Kitasato

AOYOMA'S REPORT UPON THE BUBONIC PLAGUE.

[The substance of a report made to the Journal Club of the Johns Hopkins Hospital by SIMON FLEXNER, M. D.]

[From *The Johns Hopkins Hospital Bulletin*, Nos. 66-67, September-October, 1896.]

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In October of 1894 an abstract of a report to the Journal Club of the Hospital, upon the subject of the bacillus of the plague, appeared in the Hospital Bulletin. The account there given of the micro-organism which had but a short time before been isolated from a number of cases of the black plague by Drs. Yersin and Katisato, and which was believed to be the cause of this devastating pest, was drawn from the reports of these investigators published at that time. The expedition sent by the Japanese government, at the head of which was Dr. Katisato, contained Dr. Aoyoma, whose mission it was to study the clinical and pathological features of the disease. Dr. Aoyoma became himself infected with the disease a short time after the beginning of his studies at Hong-kong, and although he recovered, the report of his studies has only recently appeared.* As was to be expected, these relate more particularly to the symptomatology and the pathological anatomy of the disease, although account is taken of the epidemiology and to a less extent of the bacteriology and of the mode of infection. In order that the first report given in the Bulletin may be in a manner complete, it is considered desirable to append an abstract of Dr. Aoyoma's recent report.

In May of 1894 the Japanese consul in Hong-kong announced to the Japanese government that the plague had appeared in Canton. Immediately following, a quarantine first of nine days and later of seven was set upon incoming ships, and Dr. Katisato, with his assistant Ishigami, and Dr. Aoyoma with his assistant Miyamoto and medical student Kinoshita, were sent to Hong-kong, where they arrived on the 12th of June. Through the kindness of Dr. Lowson they

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were permitted to arrange for their work in one of the rooms of the Kennedy Town Hospital, where on the 14th they had established themselves ready for work. Unfortunately Aoyoma and Ishigami became ill with the pest on the 28th of June, owing to which the studies which are here to be given were limited to fifteen days of active service. In this time 19 autopsies were held and 45 clinical cases studied, the latter more or less completely. In addition to these the opportunity of seeing a large number of cases in the Chinese hospitals had been embraced.

Respecting the situation of Hong-kong and the condition of the soil, its inhabitants and houses, the following may be stated: Hong-kong is one of the widest of the islands situated in the Gulf of Canton stream, and lies 142 km. southeast of the city of Canton, and 62 km. east of Macao, and is separated by a small body of water, which is used as a harbor, from the mainland. The island is mountainous, from two to five miles in length, and consists of granitic rock. Respecting the climate it may be stated that it is tropical, and the warmest months of the year are from March to November. The winter is also warm, and snow is not known in that locality.

Victoria, which is the principal town, extends from east to west along the north coast, between the sea and the mountainous background, and follows the latter, as it is built in part upon the mountain side. In the most easterly part we meet the barracks, villas, factories and the European shops. The westerly and middle parts, which are lower, are the Chinese quarters. The portion of the town which was most affected is known as Taiping-chan, which lies in the middle of the city. As regards the streets themselves, excepting that they are narrow, they are the equals of the best European streets. The houses, which are usually two stories in height and built after the European fashion, number about 7900, of which 6600 belong to the Chinese population.

The number of inhabitants of Hong-kong is difficult to ascertain and probably reaches the neighborhood of 250,000. The report obtained from the water-supply bureau gave 163,949, of whom 151,974 were Chinese. The overcrowding of the houses of the Chinese workmen has greatly increased during

the past ten years. It is stated that in the ten years from 1881 to 1891 the number of inhabitants of the city increased 41 per cent., while the houses increased only $13\frac{9}{10}$ per cent. The densest population is found in Taiping-chan, where it would appear that in a house area of 0.173 acre 3740 Chinese live. The streets of this part are very narrow, the houses are two-storied, the windows small and few in number. The houses, which are long in form, are separated by partitions into two parts, each of which is further subdivided into a number of large rooms. In the earlier times one of these rooms housed a single family, but at the present, owing to overcrowding, these rooms have been divided by subpartitions into an upper and a lower compartment, and these compartments further by upright partitions, so that several rooms have been constructed out of the original ones, in each of which a family now lives. The average size of the main room is 26x14 feet by 10 feet high, and contains eight partitions averaging 7x6 feet by 7 feet high, over which a sort of loft is often built to increase the accommodation, and in a room of this description from 16 to 25 people live.

The canalization is constructed so that one system of pipes receives the washings from the rains and the other the sewage from the kitchens, etc. The first works perfectly, whereas the other is for the most part in a very bad condition, so that stagnations frequently occur and the sewage is dammed back upon the houses.

The city itself is provided with an excellent water supply, which at certain times is even subjected to filtration. The clothing of the Chinese is hygienically to be recommended. The only difficulty to be pointed out is, that although well conceived for the purpose, it is never under any circumstances subjected to washing, which fact is equally true of their bedding. The personal habits of both the men and the women are almost beyond belief in their crudeness and neglect. Cleanliness on their part, or anything approaching it, is an absolutely unknown art.

As regards the cause of the plague, it may be said that Katisato discovered bacilli in the blood and in the lymphatic glands which differed somewhat in their morphological characters but which agreed in their cultural properties. Accord-

ing to Katisato, the bacillus which appears in the blood resembles the organism of chicken cholera, possesses a capsule, the middle portion staining very faintly; while the bacillus obtained from the lymphatic glands is somewhat longer, has rounded ends, and stains more uniformly than the other. The bacillus obtained by Yersin is stated to have rounded ends, to be easily stained with the aniline dyes, and to be decolorized with Gram's method. The ends again stain more uniformly than the middle part. According to Katisato, the organism would at times stain by Gram's method, and at others not. Aoyoma, however, observed that those contained within the lymph glands were decolorized, and those in the blood stained by this method. The number of organisms contained within the blood is usually not large, and may be so small that it is necessary to prepare a large number of cover-slip preparations in order to find sufficient for a diagnosis. On the other hand, they are found abundantly in the affected lymphatic glands.

The study of the tissues has shown that in the lymph glands a variety of bacteria may be met with. As a constant and predominating species the lymph gland bacillus of Katisato is found, although in rare cases micrococci predominate. Careful observation, however, shows within these masses greater or less numbers of the pest bacilli, the streptococci occupying the blood-vessels rather than the gland substance. The pest bacilli in the tissues stained less intensely in alkaline methylene blue solution than the streptococci, and the staphylococci least of all. It is stated that while the streptococci retain the Gram stain, the bacilli and the staphylococci do not. It is suggested by Aoyoma that the forms described by Katisato as occurring in the blood and retaining the Gram stain may have been pairs of cocci and not bacilli at all. He regards the association of the bacilli and cocci as of great importance, inasmuch as in the greater number of instances the affected glands suppurate, while a very small fraction do not. Hence it is considered that the suppuration is caused not by the plague bacilli which are always present, but through the action of pus-producing bacteria which entered along with the former or later than these; and Aoyoma has further found that in suppurating glands the plague bacilli are either much diminished in numbers or have entirely disappeared.

It may be recalled that in the first reports of Katisato and of Yersin they stated that the bacilli might enter the body first through the respiratory tract, second the digestive tract and third, excoriations of the surface. Aoyoma, on the other hand, expresses the opinion that in the great majority of cases, if not in all, the entrance is through external wounds. He points out that physicians and nurses who are in attendance upon infected individuals and spend much time in the places in which the sick are kept, rarely become infected with the disease. In this epidemic, of all such persons who were in attendance upon the sick, only three Japanese physicians and one Chinese physician became infected, the nurses having entirely escaped. During the prevalence of the epidemic 300 English soldiers volunteered to cleanse and disinfect the Chinese pest-houses. Of these only ten became affected with the disease. Thus it would appear as though an actual pest atmosphere did not exist and that the infection did not take place through the inspired air. Moreover, Aoyoma did not observe that the tracheal or bronchial glands were in a condition of intense inflammation, which he presumes would have been the case had the bacilli invaded through the air passages.

Respecting the question whether the organisms are taken into the body through the drinking water or with the food, it may be said that the Chinese do not drink unboiled water, and never under any circumstances eat uncooked foods. That portion of the town (Taiping-chan) which was most infected, and in which the hygienic conditions were the worst, received its drinking water from the general supply. It is true that Katisato was able to cause infection in mice by introducing the bacilli into their stomachs through glass tubes, but it is stated by Aoyoma that Katisato does not any longer regard these experiments as being certain proof of infection through the alimentary tract. It is noteworthy that at autopsy the lymphatic apparatus of the stomach and intestines and the mesenteric lymph glands were never found greatly inflamed, and the last contained very small numbers of the bacilli only, or in certain cases none at all. Hence it is stated that all physicians who observed this outbreak of the pest were forced to the idea that the bacilli entered chiefly through external wounds.

In the great majority of cases the deep inguinal and the axillary glands, and in a small number of cases the superficial inguinal glands, of one side were first affected and afterwards other glands became involved. This fact is explicable only upon the assumption that the organism entered through small defects of the skin which were present either on the feet or the hands; and as the working class of Chinese usually go barefoot, such small defects can easily be imagined to exist. Further, as is known, the lymphatic vessels of the feet run to the deeper and lower inguinal glands, thus exposing these first in the great majority of cases. The superficial inguinal glands receive the lymphatics of the penis and the skin over the lower portion of the abdomen, and these are but seldom primarily affected. Of the nine Japanese whom Aoyoma observed, two women showed affection of the axillary glands, one of the submaxillary glands, whereas in the other no glandular affection could be detected, notwithstanding the fact that the bacilli were found in the blood. Of the Japanese men, four showed swelling of the axillary glands, and one only of the inguinal glands. This is interesting when it is considered that the Japanese do not go barefoot. It may also be mentioned that among the Chinese the women show affection of the axillary rather than of the inguinal glands.

The wounds through which the infectious agent enters show, as a rule, no reaction. Notable exceptions to this statement are his own case, in which a lymphangitis was present, and that of his assistant, Nakahara, who succumbed to the disease and in whom lymphangitis was also observed, in both cases beginning in the hand and extending towards the axilla. Regarding the manner of diffusion of the bacilli, nothing new has been added in this report. The period of incubation of the disease is given at from two to seven days; and as regards the age and the sex of those affected, it may be said that the greater number of cases occur in young males.

The following table gives the relative proportion of men, women and children affected:

Men	62.40 per cent.
Women	19.23
Boys	8.92
Girls	9.45

It is worth noting that Aoyoma himself did not observe a single case in newly-born children or sucklings, although an English physician, Dr. Lowson, claims to have seen five or six cases among the latter.

The mortality in Hong-kong from the beginning of the disease until the 2nd of September is given as follows:

	Number Affected.	Number Died.
Europeans	11	2
Japanese	10	6
Manilanese	31	1
Urasinese	3	3
Indians	13	10
Portuguese	18	12
Malayanese	3	3
West Indians	1	1
Chinese	2619	2447

Symptomatology. The symptoms of the disease during the last plague were not, as was stated by most authors, protean, but they were quite simple. The disease began for the most part without prodromata, with a chill, or even in the first instances with pain and swelling of the glands and with succeeding chill and fever. Prodromata when present were usually short and varied in duration from a few hours to two or three days, or perhaps somewhat longer. The symptoms in the prodromal stage are prostration, headache, nausea, vomiting, loss of appetite, vertigo, and only rarely pains in the lumbar region or in the back. In the cases of the affection of the more intelligent population, even before the outbreak of the fever, slight swelling and pain were noted in the glands; whereas in the more obtuse Chinese these slighter phenomena were not noticed.

The temperature rises quickly to 39° or 40° C. or even higher, and remains high during the progress of the disease. Delirium sets in early, for the most part after the second day, and continues day and night, although in the lighter cases it may be absent during the day. On the other hand, severe cases occur in which from the beginning until death supervenes the functions of the brain are intact. The pulse is usually of good volume, as a rule dicrotic and varies in fre-

quency from 90 to 120 per minute. The spleen is palpable usually after the second or third day. It rarely can be felt more than a few cm. below the costal margins. The liver also is usually enlarged and palpable.

The urine is in most instances of dark color, cloudy, contains albumen, and does not, as a rule, give the diazo reaction. A few casts, either hyaline or granular, and white corpuscles are usually present. Very rarely the urine contains blood.

After the first or second day the glandular affection becomes more marked, and those glands first involved may reach the size of an egg. The pain increases with the growth in size, although in some cases it may be absent excepting upon pressure. The glandular affection is characteristic, inasmuch as it begins in one group and then involves in succession others, as for example first the inguinal, then the axillary, then those of the neck, and finally the submaxillary glands. The glands of the neck, of the elbow and the knee are seldom primarily affected. Only very rarely do several sets of glands become enlarged at once. Very soon after the swelling of the glands the periglandular tissues become involved and then later the skin. In the milder cases, suppuration may not occur and the swelling gradually diminish and finally disappear. On the other hand, suppuration may occur even in glands but little enlarged.

The temperature rises rapidly to 39 or 40 degrees, and in rare cases to 41½ degrees. In other instances the rise is more gradual. After remaining continuous for three or four days, there may be a critical fall, or the decrease may be gradual. In severe cases which recover the fever lasts from one to three weeks, and towards the end presents an irregular and remittent type. In not a few cases after the temperature has returned to the normal at the end of the first or the beginning of the second week there is a relapse, the fever now assuming a remittent character. The remittent fevers are suppurative; the fever is very rarely from the beginning remittent and irregular.

Actual hemorrhages into the skin were observed but once by Aoyoma, although congested areas are not infrequent. These latter areas disappear upon pressure and are believed to be caused by the bites of mosquitoes. Respecting the ques-

tion of the appearance of an exanthematous eruption, it is stated that a rapidly disappearing erythema may occur. Symptoms referable to the brain, with the exception of the delirium, were very rarely observed. Fibrillary twitchings occurred before death, and actual convulsions were seen in very rare instances. In only one case was opisthotonus observed.

In the *Foudroyante* cases death may occur before any considerable glandular swelling can be made out; in the severest cases taking place on the second day. As a rule, death occurs from the second to the eighth day, and on an average on the fourth day. As suppuration of the glands rarely occurs before the tenth day it was not observed in these more rapid cases. When death takes place late in the course of the disease it may be due to a secondary pyæmic infection. The suppuration of the glands may continue for months, so that the convalescence of the patient is rendered very slow and tedious. When suppuration does not occur the glands gradually become smaller, although the enlargement may not entirely disappear for two or three months.

Complications are stated to be quite frequent. Of these, nephritis occurs quite commonly in the severer cases. It develops as early as the third or fourth day of the disease, is accompanied with the appearance of a moderate amount of albumen in the dark red urine, and microscopically hyaline and granular casts, as well as white and red blood corpuscles, are found. Œdema was rarely seen, and when present, of light grade, and anuria was never observed. The blood which is present in the urine is not derived from parenchymatous hemorrhages, but from small extravasations into the mucous membrane of the pelvis of the kidney and the bladder. Abscess formation in addition to the lymph glands was observed in the liver, lungs and other organs in the later stages of the disease. Icterus of a light grade, and presumably of catarrhal origin, was often present; in one case it reached a very high degree, and at the autopsy it was found that the common duct had been pressed upon by a group of enlarged lymphatic glands. Serous pleuritis occurred but seldom, and seemed when present to be associated with the enlargement of the axillary glands. Pneumonia was seen in a single

instance only, but bronchitis was much more common. Rarer complications are periostitis, lymphangitis, furunculosis of the skin, phlegmons which have their origin in the suppurating glands, carbuncle, singultus, and bloody stools.

Respecting the question as to whether cases of the pest without glandular affection ever exist, it may be said that in three cases which came to autopsy and which were proven to have died of the plague, enlargement of the glands was not made out during life.

The blood presented a dark red color, and the estimation of the corpuscles showed that the red corpuscles were only inconsiderably or not at all diminished, while the white were always increased. The number of white corpuscles per cubic mm. varied from 20,000 to 200,000; a control count of normal blood in a Chinese gave 10,000 white corpuscles to the cubic mm. The increase in white blood corpuscles is in the polymorpho-nuclear neutrophilic variety. Eosinophilic cells were very rarely seen. It is stated that the blood platelets were increased in number.

During the short time that Aoyoma carried on his studies he made autopsies upon 19 cadavers. The following is in brief the result of his studies of these cases: There is not infrequently a post-mortem rise of temperature; in one case the temperature taken four hours after death in the rectum, with a thermometer which registered 43 degrees, could not be estimated because the mercury was driven to the top of the capillary tube. Post-mortem muscular contractions also occurred in a similar manner to those observed in cholera. The affection of the lymph glands in various regions of the body has already been referred to, and it remains to say that in no case did he find evidence of a primary affection of the pleural or peritoneal lymphatic glands. No matter in which part of the body the glands are primarily affected, the entire lymphatic apparatus of the body shows at least some swelling, and perhaps congestion as well. With the exception of minute ecchymoses nothing abnormal was observed in the heart. The lungs and the pleura were not the seat of inflammatory changes, although in the latter, in certain of the cases of primary axillary affection, an increased amount of fluid existed in the pleural cavity. The spleen was enlarged, and sometimes considerably

so. The kidneys showed the lesions of cloudy swelling, and often were congested. Small hemorrhages occurred in the mucous membrane of the pelvis. The liver was enlarged and hyperæmic and the seat of parenchymatous degeneration. The stomach and intestines showed more or less injection of the mucous membrane and increase of the mucous section. The pia arachnoid was as a rule hyperæmic and very œdematous. Purulent inflammations were never present in this situation. In few cases a moderate number of small hemorrhages were observed in these membranes. The fluid within the ventricles was moderately, never greatly increased. The substance of the brain showed a moderate œdema and numerous hemorrhagic points. In one instance an extravasation of blood the size of a bean was found in the medulla oblongata, and in another one of the same size occurred in the pons. The pia arachnoid of the spinal cord was hyperæmic and œdematous. Lesions were not found in the cord itself.

The increase in size of the lymphatic glands depends upon several factors, namely, hyperæmia, exudation, hemorrhage, hyperplasia of the gland cells, and great development of bacteria. The bacilli which are present are found in the earlier stages in the lymph spaces about the follicles, and later they are found within the follicles, the lymph sinuses and the medullary cords. The cells of the affected gland undergo various degenerative changes and may become necrotic. They lose their nuclei in the latter case, and a variable amount of nuclear detritus is present among the degenerated and necrotic cells. The hemorrhages are not limited to the gland itself, but may be found, as well as greater or less œdema, in the periglandular tissues. The usual fate of the enlarged glands is to suppurate, although in certain cases the swelling may disappear without suppuration and the glands return to normal; while in still others a fibroid induration may result. The suppuration is either of the nature of simple abscess formation, or preceding this there may be a necrosis of the gland substance; in certain cases the suppuration does not remain limited to the glands, but extends into the periglandular tissue. Sections of the lymph glands showed a variety of bacteria. It is stated that in the primary localization various bacteria may be associated. Among these can be distinguished

the pest bacilli and cocci, and among the latter both streptococcus and staphylococcus forms may be discovered. Aoyoma considers the association of these organisms as very important in determining the suppuration or non-suppuration of the affected glands. The spleen usually shows the presence of large numbers of bacilli, and among these more rarely micrococci. The pest bacilli were also, though not constantly, found in the interstitial substance of the kidneys and in the glomerular capillaries. They were also present in the inter- and intra-acinous tissues of the liver. The mesenteric glands sometimes contained the bacilli in small numbers; it is not stated whether or not they were found in the structures of the central nervous system.