RABBIT POX

III. Report of an Epidemic with Especial Reference to Epidemiological Factors

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(Received for publication, March 19, 1935)

Descriptions of an epidemic disease in rabbits comparable with small pox in man were given in a previous paper (1). Pearce, Rosahn and Hu (2) found that the disease was caused by a filterable virus of the pox group which was closely related to vaccine virus but not identical with either the neurotropic or dermotropic form. From their investigations, it may be inferred that the causative agent is either a variant of one or the other or a distinct virus.

The infection produced by this virus is capable of spreading among rabbits and may produce an epidemic much like small pox in man. As was pointed out in previous papers, the epidemic occurred in an animal population which had been under close observation for a period of years and contained a variety of racial types and groups which were known to differ radically in their constitutional potentialities. An unusual opportunity was thus offered for the study of epidemiological factors.

The object of the present paper is to record the essential facts concerning the origin of the epidemic, the source of infection and its spread through the colony and eventual disappearance, together with crude mortality data for different periods of the epidemic. Particular attention will be given to events of epidemiological significance preceding the outbreak. Consideration of selective variations in susceptibility which were disclosed by the epidemic will be reserved for another paper.

Composition of the Population

On Dec. 20, 1932, the colony contained 591 adults and 824 rabbits under 2 months of age. During the first 4 weeks of the epidemic, 291 living young were

born, thus increasing the exposed population to a total of 1706. These animals were distributed among fifteen pure breeds and two groups of hybrids.

With few exceptions, the animals were bred and reared in the colony and no new stock had been brought into the breeding rooms proper since the previous spring. From time to time, however, animals were purchased from outside sources for certain classes of experiments, and these were brought into contact with one division of the breeding colony. Animals under experimental observation and stocks purchased for such purposes are not included in these reports.

Most of the adults were in active breeding service during the fall and until Dec. 16 when all matings were discontinued. From that time until Feb. 17 the male population was idle. During the first 4 weeks of the epidemic, however, there were a number of pregnant females and there were nursing does during the entire period.

The population of the colony was, therefore, mixed, containing racial elements and racial crosses with strong and vigorous groups, on the one hand, and weaklings of various kinds on the other; there was a wide range of age groups, from new born to old age, and the adult members of the population were in various states of physiological activity.

Housing and Care of Colony

The animals were reared indoors and for generations had not been exposed to outdoor conditions of living. They were housed in four steam heated rooms, all filled to capacity. These rooms were equipped with automatic heat control and during the fall, winter and spring, an effort was made to maintain a temperature between 60° and 65°F. The lighting of the rooms was good but ventilation was poor.

Adults were caged separately and, as far as possible, the size of the cage was adjusted to the spacial requirements of individual animals. This was determined not only by the size of the animal, but by temperamental adaptability to spacial limitations.

The cages, in general, were of two classes; namely, individual cages for storage purposes, and breeding and nursery cages. The standard individual cage measured 22 x 14 x 14 inches and, occasionally, a slightly smaller cage was used. Several sizes of breeding and nursery cages were in use; these ranged from a cage 22 inches wide, 30 inches deep and 20 inches high to cages 69 inches wide, 30 inches deep and 26 inches high. In all cases an effort was made to give every animal as much room as possible.

Does are permitted to carry their litters from 4 to 8 weeks, rarely longer. The time of weaning depends in part upon the growth and maturity of the litter and the consequent necessity for nursing, in part, upon the condition of nursing does and the desirability of early weaning as a protection for the doe, and in part on the necessity for using the doe for the production of additional litters. In any case, young animals remain together for a period varying from 6 to 12 weeks. As a

rule, they are separated and caged at an average age of 8 to 10 weeks. In our colony sexual maturity is frequently attained as early as 12 weeks and young animals are sufficiently mature for breeding service at from 4 to 5 months if their development has proceeded normally. This varies, of course, with different breeds and with pure breeds as compared with hybrids.

On account of the composition of the population and the purposes for which the colony is maintained, the use of a diet that is adequate for all animals is neither practical nor desirable. An effort has been made to provide a diet that is adequate for standard, normal groups of animals as determined by criteria of health, reproductive efficiency and the growth and maturity of young stock. This leaves a margin for comparison between control groups and those members of the population whose requirements are greater.

Numerous systems of feeding have been tested but, at the time of the epidemic, we were using a commercial food composed of mixed grains and grain products, chopped alfalfa and mineral salts with a molasses binder. This was supplemented with hay and a free supply of water. No green food was used. This particular diet had been in general use for about a year and on the whole, had given satisfactory results.

The relation of the rooms to one another and to other animal quarters is significant. Three of the rooms occupied the east end of a floor in one building as shown in Text-fig. 1, while the fourth was on the top floor of another building at a considerable distance from the first and connected only by a series of corridors and stairways. This room was in use at the time of the epidemic as an isolation room for animals with chronic or persistent snuffles and acute cases with profuse nasal discharge. When such animals recovered, they were returned to the breeding colony, so that there was a movement back and forth between the breeding colony and the isolation quarters. These animals were, in the main, idle and were not kept under close observation.

Rooms A and B are breeding rooms. They are separated by a wide corridor; both are exposed on two sides. Room A has no communication with any other room, but in B there is a door connecting with C. This was closed by immovable cage racks, but the doorway was not sealed and there was an open space beneath the door.

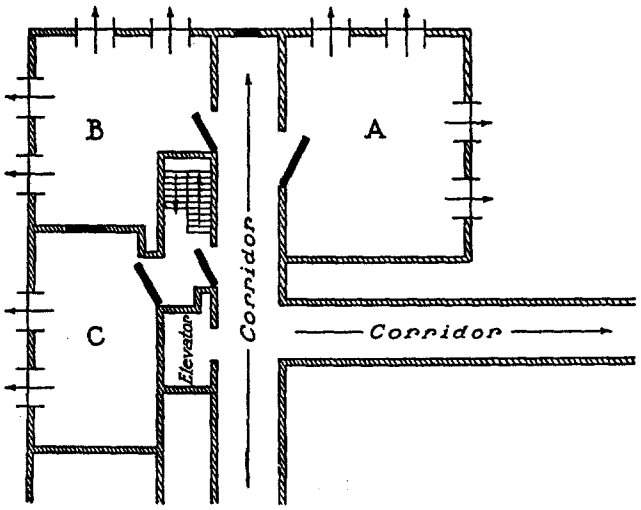
At the time of the epidemic, C was used for miscellaneous stocks, including an overflow from the breeding colony consisting of animals not in active service or of secondary value, and of mild cases of snuffles. In addition, this room contained experimental animals, some of which had been purchased from outside sources. Breeding stocks in this room were examined irregularly or only as there was occasion to use them.

Beyond C, the corridor on which the breeding rooms open continues past the doors of a number of rooms used for housing experimental animals belonging to other laboratories. This corridor is a thoroughfare for the movement of food, bedding, and the litter from cages as they are cleaned.

Rooms A and B were isolated to the extent that they were under the care of men who were assigned no other duties. But the caretaker in C divided his time between that room and others on the same floor, and thus came in contact with other animals. On Sundays and holidays, however, the regular routine was suspended and a reduced crew of caretakers went from room to room to feed and water animals, so that all isolation precautions were broken down on these occasions.

Health Supervision

The health of the colony is subject to close supervision. Animals in the breeding rooms are inspected daily. Cases of illness are noted and mortality records are kept showing the prevalence of disease and the death rate from various causes.



TEXT-FIG. 1. Plan of animal rooms.

These records are supplemented by a weekly enumeration and grading of all cases of snuffles, including animals with moist noses or slightly soiled forepaws as well as those with frank nasal discharges. Functional fitness is gauged by reproductive efficiency based on the percentage of fertile matings, abortions, still births and desertions of litters.

Experience has shown that the prevalence of snuffles and reproductive efficiency are peculiarly sensitive indicators of the health and performance of the colony and that any deterioration or improvement is almost immediately reflected by one or both of these indices, so that the routine management of the colony is based largely on evidence supplied by these records.

Pre-Epidemic Period

Health and Efficiency of the Population

In the study of epidemics, information concerning the state of the population during the period preceding the epidemic outbreak is desirable but, as a rule, is difficult to obtain. Observations covering the pre-epidemic period are, therefore, of especial interest and the results of the observations made in the present instance may be presented as events leading up to the epidemic outbreak. These include data on reproductive efficiency, the incidence of snuffles, the prevalence of gastro-intestinal disorders and the death rate from various causes.

Fertility.—As a rule, adult rabbits which have been idle during the summer or for a period of months show evidence of low fertility when first returned to active breeding service. In exceptional cases, the reduction in fertility may amount to complete sterility lasting for a month or more. This condition is accentuated by moult and low fertility is a normal occurrence during moulting periods.

When breeding is resumed in the fall, matings made during the first week or so usually give a small percentage of pregnancies; the normal expectation is from 20 to 40 per cent. The curve then rises to a level of from 60 to 80 per cent and should remain well above 60 per cent. A further rise occurs during the early spring and is followed by a fall coincident with the spring moult and the beginning of hot weather. The exact figures are influenced by the frequency with which persistently sterile animals are used and, in compiling fertility records, corrections are made on this account and no matings are used unless service is actually observed.

The records for the fall of 1932 are given in Table I and Text-fig. 2. Breeding began the last week in September and continued without interruption until Dec. 16. It will be seen that the fertility curve followed a normal course and reached a high point of 71 per cent for matings made during the first week of November. This was followed by a decided drop which, in the routine examination for pregnancy, 10 days after mating, was not detected until the middle of November. At this time, other signs of deterioration were apparent.

Similar disturbances had been encountered on other occasions and, while their true cause was not known, it had been found that they could be corrected by the administration of vitamin concentrates in excess of the normal requirement. The adult members of the population were, therefore, given brewers' yeast, cod liver oil with viosterol, and tomato juice by hand for a period of about 2 weeks. This was a laborious task and could not be carried out indefinitely and, as improvement was not as rapid or as satisfactory as usual, arrangements were undertaken for the incorporation of additional vitamins in the regular food ration. This procedure

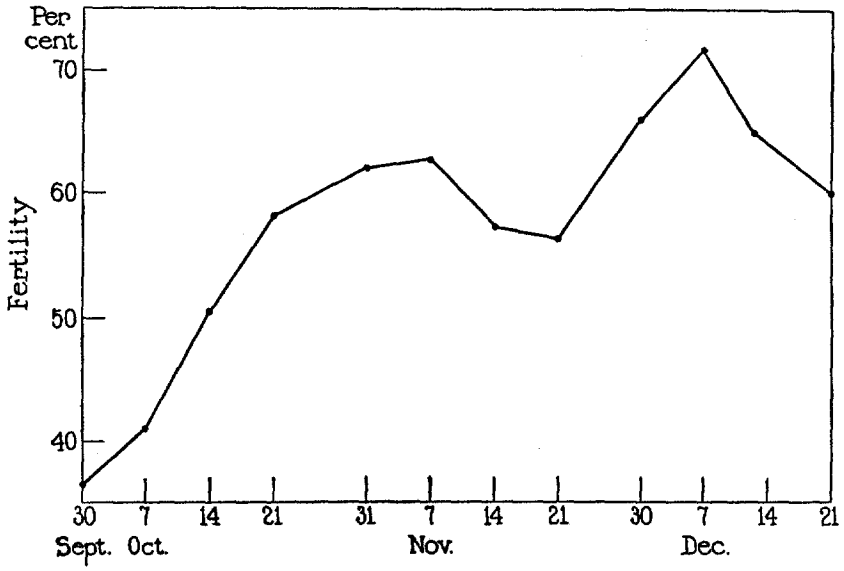
could not be put into operation before the epidemic of pox occurred. Meantime, selective vitaminization of the most seriously affected and most valuable animals was continued.

Reference to the fertility curve in Text-fig. 2 shows that there was a definite response to vitaminization. The curve rose from a low level of 51 to 56 per cent

TABLE I

Fertility during the Pre-Epidemic Period

	Sept.	Oct. 1–7	Oct. 8–14	Oct. 15–21	Oct. 22–31	Nov. 1–7	Nov. 8–14	Nov. 15–21	Nov. 22–30	Dec. 1–7	Dec. 8–14	Dec. 15–21
Matings	46	96	102	81	72	49	39	43	35	39	50	10
Pregnancies	16	38	51	51	41	35	20	24	22	32	30	6
Fertility, *per cent*	34.8	39.6	50	63	57	71.4	51	56	63	82	60	60



TEXT-FIG. 2. Fertility during the pre-epidemic period.

during the 2nd and 3rd weeks of November to 82 per cent for the first week of December. Routine vitaminization was discontinued at this time and the curve again dropped abruptly.

Abortions.—The gestation period in the rabbit varies from 30 to 32 days with a mean of approximately 31 days. Pregnancy can be diagnosed in some instances by palpation of the abdomen as early as the 8th day following coitus and, with rare exceptions, can be diagnosed with certainty by the 10th day. The term abortion

is used here to cover the loss of litters during the 21 day period after pregnancy has been established. Nothing definite is known concerning earlier interruptions of pregnancy. Abortion usually occurs during the last week of pregnancy with the birth of a premature litter, either living or dead. Occasionally, it occurs earlier and, in such cases, the products of conception are usually eaten by the doe so that the exact date of abortion cannot be determined.

No abortions occurred among the animals mated during September or the first 3 weeks of October, but the rate for subsequent matings rose from 5 per cent during the last week of November to 7.3 per cent during the 2nd week of December. From this point on the picture was complicated by the prevalence of pox. The abortion rate rose abruptly and progressively after the outbreak occurred, reaching the high point of 83.3 per cent among does mated just before the epidemic began. It is important to note that the first increase in abortions occurred among animals of the group in which a decrease in fertility was first recognized. Thus, decreasing fertility and abortion are linked together as immediate and ultimate responses to some disturbance in the animal organism.

Still Births.—In checking litters at birth, dead macerated fetuses and animals that are immature and evidently dead before birth are occasionally found. But, as a rule, it is impossible to distinguish between deaths which occur just before, during or immediately after birth. All of these represent birth losses and are classed as still births. The number of such animals varies normally in different breeds or families; in some they are of common occurrence and are most frequent among animals known to transmit certain constitutional abnormalities. Still births usually average between 2 to 5 per cent of the total number of young born and are limited to few litters.

No significant deviation from the expected percentage of still births was found during the pre-epidemic period, but toward the end of this period, there was a definite increase in the proportion of litters containing still born young. That is to say, the condition was more widespread than usual.

Desertions.—Neglect, desertion or the destruction of litters at birth or during the first week of life is a phenomenon of considerable interest. The preparation for the birth of a litter and the care given the litter at birth and during the first few days thereafter are expressions of racial, familial and individual characteristics, and any deviation from the usual course of events in a given animal is a peculiarly sensitive index of the true state of health of that animal. To appreciate this fully, the individuality of the animal must be known, but the failure of any animal to perform these functions adequately, or the manifestation of cannibalism, may be accepted as conclusive evidence of abnormality. In some instances, it is a disinclination, in others an inability to care for the young and in still others a morbid appetite which leads to desertion on the one hand, and cannibalism on the other. In the great majority of cases these expressions of abnormality can be abolished by appropriate treatment (3).

An analysis of maternal behavior in relation to losses by desertion is too compli-

cated to be attempted here. It is sufficient to say that during October and November desertions were only occasionally encountered, and most of these occurred in a family of closely inbred animals which rarely nurse their own young but, as a rule, will rear foster litters. Throughout the remainder of the pre-epidemic period, however, there was a progressive increase in desertions on the part of does that normally raise large, healthy litters, and this included some of the most dependable animals in the colony.

This was regarded as convincing evidence of the prevalence of some condition which was undermining the health of the colony and was the main reason for the decision to stop breeding operations on Dec. 16, or about 2 weeks before the first case of pox was found in the breeding colony. It will be noted again that this manifestation of abnormality occurred in the same group of animals previously identified with diminished fertility and increasing abortions. While these three measures of the functional status of the female population of the colony are separated in time of expression, they are all connected with some disturbance in the health of the community dating back to the middle of November, or more than a month before the outbreak of pox occurred.

Prevalence of Snuffles.—In considering the significance of snuffles as an index of health, it should be pointed out that the great majority of rabbits are carriers of *Bacterium lepisepticum* or *Bacterium bronchisepticum*, or both. So called snuffles-free colonies may be established and maintained by employing suitable precautions. However, no such precautions were taken with this colony as we preferred to utilize snuffles as a constitutional index. Considerable time has been devoted to study of the disease with especial reference to the factors which influence susceptibility.

Briefly, it has been found that, in the main, snuffles is a disease of adolescent and adult life. Nursing young are peculiarly insusceptible, but susceptibility increases with weaning and reaches a maximum at puberty. After full sexual development is attained, the presence or absence of snuffles is a function of health and vigor.

The incidence of the disease varies greatly in different breeds or family groups. There are some groups of animals in the colony which are so susceptible that, with rare exceptions, every animal develops a nasal discharge by the end of the 5th month of life. On the other hand, there are some in which snuffles is rarely seen at any time. Between these extremes, however, snuffles is variable and is subject to the influence of numerous factors. For example, moulting is always preceded or accompanied by an increase of wet noses or frank nasal discharges. Males that are used too often for service and does that are bred too frequently or made to carry litters too long are apt to develop snuffles. On the other hand, idle females that are excessively fat and indolent are frequently affected. In such cases the condition is often relieved by pregnancy and lactation.

A similar situation obtains with respect to spacial requirements. With many animals, snuffles is merely a response to overcrowding or to too close confinement

in small cages and can be relieved by a suitable readjustment of cage accommodations. Overheating of rooms and unseasonable weather are also factors of importance.

The presence in the colony of animals with frank nasal discharges is a factor of uncertain significance. A limited isolation has been practiced as a presumptive measure of protection to young stock, but it has never been possible to remove all animals with nasal discharges from the breeding rooms. There is, however, no evidence to show that the presence of such animals has any material influence on the actual prevalence of snuffles.

The evidence available indicates that the prevalence of snuffles represents an expression of inherent susceptibility on the one hand, and the action of environmental factors which affect the functional efficiency and the health of the animal on the other. In our colony, it is a disease of no particular consequence except in certain racial groups, and rarely are other cases encountered which will not respond to simple methods of dietary and hygienic treatment.

TABLE II

Incidence of Snuffles during Pre-Epidemic Period

	Oct. 22	Nov. 9	Nov. 15	Nov. 21	Nov. 28	Dec. 7	Dec. 14	Dec. 21
Snuffles, *per cent*.....	14.7	13.9	12.0	13.6	13.6	15.5	17.4	23.6

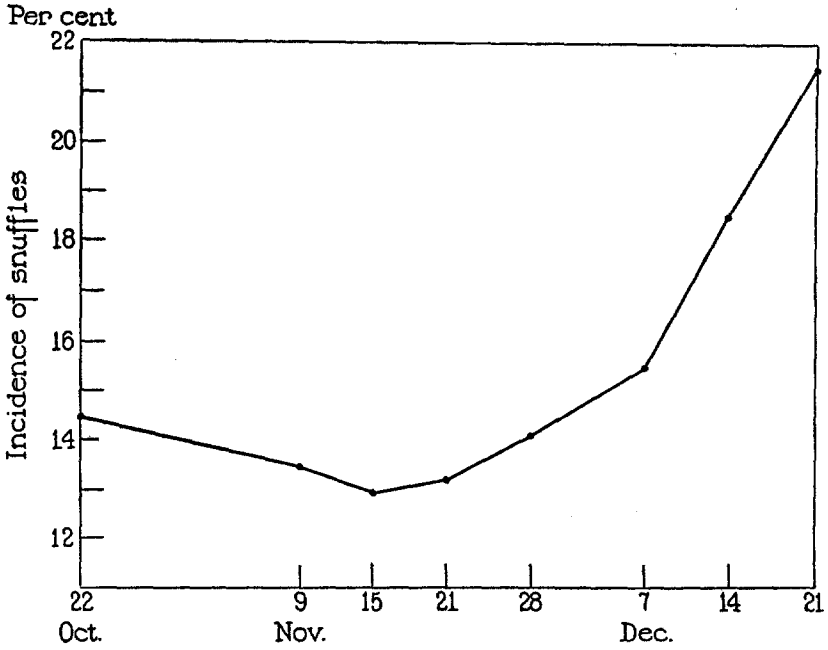
The incidence of snuffles from Oct. 22 to Dec. 21 is given in Table II. These figures are based on the adult population and include every case of wet nose in the colony. The values for the first three checks represent a basic level and are attributable mainly to animals with more or less persistent snuffles. The slight decline shown on Nov. 15 was referable, in large part, to the weeding out of some of these animals; the few new cases that developed were offset by recoveries. Other animals were discarded later, but there was a gradual increase in new cases, culminating in a sharp rise during the 2nd and 3rd weeks of December when nearly a fourth of the colony was affected. During this period the severity of the disease increased, cases began to appear in the young stock and there was a rise in the death rate from pneumonia in both classes of animals. After Dec. 21, snuffles checks were discontinued as cases of simple snuffles could not be distinguished with certainty from incipient cases of pox.

This series of observations again indicated the presence of some disturbing influence in the colony which, in this instance, assumed the form of a definite increase in the incidence and severity of an upper respiratory infection and an increase in the death rate from pneumonia. This sharp rise occurred more than 2 weeks in advance of the outbreak of rabbit pox and coincided with an equally sharp decline in the fertility of the colony as shown in Text-figs. 2 and 3.

Gastro-Intestinal Disorders.—Gastro-intestinal disorders varying from mild and transient cases of slobbers and diarrhea to chronic progressive and acutely fatal

affections constitute the most serious group of diseases with which we have had to contend. Affections of this class are most frequent in young animals and account for the great majority of deaths during the first 3 or 4 months of life. They are less serious in older animals but, at times, the mortality in adults is also high. No age group is exempt and even animals 1 to 3 weeks old, dependent entirely upon nursing, are subject to periodic outbreaks of a highly fatal nature.

The etiology of this class of disorders is uncertain. By some they have been attributed to improper feeding or to the feeding of green food and to parasitic infections, particularly coccidiosis. Neither of these conditions, however, is a



TEXT-FIG. 3. Incidence of snuffles during the pre-epidemic period.

factor of primary importance in our colony; coccodiosis is extremely rare and green food is not used. From investigations extending over a period of years, it has been found that, on a standard diet, gastro-intestinal disorders are of variable frequency and severity. Incidence and mortality are highest in hot weather, but for unknown reasons serious outbreaks occur at other times. It has been found also that, in certain stocks, gastro-intestinal disorders are rare at any time while, in others, incidence and mortality are comparatively high at all times and under all circumstances. Diet in the form of vitamin concentrates or the use of a suitable foster mother is the most potent factor in influencing these affections experimentally. In brief, the information obtained so far indicates that there are at

least two groups of factors concerned in the periodic outbreaks of these disorders, the one an hereditary predisposition and the other a variation in dietary requirement which is determined by unknown environmental factors.

Mortality records for the period preceding the outbreak of rabbit pox show that there were no deaths from gastro-intestinal disorders prior to Nov. 16. There was one death in a young animal on this date from acute bloat, another on the last day of the month and two the first week of December (Table III). This is a low normal expectation and covers a period in which there was not a large number of highly susceptible young animals in the colony. During the 2nd and 3rd weeks of December, the rate rose rapidly and there were six deaths among adults. This rise continued for 2 weeks after the first case of pox appeared and then decreased as the epidemic reached its height. These relations are shown in Text-fig. 4.

TABLE III

Mortality from Gastro-Intestinal Disorders in Young and Adult Stock

	Nov. 16–22	Nov. 23–29	Nov. 30–Dec. 6	Dec. 7–13	Dec. 14–20	Dec. 21–27	Dec. 28–Jan. 3	Jan. 4–10	Jan. 11–17	Jan. 18–24
Young stock										
Deaths	1	0	3	4	25	35	43	26	8	2
Mortality, *per cent*	0.13	0	0.37	0.49	3.07	4.32	5.62	3.88	1.69	0.69
Adult stock										
Deaths	0	0	0	0	6	4	0	0	1	0
Mortality, *per cent*	0	0	0	0	1.01	0.68	0	0	0.19	0

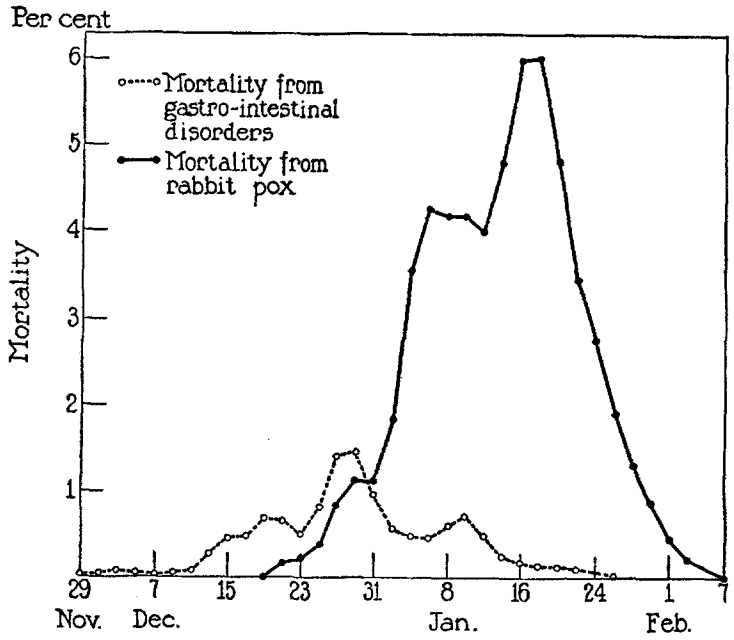
Miscellaneous Signs of Deterioration.—Besides the criteria of health mentioned above, there were other indications of a widespread and profound disturbance of the health of the colony which cannot be recorded in detail. It may be said, however, that there was a recurrent moult among the adults in late November and early December. Matings were obtained with difficulty due to a depression of sexual characters of both males and females. At the same time young animals showed retarded growth and absence of customary thriftiness. Signs of retarded and abnormal development, such as primary nakedness or subnormal development of the hair with deficient pigmentation which are usually limited to certain family groups, were found widespread in full term litters.

Birth abnormalities such as calcification defects in the bones of the calvarium or complete absence of calcification with resulting hydrocephalus and abnormal development of the jaws with malocclusion of the incisor teeth are of sporadic occurrence in certain groups of constitutionally defective animals. These conditions have a genetic background, but their expression is largely determined by environmental factors. In other animals, functional disorders of a lethal character

occur with more or less regularity, but the time of appearance and the severity of these affections are materially influenced by environmental factors. During the pre-epidemic period, birth abnormalities occurred with increased frequency, while lethal deficiencies progressed more rapidly to a fatal termination.

The Epidemic

The unfolding of these signs of physical and functional deterioration, at first gradual and then more rapid, had been watched with great concern. When it became apparent that efforts to improve the



TEXT-FIG. 4. Comparison of pox and gastro intestinal mortality rates.

condition of the population by dietary and hygienic measures were not attended with the usual success, breeding operations were suspended as a last resort. This was done on Dec. 16 and the first typical case of pox was found in a young rabbit in Room B on Dec. 28.

The infection spread rapidly through this room with cases developing simultaneously in all locations. There was no evidence of spread by contact or proximity from a primary focus of infection but, at the outset, the main focus appeared to be in the rear of the room adjoin-

ing Room C, and during the early part of the epidemic, the incidence of infection and mortality was highest in this group of cages.

Scattered cases of pox were found in A soon after they appeared in B. In this room, however, which contained a larger proportion of adult animals and was less crowded than B, the infection spread more slowly and the peak of the outbreak was not reached until the disease in B was well on the decline. There were comparatively few deaths in C and, for the most part, those in D occurred before the nature of the disease had been recognized.

The incidence of new cases could not be followed and recorded day by day. The only accurate record of the course of the epidemic is derived from the mortality records. Dead animals were collected daily, records of their death were made and autopsies performed. The data obtained in this way are given in Table IV and Text-fig. 4.

TABLE IV

Pox Mortality

	Dec. 20–25	Dec. 26–31	Jan. 1–6	Jan. 7–12	Jan. 13–18	Jan. 19–24	Jan. 25–30	Jan 31–Feb. 5
Deaths	7	45	127	139	166	93	28	5
Mortality, *per cent*	0.5	3.3	9.8	12.4	17.4	12.2	4.0	0.7

The epidemic, recognized as such, began Dec. 28 and ended Feb. 5. It will be noted, however, that the record begins with Dec. 20, more than a week before the first clinically typical case of pox was found in the breeding rooms. A review of autopsy protocols in the light of subsequent experience showed that deaths from pox, clinically unrecognized because of the absence of external lesions, occurred in Room B on that date. Deaths which occurred in Room D as early as Dec. 12, and at the time were attributed to pneumonia, probably resulted from pox infection but are not included. Moreover, there were deaths during February and even later which were due indirectly to rabbit pox, but none of these are included in the data given above. The mortality curve for the period (Text-fig. 4) is typically that of an epidemic. The only irregularity is shown at Jan. 12 and this is referable to the superimposing of what amounts to two closely related epidemics, the one in Room B and the other in Room A.

Of the 1706 animals constituting the population during the epidemic period, 393 were killed or died of various causes including desertion, diarrhea and miscellaneous disorders and are not included in the determination of the pox mortality. During the period from Dec. 20 to Feb. 5, 610 animals died of rabbit pox, giving a mortality of 46.4 per cent. Many others were so seriously affected that they subsequently

died or were killed in the reorganization of the colony. Actual losses attributable to the epidemic were, therefore, much higher than the figures given above would indicate.

In discussing the origin of the epidemic, reference will be made to peculiar affections which preceded and followed the epidemic outbreak. It is not known whether these conditions were referable to pox infection, but it is certain that the epidemic began and ended with cases of infection which could not have been recognized as pox except by their association with typical cases of the disease. Thus, the first deaths were ascribed to pneumonia of a virulent type. These animals showed a profuse blood-stained discharge from the nose with massive consolidation of the lungs, but no characteristic focal lesions as in typical cases of pox. The evidence available, however, indicates that these were cases of pox infection. Moreover, during the 4th week of December, there occurred a number of deaths in Room B among young animals which showed signs of an acute gastro-intestinal disturbance, but no clinical evidence of pox infection. At autopsy, however, the focal lesions afterwards found to be characteristic of the disease were discovered in their internal organs. The first death of this kind occurred on Dec. 20 and it was more than a week before typical external lesions appeared in affected animals. Toward the end of the epidemic, on the other hand, mild cases of infection were common with a tendency to monosymptomatic affections difficult to recognize or easily confused with some other disease. Prominent among these were cases of keratitis and iritis with or without the production of glaucoma.

It can be said, therefore, that the time of the actual appearance of the infection in the colony and of its final disappearance are unknown. The disease began insidiously and died out in an equally obscure manner, leaving behind a train of affections suggestive of pox but not definitely established as cases of pox infection. On the basis of the distribution of lesions, three phases in the history of the infection could be recognized. At first the disease was entirely visceral, appearing as a fulminating pneumonia on the one hand and as an acute affection of the gastro-intestinal system with numerous focal lesions on the other. Later, with involvement of the skin and all organ systems, the infection assumed its typical form. Toward the termi-

nation of the epidemic, visceral lesions were less numerous and manifestations of infection were limited almost entirely to the skin.

Origin and Spread of the Infection

When the condition of the colony became so serious that we were forced to discontinue breeding operations, a systematic examination of all animals was made for evidence of any obscure disease which might have been overlooked in the course of routine observation. These examinations were continued day by day with attention centered on the breeding rooms, but for some time nothing definite was found. Suspicion was first aroused by a sudden increase in the mortality from what appeared to be pneumonia among the animals with snuffles in the isolation room (D). These animals became acutely ill; some showed a profuse blood-stained discharge from the nose or the formation of thick brown crusts about the nares with marked respiratory distress followed by death in a few hours or by gradual recovery. At autopsy the outstanding condition was a massive pneumonia. There were no typical pox lesions, either external or internal. Examination of several males in process of recovery showed, however, that these animals had a granular orchitis undergoing resolution.

The significance of this finding was not appreciated at the time, but it was known that we were not dealing with an ordinary pneumonia. These were undoubtedly atypical cases of pox. As was mentioned above, the animals in this room were not subject to systematic observation and the time of occurrence of pox in this group can be fixed only with reference to the flare up of pneumonia. The first death of this kind occurred Dec. 12. Typical cases of pox were never found among the breeding stocks in this room, but did occur in a group of experimental animals which had been inoculated with material taken from an animal in this room. The presence of the virus was thus definitely established.

In this connection it is also of interest to note that before the presence of a contagious disease was recognized, several animals were transferred from this room to the breeding rooms; others were brought into the room for mating and then returned to their own quarters. None of these animals, however, developed pox until the epidemic was well advanced. Later, a litter of young 13 days old was taken from a

doe that had just died with pneumonia and transferred to a foster mother in A. A number of these animals died within 48 hours and they also showed pneumonia, but the doe which had fostered them and her own young were among the last in the colony to develop pox. The bearing of these transfers on the outbreak in the breeding rooms is, therefore, uncertain. It is of further interest in this connection that the mortality in D was not high and that the fulminating cases of pneumonia were largely limited to a group of Belgian hares and French silvers which were subsequently found to be among the most susceptible breeds.

The animals in Room C were not examined until after the first typical case of acute infection had been found in B. But, at this time, several cases were found. In addition, there were a number of animals with crusted and healing papular lesions of the skin and with lesions of the testicles in process of resolution. From these findings, it was evident that the disease had been present in mild form in this room for some time, thus establishing a second focus of infection antedating the outbreak in the two breeding rooms. It is possible, therefore, to trace the outbreak in the breeding rooms to either or both of these sources of infection.

The question then arises as to whether the infection in these rooms had an independent origin or spread from one to the other. This question cannot be answered with certainty. The evidence available indicates that there were two independent sources of infection which, in one case (Room D), gave rise to an acute fulminating type of infection and, in another (Room C), to a distinctly milder form of disease. The disease apparently developed at about the same time in both rooms and it was at least a week or 10 days before it spread to the breeding rooms.

The origin of the virus is also a matter of some uncertainty, but it is highly probable that in both cases infection originated from a passage virus. During the autumn, animals inoculated with neurovaccine and dermovaccine were kept on a lower floor of the building in which Room D is located and in rooms only a short distance down the corridor from the breeding colony. There was no report of a spontaneous spread of infection in any of these rooms until after the epidemic developed in the breeding colony, but it is known that in at

least one of them a disease presenting the clinical characteristics of rabbit pox was present earlier in the fall.

Isolation of inoculated animals is a difficult matter and ordinarily few or no precautions are taken to prevent the spread of the less harmful virus or bacterial infections among the animals of a given room or from one room to another. Caretakers provide a ready means for the dissemination of highly contagious material. In spite of this, serious outbreaks are comparatively rare. In the present instance, however, all available evidence indicated that from the passage of some virus, spontaneous spread did occur among the animals in one or more of these rooms. Eventually, the virus was transported in a highly virulent form to the nearest outposts of the breeding colony which was not protected in any way against outside infection. Spread of the infection continued from one room to another until practically the entire rabbit population of the Institute had been exposed, regardless of location or distance from the original source of infection and despite all efforts to quarantine or isolate groups of animals known to have been infected or exposed. The order of occurrence of outbreaks in various rooms and their relation to possible sources of infection are not known, since the recognition of the disease, in all cases, followed the discovery in the breeding colony.

Termination of the Epidemic

The course of events during the terminal stages of the epidemic brought out several points of epidemiological interest. As is usual during the early stages of an epidemic, the infection was highly contagious and the mortality correspondingly high, while, in the terminal stages, contagiousness diminished and the mortality was low. All of the adults and all of the young born prior to the epidemic except those that died of other causes developed pox. The same is true of all litters born during the early stages of the epidemic. There were, however, several instances of litters born after the epidemic was well under way in which no typical case of pox developed, and still others in which some animals developed typical cases of disease while other animals, despite the most intimate exposure, remained free from signs or symptoms of infection. In a third group of animals, known to have been exposed soon after birth, the incubation period was greatly

prolonged and lesions did not develop for several weeks; these infections were comparatively mild and were among the last cases of the epidemic. In most, if not all, of these exceptional cases the mother contracted the disease before or shortly after the birth of the litter and was not seriously affected. This sequence is apparently significant and suggests a passive protection from an immune mother. Still, the apparent change in contagiousness and definite decrease in the severity of the disease are difficult to explain.

The present tendency is to assume that conditions of this kind are brought about by a process of gradual immunization through exposure of the population to subinfecting doses of the etiological agent. In the present instance, however, there were comparatively few animals that escaped demonstrable infection, and the epidemic ended only after practically the entire population had contracted the disease. The few animals that apparently escaped infection were born after the epidemic began and were of an age found ordinarily to be highly susceptible. Some of them may have had extremely mild or asymptomatic infections or they may have become immune in the manner indicated above, which seems improbable. On the other hand, they may have been protected by nursing an immune mother, a passive rather than an active immunity.

At the time, it was not possible to carry out tests to determine whether the evident refractoriness of animals known to have been exposed was due to a specific immunity or to other causes. A year later, the immunity of some of these animals to vaccine virus was tested by Pearce, Rosahn and Hu as a part of an extensive series of experiments on the relation of vaccinia to rabbit pox. Vaccination showed that most of them were susceptible, but the significance of these findings is uncertain. The tests showed the condition of the animals at the end of a year and, at that time, their immunity was not of the same order as the immunity found in animals known to have recovered from rabbit pox. However, since the immunity produced by vaccination may be of short duration, it is also possible that these animals may have been protected by a transient immunity in the first instance, and the termination of the epidemic could still be explained by the development of a specific immunity in the entire population.

This explanation might appear to be the logical one if nothing more were known concerning the epidemiology of this disease. There was, however, a previous epidemic in 1930. In this instance, comparatively few animals contracted the disease and most of these recovered. At the time of the second epidemic, there were many animals in the colony that had passed through the first epidemic but none that were known to have had the disease. These animals proved to be just as susceptible to pox as the normal unexposed population so that, if they were protected in the first instance by a specific immunity, the immunity was again of short duration and afforded no appreciable protection against a second exposure.

Still a third epidemic of this disease occurred during the winter of 1933–34. This epidemic pursued a course like that of the first. It developed among experimental animals in a room containing a portion of the breeding colony, but its spread was limited and the mortality low. In this instance, young animals in the room were tested by Pearce, Rosahn and Hu immediately after the epidemic and found to be as susceptible as unexposed controls, so that the failure of the infection to spread could not be attributed to active immunization.

Finally, toward the end of the epidemic under consideration two experiments were carried out with young animals of the most susceptible age. These were obtained from outside sources and had not been exposed to rabbit pox. They were brought into the breeding rooms and exposed to infection by placing them in intimate contact with infected animals. All of them developed pox of a mild form but there were no deaths in a group of twelve animals. At the height of the epidemic the mortality among animals of this age group was upwards of 70 per cent. It is evident, therefore, that while the contagiousness was still high, the severity of the disease produced by natural infection was greatly diminished in animals which possessed no specific immunity.

These results, taken in conjunction with other evidence, cast considerable doubt on the significance of active and progressive immunization as the cause of the terminal abatement in the severity of the disease or as the sole cause for the termination of the epidemic. Old and young animals shared alike in the diminished severity of the disease which marked the terminal stages of the epidemic, and the evi-

dence available indicates that this characteristic change in the course of events was not due entirely, if at all, to a specific immunity but to some other group of factors which affected the entire population in a non-specific manner.

Epidemiological Considerations

The epidemic described is typical of epidemics in human populations and one of the chief points of interest is the opportunity afforded for a consideration of the rôle of epidemiological factors other than those concerned directly with the infectious agent. Accurate information of this kind is extremely difficult to obtain in human epidemics. It has been shown, however, that epidemic outbreaks in animal populations under experimental control are profoundly influenced by factors affecting the host as well as by factors which operate through the infecting organism (4). In experimental epidemics, efforts are directed toward the creation of known conditions and the maintenance of control so that the influence of given factors may be determined with accuracy. There is still some uncertainty, however, as to the conditions that actually prevail in spontaneous outbreaks and the relative importance of various epidemiological factors. Study of the present epidemic provides some information bearing on these points. The evidence collected is of two kinds. First, numerical data derived from systematic observations covering a long period of time and second, estimates of conditions based on judgment, both of which were originally intended to supply information concerning the health and activity of the community.

Reference to the data given above shows clearly that the reproductive activities of the adults in the population were not normal and that for a long time prior to the outbreak of rabbit pox the functional efficiency of these animals was on the decline. That this was not merely a disturbance of reproductive function is shown by parallel observations on the prevalence of disease.

The snuffles index is of particular interest in this connection. It concerns the same elements of the population and records the prevalence of a disease which is constantly present in the community. Here again, it was found that the severity and incidence of this disease began to increase well in advance of the pox epidemic with a

sharp rise immediately preceding the outbreak. There was, moreover, a definite spread of this disease to a portion of the population which is ordinarily insusceptible and this was associated with an increase in the death rate from pneumonia arising from infection with the same group of organisms.

Among the young animals, there was also evidence of low vitality indicated most clearly by the prevalence of gastro-intestinal disorders and deaths directly referable to these disorders. Here again, a disease which is ordinarily limited to certain elements of the population broke over the usual boundaries and caused the death of adults as well as young animals. The incidence of this disease also increased abruptly just previous to the epidemic invasion.

The significance of other abnormalities mentioned above need not be emphasized here. It is sufficient to say that the deterioration of the colony as evidenced by diminished functional efficiency and increased susceptibility to disease was unmistakable.

Experience has shown that for the most part conditions such as prevailed in the community prior to the epidemic are influenced by three groups of factors; namely, diet, cage accommodation or mode of living and climate or weather. Two of these are subject to control and their influence has been tested repeatedly.

The dietary aspect of these conditions is of particular interest. Some of the conditions do suggest a dietary deficiency. There is no reason, however, to assume that a diet found to be adequate for control or standard normal animals of the population was directly responsible for the sudden development of these abnormalities. It is true that the administration of vitamin concentrates usually affords relief in such a situation, but this has been interpreted as evidence of a variation in the vitamin requirement of the animals which results from fluctuations in unknown environmental factors.

It is important to note also that relief may be obtained by other means than diet. Adjustment of cage accommodations with improvement in the conditions of living has been found helpful in many cases. The conditions under consideration, therefore, cannot be regarded as dietary deficiencies in the usual sense. They are, rather, states of diminished vital capacity due to unknown causes, but susceptible of relief by improvement in the conditions of living in which diet plays a very important part.

It is of interest in this connection to note the variations in the disease picture which occurred in different epidemic stages. The first animals to contract the infection reacted with the production of a fulminating pneumonia and for some time the specific lesions of the disease were entirely visceral in distribution. During the height of the epidemic, lesions were widespread and cutaneous lesions formed the most typical clinical feature. Toward the end, however, visceral lesions were infrequent, there was a marked tendency to monosymptomatic affections and, in many cases, characteristic skin papules could be found only after a most extensive search. Similar variations in the disease picture are commonly found in human epidemics and suggest either a variation in the disease-producing properties of the infecting agent or a changing status on the part of the population.

In the present instance there was unmistakable evidence of an increased resistance in the animals during the terminal stages of the epidemic. This could hardly be explained on the basis of a specific immunity since the infection produced in animals of a highly susceptible age which had never been exposed to this infection was relatively harmless. It would have been desirable to have tested the status of the colony by the methods used in the pre-epidemic period. However, there was no means of gauging the functional efficiency of recovered animals until breeding operations were resumed. It was then found that fertility was surprisingly high, rose steadily to 100 per cent and for some time thereafter maintained an unprecedentedly high level. Among the earlier litters, however, there were still a considerable number of still born and non-viable young which were attributed to persistent abnormalities of the generative tract. But, on the whole, there was a striking improvement in reproductive efficiency and snuffles checks which were resumed about the same time showed a very low incidence of this disease.

It is impossible to prove or disprove a causal relation between the prevalence of a widespread and profound disturbance of the population and the occurrence of a devastating epidemic, or a relation between the terminal abatement in the severity of the disease and the coincident increase in resistance followed by general improvement in the condition of the population. But experiments carried out in these laboratories some years ago showed that the organic constitution of the rabbit is subject to a series of orderly variations which tend to

follow a seasonal course, modified by prevailing meteorological conditions (5). It was also found that susceptibility to experimentally induced disease varied with the prevailing condition of the animal organism and that both the organic constitution and the functional response to disease could be affected by modifying environmental conditions under experimental control. The question arises as to whether similar relations may not affect spontaneous outbreaks of disease.

Small pox is a winter disease and so also is rabbit pox. The evidence available indicates that rabbit pox is produced by a virus originating from vaccine virus. From the time the breeding colony was first organized (1929), it has been exposed to infection from inoculated animals in other laboratories through the same channels of communication which gave rise to the epidemic under consideration. So far, three epidemics of pox have occurred; two of them were mild and one was of devastating severity; two began during the 3rd week of December and the other in February. These facts indicate, on the one hand, a decided preference for the winter months and, on the other, a striking variation in the severity of disease on different occasions. Obviously, such peculiarities as these cannot be accounted for either on the basis of chance exposure to vaccine virus or by specific immunity. In view of the conditions which have existed over a period of years, it is even probable that exposure, comparable with that which gave rise to the epidemic reported, may have occurred repeatedly without producing a single typical case of disease. This is apparently in accord with the experience of those who have kept rabbits inoculated with vaccine virus in close proximity to animals that are not immune to this virus.

It is evident, therefore, that the chance introduction of vaccine virus into a non-immune population is not sufficient in itself to determine the occurrence of a severe epidemic; favorable conditions for the propagation of the infection are also essential. These probably include factors which favor an alteration in the pathogenic properties of the infecting organism, on the one hand, and diminished resistance of the host, on the other. Apparently, these two conditions are closely related and it is not improbable that both are referable to the operation of factors on the animal organism and they may be expressions of a common cause.

The experiments carried out by Pearce, Rosahn and Hu showed

that the virus isolated from the epidemic was related to vaccine virus but decidedly more virulent than the passage strain of neurovaccine with which it was compared and far more virulent than the dermovaccine. Under passage conditions this virulence was retained for a period of 9 months (January to September). During this time the infection in the colony died out. These results would indicate that under conditions of natural passage some alteration in the pathogenic properties of the pox virus had occurred. The characteristic properties of this virus are capable of perpetuation by parenteral inoculation, but when left to natural passage under conditions such as prevailed during the epidemic, reversion to a less virulent condition tends to occur and spread of the infection ceases.

One may conclude, therefore, that the decisive factors in the series of events associated with the development and termination of an epidemic are factors which affect the population. It has been shown experimentally that in the case of the rabbit, profound changes in organic constitution are induced by environmental factors and that susceptibility to disease varies accordingly. The series of events preceding the occurrence of the epidemic reported were expressions of a serious disturbance in the animal organism induced by some unknown environmental influence which is commonly operative at that period of the year but in this instance was of more than usual severity. The old idea of an "epidemic constitution" may find an explanation in the development of environmental conditions which affect the functional efficiency and disturb the health of a community and thus create conditions favorable to the spread of devastating infections. It is reasonably certain that factors of this kind played an important rôle in the epidemic of rabbit pox which has been reported.

SUMMARY

A devastating epidemic of rabbit pox in a breeding colony was studied with especial reference to factors of epidemiological significance.

The evidence obtained indicated that the epidemic originated among animals inoculated with vaccine virus and that the infection was spread to the breeding colony by caretakers. The epidemic began insidiously with atypical cases of visceral disease followed by typical

cases of pox and terminated as a mild cutaneous disease with scattering monosymptomatic affections of various kinds, difficult to recognize as cases of pox infection.

An analysis of data concerning the health and functional efficiency of the population and the immunity of exposed animals showed that the epidemic of rabbit pox was the terminal event in a series of progressive disorders which began fully a month before the first case of pox occurred. In like manner, the terminal decrease in the severity of the disease and the eventual termination of the epidemic appeared to be referable to an improvement in the condition of the population rather than to a specific immunity acquired by exposure to infection.

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