A unique condition of the rabbit, designated premature or early senescence, was one of the inherited disease complexes which occurred in a breeding colony maintained in this laboratory for studies on constitutional problems (1). The senile appearance of many individuals was striking, a rabbit 1 or 2 years of age resembling a much older rabbit in such respects as an irregular unkempt coat, dry scurfy or scaly skin areas, and an increasingly poor nutritional state. The basis of the condition was a degeneration of greater or less degree and distribution. In a considerable proportion of cases, a progressive general deterioration developed that was rapidly progressive in character and fatal within a year or so while in other rabbits it was comparatively mild. The pathologic findings, particularly those in the cardiovascular, renal, and endocrine systems, were impressive features.

The first example of the condition occurred in a pure bred Belgian hare, the daughter of parents purchased as one of the foundation stocks of the colony; other examples which later developed in the Belgian group included in their ancestry one or both parents of the first case. At the time, the essential nature of the complex was not suspected but its identification in these early cases later became certain after the results of subsequent experiments were available. At first, interest in this group of rabbits was centered on an inherited disorder of nurslings which was lethal in a few days or weeks and also on a peculiar soft rusty-colored coat condition which developed in some of the rabbits of this stock. These individuals tended to be rather frail and short lived and it was thought that they might represent a mild form of the lethal nursling disorder.

The situation was further confused by the occurrence in this particular Belgian line of a diminutive form characterized at birth by a pale parchment-like wrinkled skin and deficient hair growth. Many of these young were non-viable but some were raised. As adults, these rabbits were generally rather small and their coats usually became soft, darkish or rusty brown in color and with a tendency toward sparseness or thinning. These characteristics were responsible for the name given the rabbits, Downy-Rusty-Dwarf or D.R.D. for short. It so happened that certain D.R.D. rabbits were
the first transmitters of the lethal condition of nurslings just mentioned and this association continued for some time. There were still other disorders in this Belgian family and meanwhile, all attempts to continue it in pure line were unsuccessful. Other Belgian stocks and also other pure breeds, principally English and Dutch, were introduced into the line from time to time in an effort to continue it and to preserve as many of the abnormalities as possible.

For a considerable period the results of breeding experiments with these several groups emphasized principally the lethal nursling disorder. Eventually, however, in the progeny of two F1 hybrid sisters, it was found that a separation of the fatal nursling affection and the downy-rusty coat condition had occurred. The downy-rusty condition was next established as an hereditary entity and in due course it became evident that it included as its most important feature the comparatively early development of senescence manifestations. Further studies showed, it should be pointed out, that neither the peculiar downy-rusty coat nor the diminutive form, that is the original D.R.D. characters, was an integral part of the premature senescence complex.

Interest in this complex in the rabbit with its characteristic manifestations, pathologic findings, and hereditary association was heightened by the possibility that it might have a place in the study of problems of aging in man and other species. Accordingly, a comprehensive series of investigations was planned and although some parts of it had to be curtailed and others omitted altogether, studies were carried out more or less continuously over a period of 15 years, the results of which will be reported in this and other papers.

The investigations were of three principal categories. First, the condition in its various forms and gradations was studied in a large number of rabbits throughout life with particular attention paid to the character and course of general deterioration and of the external or local manifestations. In addition blood-chemical and histological studies on certain animals were made. Extensive breeding experiments were an essential part of the entire program. Second, postmortem examinations were carried out and representative histologic material was studied. Third, an analysis of pedigree records and of the results of breeding tests was undertaken to obtain information on the mode of inheritance of the condition.

For descriptive purposes, a chronic and an acute form of the premature senescence complex are reported, the cases being classified on an age-survival basis of 2 years 6 months. This is a convenient although arbitrary division, for there were gradations between an obviously chronic and an obviously acute condition and furthermore, a change from one type to the other in a particular rabbit sometimes occurred.

The chronic condition included two principal types of cases. The first type comprised the rabbits which developed a slowly progressive but on the whole well marked deterioration that eventually became severe and rapidly fatal in a considerable number of instances. The local manifestations were often of a protracted character but with a definite tendency toward regression and healing and subsequent relapse. The second type comprised the cases in which the general degeneration was comparatively minor and the external manifestations mild. Remissions were frequently observed and were prolonged in many instances and in some cases apparent recovery took place.
The acute condition was represented by the rabbits which did not survive to the age of 2 years 6 months. These cases developed a comparatively rapid progressive deterioration with a frequently fatal outcome with correspondingly severe local manifestations. In addition to the adult members of this group were much younger rabbits, nurseries, and young adults, the so called juvenile cases, which will be discussed separately.

The chronic form of premature senescence is described in the present paper and the acute form in adult rabbits in the following report (2). Later papers will contain a description of the condition in young rabbits, the results of blood-chemical determinations and of hematologic examinations, the gross and microscopic pathologic findings, and an analysis of genetic data.

Materials and Methods

The nucleus of the premature senescence stock comprised 6 pure bred Belgian hares: a downy-rusty coated female, subsequently identified as the first senescence case and her unaffected sister, their unaffected brother belonging to a second litter from the same parents, 2 unaffected half-sisters, the daughters of the same sire and a Belgian doe of an unrelated line, and finally the sire himself. These rabbits were interbred and bred to Belgian rabbits of other lines as well as to other pure bred racial stocks in which, as far as was known, the several functional disorders observed in this particular Belgian family did not occur. As soon as the downy-rusty condition became established as an entity and the development of early senescence was recognized, the stock was increased by interbreeding as well as by extensive outcrossing. Thus it came about that much of the stock was of a mixed or mongrel character, in which various breeds were represented.

The material, on which the description of premature senescence in the rabbit is centered, comprises a selected group of 185 adult rabbits, 93 males and 92 females, in which 20 generations of the condition are represented. Each rabbit was carefully observed throughout life and was examined postmortem. A larger number of adult cases actually occurred but those insufficiently observed in one or another respect were not included. Of the total number of rabbits, 106 are discussed in the present paper as 53 chronic, 40 as probable chronic, and 13 as recovered cases, respectively (Table I); 79 rabbits classified as acute cases are considered in the following paper (2).

The other rabbits of the colony, which belonged to both normal and abnormal stock, served as control material. The various constitutional problems under investigation involved a large proportion of the entire population. Many litters and groups of rabbits assembled for particular experiments were constantly under close observation and in addition repeated population surveys were made at regular intervals. Most of the problems studied had their inception in disorders or abnormalities first observed in certain family groups of the colony and many of them occurred in the Belgian group under present consideration. In certain racial groups, notably the English breed, abnormal conditions were comparatively rare or insignificant. The largest segment of the population comprised hybrid and mongrel rabbits of mixed ancestry. A considerable number of them together with representatives of pure bred stocks were under observation for 3 years or longer.

In all the work with the premature senescence stock, a detailed description of the young and the mother and body weight determinations were recorded at the first examination of the litter within a few hours of birth. In subsequent examinations of the nurseries carried out 2 or 3 times a week, particular attention was paid to the appearance, nutritional state, and
growth of the young and to the physical condition and nursing status of the doe. Fostering some or all of a litter was carried out not infrequently, for poor care of their young or an inadequate nursing capacity was often observed in does of the Belgian breed and in does of predominately Belgian blood. Litters were usually weaned at 7 or 8 weeks of age and at 3 or 4 months of age the rabbits were separately caged, as was the custom throughout the colony. Adult members of the premature senescence stock were examined at approximately fortnightly intervals except those individuals with active manifestations which were examined more frequently. Finally, a postmortem examination was carried out on practically every rabbit and representative tissues saved for microscopic study. All rabbits that were killed received an injection of air in a marginal ear vein.

The entire population of the colony was fed the same diet consisting of a standard pellet preparation of the best quality obtainable, timothy and alfalfa hay, and a constant water supply. Supplementary feeding of fresh cabbage and carrots was carried out during the winter months. An excellent state of health was maintained throughout the colony.

RESULTS

The condition which we have termed premature senescence in severe form expressed itself in the development of various external or local manifestations,
often at an early age, of a progressive and pronounced general deterioration. The most prominent local manifestations, to be described in detail further on, were degeneration of the coat and skin, lesions of the eyes and feet, and reproductive abnormalities; the symptoms of a general or systemic degeneration including muscle atrophy and fat depletion, a declining body weight, emaciation, weakness, and finally a fatal termination. A senile appearance, quite striking in some cases, was due largely to the degenerative changes of the coat. In addition to this severe disorder, there were frequent examples of moderate and minor types in which the local manifestations were less numerous and of a generally milder character while general deterioration, if indeed it occurred, was likewise mild and self-limited. Recovery of some cases apparently occurred.

The classification of a chronic form of premature senescence has been made, as has already been stated, on the basis of survival to 2 years 6 months of age. Certain other cases, which would probably have survived to this age or longer, have been included for present consideration. Data for the total group of 106 cases on the grade or severity of the senescence complex, the survival age, the particular outcome, and the serious complications encountered are summarized in Table I and will first be discussed. Then follows a description of the external or local features and the course of general deterioration.

There were 18 rabbits (Table I) which developed a severe progressive degeneration with active manifestations and which lived from 2 years 6 months, to 4 years of age or older; 7 of the 8 deaths were ascribed directly to the senescence condition while in 1 rabbit there was a complicating lung abscess. Of the 10 rabbits which were killed, death appeared to be imminent; none showed a complicating condition.

Of the 14 rabbits with a somewhat less severe senescence (Table I), all showed active manifestations for similar age periods of from 2 years 6 months, to 4 years or older and a fatal termination was expected although it was not as imminent in all cases as in the previous group. Of the 12 rabbits killed, 1 had a complicating toxemia of pregnancy (3, 4) and another an accidentally injured spine. The direct cause of death of 2 rabbits was a lung abscess in one and an acute gastroenteritis in the other.

There were 61 rabbits which developed a comparatively mild senescence that did not seriously interfere with the general health of the rabbits (Table I). Remissions of general and local manifestations were relatively frequent but degenerative features were present at the time of or shortly before the conclusion of the observation period. Of the 21 older rabbits followed for age periods corresponding to those in the severe and moderately severe senescence groups, there were 5 serious complicating conditions: an extensive bronchitis, a subcutaneous abscess of the supraorbital region, 2 mammary carcinomas with metastases, and an acute gastroenteritis. There were 11 rabbits observed for a slightly shorter time; that is, an age period of from 2 years to 2 years 5 months, and in 3 animals, the picture was complicated by a bronchopneumonia, an acute toxemia, and a subcutaneous abscess of the face and neck.

There has also been listed in the group of chronic mild cases 29 rabbits which strictly speaking should not be included for they were followed for less than the prescribed period; 26 were observed for age periods of from 1 year 6 months, to 1 year 11 months, and 3 from 1 year to 1 year 5 months. However, the general character of the manifestations was comparable to that shown by the older rabbits in this group and it was thought probable that the condition would not have become more severe. Of the 29 rabbits, 21 were killed, 2 because of
complications, a torticollis and an accidentally injured spine respectively, and 19 for post-mortem material or because of space requirements. Eight rabbits were found dead, all with such serious complications as pneumonia, mediastinal abscess, and toxemia of pregnancy.

There were 13 rabbits which had shown no evidence of senescence degeneration for at least 6 months before final disposal; they had either recovered from earlier manifestations or were in a long remission period. For the most part these earlier features were of a mild or minor character and in the case of the 5 rabbits observed for ages of from 2 to 4 years, recovery seemed certain. The cause of death in 2 younger animals was an acute gastroenteritis.

The above data on 106 rabbits, in which manifestations ascribed to the development of premature senescence were observed, can be summarized as follows: Of 53 rabbits with active manifestations of the complex at 2 years 6 months, to 4 years of age and classified as examples of a chronic condition, 32 rabbits showed a severe or moderately severe progressive deterioration which either caused the death of the animal or almost certainly would have done so within a short time. In 21 rabbits also observed for comparable age periods and in 11 others followed for a slightly shorter time, the character of the degeneration was comparatively mild and a change to a severe condition appeared unlikely. Some of these 32 animals would probably have recovered, as was thought to be the case in 5 rabbits observed for age periods of from 2 years to 3 years 11 months. Of the remaining 37 rabbits followed for the shorter age periods of 1 year 6 months, to 1 year 11 months, 29 continued to show minor although active features while 8 were either in a long remission period or had recovered.

In the entire group of 106 rabbits, serious complicating conditions were found in 25 rabbits, an incidence of 23.6 per cent, but 15 of them occurred in 50 animals followed for the shorter age periods, an incidence of 30.0 per cent. Of the 56 cases under observation for at least 2 years 6 months, 10 rabbits showed serious complications or an incidence of 17.9 per cent.

The senile appearance was largely determined by degenerative changes of the coat and in the severe or moderately severe chronic condition, it was usually well defined by 2 years of age. All 32 rabbits with these grades of senescence (Table I) acquired this appearance: in 10 it was marked, in 14 moderate, and in 8 comparatively slight. Of the 21 rabbits classified as mild chronic cases, 3 had a moderate and 8 a minor senile appearance; and of the 11 mild cases followed to the 2 years to 2 years 5 months, age period, 3 developed a slight or suggestive senile appearance.

The coat was affected in practically all cases. The early changes were a loss of sheen together with dryness and thinning and were usually noted in the first weeks or months of life. Irregularities of coat length and thickness were later developments. A ruffled coat and one with patches of rough or harsh fur usually on the back and sides of the body were quite common. Various degrees of patchy thinning or sparseness practically always occurred and often small areas of alopecia. These changes were usually first observed on the ventral surface of the body and the inner surfaces of the thighs with a somewhat later involvement of other regions. On the head the coat changes were less frequent and less pronounced than those on the body and legs and
were usually limited to small patches of roughened fur and thinning, particularly at the base of the ears. Quite large areas of sparseness of fur in the posterior cervical region, however, were not infrequent while thinning of the fur on the external surface of the ears was often seen. In older cases especially, a medium or pronounced taggy condition of the coat on the body and legs was quite common. There was a marked tendency for colored fur to develop a rusty tint and red or reddish-brown coats often became a deep mahogany color. In a few instances the fur of the head and face became definitely grizzled. It should be emphasized that there was little uniformity in the degenerative changes of the coat from one rabbit to the next. The age at which the first changes were noted, the time required for their development, the size and number of affected areas, and the degree and duration of involvement, all these features showed marked variability. As was also the case with other manifestations, improvement of the coat frequently occurred although in well marked cases these phases, as a rule, were temporary. The following excerpts from case records illustrate the various coat manifestations:

100-2, a pure bred, downy-coated Belgian doe, whose photograph appears in Fig. 1, was the first example of hereditary premature senescence. The coat at birth was thin and streaked and by 6 months of age it was irregular and ruffled. At 2 years 1 month, it was markedly irregular with numerous small areas of thinning on the body and upper hind legs, as is shown in the photograph; there was also marked thinning on the under surface of the body. The red color had darkened and a definite rusty tint subsequently developed. Lesions of the eyes (Figs. 2 and 3), to be described later, contributed to the senile appearance.

X10008-1 had a rather thin, downy coat as a nursling and young adult. At 2 years of age, the fur on the head was distinctly grizzled and the body coat was short and irregular; in the next 10 months it became markedly ragged. There then followed a short period of definite improvement during which the photograph in Fig. 4 was taken. The moderately senile appearance, however continued.

X9723 had a short, downy, rather thin uneven coat from birth. As a young adult the irregularities became more marked and a definite rusty color developed. The photographs taken at 2 years 5 months, 3 years 1 month, and 3 years 5 months, respectively (Figs. 5 to 7) show the persistence of moderate irregularities. The appearance of senility was recorded as being marked at 2 years 5 months; it was less prominent later. Lesions of the eye (Figs. 8 to 10) and of the ears (Fig. 11) also developed.

X10169-1 was recorded as having a moderately senile appearance at 1 year 10 months of age, the red downy coat had a well marked rusty tint and showed some irregular thinning, and the fur on the head and face was grizzled. There was a rather slow coat deterioration at first, as indicated by the photograph in Fig. 5 taken at 2 years 4 months of age, but later it was more rapid with well marked changes. The state at 2 years 10 months, at which time the general degeneration was pronounced, is shown in Fig. 12. Lesions of the eye (Figs. 13 and 14) and of the ears (Fig. 15) were prominent features.

X16212-1 had a moderately senile appearance at 2 years 8 months of age (Fig. 16); the severe progressive senescence condition was characterized by periods of incomplete remission and exacerbations of manifestations. The downy reddish coat was thin at birth and had a deep rust color at 4 months of age. Eye and ear lesions developed and hock involvement was marked (Fig. 17).

X25821-1 had a coat of normal quality which was harsh, dry and irregular at about 2 years of age. At 2 years 11 months, (Fig. 18) these changes had become more pronounced, there were several large tags on the body and legs, and the external surfaces of the ears and
the posterior cervical region were partially denuded. Chronic hock lesions were present (Fig. 19).

X24406-3 at 4 years of age (Fig. 21) showed a fair to moderate degree of coat degeneration which had remained in about the same condition for more than a year. The large areas of thinning were prominent and around the ears and at the base of the ears the fur was very sparse. The deep rusty tint of the red portions of the downy coat was conspicuous.

X23999-1, at 5 years 4 months of age (Fig. 22), showed a very marked degeneration of the coat which was normal, not downy, in type. The fur generally was ruffled, of a very uneven length, harsh, and very dry with areas of thinning and some tagginess. The color was a mahogany red. On the head and face the fur was definitely grizzled and short and at the base of the ears, quite thin. These changes first appeared at about 3 years of age and the rate of progress was slow but the senile appearance of the rabbit was well established a year later.

X23998-1, at 4 years 7 months of age (Fig. 23), had a very deteriorated coat which was of the usual normal quality. The senile appearance was quite marked. The fur was dry, harsh, and irregular with numerous tags and matted areas; on the ventral surface of the body and inner surfaces of the legs it was sparse. The color generally was a dark rusty red but on the head it was slightly grizzled. These changes, first noted at 2 years of age, developed slowly.

X24000-1, at 4 years 7 months of age, showed a moderate degeneration of the downy coat (Fig. 24). There were large areas of irregular thinning, patches of harsh fur and some tagginess; the color was a deep rusty red. On the face, at the base of the ears, and on the ventral surface of the body and the inner legs areas, the fur was quite sparse.

The skin of rabbits, which developed a protracted senescence of a severe or moderately severe type, became dry and often slightly scurfy and a more abundant branny desquamation was usual in areas of well-marked coat deterioration. Considerable accumulations of yellowish or silvery scales were commonly found in patches of partial or complete alopecia, the parts most frequently affected being the plantar and palmar surfaces of the feet, the ears, and the neck. As the senescence condition progressed, the skin generally became thinner than normal, with a loss of tone. As was the case with the coat, there was great variability in the manifestations but in well-marked chronic cases, some change was practically always found by 2 years of age. The following examples were typical:

In 100-2, whose photograph at 2 years 1 month of age appears in Fig. 1, very fine scaling of rather large areas of the body was recorded at 2 years 6 months. An accumulation of dry scales on the right upper eyelid is shown in Fig. 3. In X9725 a scurfy condition of the nape of the neck was present at 3 years 1 month when the photograph in Fig. 6 was taken; other areas were similarly affected later. In X10169-1, at 2 years 10 months of age (Fig. 12), the skin was dry, lacking in tone, and showed a fine branny scaling in sparse fur areas. In X24406-3, at 4 years of age (Fig. 21), there was a fairly extensive scurfy condition of the body skin. In X24000-1, whose photograph at 4 years 7 months is depicted in Fig. 24, the skin was thin and dry, but was otherwise apparently normal; previously, however, beginning at 2 years 7 months of age and continuing for 3 or 4 months, a widely distributed fine branny desquamation was one of several actively progressive manifestations.

Both skin surfaces of the ear were affected in a manner similar to other skin areas, but rather often the degree of involvement was pronounced. The outer surface was more frequently and more considerably affected than the inner and abundant scaling was accompanied by marked thinning of the fur. The scaling usually had a uniform distribution but instances of a patchy or a circinate type were also seen. The development of dermatosis generally coincided with or followed the establishment of well-marked coat and skin degenerative changes and although its duration was variable,
pronounced examples might persist for weeks. Regression and relapse also occurred as with other manifestations. In older cases, thinness of the ears was often prominent and in addition, a central longitudinal crease developed fairly frequently (Figs. 18 and 23). Of the 32 examples of severe or moderately severe chronic senescence, a well marked ear dermatosis developed in 13 rabbits; of the 32 mild chronic and probably chronic cases, a similar condition occurred in 4 rabbits; and in 29 mild cases observed up to 2 years of age, the ears of 6 rabbits were affected (Table I). Two examples will serve to illustrate the character of the condition.

The ears of X9725 at 3 years 5 months of age showed an outspoken dermatosis, both diffuse and patchy in character (Fig. 11), which had been present for 3 months. There was a widespread distribution of extremely fine branny scales and a speckling of small oval or round patches of silvery scales. The latter type in particular was more abundant on the external surface which was also almost completely denuded of fur in its central portion. A deep longitudinal crease in the distal half of the ears may be seen.

The photograph of the ears of X10169-1, shown in Fig. 15, was taken at 2 years 10 months of age. A week previously there was a diffuse fine silvery scaling chiefly on the inner surface over the outer third of the ears; within a few days the ears became slightly reddened and the scales much larger, some measuring up to 1 cm. in diameter. Some were circinate in form. The scales were found over the entire internal and external surfaces and were particularly prominent in the outer third of the inner surface (to the left in the photograph) where the earlier scaling had been prominent. The external surfaces were almost denuded of hair.

The feet were frequently affected. Lesions of the plantar surfaces of the hind feet were frequent and often comparatively early manifestations that is, in the 1st year, while those on the palms of the forepaws occurred less frequently and usually at a later age. The character of the hind feet or hock lesions varied from a cutaneous thickening or callus to a large fleshy or granulomatous mass measuring up to 1.5 or 2.0 cm. in diameter and 1 cm. or more in thickness. In typical form this lesion began as a small firm nodular swelling which increased in size sometimes very rapidly, the skin becoming thin and reddened; ulceration took place with oozing and bleeding and eventually the surface was covered with a thin or thick crust. Ulceration of smaller nodules was less frequent. The largest nodules were generally solitary but 2 or more smaller ones were common. The usual location was in the central and proximal tarsal area but sometimes small nodules were found in the distal tarsal and the metatarsal areas and along the tarsal margins. Partial or complete denudation of fur often accompanied the nodular lesion as well as a simple callus. The duration of these lesions was very variable, regression and healing of large granulomatous nodules sometimes taking place in a few weeks.

The lesions ordinarily found on the palms of the forepaws varied from cutaneous erosions and occasionally small nodules to a diffuse swelling of the skin and subcutaneous tissue of the area adjacent to the base of the toes. The skin became shiny and red, and oozing and bleeding, and the formation of small crusts followed. The area thus involved was sometimes quite large and extended over the metacarpals. This type of lesion was also seen on the hind feet, generally in severe cases.

The incidence of lesions of the feet in the several groups of chronic senescence rabbits referred to in Table I was as follows: Of 32 rabbits which developed a severe or moderately severe condition, 23 showed well marked lesions, 6 with involvement of both hind and forefeet and 17 with involvement of the hind feet only; various degrees
of plantar cutaneous thickening were noted in 5 rabbits. Of the 32 rabbits with a mild chronic and probably chronic senescence, nodular lesions of the hind hocks developed in 15 animals; there were no instances of forepaw involvement, and 6 rabbits showed minor plantar cutaneous thickenings. Of the 29 rabbits with a mild senescence, followed up to the age period of 1 year 6 months to 1 year 11 months hind hock nodular lesions of a generally mild character were observed in 15 and cutaneous thickenings in 5 rabbits, respectively. Of the 13 recovered cases followed for variable periods, hind feet lesions were noted in 6 rabbits. There was 1 instance of minor forepaw involvement, and 3 instances of minor plantar calluses.

An example of the large fleshy granulomatous lesion as well as the more diffuse type is shown in the photograph of X16212-1 at 2 years 8 months of age (Fig. 17). At 4 months of age, thin crusted red swellings were noted on both plantar surfaces and a month later granulomatous nodules had developed; at 1 year there were bare areas on both hocks and a superficial oozing erosion about 1.5 cm. in diameter on the right metatarsal region and a smaller similar area on the left tarsus covered with a callus which extended to the heel; 4 months later both plantar surfaces were healed with residual bareness and slight redness and thinness of the skin on the left surface. At 2 years 4 months of age, pronounced fleshy lesions on both hocks had developed, that on the right foot was crusted while the nodule on the left foot was covered by a thick callus; the front feet now showed bare reddened cutaneous patches covered with thin scabs. There was a marked increase of all the lesions during the next 3 months. As is shown in Fig. 17, there was a very large granulomatous lesion on the right hock covered with thick brownish crusts and on the left hock a smaller crusted mass with a clearly outlined darkish callus extension over the heel. At the base of all the toes were areas of cutaneous thickening covered with a thick callus and similar lesions were found on the palms of the front feet. Except on the granulomas the fur showed little thinning and on the left hock it was clipped for the photograph.

Another foot lesion is shown in the photograph of X25821-1, 2 years 11 months of age, reproduced in Fig. 19. Plantar involvement began at 2 years 6 months of age with cutaneous thickenings which soon ulcerated and bled and then became crusted. A little later these areas developed into indolent shallow, somewhat fibrous-feeling nodules which continued to ooze and bleed. There was little change in their appearance over a 3 to 4 month period. At about 2 years 9 months of age the skin of the palmar surface of the forepaws showed several small red thinned patches which bled and became crusted. The senescence of this rabbit was rather mild with a late onset and slow progression until about 2 months prior to the time of the photograph when the physical deterioration became rapidly worse. A fatal outcome was certain a week after the photograph was taken, and the rabbit was killed.

Eye manifestations were frequent, the most common being an ophthalmia with swelling and reddening of the eyelids and excess lacrimation; in the acute phases, a mild conjunctivitis of the lid was common and sometimes of the bulb. As a rule the onset was in the first year and frequently in the first weeks of life, particularly in the rabbits which developed a well marked senescence. The degree and duration of symptoms were variable but involvement lasting several weeks was not uncommon and acute exacerbations or repeated attacks often occurred. Eventually the lids became thickened, sometimes with puckering and with irregular or granular margins.

The incidence of ophthalmia in the cases summarized in Table I was as follows: in 28 or 88.0 per cent of the 32 severe or moderately severe chronic cases; in 18 or 56.0 per cent of the 32 mild chronic and probably chronic cases; in 16 or 55.0 per cent of the 29 mild cases observed in the shorter age period of 1 year 6 months to 1 year 11 months; in 7 or 54.0 per cent of the 13 recovered cases.
Lesions of the cornea also developed, most frequently in the severe cases and generally in the 2nd or 3rd year. As a rule both corneas were affected, lesions of the second cornea usually following those of the first within a few days. In most instances, the first change noted was a slight roughening of a small area of the corneal surface followed in a few days by the development of one or more small greyish granulomatous nodules; a faint haze of the cornea in and about the area practically always occurred and with the growth of the nodules, this might become pronounced. The smallest nodules were just visible as elevated greyish points while the largest, which sometimes represented a fusing of smaller nodules, might attain a diameter of 5 mm. Occasionally the pericorneal and conjunctival blood vessels in the neighborhood of the granuloma were congested. Not infrequently the nodular mass ulcerated and in some cases tiny residual pits in the cornea remained for a short time after regression and disappearance of the granulomatous tissue. There were also a few instances of small residual corneal opacities which were more or less permanent. The duration of corneal lesions was variable, ranging from a few days to upwards of 1 or 2 months in the case of the largest granulomas and a recurrence of the nodules was observed in several cases.

Of the 18 rabbits with a severe chronic senescence (Table I), 8 or 44.4 per cent developed corneal lesions; of the 14 with a moderately severe chronic condition, there were 2 instances or 14.3 per cent. In the other four groups cited in Table I, the incidence of corneal involvement ranged from 3.5 to 18.1 per cent.

A photograph of a large granuloma on the right cornea of 100-2, aged 2 years 7 months is shown in Fig. 2; there had been an unusually rapid growth of the mass during the previous week. The chronic thickened condition of the lids is well shown. The photograph in Fig. 3 taken at the same time shows the appearance of the left eye; on the cornea were several small grey elevated areas which had first been noted 24 hours previously and there was also a conjunctivitis which had been present for 2 weeks.

The three photographs in Figs. 8 to 10 illustrate successive phases of eye involvement in X9725, a case of chronic severe senescence. Both eyes were similarly affected. The photograph in Fig. 8, taken at 2 years 3 months of age, shows the marked swelling of the lids especially the upper and the irregular clouding of the cornea together with 5 central opaque points of granulomatous tissue. The second photograph in Fig. 9, taken 2 months later, shows that the acute ophthalmia had subsided considerably; several small corneal scars can just be made out. The third photograph in Fig. 10 was taken a year later, at 3 years 5 months of age, and shows a recurrent granulomatous keratitis; the cornea was diffusely clouded and there were 2 small nodular areas which are visible just below the area of light reflection.

The photographs in Figs. 13 and 14 of the left eye of X10169-1, a case of chronic severe senescence, were taken 2 months apart. The right eye was similarly affected. At 2 years 2 months of age (Fig. 13) there was a large central area of clouding of the cornea in the center of which was a small opaque spot. The eyelids were swollen and the margins granular. Within 3 weeks an ulcerated granulomatous mass had developed in the cornea and its appearance 5 weeks later is shown in the photograph in Fig. 14.

Certain reproductive abnormalities occurred. The actual incidence of these conditions, infertility for example, is not known because comparable breeding tests could not be carried out for various reasons. The testing of females, for instance, was restricted by their relatively short reproductive span as compared with that of males as well as by the periods of pregnancy and nursing. In addition the sex distribution of groups might be affected because of the necessity of including a disproportionate number of either sex for observational data or for other reasons. Of the 106 rabbits
described in this report, there were 58 males and 48 females. The records available show that all the reproductive abnormalities under consideration were represented in the four groups of chronic senescence rabbits summarized in Table I, with the highest incidence in the severe or moderately severe cases.

Infertility of various degrees occurred rather frequently in both sexes. It was observed not only in circumstances of pronounced physical deterioration, as was to be expected, but also in rabbits whose general condition was good. On the other hand, fertility was preserved in some individuals whose general physical degeneration was well marked. Infertility was also associated with an adipose condition which was a comparatively frequent occurrence in senescent female rabbits, less frequent in males. There was considerable variability in the age at which infertility was noted, some instances occurring early in the rabbit's breeding history but the majority occurred later, that is, around 1 year of age and older. Its duration was also variable, ranging from a few weeks to several months and repetitions of such periods were not unusual. Sterility occasionally developed.

The breeding record of the male rabbit, X10008-1 (Fig. 4), was normal up to 2 years of age; there then occurred a 6 weeks' period of infertility (8 consecutive matings), which was followed by a resumption of fertility. During the 3rd year there was a progressive increase in the coat deterioration, and large hock granulomas and corneal lesions developed. A 2nd infertile period occurred at 2 years 11 months of age (7 consecutive matings in 2 weeks) and during the remaining 7 months of life, infertility was the rule (12 matings with 3 pregnancies). General physical degeneration first became serious about the time of the second infertile period and progressed fairly steadily at a moderate rate.

An example of infertility and ultimate sterility was furnished by the male rabbit, X11061-1. Breeding began at 8 months of age and during the following year he was bred 26 times, only 7 of which matings were fertile. From 1 year 11 months, to 2 years 8 months of age, 23 matings resulted in 10 pregnancies and 13 non-fertile matings and this period of comparative fertility was followed by complete sterility (20 non-fertile matings in 5 months). A senile appearance, particularly of the head and face, was noted at 1 year 8 months of age; during the next 10 months, the degeneration of the coat increased, foot lesions developed, and short periods of general deterioration with muscle atrophy and loss of weight occurred. At 2 years 10 months of age, when progressive physical deterioration was well established, sterility had already been present for 2 months (8 non-pregnant matings).

There were occasional striking instances of the preservation of fertility under conditions of a well established general degeneration. In the male rabbit, whose case record is summarized on page 498 and whose photographs appear in Figs. 16 and 17, general deterioration began at about 1 year 10 months of age and progressed fairly steadily to a condition of marked cachexia and emaciation at 2 years 10 months of age; there was a loss of 600 gm. in body weight in the year. However, the rabbit continued to be fertile until the last 2 months of life.

Reproductive abnormalities in female rabbits included, in addition to infertility, the conditions of absorption and of retention of the products of conception, premature and delayed parturition, still-born young, desertion and destruction of the young, and peculiar lactation reactions such as premature engorgement, excessive mammary reaction, pseudolactation, and a reduced or even an absent engorgement. There were also instances in which the doe's milk was satisfactory for the young of another litter but not for her own young which, however, thrived when fostered by another doe.
There was great variability in the incidence of these several features but all of them were represented in the various grades of chronic senescence, most frequently in the severer grades (Table 1). A tendency toward the repetition of any of these abnormalities was noted and the association of lactation abnormalities with desertion or destruction of the young was a common finding. There were instances of such conditions as repeated fetal absorption and persistent pathological findings, as for example, cystic endometritis but this was by no means a constant rule.

The doe, X11779-2, was bred 6 times from 5½ months to 1 year of age; there were 4 litters which the doe destroyed or deserted and 2 non-fertile matings. Beginning at 1 year 6 months of age, there were 7 consecutive non-pregnant matings in 2 months with the 8th mating resulting in pregnancy. The newborn young were placed with another mother and the doe given 4 fosters. Following the birth of the litter, the breasts showed an excessive engorgement which persisted for about a week, but the fosters were well fed and given excellent care for 3 weeks when they were removed to release the doe for further breeding. A week later the breasts were again engorged and a mating made at this time was infertile. During the next 3 months, 2 litters were born, the first comprised 2 healthy and 2 macerated individuals and the other, 3 still-born young. After a rest period of 4 months the doe, at 2 years 5 months of age, was distinctly adipose. She was bred 5 time during the next 5 months; 2 matings were non-fertile and 12 days after 1 of them there was a moderate, irregular mammary engorgement. There was 1 litter of 2 still-born young and 1 instance of fetal absorption almost at term accompanied by a pronounced mammary reaction and a generally ill state lasting several days. With the 3rd pregnancy an acute toxemia developed on the 27th day together with a repetition of marked breast engorgement and an excessive secretion of milk, death occurring on the next day. The manifestations of a moderately severe senescence included coat deterioration, lesions of the feet, ulcerative keratitis, and ear dermatosis; the appearance at 1 year 4 months of age was decidedly senile. The adiposity, which was predominately of the shoulder girdle type, was pronounced and persisted to the end, and general deterioration, to which the reproductive abnormalities might be ascribed, had not progressed to any considerable degree.

The development of general degeneration was the most striking as it was the most significant manifestation of the premature senescence condition and the degree or severity of the condition was largely determined by its character. In severe form it pursued a progressive course characterized by a decreasing body weight, cachexia, emaciation, and a fatal termination. However, there were usually periods, especially in the early phases, in which the decline was temporarily halted with stabilization of body weight or a definite improvement might take place. There were also many examples of less severe grades including those of mild degree and short duration, from which apparent recovery occurred. In the majority of chronic cases the onset of the decline as indicated by symptoms of a general nature was in the 2nd year, while its duration was extremely variable and ranged from a few weeks to a year or more.

The first evidence of general degeneration was practically always a sustained loss of body weight for several weeks, as for example, some 200 gm. or more over a 3 or 4 weeks period, and often associated with but sometimes preceded by muscular atrophy. In the 18 severe and the 14 moderately severe cases referred to in Table I, these developments usually occurred at from 2 to 3 years of age. Further decreases in weight followed, generally in a step-like fashion, with reduction of subcutaneous fat. Of the greatest significance from the standpoint of the physical state of the animal and in assessing the progressive character of the general degeneration was a wasting or atrophy of the muscles, those of the lumbar region being almost always the first
affected. Other muscle groups also became involved, particularly those of the thighs and upper forelegs. An occasional instance of wasting of the facial muscles was seen. A peculiar combination found mostly in female cases comprised muscle atrophy and adiposity, preeminently of the shoulder girdle type. The body weight of such individuals might remain relatively stabilized for several weeks, although the degree of muscle involvement was pronounced and the superficial fat in other regions definitely reduced.

As general degeneration progressed, the rabbit became increasingly thin. Loss of appetite, however, was a very variable symptom; it did not commonly precede the early weight losses nor necessarily accompany the later ones until the animal's general condition had worsened considerably. The gastrointestinal functions, too, were similarly maintained. The association of infertility with a failing physical state was a common, although not constant, finding as has already been mentioned. In the later stages of severe deterioration, emaciation was usually marked and although apathy was quite often and stiffness of movement was not infrequently observed, there were also a few gaunt individuals with surprising vigor and activity. The development of weakness and a disinclination to move marked the beginning of the end. In 21 of the 32 severe or moderately severe cases (Table I), death occurred or was imminent at from 2 years 6 months, to 3 years 11 months, and in 11 rabbits at older ages.

The sequence of events of progressive degeneration in a severe chronic case, X16212-1 (Figs. 16 and 17), is summarized in the following tabulation. There was one long remission beginning at 1 year 4 months of age and a short period of general improvement at 2 years of age. Infertility was not observed until the last 2 months.

| Age (yr.-mo.) | Body weight (gm.) | General condition | Manifestations of senescence |
|--------------|------------------|------------------|-----------------------------|
| Birth        | 58               | Good             | Thin coat. Slick skin. Ophthalmia. |
| 0-5          | 1775             | Excellent        | Rusty irregular downy coat. Active hock granulomas. |
| 1-0          | 2775             | "                | Large hock lesions regressing. |
| 1-4          | 2925             | "                | Coat improved. Hocks healed with thin red calluses. |
| 1-6          | 3300             | "                | Minor coat degeneration and ophthalmia. |
| 1-8          | 3100             | Good             | Slight muscular wasting. Slight senile appearance. |
| 1-9          | 3350             | Improved         | Minor ear dermatosis. |
| 1-10         | 3000             | Fair             | Muscular wasting. Fat depletion. Coat degeneration increasing. Bare hocks with callus. |
| 2-0          | 2950             | Improved         | Well marked senile appearance. |
| 2-4          | 2900             | Fair             | Ragged thin coat. Ear dermatosis. Marked ophthalmia. Pronounced recurrent hock granulomas. Bleeding erosions on palms. |
| 2-5          | 3000             | Improved         | Active feet lesions increasing rapidly. |
| 2-7          | 2725             | Fair             | All lesions increasing. Stiffness. Photographed (Figs. 16 and 17). |
| 2-8          | 2500             | Poor             | Marked muscular wasting. Somewhat weak. Thin. |
| 2-9          | 2400             | "                | All manifestations increasing. |
| 2-10         | 2400             | "                | Lesions increasing. Marked stiffness and weakness. Emaciated. Killed. |
In contrast with the foregoing type of degeneration characteristic of many well marked cases of chronic premature senescence, was another less frequent type illustrated by the following summarized record of the male rabbit, X24000-1 (Fig. 24). The second and serious exacerbation of local and general manifestations beginning at 3 years 7 months of age was succeeded by a remarkable improvement lasting for some 7 months. Pathologic findings, however, indicated that this remission would not

| Age | Body weight | General condition | Manifestations of senescence |
|-----|-------------|-------------------|-----------------------------|
| yr.-mo. | gm. | Excellent | Minor coat deterioration and ophthalmia that developed at 1 mo. |
| 0-5 | 1875 | Good | No essential change. |
| 0-8 | 2300 | Improved | Wasting of lumbar muscles. Marked coat thinning. Moderate ophthalmia. Scant serous nasal discharge, but swelling congestion and vesicular dermatitis of large areas on the upper lips. Moderately senile appearance. |
| 1-5 | 2100 | Good | All manifestations regressing. |
| 1-7 | 2300 | Excellent | Minor coat deterioration and ophthalmia. |
| 2-11 | 2800 | Good | Moderate muscular wasting and fat depletion. |
| 3-7 | 2400 | Poor | Marked muscular wasting and fat depletion. Weak. Marked, irregular, and thinned coat. Scurfy skin. Ear dermatosis. Recurrence of lip dermatosis. Marked ophthalmia. Large bare congested areas on plantar and palmar surfaces. |
| 3-11 | 2250 | " | Lesions have not increased. Lively. |
| 4-0 | 2100 | Excellent | Very dry irregular taggy coat with thinned areas. General branny cutaneous desquamation. bare areas with scaling at base of ears. Minor ear dermatosis. Bare hocks with thin calluses. Moderate ophthalmia. |
| 4-4 | 2550 | " | Manifestations not increasing. |
| 4-6 | 2800 | Excellent | No essential change. Photographed (Fig. 24). Killed. |

Rabbit X25017-2

| Age | Body weight | General condition | Manifestations of senescence |
|-----|-------------|-------------------|-----------------------------|
| yr.-mo. | gm. | Good | Suspicious coat features and ophthalmia. |
| Birth | 49 | Excellent | Moderate coat degeneration. Swelling and congestion of lids. |
| 0-2 | 1250 | Good | Coat degeneration increasing. Slight ophthalmia. |
| 0-8 | 1800 | Fair | Fair coat and eyelid involvement. |
| 1-2 | 2100 | " | Plantar thickenings with erosions, oozing, and bleeding. |
| 1-7 | 2000 | Excellent | Fair grade plantar lesions with denuded surfaces. |
| 1-10 | 1950 | " | Plantar lesions almost healed. |
| 2-0 | 2000 | Good | Fair grade coat degeneration. Slight lid involvement but marked lacrimation. Minor ear dermatosis. Large bare scaly indurated areas on plantar surfaces. |
| 2-7 | 2100 | " | No essential change. Photographed (Fig. 20). |
| 3-8 | 2150 | Excellent | No essential change. Killed. |
have continued much longer. Beginning at 3 years of age sterility was practically complete (17 non-fertile and 1 fertile mating).

An example of a mild type of premature senescence with minor local manifestations is given in the preceding tabulated record of the male rabbit, X25017-2 (Fig. 20). Toward the end of the 2nd year there was a short period of insignificant general degeneration that was succeeded by a long period of good physical condition. Infertility was noted when breeding was begun at 7 months of age (5 non-fertile matings in 1 month) and subsequent tests showed a variable fertility (10 non-fertile and 5 fertile matings).

RECAPITULATION AND DISCUSSION

A chronic form of hereditary premature senescence of the rabbit has here been described. Twenty generations of the condition are represented in the group of 185 rabbits that provided the principal material of this and the next report, and of this number 106 rabbits developed the chronic and 79 rabbits the acute form respectively (2). This classification was based on the survival or probable survival of cases to the age of 2 years 6 months. Depending upon the character of the local manifestations but more particularly that of general degeneration, three grades of the condition were recognized. Of 53 rabbits, 18 or 34.0 per cent developed a severe, 14 or 26.4 a moderate, and 21 or 39.6 per cent a mild chronic senescence respectively (Table I). The actual incidence of the mild grade was undoubtedly higher as indicated by 41 comparable cases observed for shorter periods. In addition there were 13 examples of recovery, or possibly of a long remission, from a mild condition.

The manifestations included external or local features that developed for the most part in the 1st or 2nd year. Their number, course, and duration varied considerably from case to case and a definite tendency toward recurrence was observed. Degeneration of the coat, which occurred in practically all cases, was usually noted in the first months and as it increased, there was usually a fine desquamation of the skin. In older well marked cases, the skin tended to be thin, lax, and inelastic. The skin of the ears often showed a conspicuous scaling. Lesions on the plantar and palmar surfaces of the feet were of frequent occurrence and these varied from cutaneous thickenings and calluses to erosions and large fleshy granulomatous nodules with involvement of the subcutaneous tissue. Ophthalmia was an almost constant feature and lesions of the cornea, usually granulomatous nodules, were fairly common. Infertility of both sexes was frequent and in the does, various abnormalities of lactation and of pregnancy, as for example fetal resorption, occurred rather often.

A more or less profound degeneration of a general nature characterized severe and moderately severe grades of senescence. The degeneration pursued an overall progressive course, usually however, with one or more interruptions or remission periods. Muscle atrophy and fat reduction, a declining body weight,
emaciation and weakness, and a fatal outcome were conspicuous features. More moderate grades of bodily decline were characterized by a less overwhelming and less rapidly progressive degeneration that might be halted for relatively long periods but in many instances a recurrence of symptoms eventually took place and in these circumstances, deterioration proceeded rapidly. In the mild grade of premature senescence, there was only an occasional example of these general symptoms and they were minor, of short duration, usually non-recurring and in any event, non-progressive. Bodily health and vigor were well preserved.

It may be asked whether the cases classified as examples of mild hereditary premature senescence did in fact represent this condition or whether their abnormal features were unrelated to it and consequently had no significance in the present connection. The criteria that were applied to this classification of these rabbits were: first, that all of them belonged to the premature senescence stock, with its potentialities of severe degeneration; second, each rabbit developed at an age comparable to that observed in the more severe examples, some local or visible manifestations indistinguishable in kind although not necessarily in degree, from those associated with the severe forms of the condition; and third, that in certain initially mild cases there did develop eventually a typical, usually rapidly progressive, general degeneration.

The first indication of the presence of hereditary premature senescence was the occurrence of external or local degenerative manifestations, the most frequent being deterioration of the coat and ophthalmia. The time of onset of these external features and their incidence for the 106 cases summarized in Table I was: during the 1st year in 55 cases or 52 per cent; during the 2nd year in 46 cases or 43 per cent; and during the first half of the 3rd year in 5 cases or 5 per cent. There were a good many cases in which manifestations were noted in the 1st weeks of life and in 38 of the 106 cases or 36 per cent, they appeared before the age of 5 months.

Evidence of a serious nature such as a declining body weight and persistent muscle atrophy that suggested the operation of severe systemic injury usually developed after the initial local manifestations, most frequently in the 2nd year. This was the case in 22 or 69 per cent of the 32 examples of severe or moderate senescence cited in Table I; in the remaining 10 cases the symptoms occurred in the 3rd year.

The comparison of the character and sequence of events in well marked senescence cases with that of mild cases is of particular interest from the standpoint of the nature and extent of the underlying condition. First, there was a somewhat higher proportion of mild cases that developed local manifestations earlier than the more severe cases, that is, 34 or 55.7 per cent of 61 mild cases developed these features during the 1st year as compared with 12 or 37.5 per cent of 32 severe and moderate cases. From this result alone, there was no rea-
son to suppose that a considerable number of the mild cases would not have
turned out to be severe cases. But opposed to this conjecture was the fact that
for the most part the character of the early manifestations was less marked than
that of the manifestations of the more severe cases. By the end of the 2nd year
local manifestations had developed in all rabbits with severe and moderate se-
nescence and in all but 3 rabbits with mild senescence and in these rabbits they
developed in the next 6 months. However, in none of the mild cases had pro-
gressive general degeneration developed, whereas in the severe cases, general
deterioration was plainly evident.

From the character of the progressive general degeneration there seemed to
be no question that vital processes or mechanisms essential to the maintenance
of bodily health were involved to a profound degree and postmortem studies
showed that important organs and tissues were adversely affected. But the fact
that mild grades of senescence occurred raises questions on the essential nature
of the underlying condition. In mild cases, was this condition limited to the tis-
sues involved in the local manifestations or was it more widespread with vital
organs also affected but to a comparatively slight degree? Or might mild se-
nescence represent a successful recovery from a considerable involvement of
these organs which had not, however, reached the point of an exhaustion of
their margin of reserve. There was little evidence to suggest that this point was
approached in the majority of mild cases but there were a few instances of re-
covery from a considerable degree of general degeneration, as for example, in
rabbit X24000-1 (see table on page 499). On the other hand there were cases
which developed progressive general degeneration after comparatively long
periods of good bodily health and comparatively minor local manifestations.

These and other related questions can only be referred to now for they can be
more profitably discussed after the pathologic observations have been described.

SUMMARY

The occurrence of hereditary premature senescence in a family of pure bred
Belgian hares belonging to a rabbit-breeding colony organized for the investiga-
tion of constitutional problems, has been described. Representatives of 20
generations of the complex have been studied. The condition was a degenera-
tion of variable degrees of severity and two principal forms were recognized, the
acute and the chronic, the chronic being the more frequent. The chronic form
has now been described in terms of the principal local or external manifestations;
that is, degeneration of the coat and skin, lesions of the eyes and feet, and re-
productive abnormalities, and of the general deterioration which in severe cases
pursued a progressive course characterized by muscle wasting, fat reduction,
emaciation, weakness, and death. The acute form will be described in the next
paper (2).
Editor's Note.—Completion of the detailed histological studies that would have added another dimension to the fullness of this thorough description was prevented by the death of Dr. Pearce.

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The photographs were made by Mr. J. A. Carlile.

**PLATE 29**

**FIG. 1.** 100-Z, a pure bred Belgian hare 2 yrs. 1 mo. old, in good physical condition, the first example of the “downy-rusty-dwarf” or D.R.D. complex, later identified as hereditary premature senescence. She was a small, rather short, lean animal but not a dwarf, with long slender legs. The very dark rich red coat was short, irregular, and soft with practically no ticking; the prominent thinned areas were well shown. The skin was inclined to be dry and slightly scaly. The plantar and palmar surfaces of the feet showed cutaneous erosions of moderate degree. During the year after this photograph was taken, the peculiar coat changes, particularly the areas of thinning, became increasingly pronounced and this together with a gradual body weight loss and eye lesions (Figs. 2 and 3) contributed to a moderately senile appearance. The rabbit died at 3 yrs. 1 mo. of age from rabbit pox.

At 6 weeks of age, there was a rather severe bilateral conjunctivitis with scaled lids that gradually subsided leaving swollen slightly reddened lid margins which became thickened, wrinkled, and somewhat nodular. Occasional crackerations of congestion and swelling of the lids were noted. At 2 yrs. 3 mos. of age, the left eye showed a pronounced purulent inflammatory condition with no apparent cause. The purulent inflammation subsided within a week leaving an opaque cornea, pericorneal congestion, and small pannus, and a marked lid conjunctivitis with congested wrinkled lid margins; the right eye was unaffected. A fortnight later, the residual opacities in the left cornea became swollen elevated areas (Fig. 2), while the right cornea showed an extensive granulomatous ulcer and the deformed lids were inflamed. The appearance of the right eye 6 days later is shown in Fig. 3. Within 2 mos. the granulomas of both corneas were healed with residual scars.

**FIG. 2.** Left eye of 100-Z, 2 yrs. 7 mos. old, the rabbit shown in Fig. 1. Note the swollen elevated areas on the grey opacities of the cornea, first observed 24 hrs. previously. The chronic deformed condition of the lids is also shown together with the swelling and congestion of a conjunctivitis of 2 weeks standing.

**FIG. 3.** Right eye of 100-Z, 2 yrs. 7 mos. old, the rabbit shown in Figs. 1 and 2. Note the large granulomatous mass in the cornea which had developed a week before. The lids were thickened and the margins irregular and nodular. On the skin surface of the upper lid there was an accumulation of dry scales. × 7.

**FIG. 4.** X10088-I, on the left, a male of predominantly Belgian blood, 3 yrs. 1 mo. of age, an example of well marked premature senescence with an initially slowly progressive degeneration that eventually became rapid and fatal at 3 yrs. 6 mos. As a nubbling and young adult the rather thin downy coat and minor ophthalmia with residual thickening of the lids were features of interest. At 2 yrs. of age the appearance of senility was slight but definite. The rusty colored short thin soft coat was becoming irregular and on the head the fur was grizzled; the physical condition was good and the breeding record showed normal fertility. During the 3rd year various degenerative features developed: On the plantar surfaces of the hind feet large swollen, edematous areas covered by thin crusts and smaller similar lesions developed on the palms of the forepaws; all these granulomatous swellings eventually ulcerated, regressed, and healed. The coat became markedly ragged, infertility was the rule and wasting of the lumbar muscles, fat depletion, and loss of weight occurred. This period of actively progressive degeneration lasted for about 8 mos. and was followed by some improvement, chiefly in the condition of the coat and increased body weight, for about 2 mos. An occasional fertile mating was obtained. The weight was 2975 gm. at 2 yrs. 10 mos. and 2775 gm. at 3 yrs. 1 mo., when this photograph was taken. Note that the animal was not perfectly nourished, the coat was somewhat irregular, the eyes droopy, and the lids swollen. There were small granulomatous nodules on both corneas and large raw areas on the denuded palmar and plantar surfaces.

**BE31-1,** on the right, a male, 6 yrs. 1 mo. old, that is, twice the age of the senescence rabbit on the left, was in excellent physical condition, well preserved with a good coat and bright eyes. All the feet were sound. Fertility was normal. This rabbit was a Belgian-English cross, the son of pure bred parents; the father belonged to the Belgian family from which the hereditary premature senescence stock was extracted.
(Pearce and Brown: Hereditary premature senescence of rabbit. I)
Fig. 5. X9725, on the right, a female, 2 yrs. 5 mos. of age, in good physical condition, was an example of chronic premature senescence of moderate grade. The coat was a rusty red, soft or downy, short, thin, and somewhat irregular; it was sparse in the first weeks and months of life. The eyelids were moderately swollen and there were corneal scars; marked ophthalmia and keratitis had developed 2 mos. previously (Figs. 8 and 9).

X10169-1, on the left, a female, 2 yrs. 4 mos. of age and weighing 2750 gm., was an example of severe premature senescence. Coat degeneration and ophthalmia were noted as a nursling. At 1 yr. 10 mos. the fur on the head and face was roughened and grizzled and the general appearance was moderately senile; on the hocks were bleeding and thinly crusted areas. A series of marked degenerative manifestations developed which included recurring ophthalmia and diffuse keratitis with granulomas and ulcers and residual scars, large granulomatous lesions of the hocks, pronounced coat deterioration, ear dermatosis, abnormal mammary engorgements, and cystic mastitis and infertility. At 2 yrs. 2 mos. muscular wasting, fat depletion, and a marked weight loss were observed and general degeneration progressed fairly rapidly with minor interruptions. The advanced deteriorated condition with extreme muscular wasting at 2 yrs. 10 mos. is shown in the photograph in Fig. 12 which was taken 2 weeks before death.

Fig. 6. X9725, on the left, 3 yrs. 1 mo. of age, body weight 2925 gm., the same rabbit shown in Fig. 5. The principal events in the 8 mos. since the previous photograph were increased coat deterioration, recurrent ophthalmia with granulomatous keratitis, the recent development of pronounced hock lesions, cystic mastitis, relative infertility, and a slowly progressive muscular wasting. There was a minor weight loss but an increasing weakness. When this photograph was taken, however, she was posed in a sitting position without difficulty.

X12896-2, on the right, 2 yrs. 1 mo. old, was an F1 hybrid daughter of the doe on the left, X9725. Her appearance showed nothing unusual except extreme adiposity; she weighed 5800 gm. Sterility was associated with her adipose state which developed at about 1 yr. 6 mos. of age.

Fig. 7. X9725, on the left, 3 yrs. 5 mos. of age, body weight 3400 gm., the same doe shown in Figs. 5 and 6. During the last 2 mos. a remarkable improvement had occurred spontaneously and the condition was described as excellent when this photograph was taken. There had been a moderate gain in body weight and there was now no evidence of weakness. The feet lesions had regressed rapidly and were almost healed and the coat had become much smoother, glossier, and more uniform. There was less inflammatory reaction in the eyelids and corneas and possibly smaller corneal granulomas. The mammary tissue had become essentially normal. In the ears, however, an outspoken dermatosis, diffuse and patchy in character, had developed on both inner and outer surfaces. This period of remission lasted about 3 mos. and was followed by a reactivation of lesions, particularly those of the eyes and hocks. The rabbit was killed shortly thereafter, at 3 yrs. 7 mos. of age.

X11098, on the right, 2 yrs. 10 mos. old, body weight 2750 gm., was a lean, slender animal whose appearance was normal. She was an F1 hybrid daughter of X9725 (Figs. 5 and 6), as was X12896-2 (Fig. 6), and both these F1 litters had the same sire.

Figs. 8 to 10. Photographs of the left eye of X9725, the rabbit shown in Figs. 5 to 7, taken at 2 yrs. 3 mos., 2 yrs. 5 mos., and 3 yrs. 5 mos. of age respectively, to show various phases of eye involvement. Both eyes were similarly affected. At 2 yrs. 3 mos. of age (Fig. 8) there was a very marked ophthalmia with swollen congested lids and a slight mucopurulent sticky exudate over the cornea and lid margins; the cornea was irregularly clouded with slight roughening over the central area where there were 5 points of opacity, an apparent healing by granulation of an earlier ulceration; the conjunctival vessels were congested. Two months later (Fig. 9) the acute manifestations had somewhat subsided, the lids were still thickened and puckered, and there were residual corneal scars. During the following months there were recurrent attacks of ophthalmia with exudate and the development of corneal granulomas. At 3 yrs. 5 mos., (Fig. 10) there was a granulomatous keratitis; 2 focal points and a diffuse clouding are visible below the area of light reflection in the photograph.

Fig. 11. Photograph of the ears of X9725, the rabbit shown in Figs. 5 to 10, taken at the age of 3 yrs. 5 mos., the same age as in the photographs in Figs. 7 and 10. There was an advanced dermatosis of the inner (on the left) and the outer (on the right) surfaces of both ears, first noted 4 mos. previously. The condition was diffuse and patchy in character, of an irregular mosaic pattern, and there was a profusion of fine silvery scales. The rugged condition of the margins resulted from injury incidental to early matings.
(Pearce and Brown: Hereditary premature senescence of rabbit. I)
PLATE 31

Fig. 12. X10169-1, on the left, 2 yrs. 10 mos. old, body weight 2075 gin., the same doe shown on the left in Fig. 5 at 2 yrs. 4 mos. During the intervening 6 mos. the general degeneration had become marked, muscular atrophy was pronounced, and the animal was wasting away to skin and bones. The extreme emaciation and the ragged thin condition of the coat are well shown. There was a marked scaly dermatosis of both surfaces of the ears (Fig. 15) and a residual clouding of the right cornea and scarring of the left cornea. Earlier photographs of the left eye are shown in Figs. 13 and 14. The plantar surfaces of the hocks were partly denuded of fur and covered with thin scaly crusts. The previous well marked cystic mastitis had regressed almost completely. She was bred 17 times, the first at 5 mos. and the last at 2 yrs. 4 mos. of age; there were 13 non-pregnant matings and none of the 4 pregnancies progressed to term. This photograph should be compared with the one on the right, of a normal appearing female of the same age, X10347-3, in excellent physical condition.

Figs. 13 and 14. Photographs of the left eye of X10169-1, the rabbit depicted in Figs. 5, 12, and 15, taken at 2 yrs. 2 mos., and 2 yrs. 4 mos. of age respectively. A faint clouding of the lower segment of both corneas, first noted at about 1 yr. 9 mos., developed slowly. At 2 yrs. of age there was an irregular opaque band in the right lower cornea, the surface of which was still smooth. In the left lower cornea a much more extensive condition comprised a diffuse but irregular clouding with lines of vessels extending from the lower margin and an opaque slightly salmon-colored material in the depths; in the center of the cornea was a clearly defined opaque depression 2 to 3 mm. in diameter, which became an ulcer. Lacrimation was profuse. Fig. 13 shows the appearance of the left eye 2 mos. later: In the center of the cornea was a small reddish opaque spot 2 to 3 mm. in diameter surrounded by an opaque grey halo which covered practically the entire pupillary area; the lid margins were granular. The corneal area became granulomatous 3 weeks later and a recurrent ulcer developed. The continued activity of the lesion is shown in the photograph of Fig. 14. Similar lesions developed in the right cornea. At 2 yrs. 10 mos. of age the ulcers had healed with residual corneal clouding.

Fig. 15. Photograph of the ears of X10169-1, the rabbit shown in Figs. 5, 12 to 14, taken at 2 yrs. 10 mos. of age, at the same time as Fig. 12, to show an extensive marked early dermatosis of both internal (on the left) and external (on the right) surfaces which had developed very rapidly. A week previously diffuse silvery fine scales were noted, chiefly on the inner surfaces over the distal third of the ears. When this photograph was taken, the ears were slightly reddened, the scales were larger and some of them were circinate with areas measuring as much as 1 mm. in diameter. The scales were found in profusion over the entire internal and external surfaces and were particularly prominent in the part of the ear extending from the natural fold of the ear to the posterior margin. The external surfaces were almost denuded of hair.

Fig. 16. X16212-1, on the left, a downy-coated male, 2 yrs. 8 mos. old, weight 2725 gin., in fairly good condition; an example of a chronic progressive premature senescence with repeated exacerbations of manifestations. The observations on this rabbit are summarized on page 498. When this photograph was taken, the active manifestations included a taggy dirty coat, swollen granular eyelids and excess lacrimation, scaly dermatosis of the ears with small papules, large crusted hock lesions (Fig. 17) and similar lesions on the front feet, muscular wasting, fat depletion, and a weight loss of 625 gm, from the high value of 3350 gm. recorded 10 mos. previously.

X21153-1, on the right, a son of X16212-1 on the left, 8 mos. of age, in good physical condition. The appearance was normal except for minor ophthalmia and calluses on the hocks.

Fig. 17. Photograph of the plantar surface of the hind feet of X16212-1, the rabbit depicted in Fig. 16 and photographed at the same time, that is, at 2 yrs. 8 mos. of age. On each hock was a large fleshy granuloma with an ulcerated surface covered with a dark brownish-black crust. Hock granulomas first developed at 4 mos. of age; they pursued an active course for several months and then regressed and healed with thin calluses by 1 yr. 4 mos. They recurred a year later, that is, 4 mos. before this photograph was taken. Crusted eroded areas developed at the base of the toes.
(Pearce and Brown: Hereditary premature senescence of rabbit. 1)
Fig. 18. *X25821-1*, a male, 2 yrs. 11 mos. of age, weight 3100 gm., was an example of a mild to moderate grade senescence, slowly progressive in character until about 6 weeks before this photograph was taken when an abrupt physical deterioration took place. Beginning at about 2 yrs. the coat of normal quality became dry, harsh, irregular, and taggy, and eventually very sparse over the ventral surface of the body and the inner surfaces of the upper legs. The dry skin showed a fine branny desquamation. At 2 yrs. 3 mos. marked lacrimation was conspicuous and the eyelids became thickened and the margins granular. On the mucocutaneous border of the nares and adjoining upper lip regions, the areas were swollen and the red and slightly moist surfaces were speckled with tiny clear vesicles and very small thin crusts; there was only a very scanty clear watery nasal discharge. This condition which was occasionally seen in rabbits of the senescence stock did not resemble that of the usual “snuffles” in the rabbit. At 2 yrs. 6 mos. of age, the hocks showed areas of cutaneous thickening which later became ulcerated nodules with crust formation and erosions of the palmar surfaces of the front feet developed. The ears became parchment-like, there was a slight branny desquamation and a pronounced longitudinal crease had developed. The rabbit was well preserved up to 2 yrs. 9 mos., at which age he weighed 4000 gm.; 2 mos. later when this photograph was taken he weighed 3100 gm. There was well marked wasting of the lumbar and thigh muscles and moderate fat depletion, apathy and weakness were noted, the coat, eye, nasal, and hock (Fig. 19) manifestations were increasing and the nasal discharge had become slightly purulent. The reproductive record was unusual. Breeding began at 6 mos. of age and up to 1 yr. 10 mos. only 3 of 17 matings were fertile. These followed one another after 8 non-fertile matings. Of the 10 matings in the next year, 5 were fertile and 1 of these was made at the time the marked physical deterioration began.

Fig. 19. Photograph of the plantar surface of the hind feet of *X25821-1*, the rabbit shown in Fig. 18 and taken at the same time, that is, at 2 yrs. 11 mos. of age. The skin of the tarsal areas was somewhat diffusely thickened and near the left heel was a moderate sized firm shallow swelling covered with a brownish red irregular crust, another rather small crusted nodule in the middle and a third one in the distal tarsal region. In the same locations on the right plantar surface were three similar, somewhat smaller, lesions almost obscured by the fur. The onset of hock lesions was at 2 yrs. 6 mos. of age, 5 mos. before the photograph was taken; their progression was slow but steady.

Fig. 20. *X25017-2*, a downy-rusty coated male, 2 yrs. 11 mos. of age, in good physical condition, body weight 2200 gm., an example of chronic premature senescence of a mild grade. A tabulated summary of observations is given on page 499. The rabbit was rather small and chunky but not a dwarf. At birth the coat was thin and the skin wrinkled and somewhat parchment-like; the opening of the eyelids was delayed and in the nursing period, ophthalmia was frequently noted. The eyelids gradually became thickened and the margins puckered. At 1 yr. 7 mos. the plantar surfaces of the hind feet showed cutaneous thickenings and erosions with oozing and bleeding; in the next 3 mos. a flat nodular lesion developed on each hock which regressed and was practically healed at 2 yrs. of age. At 2 yrs. 3 mos. of age the senile appearance was slight but definite; the coat showed patches of thinning and the rusty color was well developed. At 2 yrs. 7 mos. the thinning of the coat had increased, there was a scaly dermatosis on the external surface of the ears, and on both plantar surfaces large bare indurated areas covered with a profusion of thin yellowish adherent scales. The condition was essentially unchanged 4 mos. later when this photograph was taken. During the remaining 9 mos. of observation, the only changes of note were a moderate increase in the deterioration of the coat and the ear dermatosis and an almost constant excess lacrimation. The physical condition continued to be good.
(Pearce and Brown: Hereditary premature senescence of rabbit.)
FIG. 21. X24406-3, a downy-coated male, aged 4 yrs., body weight 2200 gm., in good physical condition, was an example of a mild protracted senescence. The irregular coat with prominent areas of thinning on the face, neck, body, and legs is well shown; at the base of the ears was a small area of alopecia and around the eyes was an encircling band of sparse fur. The dark portion of the coat was a very deep rusty-red color. At birth the coat was thin and streaked and recurrent ophthalmia was observed. In the 2nd year, the condition of the coat had greatly improved but by 3 yrs. of age deterioration was resumed and the appearance was described as slightly senile. At 3 yrs. 9 mos. both plantar surfaces showed large bare areas, the skin was dry and moderately thickened and there was a central area of reddening covered with thin, tightly adherent scales. There was also a fine branny dermatosis on the partly denuded external surface of both ears. During the next month, heavy crusted calluses developed on both hocks.

FIG. 22. X23999-1, a male aged 5 yrs. 4 mos., body weight 3050 gm., an example of a very slowly progressive chronic senescence of moderate grade and late onset. At about 2 yrs. 8 mos. of age, the normal, not downy, coat became harsh, dry, and irregular with areas of thinning and at 4 yrs. of age, the taggy appearance, especially on the hind quarters and exterior thigh surfaces, was conspicuous. Both plantar surfaces showed marked cutaneous thickening and the eyelids were slightly but definitely thickened with moderately granular margins. During the next year, large heavy hock calluses and marked stiffness and restricted motion of both hind legs developed, a disinclination to move was noticeable, the coat became very dry, taggy, and irregular, dandruff was conspicuous and both surfaces of the ears showed an extensive dermatosis with fairly large silvery scales. Periods of infertility beginning in the 2nd year were observed. The body weight was well maintained, but at the time of this photograph considerable muscle atrophy had occurred over an 18 mo. period.

FIG. 23. X23998-1, a male 4 yrs. 7 mos. old, weighing 3500 gm., an example of a very protracted senescence of an initially mild grade and slow development that eventually changed to a rapidly progressive degeneration with a fatal termination 1 mo. after this photograph was taken. As a nursling and for the first 2 yrs. of life there was nothing remarkable in his appearance. He grew to be a large heavy boned well nourished animal with a reddish normal, not downy, coat. At 2 yrs. 7 mos. of age, the body weight was 4450 gm. and the general condition was excellent. The coat was beginning to be matted and taggy and the eyelid margins were thickened and granular. At 3 yrs. of age the physical condition was still good but a weight loss of 400 gm. had occurred, on each cornea was a small suspicious area thought to be an incipient ulcer, and the coat showed considerable thinning. Small granulomatous corneal masses developed which healed with residual scarring in about 2 mos., the coat became extremely taggy and harsh, the plantar surfaces became bare and calloused, infertiltity developed, and the body weight continued to decline. At 4 yrs. of age the movement of both hind legs was stiff and restricted. When this photograph was taken, the markedly deteriorated coat showed considerable tagginess and on the ventral surface of the body and inner thighs, an extremely sparse condition. The skin generally was dry with a branny desquamation. The hock calluses were heavy and on the palmar surfaces of the front paws were large red ulcerated areas. The stiffness of the hind legs had greatly increased. Considerable muscle atrophy and fat depletion had occurred and the body weight had decreased to 3500 gm. During the following month, the weight loss continued, movements became very limited, and an increasing weakness developed. When death occurred at 4 yrs. 8 mos. of age, the body weight was 3000 gm.

FIG. 24. X24000-1, a male 4 yrs. 7 mos. old, in good condition, body weight 2800 gm., an example of a moderate chronic slowly progressive senescence with remissions. A tabulated summary of observations appears on page 499. A remission period had lasted about 5 mos. when this photograph was taken. The senescence features present at this time were a moderate coat deterioration, dry indurated bare areas on the plantar surfaces of the hind feet, and slightly thickened eyelid margins. The downy coat was dry and somewhat irregular with areas of thinning and a few tags; it was sparse on the face, the ventral surface of the body, and on the inner thighs and upper forelegs.
(Pearce and Brown: Hereditary premature senescence of rabbit. I)