

FAMILIAL MAMMARY TUMORS IN THE RABBIT

I. CLINICAL HISTORY

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PLATES 10 TO 12

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Spontaneous tumors of the breast are known to occur with high frequency in certain species of animals, notably the mouse and the dog but, on the other hand, very few cases have been reported in the rabbit. A report from this laboratory in 1938 cited 10 cases (1) but aside from this series only 3 instances could be found in a review of the literature (2-4). These were accidental findings and there were no clinical notes or antemortem pathological studies to correlate autopsy findings with factors which might have thrown light on the origin of the tumors.

The study of breast tumors in the rabbit to be reported in this and succeeding papers represents a development of planned experiments which constitute one phase of a more comprehensive investigation of constitutional problems based on an animal population of known composition. It is necessary to refer briefly to the origin and development of this work so that the study of the tumors may be viewed in proper relation to other experiments.

General Plan

This series of investigations had its inception in 1929 with the organization of a breeding colony for the study of constitutional problems (5). At that time no known material was available for the study of spontaneous neoplastic diseases in the rabbit and it was hoped that among the animals comprising the population suitable material could be developed. Animals of presumptive tumor age were given a place in the colony organization and routine examinations were made for the purpose of detecting neoplastic conditions. The study of breast tumors and of other neoplastic diseases began, therefore, as a population survey.

The first breast abnormality was found in the fall of 1930 in a Belgian hare purchased as foundation stock. This was a cystic condition comparable with that to be described in connection with Fig. 4, but complicated by an extensive suppurative process, which eventually necessitated the disposal of the animal. A pure bred son and daughter

together with their sire and 2 other daughters from an outcross mating constituted the nucleus from which the present tumor stocks were developed.

The inherent tumor potentialities of these animals were unknown but the recognition of other functional disorders had marked this family of Belgian hares as the most important group in the colony. It was also the most difficult to maintain. Every effort was made to perpetuate the line in pure form but this was impossible and from time to time other strains of Belgians were introduced and crossed with the original line. Outcrosses with other racial groups were also made in connection with the study of the functional disorders mentioned above. The family of animals from which the study of breast tumors was eventually developed thus consisted of a small group of pure Belgians and a much larger group of hybrids composed chiefly of primary crosses between English and Belgian stocks and animals derived from further crosses of these hybrids among themselves and with the parent Belgian line.

English rabbits were selected for the crosses because they represented the nearest approach to normal of any racial group in the population and a type nearest that of the Belgian. It was subsequently discovered, however, that in this way one breast tumor line was crossed with another. The English population was later found to be a second source of breast tumors but, as will be pointed out, tumors of the two lines differ in type and in the age of development.

No mammary tumors were detected until 1934. Small groups of animals from numerous racial and family groups had been held for observation over periods of several years as parts of the working population. On several occasions, heavy losses occurred from outbreaks of epidemic disease and in all cases the Belgian population suffered most so that potential tumor animals were continually lost before reaching tumor age.

In the spring of 1934, the first abnormality of the present series, which consisted of a cystic breast condition, was discovered in the course of a routine population check. The animal was used at once for the breeding of F₁ hybrids, while its nearest relatives were preserved to provide material for tumor studies if the subsequent course of events in this animal should warrant such an undertaking.

In 1935, the colony was moved from New York to Princeton and in a short time after other animals developed mammary tumors. These occurred not only in the Belgian population but also in the family of English rabbits referred to above and in hybrid crosses. Meanwhile, the condition in the first animal progressed to cancer.

With the material thus provided, plans were made for a more direct and comprehensive investigation of the genesis of spontaneous neoplasia. Genetic studies¹ and transplantation experiments were included in this program. Tumor animals were used for F₁ and backcross matings. On the basis of evidence obtained from an analysis of pedigrees, matings among other animals of this group were made with a view to increasing the number of probable tumor animals. For a while, the English as well as the Belgian line was developed; but both lines could not be accommodated and eventually work with the English stocks was discontinued as available evidence indicated that these animals would have to be held from 1 to 2 years longer than the Belgians before end results could be obtained.

¹ Genetic experiments are being conducted by Dr. Pearce and consideration of the influence of hereditary factors in these papers will be limited to a pedigree analysis.

It has been necessary to pursue these studies as experiments coordinated with other problems. Still, it was believed that the study of neoplastic diseases in relation to other functional disorders in the general population possessed some advantages. Tumors of the breast have been investigated, therefore, as a population study with especial reference to the bearing of inherent constitutional peculiarities on the genesis of mammary tumors. It so happens that the family group concerned presents the greatest variety of functional disorders of any group in the entire population and any effort to determine whether these associated conditions possessed significance would require a control such as that supplied by the remainder of the population. Moreover, it seemed that this method of procedure placed the problem on a footing more nearly comparable with conditions surrounding the development of cancer in human populations, with the added advantage of a more intimate knowledge of members of the experimental population and the opportunity to employ measures of control as circumstances demanded.

In this connection, it should be pointed out that what has been said with reference to the association of breast tumors and functional disorders is equally applicable to other neoplastic diseases which have been encountered in this laboratory. In practically all cases, interest in some striking or profound functional disorder has prepared the way for the discovery of the neoplastic condition. In other words, tumors have developed largely in that portion of the population which is classed as abnormal rather than among the so called normal groups. This may be merely coincidence but it was noted in the case of uterine tumors and its significance will be considered in connection with breast tumors.

During the past few years a comparatively large number of spontaneous tumors of the breast has been obtained. The tumors have been investigated systematically through their entire course of development, including a clinical study of breast changes, the gross and microscopic pathology of the conditions as revealed by biopsy at frequent intervals and complete autopsies on those animals which have died or have been killed. In addition, an effort has been made to correlate the results thus obtained with the functional behavior of the host.

The present paper will be limited to the clinical aspects of spontaneous tumors. This will be followed by a second paper dealing with gross and microscopic pathology, while a third paper will be concerned with coincident changes in other organs and with other factors which may have influenced the occurrence and course of the spontaneous growths. The successful transplantation of the tumors and their growth characteristics in animals of the same and of foreign species will be described at a later date.

Materials and Methods

The organization and management of the colony has been described elsewhere and need not be repeated here (6). It should be noted, however, that the management of the tumor-producing part of the population differed from that of the colony as a whole in only two respects, namely, the use of extraordinary precautions to safeguard tumor animals and the feeding of green food to this group at more frequent intervals, particularly during the past year

The material for this study was derived from several classes of experiments. As already stated, long series of breeding experiments were carried out in an effort to concentrate or fix inherent constitutional characters in numerous pure bred lines of rabbits. When a source of tumor material had been found in this way, a second series of breeding experiments was undertaken to preserve this material and to provide a more abundant supply of tumors.

Another class of experiments was directed toward the correlation of clinical and pathological alterations in breast tissues from the earliest recognizable changes to the development of neoplasia and eventual malignancy. Such experiments involved systematic examinations of large numbers of animals with the performance of biopsies at frequent intervals on those found to have developed mammary abnormalities. Biopsies were done under ether anesthesia. In conjunction with these experiments, attempts were made to transplant selected tumors at various stages in their development as a biological criterion of self sufficiency or capacity for independent growth. Experiments of a converse nature were also undertaken to determine the response of tumor-bearing animals to the transplantation of their own or of another tumor capable of growing in normal animals.

A third class of experiments was carried out in an effort to determine whether any relation existed between the occurrence and subsequent course of mammary tumors on the one hand and inherent functional disorders or disturbances of normal function on the other. These experiments have followed two directions: first, a comparison of tumor-bearing lines and tumor-bearing animals with non-tumor-bearing stocks on a genetic basis, and second, a comparison of the functional behavior of tumor animals of a given group with animals which did not develop tumors. Comparisons of the second type have been concerned chiefly with reproductive phenomena. In addition, the influence of reproductive cycles and the relation of disturbances in these functions to the occurrence of mammary disorders, the relation of mammary disorders to the occurrence of neoplasia and the evolution of malignancy have been investigated.

Thus far 29 animals presenting mammary abnormalities known to be connected with the development of neoplastic changes have been studied for various periods of time. 11 of these died of intercurrent disease or were killed before the ultimate outcome of the condition could be determined. 7 additional animals are still under observation, while in a third group of 11 animals the breast changes were followed from an early stage to cancer; 10 of these animals have come to autopsy and 1 is still living.

This group of animals does not represent the ultimate incidence of breast tumors in the population or the probable end result of the breast condition in all cases. A preliminary period of observation was fixed at 3 years, but many animals were discarded before the expiration of this period because they could not be used for breeding purposes. Others were discarded at the age of 3 years if no abnormality had developed and they could not be used advantageously for other purposes. The time limit was based on the behavior of the Belgian population. It is certain, therefore, that some animals were eliminated which would have developed tumors if they could have been held for further observation. In like manner, some animals with breast tumors died from intercurrent disease; others became debilitated or developed conditions which overshadowed the tumor growth and were killed when it appeared that no further information could be obtained or that the animal might die at a time when an autopsy could not be performed.

In the first group of cases studied, clinical examination was supplemented by biopsy

at such times as clinical changes in the breast seemed to warrant, but the study of material obtained in this manner showed that a considerable period of time separated the occurrence of microscopic structural alterations and the appearance of indicative clinical signs. The material was not sufficient to fix the exact time limits of the various histological stages of the disorder and an attempt was made in recent cases to determine more precise time relations by performing biopsies at more frequent intervals. Biopsies were performed in the periphery of the breast in order to minimize damage to the main ducts and to avoid histological alterations which might result from interference with proper drainage during lactation.

Complete autopsies were performed in all cases and all organs were sectioned and studied microscopically. Routine biopsy and autopsy sections were fixed in Petrunkevitch's solution and pituitary glands were fixed in Susa's solution. General sections were stained with hematoxylin and eosin and pituitary glands with a modification of Mallory's aniline blue method. Contiguous breast sections were stained with hematoxylin and eosin and with Weigert's elastic tissue stain.

Clinical Classification of Tumors

Two distinct morphological types of tumor which differ in mode of development and biological characteristics have been observed in the breasts of rabbits. A distinctive antecedent mammary history further differentiates one type and is used as a basis of classification in the presentation of data in Tables I and II. Table I records cases with complete, as well as incomplete, clinical courses and, in the latter class, a number of animals without neoplasia but with early breast changes are included. On the other hand, all animals bearing tumors of the type listed in the second table have died and no new instances have been discovered.

The development of neoplasia was preceded by a history of cystic disease in 19 cases, while in 4 cases no antecedent mammary changes were observed. In 2 instances the presence of tumor was first noted at autopsy and while the course of the disorder was not followed during life, the coexistence of advanced cystic disease suggested a developmental history similar to that of the first group of cases.

Tumors Originating at the Site of Preexisting Cystic Disease

The course of the mammary disorder leading to neoplasia was under clinical observation from the inception of cystic changes in the majority of cases. The sequence of events throughout the period of study was similar in all cases and, in instances in which death occurred before invasion, the similarity of the observed developmental course suggested that with continued life these growths would also have become cancerous. In order to avoid repetition, therefore, individual case histories will not be cited in the present section but will be dealt with collectively and the disorder will be

TABLE I
Tumors Originating at the Site of Preexisting Cystic Disease

No.	Age at inception of disorder	Nature of first abnormality	Period of observation	Eventual fate	Condition at death	Terminal or present status
	<i>mos.</i>		<i>mos.</i>			
B16-2	29	Cystic disease	25	Killed	Moribund	Adenocarcinoma with metastasis
B178	25	" "	19	"	Failing	Adenocarcinoma
B234-3	30	" "	7	"	Moribund	Medullary carcinoma with metastasis
B240-2	29	" "	16	Died		Adenocarcinoma with metastasis
B346-3	27	" "	13	Killed	Moribund	Anastomosing papillomata
B348-1 (BE)	20	" "	7	"	Good	Adenocarcinoma
BE28-3	36	" "	6	"	Moribund	Anastomosing papillomata
BE44-2	29	" "	2	Died		Adenocarcinoma
X1966-4	38	" "	9	"		Sessile epithelial neoplasia
X5074-2	27	" "	7	Killed	Moribund	Anastomosing papillomata
X6106-3	17	" "	21	Died		Adenocarcinoma
X9755-3	10	" "	11	"		Anastomosing papillomata
X2594-3	36	" "	7	Killed	Good	" "
X1984-4	43	" "	8	"	"	Uniradicular papillomata
X1539-1	35	" "	17	"	Poor	Anastomosing papillomata
B249-3	35	*		"	"	Small solitary anastomosing papilloma
B306-3	23	*		"	"	Sessile epithelial neoplasia
EB2-2	29	Cystic disease	29	Living		Adenocarcinoma
BE75-6	43	" "	4	"		Sessile epithelial neoplasia
X5943-9	44	" "	3	"		Anastomosing papillomata
X7634-6	33	" "	3	"		Cystic disease
X7768-3	30	" "	6	"		" "
X8157-1	19	" "	16	"		Anastomosing papilloma
X10169-1	11	" "	15	"		Cystic disease
X10557-3	10	" "	16	"		" "

* Breast abnormality in which cystic changes predominated, first discovered at autopsy.

TABLE II
Tumors Not Associated with Preexisting Cystic Disease

No.	Age at inception of disorder	Nature of first abnormality	Period of observation	Eventual fate	Condition at death	Terminal or present status
	<i>mos.</i>		<i>mos.</i>			
B57-2	47	Tumor	3	Killed	Good	Adenoma
E33-5	51	"	16	Died		Adenocarcinoma with metastasis
E126-2	34	"	12	Killed	Poor	Adenocarcinoma
T36-1	42	"	16	"	Moribund	Adenocarcinoma with metastasis

described as it occurred in typical progressive instances beginning with cystic disease and terminating with metastasis.

The sequence of events was also followed by biopsy and examination of the tissue shows the advance of the disease in three more or less distinct stages which offer a convenient division of the clinical course for descriptive purposes. It should be emphasized, however, that, while the different stages apparently form parts of a continuous disease process, great variation occurs in the rapidity of progress from one phase to another and under certain conditions the disorder may be arrested for long periods of time in any one of its developmental stages. The factors influencing this variation have been the subject of special study and will be discussed in a later section together with other pertinent findings derived from an investigation of individual cases.

Cystic Disease.—The first indication of breast abnormality may occur either as a sudden and intense engorgement involving the entire mammary system (Fig. 1) or as a slight granular enlargement in a segment of a single gland. Such engorgement, so far as known, is associated with a recent infertile mating, or an estrous period, while the primary granular changes are found in resting animals. The failure to note preliminary engorgement in the latter cases, however, does not preclude its possible occurrence in a masked form during a preceding period of pregnancy hypertrophy or lactation. In any case, the ensuing sequence of events proceeds in a similar manner.

Engorgement may persist and increase in severity for 2 or more weeks (Fig. 2). The breast tissue appears white through the stretched skin but, toward the end of the period the distended glands become translucent, and clear, colorless fluid instead of milk may be expressed from the nipples. Biopsy shows the presence of large, dilated spaces filled with thin white or colorless fluid. The mammary tissue is delicate, easily torn and not fibrous. Many of the dilated spaces intercommunicate and operation usually results in a temporary collapse of the breast with recurrent distension following in a day or two.

The engorgement subsides suddenly in the majority of cases and resolution may take place within the course of a few days. There may be a complete return to a normal condition but occasionally the breasts remain enlarged (Fig. 3). In such cases, the glands are soft and doughy to palpation and operation shows an increase in parenchyma with a small amount of fluid secretion. Usually extremely small granular thickenings may be found on careful examination in the periphery of one or more breasts following subsidence of the primary distension.

The engorgement eventually reappears after a variable period during which the animal may or may not have been remated. In the majority of cases, the above mentioned relationship to mating obtains and if pregnancy results, pregnancy hypertrophy and lactation follow the primary engorgement and the resulting litter nurses and appears to thrive. In instances in which the engorgement recurs during a resting phase, its appearance has been observed to coincide with manifestations of heat and its resolution to follow a fertile mating. In still other cases the subsidence of engorgement has been found to occur simultaneously with a deterioration in the general health of the animal and its reappearance to follow a gain in weight and a return to better physical condition.

The cycle of engorgement and return to normal may be repeated a number of times before residuary changes are noted, but eventually minute shotty nodules persist. The nodules may be scattered in small groups throughout the mammary tissue with no constant relation to the architecture of the breast and may remain as isolated lesions throughout the early course of the disorder. In other regions the nodules are aggregated in firm, granular areas which occupy a small, peripheral mammary segment and, with progress of the disease, gradually extend to form a flattened pancake-like mass with distinct borders which encompass the greater part of the gland (Fig. 4). It should be emphasized that the granular changes are not localized but occur throughout the mammary tissue. All regions are not equally affected and, while the changes in some breasts produce masses apparent to the naked eye, their presence in other glands can only be determined by careful palpation.

With enlargement of the nodules their cystic nature becomes apparent: many appear blue but others show no color through the shaved, overlying skin. Fluctuation can be elicited and, occasionally, rupture with a discharge of clear fluid from the nipple results from excessive pressure applied during palpation. Individual cysts may attain a diameter of 2 cm. or more, but smaller cysts ranging to a pinhead in size make up the bulk of the larger breast masses. The nipples are occasionally affected by the cystic change and may be greatly distended with the skin stretched to paper thinness. Rupture and collapse with a spurt of colorless fluid follows minor trauma in such cases.

At biopsy, individual cysts are intimately attached to surrounding tissues and cannot be shelled out. The blue cysts are thin walled and easily ruptured, while other cysts are thick walled and resist considerable pressure. The large pancake-like masses of granular tissue are easily distinguished from normal breast. They appear greyish brown in color with small lighter and darker focal areas and are well demarcated from the surrounding tissues by clear cut, rounded borders. Their substance is made up of numerous small, cystic nodules which on section may contain clear, colorless fluid or dark brown, inspissated material.

The clinical picture does not remain constant but is characterized by periods of progression and regression. Engorgement may recur at any time and obscure the cystic changes. It may be generalized or localized to a single region and its subsidence is associated with the appearance of new cysts and an increase in the size of existing nodules. Large dilated areas filled with milk persist for considerable periods of time and the secretion becomes thick and semisolid. Periods of regression during which existing cysts decrease in size and may entirely disappear occur without any observable change in the condition of the animal. In other instances temporary regression is associated with a decline in physical condition and is succeeded by recurrence following recovery.

The stage of cystic disease is of extremely irregular duration but eventually, biopsy examination shows the presence of neoplasia in widely scattered areas.

Stage of Non-Invasive Neoplasia.—It is not possible to detect beginning neoplasia clinically. The process occurs with equal frequency in microscopic and in large cysts and the size of individual nodules or the extent of breast involvement cannot be used as criteria in this respect.

In advanced cases, nodules which were previously soft and cystic become firm and non-fluctuant and occasionally bloody fluid can be expressed from a nipple. The masses in individual breasts increase at an unequal rate but, at this stage, the involvement of

all mammary tissue is obvious to casual examination (Fig. 5). The enlargement of some breasts is no greater than is observed in normal lactation but others become pendulous and attain such a size that they are not raised from the cage floor when the animal is erect and, as a consequence of continuous trauma incident to normal activity, may become infected.

At biopsy, the breast tissue is extremely irregular in appearance. Cysts of all dimensions ranging from 3 cm. in diameter to the size of a pinhead are found in close proximity. Some are completely filled with greyish, fleshy tissue, others show mural excrescences of the same description and still others contain only clear fluid or thick, brown, inspissated material. The intercystic tissue is firm and fibrous.

Engorgement may recur during this stage but is usually localized in one or more breasts. Resolution is followed by the appearance of a fresh crop of cystic nodules and all stages of the disorder from minute, granular thickenings to large, firm, pendulous masses may be found in a single animal. The degree of visual breast involvement and the size of individual masses vary widely. Large nodules which on histological examination have shown neoplastic growth may be reduced to a small fraction of their previous mass in the course of a few weeks and, on the other hand, may enlarge with equal rapidity. A particular mammary region may show the most pronounced lesions at one period, but at a subsequent examination less than 1 month later, the site of predominant involvement may be shifted to a different area.

After a variable period of time during which the condition in one or more breasts becomes stabilized, microscopic examination shows areas of active invasion. This occurrence may not be reflected in indicative physical changes for a considerable period of time but eventually signs of invasive growth dominate the clinical picture.

Stage of Invasive Neoplasia.—Retraction of the nipple, fixation to the skin and muscle and an increased growth rate are the characteristic clinical features of this stage (Figs. 6 and 7). Small areas of softening may occur and ulceration of the overlying skin frequently follows. Such alterations usually appear in the breast in which antecedent physical changes were most pronounced and may be entirely limited to that breast, but occasionally other glands in remote, as well as adjacent, positions show signs of invasive growth.

The main tumor mass increases at an uneven rate with periods of reduced and accelerated growth which correspond with the general physical condition of the animal and to a lesser but detectable degree with the season of year. The mass may present a firm, nodular surface with areas of board-like hardness or rounded contours with a soft, doughy consistency depending on the histological type of growth. It is a characteristic feature of the condition that the growth of nodules in other breasts is slow and abortive in the presence of a rapidly increasing tumor mass. In the final stages, therefore, the typical picture is that of a single, large, rapidly growing mass with smaller, less active nodules scattered throughout the remainder of the mammary system (Fig. 8). Metastatic areas of growth can often be palpated in the regional lymph nodes.

At biopsy, the main mass may be fleshy or fibrous and present areas of cyst formation or of necrosis. Nodules in other breasts may be purely cystic or filled with fleshy tissue limited to the cyst wall or extending diffusely into the surrounding region.

The animals exhibit no sign of cachexia other than a progressive loss of weight and generally remain alert and active until shortly before death. The duration of the dis-

order is extremely variable. The entire clinical course from the beginning of cystic changes to death with metastasis was completed in 7 months in one instance and was prolonged to 25 months in another.

Tumors Not Associated with Preexisting Cystic Disease

Tumors of this class are less common and at the present time only four have come under observation. The differentiating developmental feature of these growths is the absence of preexisting cystic disease, but it should be emphasized that during their course cystic changes frequently occur in structures formed by the tumor elements and are occasionally found in the neighboring mammary tissue. These changes remain inconspicuous, however, and their detection depends on microscopic examination.

In their earliest stages the tumors appeared as solitary, pea-sized, elastic nodules freely movable in normal breast tissue. In all but one instance the neoplastic process remained confined to a single nodule and other breasts were not involved except by extension from the primary growth. This case, however, was characterized by the occurrence of numerous, smaller, rounded masses scattered throughout the mammary tissue and resembling the main growth in all physical characteristics.

One animal was killed after 10 weeks of observation when the nodule had reached a diameter of approximately 2 cm. The remaining animals were held from 12 to 16 months but in no instance did the tumors attain a size comparable with those of the previous series. Growth was slow but progressive and the periods of acceleration and retardation which characterized the preceding tumors were not apparent. The nodules remained firm, rounded and elastic and attachment to surrounding structures did not occur until a late stage.

In one instance a metastatic nodule appeared in a breast of the opposite side, 10 months after discovery of the primary tumor (Fig. 9) and in this case and in one other, visceral metastases were found at death after a clinical course of 16 months.

SUMMARY

The clinical histories of two different types of familial mammary cancer in the rabbit have been described. In one type, the first clinical sign of breast abnormality was a sudden and intense engorgement and thereafter the disorder passed through stages of cyst formation and benign neoplasia to cancer with metastasis. In the second type, neoplasia originated in clinically normal breast tissue and there was no history of antecedent mammary abnormality.

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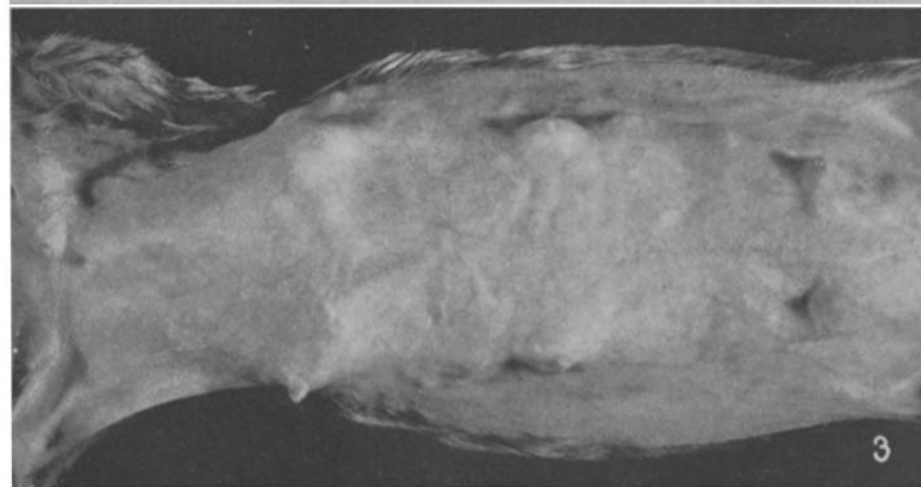
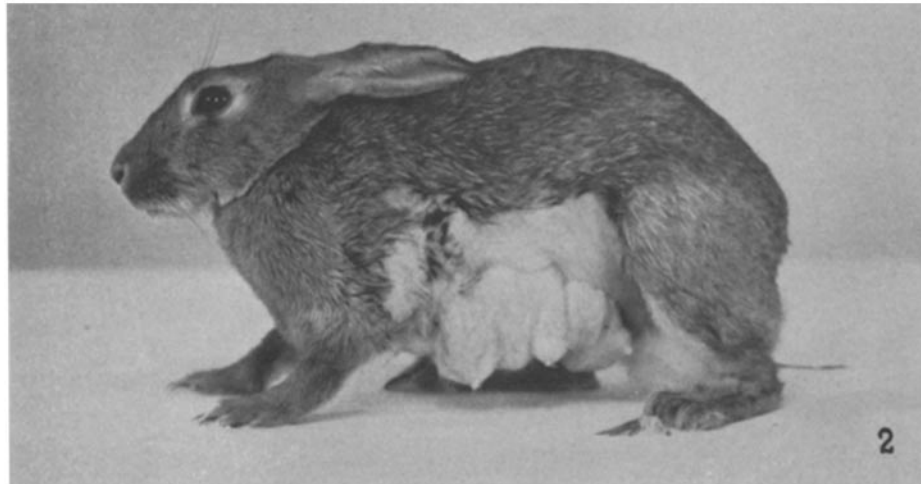
EXPLANATION OF PLATES

PLATE 10

FIG. 1. X10169-1. Primary engorgement involving the entire mammary system. The trauma in the third right breast is a result of a recent biopsy examination. $\times 0.4$.

FIG. 2. X6106-3. Persistent, increasing engorgement.

FIG. 3. X6106-3. Photograph taken 1 month later. The acute engorgement has subsided but all breasts show residual enlargement. Beginning granular changes are present in the peripheral region of many glands and the nipple of the fourth left breast shows typical cystic dilatation. $\times 0.4$.



Photographed by J. A. Carlike

(Greene: Familial mammary tumors in rabbit. I)

PLATE 11

FIG. 4. X8157-1. Photograph taken 4 months after inception of the disorder. Many breasts show residual enlargement and contain isolated cystic nodules. The fourth right breast contains a mass of characteristic hypertrophic, granular tissue. The first breasts of the two sides are not shown in the photograph. There is a supernumerary breast on the right side. $\times 0.4$.

FIG. 5. B178. Photograph taken 6 months after inception of the disorder. The tumors in the third breasts of both sides are firm, non-fluctuant and freely movable. Biopsy examination demonstrated the presence of non-invasive neoplasia. Other breasts contain smaller neoplastic nodules, cysts and localized areas of engorgement. $\times 0.35$.

FIG. 6. B240. Photograph taken 7 months after inception of the disorder. The tumor in the third left breast has invaded the skin and appears externally in two areas. Despite local invasion the animal remained in good physical condition and death with metastasis did not occur until after the lapse of a year. The changes in other breasts had almost completely regressed but subsequently reappeared. $\times 0.55$.



Photographed by J. A. Carlile

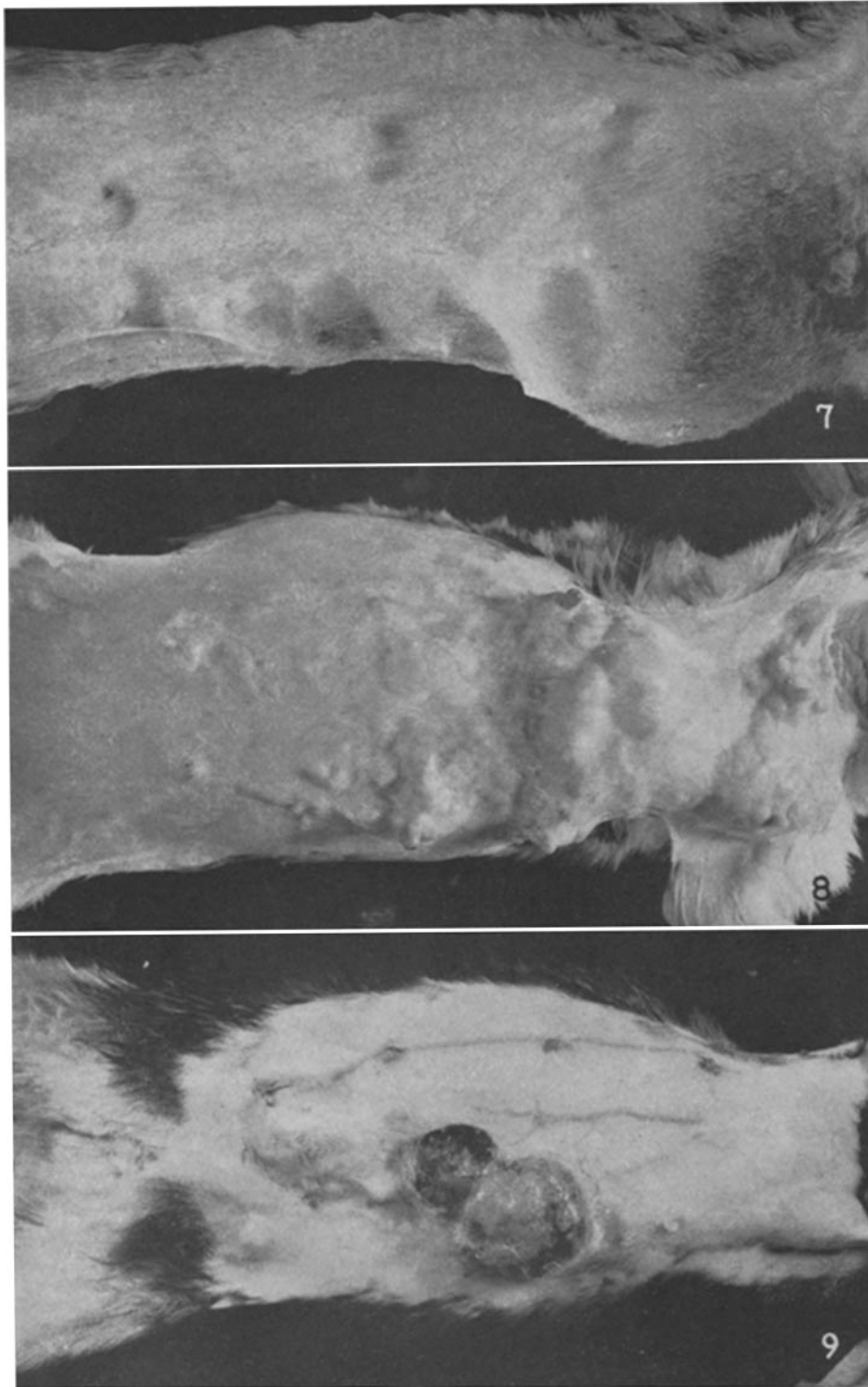
(Greene: Familial mammary tumors in rabbit I)

PLATE 12

FIG. 7. B234-3. Photograph taken 7 months after inception of the disorder. The mass in the first left breast is soft and doughy in consistency. Microscopic examination showed the presence of a medullary carcinoma. Death with metastasis occurred 2 weeks after this picture was taken. $\times 0.55$.

FIG. 8. EB2-2. Photograph taken 26 months after inception of the disorder. All stages of the disorder are present in different regions. Directly below the second right breast is an area of engorgement. Nodules, scattered throughout the mammary system, are purely cystic in character or contain multiradicular papillomata. The first left breast is the seat of an invasive growth. The rabbit is living at the present time and the mammary disorder has been present for 29 months, exactly half the animal's life. $\times 0.4$.

FIG. 9. T36-1. Photograph taken 16 months after discovery of the primary tumor nodule. The primary tumor is the lower mass shown in the picture, while the upper mass is a secondary growth of 6 months duration. A direct lymphatic extension from the primary to the secondary tumor was traced at autopsy. The primary growth shows no clinical evidence of malignancy but the secondary tumor has invaded the skin and is attached to the underlying muscle. Other breasts are normal in appearance. Metastases are present in the lymph nodes of the left axilla and groin. $\times 0.4$.



Photographed by J. A. Carlile

(Greene: Familial mammary tumors in rabbit. I)