., 27, 493-497.

Rowland, S. (1914a). Reports on plague investigations in India. The influence of cultivation in serum-containing media upon the virulence and immunising properties of the plague bacillus. J.Hyg., Camb., 13, Plague Suppl., 403-411.

Rowland, S. (1914b). Reports on plague investigations in India. The morphology of the plague bacillus. J.Hyg., Camb., 13, Plague Suppl., 418-422.

Schutze, H. (1925). Plague immunisation in guinea pigs and rats. Br.J.exp.Path., 6, 207-210.

Schutze, H. (1932a). Studies in B. pestis antigens: I. The antigens and immunity reactions of B. pestis. Br.J.exp.Path. 13, 284-288.

Schutze, H. (1932b). Studies in B. pestis antigens: III. The prophylactic value of the envelope and somatic antigens of B. pestis. Br.J.exp.Path., 13, 293-298.

Schutze, H. (1939). Studies on B. pestis antigens as prophylactic agents. Br.J.exp.Path., 20, 235-244.

Simpson, W.J. (1905). A treatise on Plague. Cambridge, University Press.

Smidt, F.P.G. de (1929). Laboratory notes on plague in Kenya. J.Hyg., Camb., 29, 201-218.

Smith, H. and Packman, L.P. (1966). A filtered non-toxic plague vaccine which protects guinea pigs and mice. Br.J.exp.Path., 47, 25-34.

Sokhey, S.S. (1939). Experimental studies in plague. 4. Experimental animal of choice for plague work. Indian J.med.Res., 27, 341-352.

Sokhey, S.S. (1940). The capsule of the plague bacillus. J.Path. Bact., 51, 97-103.

Spivack, M.L., Foster, L., Larson, A., Chen, T.H., Baker, E.E. and Meyer, K.F. (1958). The immune response of the guinea pig to the antigens of Pasteurella pestis. J.Immun., 80, 132-141.

Sprunt, D.H. and Camalier, W. (1942). Reduction of pulmonary resistance to infection by circulating toxins. Archs Path., 34, 801-806.

Stamp, Lord. (1947). The preservation of bacteria by drying. J.gen.Microbiol., 1, 251-265.

Strong, R.P. (1906). Vaccination against plague. Philipp.J.Sci., 1, 181-190.

Strong, R.P. (1907). Studies in plague immunity. Philipp.J.Sci.B. Med.Sci., 2, 155-331.

Smidt, F.P.G. de (1929). Laboratory notes on plague in Kenya. J.Hyg., Camb., 29, 201-218.

Smith, H. and Packman, L.P. (1966). A filtered non-toxic plague vaccine which protects guinea pigs and mice. Br.J.exp.Path., 47, 25-34.

Sokhey, S.S. (1939). Experimental studies in plague. 4. Experimental animal of choice for plague work. Indian J.med.Res., 27, 341-352.

Sokhey, S.S. (1940). The capsule of the plague bacillus. J.Path. Bact., 51, 97-103.

Spivack, M.L., Foster, L., Larson, A., Chen, T.H., Baker, E.E. and Meyer, K.F. (1958). The immune response of the guinea pig to the antigens of Pasteurella pestis. J.Immun., 80, 132-141.

Sprunt, D.H. and Gamalier, M. (1942). Reduction of pulmonary resistance to infection by circulating toxins. Archs Path., 34, 801-806.

Stamp, Lord. (1947). The preservation of bacteria by drying. J.gen.Microbiol., 1, 251-265.

Strong, R.P. (1906). Vaccination against plague. Philipp.J.Sci., 1, 181-190.

Strong, R.P. (1907). Studies in plague immunity. Philipp.J.Sci.B. Med.Sci., 2, 155-331.

Surgalla, M.J., Beesley, E.D. and Albino, J.M. (1970). Practical applications of new laboratory methods for plague investigations. Bull.Wld Hlth Org., 42, 993-997.

Taylor, G. (1933). Haffkine's plague vaccine. Indian med.Res.Mem., 27, 1-120.

Thompson, W.R. (1947). Use of moving averages and interpolation to estimate median-effective dose. Bact.Rev., 11, 115-145.

Walker, D.L., Foster, L., Chen, T.H., Larson, A. and Meyer, K.F. (1953). Studies on immunization against plague. V. Multiplication and persistence of virulent and avirulent Pasteurella pestis in mice and guinea pigs. J.Immun., 70, 245-252.

World Health Organization Expert Committee on Plague, (1970). Fourth Report. Tech.Rep.Ser.Wld Hlth Org., No. 447, 1-25.

Wu Lien-Teh, Chun, J.W.H., Pollitzer, R. and Wu, C.Y. (1936). Plague: A manual for medical and public health workers. Shanghai.