STUDIES BASED ON A MALIGNANT TUMOR OF THE RABBIT.

V. METASTASES.

PART 1. DESCRIPTION OF THE LESIONS WITH ESPECIAL REFERENCE TO THEIR OCCURRENCE AND DISTRIBUTION.

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PLATES 25 TO 29.

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In previous reports (1, 2), dealing with phenomena of tumor growth and the clinical effects observed in tumor-bearing animals, reference was made to the frequent occurrence of metastases following intra-testicular transplantation and their absence after other methods of inoculation, and it was pointed out that this was one of the outstanding differences in the results obtained by the use of various methods of transplantation. It was further noted that no constant relationship existed between the rate of growth or the size attained by the primary tumor and the occurrence of metastases in distant organs, but that the development of metastases and the malignancy displayed by the tumor were more closely related to persistence of growth or the ability of the animal to confine the growth to a given area, and hence to the function of animal resistance.

If one may consider metastases from this point of view, a study of the phenomena of metastasis of a given tumor in a large series of animals, should not only throw some light upon those conditions which contribute to or prevent the occurrence of metastases but upon the more fundamental problem of the nature and mode of operation of animal resistance. Such a study has been undertaken, and the results, in as far as they pertain to the occurrence or non-occurrence of metastases, will be reported in this and the two following papers.
On account of the scope of the investigation and the volume of the material used, it will be necessary to divide the report dealing with metastases into three parts. The first two papers will be devoted to a description of the lesions and the circumstances of their occurrence as a further contribution to the picture of the disease produced by this tumor and as a basis for the discussion of factors which influence the occurrence and distribution of metastases. This last phase of the subject will be reserved for Part 3 of the paper.

Methods and Material.

The material upon which this study is based consists of a series of 191 rabbits from the first twenty generations of transplantation in which the phenomena of metastasis were studied in relation to the growth of the primary tumor, the clinical course of the disease, the occurrence of changes in other organs and tissues, and a number of other factors such as the age and breed of the animal, the generation of the transplant, and the season at which the inoculations were made, all of which are known to exercise some influence upon the course of the disease. For the most part, the animals were derived from experiments which were conducted primarily for the study of the disease as a whole, and hence from the single point of view of metastases, the material is not so well distributed as might be desired, but all animals have been excluded where any objection might be raised to their use. The animals fall into two general groups: first, animals killed at regular intervals of from 1 to 4 weeks after inoculation, and second, animals that died or were killed at various periods during the progress or resolution of the growth or after apparent recovery had taken place, the time ranging from 2 weeks to 7 months from the date of inoculation. For statistical purposes, however, the time limits have been fixed at between 3 and 28 weeks.

All animals received a unilateral testicular inoculation, and with two exceptions, no experimental procedure was employed which in itself might influence the course of events. The exceptions mentioned included one group of four rabbits which had one testicle removed before inoculation and a group of five rabbits that were inoculated with material that had been subjected to repeated freezing and thawing with a consequent prolongation of 2 to 3 weeks in the period of incubation. Otherwise, the variables which figured in the results were those of age, breed, length of survival, and such unavoidable differences as might exist in the quality of material used for the inoculation of different series of animals and the time (season) at which the experiments were carried out.

In reporting the results of this investigation, estimates of incidence and distribution will be based upon metastases which could be detected clinically or at autopsy or to gross as distinguished from microscopic lesions. In estimating the actual incidence of metastases, all animals showing active, regressing, or healed
lesions have been regarded as positive, but in classifying lesions on a time basis, it has been necessary to disregard clinical observations as to the time of occurrence of certain groups of metastases and to eliminate healed lesions, since these cannot be properly correlated with autopsy observations. The time given in such classifications unless otherwise indicated is that at which the postmortem examination was made.

The method of presentation employed is based upon the animal as the prime factor in determining the course of the disease. Lesions are described from the point of view of the peculiarities of the growth and the reaction which occurs in individual organs and tissues, and the circumstances of their occurrence are analyzed with reference to time and to the character and progress of the disease, the object being to bring phenomena of metastasis into as close relationship as possible with those conditions which determine the course of the disease.

Many of the facts in regard to metastases are represented graphically, and for this purpose, two simple methods of charting have been used, both of which are intended to represent relative rather than absolute values. The animals studied are immediately divisible into two main groups, positives and negatives. While we are equally concerned with both groups, our interest is at present centered upon those animals in which metastases occurred. Hence in order to avoid undue distortion of the picture presented, it is necessary to eliminate negative animals and to record the results of incidence of different classes of metastases upon a relative basis.

Moreover, the mere presence of metastatic growths may in itself be misleading and the further consideration of the number of foci affected has been introduced in order to give the added idea of the severity of disease as expressed in terms of the incidence and distribution of metastases in any group of animals or tissues. In like manner, the general curve of metastatic involvement has been used in many places as a background for comparison with the curves of individual organs in order to preserve the idea of the relation of metastases in individual organs to the disease as a whole.

**Incidence and Distribution of Secondary Growths in General.**

In taking up the subject of secondary growths arising from this tumor, it seems well to emphasize the fact that the tumor under consideration has at all times exhibited a tendency to a diffuse growth with a perivascular arrangement of cells and that invasion of blood vessels and lymphatics has occurred almost from the beginning of the growth or within 7 to 10 days after inoculation. It is obvious, therefore, that some dissemination of cells must have occurred in practically all animals with actively growing primary tumors, and yet, among the animals studied, secondary tumors were found in only 114, while the
remaining 77 animals showed no visible extension of the growth beyond the body of the inoculated testicle. It would appear from this, that dissemination of tumor cells does not necessarily imply the development of gross lesions, and this fact is of the foremost importance, since in studying phenomena of metastasis, one is concerned fully as much with the absence of metastases as with their presence.

For convenience, the tumors which developed from a primary growth in the testicle have been divided into three classes, (1) local or regional extensions, (2) implantations on serous surfaces, and (3) metastases to distant parts of the body arising by way of the blood vessels or lymphatics. This grouping is intended primarily to indicate degrees of independence and distribution rather than the exact mode of origin, which in reality is one of the problems with which we are concerned.

The mean incidence of secondary growths for the entire group of animals was 60 per cent, and at one time or another metastases occurred in nearly all parts of the body, as shown in Text-fig. 1, which gives the relative frequency of involvement of various organs and tissues in 114 animals. There were great variations, however, in both the incidence and distribution of metastases, and, while it is not intended to take up this phase of the subject in detail, the fact should be noted that at different times and in different series of animals, the incidence of metastases varied between a minimum of about 25 per cent and a maximum of 100 per cent and that the distribution of the lesions was subject to equally marked variations. These features of the subject will be discussed when the factors are considered which have influenced the growth and malignancy of the tumor during the course of transplantation.

Gross lesions were found as early as 2 weeks after inoculation, and in some instances, actively growing metastases were still present in animals killed as late as 7 months after inoculation. The curve of incidence of all classes of lesions as determined by postmortem examination at periods of from 3 to 28 weeks after inoculation is given in Text-fig. 2. If this chart is considered with reference to the development of the primary tumor and the subsequent course of the disease in different classes of animals, it possesses a significance which is not otherwise apparent, and since this form of chart will be used with reference to metastases in individual organs, it may be analyzed in some detail.

In the first place, two conditions are represented. The upper curve indicates the proportion of the animals examined at any time in which secondary growths were found, and may be spoken of as the curve of animal incidence. The lower curve represents the relative number of foci involved as compared with a theoretical possible involvement which was determined by the distribution of metastases in all animals examined thus far, and represents both the extent and distribution of lesions. In order to facilitate comparison of these two curves, the scale of the second curve has been multiplied fivefold.
Text-Fig. 1. Relative incidence of secondary tumor growths in different organs and tissues.
A consideration of the conditions found at 3 weeks will show that a great majority of the animals (77 per cent) showed secondary growths but few foci were affected (3.08 per cent). From the 3rd to the 5th weeks, corresponding with the time during which many animals show either an arrest or regression of the primary tumor, fewer animals showed metastases, but those in which metastases were found, showed a decided increase in distribution or the number of organs affected. From this point onward, the two lines proceed almost parallel with a rapid increase in both the incidence and distribution of metastases until the maximum height is reached at the 7th week. There is then a marked reduction in both curves extending over a period of several weeks followed by a slight rise with a second drop after which the changes that occur are of minor degree and affect animal incidence rather than the distribution of metastases, but there is a distinct upward trend in the curve of incidence.

Text-Fig. 2. Relative incidence and distribution of metastases, plotted with reference to time.

These changes are all reflected in the course of the disease. The initial drop in the curve of incidence indicates that early metastases may undergo resolution in some animals at the same time that retrogressive changes take place in the primary tumor. The rapid rise in the curves between the 4th and 7th weeks corresponds with a renewal of activity in the primary tumor and the appearance of cases of fulminating malignancy. The apparent increase in the curve of incidence is doubtless somewhat exaggerated owing to a preponderance of deaths at this particular time but this is a characteristic feature of the disease. The drop which occurs from the 7th to the 10th weeks is due in part to elimination by death and in part to recovery of a second group of animals. The wide discrepancy between incidence and distribution as shown at the 8th and 9th weeks is almost a repetition of the condition at the 3rd and 4th weeks and is doubtless attributable to the same causes. Subsequent elevations in the curve of incidence are attributable to recru-
descence of activity and more slowly progressive types of disease which, as may be seen, mature at intervals of approximately 4 weeks. The flattening out of the curve of distribution which occurs during the latter half of the period of observation is of especial importance since, as will be shown later, the maintenance of this particular level is due to the almost constant involvement of one group of organs and of conditions which suggest the development of a selective distribution of cells or an immunity in certain tissues which is not shared by others.

The facts which have been brought out show the general tendencies which exist with reference to the occurrence of secondary growths as a whole. It has been found, however, that the conditions which favor the development of metastases are not the same for all organs or tissues, and in order to obtain a clearer conception of the underlying causes for these differences it will be necessary to consider the lesions of different organs individually.

**Local or Regional Extensions.**

While in many animals, the primary tumor was at all times confined within the testicle, the growth not infrequently invaded the tunics and spread to adjacent tissues or extended outward along the lymphatics and blood vessels either in the form of fairly discrete nodules connected by more or less distinct lines of tumor growth, or as masses continuous with the primary tumor. The resulting lesions, therefore, were of two kinds, but with no sharp line of distinction between them. The picture presented varied in different animals. In some, there were small nodular masses on the outer surface of the tunics, and occasionally the growth involved the scrotum as well. More often there were discrete nodules distributed along the cord, or the growth extended upward into the abdominal cavity in the form of large, irregular masses which not infrequently involved the tissues about the inguinal canal and the lower abdominal and pelvic regions. Examples of the conditions present in cases of this kind may be seen in Figs. 1 to 3, which show varying degrees of the processes described.

These outgrowths from the primary tumor were at times very limited in extent or were confined to the lower abdominal and pelvic regions. As a rule, however, the growth continued upward in the retroperitoneal tissues along the midline of the body or along the outer margins of the lumbar muscles (Figs. 1 to 3). In these cases, the direct connection with the primary tumor was usually lost. The growth assumed the form of discrete nodules distributed along the line of the lymphatics
with numerous metastases in the retroperitoneal lymph nodes and in the perirenal tissues, and not infrequently, this chain of lesions extended upward in the midline to the base of the neck with the formation of metastases in the retropleural tissues and in the mediastinum.

Growth of the several types described were of frequent occurrence as may be seen by reference to Text-fig. 1. Out of a total of 114 animals, there were only 14, or 12.3 per cent, in which the only secondary growths were confined to the tissues immediately surrounding the primary tumor. Extensions up the cord of the inoculated testicle occurred, however, in 39.6 per cent of the animals, and it is important to note that the retroperitoneal tissues were involved with even greater frequency (41.4 per cent), while secondary growths were comparatively rare in either the tunics or the scrotum.

Extension of the primary tumor up the cord and the development of isolated nodules in the epididymis and cord were usually the first clinical signs of malignancy and were frequently recognizable by the end of the 3rd or 4th week after inoculation. In like manner, metastases to the retroperitoneal tissues occurred as early as 2 to 3 weeks after inoculation, or at about the same time and with the same frequency as pulmonary metastases, which shows not only that the cells began to be disseminated at a very early period but presents a striking parallelism in the initiation of metastases by way of the blood vessels and lymphatics.

Lesions of this class rarely gave rise to serious disturbances. In several animals, there was obstruction to the right ureter with the production of a hydronephrosis, and in one instance, a growth in the pelvis caused complete obstruction at the neck of the bladder.

**Implantations.**

Invasion of the tunics and extension of the primary tumor into the lower abdominal cavity were productive of conditions which might be regarded as peculiarly favorable to the development of implantation metastases but lesions of this class were by no means so frequent as might have been expected. In fact, they were less frequent than metastases to the retroperitoneal tissues or to such organs as the lungs and the kidneys, where the distribution of tumor cells was effected either by the lymphatics or the blood stream (Text-fig. 1).

In some instances, there were innumerable masses of tumor growth distributed through all parts of the abdominal cavity, as in Fig. 1, but these cases were comparatively rare. As a rule, there were only a few lesions present, and while some of them were as large as 8 to 10 cm. in their greatest diameter, they were usually small and rarely exceeded 1 to 2 cm. in diameter.

These growths occurred most often in the omentum and mesentery but were almost as frequent over the surface of the intestine and diaphragm together with...
adjacent parts of the abdominal wall. The stomach and bladder were rarely affected and metastases were less frequent on the small intestine than on the cecum and colon. The surface of the spleen was affected in only one animal, and as far as could be determined, there were no implantation metastases on the liver.

In like manner, metastases were less frequent over the lateral and ventral surfaces of the parietal peritoneum than in the pelvic and diaphragmatic pouches, the flanks, or the lumbar regions. Another peculiarity of these lesions was a tendency to localization along the course of blood vessels and lymphatics, as may be seen in Fig. 1, which suggests that in reality some of the lesions classed as implantation metastases may have arisen from cells within blood or lymph vessels. This applies especially to mesenteric metastases.

There were a few implantation metastases on the parietal pleura, but again these lesions were rare as compared with the incidence of metastases in the lungs which involved the pleural surfaces. The evidence available, therefore, would indicate that successful implantation of tumor cells on serous surfaces was accomplished with difficulty, and that the hindrance to growth was much greater than that encountered in either the lymphatics or the blood vessels.

Although implantation metastases were of frequent occurrence and occasionally reached a very large size, there was only one instance in which death could be attributed to a growth of this kind. In this animal, an unusually large tumor developed in the mesentery and eventually gave rise to an intestinal infarction.

Metastases in Distant Parts of the Body.

By far the greatest number of secondary tumors, and those of chief importance, were located in parts of the body which were inaccessible to cells from the primary tumor except by passage through lymphatics or blood vessels. Lesions of this class occurred in 100, or 52.3 per cent, of the 191 rabbits studied, while their relative frequency in animals with secondary growths was 87.7 per cent.

Metastases of this class occurred in nearly all parts of the body, as may be seen by reference to Figs. 1 to 4 and Text-fig. 1 which gives the distribution according to incidence in different organs or tissues. The sites of greatest frequency were the kidneys, the lungs, the suprarenals, the lymph nodes, the liver, the eyes, the muscles, the bones, the heart, and the tissues of the mediastinum. In contrast with the high incidence shown by the organs enumerated, it will be noted that metastases occurred very rarely in certain other organs such
as the uninoculated testicle, the spleen, and the thyroid, while no metastases were found in such organs as the brain and spinal cord or the salivary glands.

In like manner, the lesions were confined almost entirely to the trunk, the head and neck, and the proximal segments of the extremities; as far as is known, there were no metastases in the ears or tongue or in the feet. In general, it appeared that the frequency of metastases diminished with the distance from the central axis of the body, and this was not entirely attributable to the nature of the tissues composing these parts, since metastases were comparatively frequent in tissues of the same order but nearer the body axis.

On account of the importance of this group of metastases, it will be necessary to consider them in greater detail than those of the two preceding groups. In describing these lesions, emphasis will be placed upon the time relations of metastases in different organs and tissues both with reference to one another and to the course of the disease. The order in which different organs or tissues will be taken up has been determined by the relationships which obtain as expressed in the circumstances under which metastases occurred.

**Lungs.**—Pulmonary metastases were usually small discrete nodules of a grayish white or opalescent appearance; they were usually firm and rarely showed either hemorrhage or necrosis. They were more numerous in the lower than the upper lobes and exhibited a tendency to localize in the pleura (Fig. 3). Occasionally, the lungs were thickly studded with these nodules, but as a rule, they were few in number and widely scattered. Among animals with metastases, the lungs were affected in 36.8 per cent. The time relations of these lesions with reference to the progress of the disease are especially interesting and can be shown best by means of a chart which records the relative incidence of pulmonary metastases in different groups of animals showing secondary growths, autopsied at from 3 to 28 weeks after inoculation (Text-fig. 3).

In general, the chart shows a three period elevation with a decrease in the extent of each succeeding rise which gives the curve a downward slope from the point of greatest elevation between the 4th and 7th weeks. These features of the curve may be emphasized, since they are typical of a condition which obtained with a number of organs while in striking contrast with the curves of others.

The actual time of occurrence of metastases in the lungs or other organs can be stated only in a general way. It may be seen from the relative position of the two curves in Text-fig. 3 that lung metastases occurred ahead of the general involvement of other organs. The earliest pulmonary metastases were noted 2 weeks after
inoculation. At the end of the 3rd week, they were more frequent than metastases in any other part of the body, except in the immediate vicinity of the primary growth. Moreover, while there was a reduction in relative frequency during the later periods of observation, pulmonary metastases were still comparatively frequent in all groups of animals up to the 16th week. After this, they were of sporadic occurrence, and the cases observed were without exception among animals of the first few generations in which the disease progressed much more slowly than at present. This fact should be mentioned because an effect of the same kind has been introduced into several other curves, notably those of the kidney and liver. In reality, there is considerable evidence to show that pulmonary metastasis were of more frequent occurrence than the actual figures would indicate and that they not infrequently underwent spontaneous resolution without leaving any gross evidence of their previous existence. The features of pulmonary metastases which

![Text-fig. 3. Relative incidence of lung metastases as compared with general distribution of secondary growths, at different intervals of time after inoculation.](image)

are of especial interest are their early occurrence and relatively high frequency during the very early stages of the disease, as contrasted with the occurrence of few lesions of small size, and their tendency to diminish in frequency during the later periods of observation. After the first few weeks, during which they occurred in all classes of animals, they were in general lesions of severe rather than of mild forms of disease.

**Liver.**—The growth in the liver varied greatly in different animals. In most instances, there were a few large or medium sized nodules measuring from 0.5 to as much as 2.0 cm. in diameter. Individual lesions were of a soft, medullary consistency and not infrequently showed hemorrhage and necrosis, but they were rarely enclosed by a connective tissue capsule, except in animals with a long standing tumor growth. In a few instances, partially or completely healed lesions were found.
Not infrequently the liver showed a most extensive metastatic involvement with innumerable large or small nodules distributed through all parts of the organ as shown in Figs. 5 and 6. These conditions corresponded with differences in the rapidity with which the disease progressed and from this standpoint are illustrative of similar differences which existed in other organs, especially the kidneys. The growth in these cases was associated with a marked enlargement of the liver. The weight of the organ per kilo of body weight was at times increased as much as two or three times that of the normal animal. This change was also proportional to the rapidity with which the disease progressed.

The curve of incidence of liver metastases (Text-fig. 4) shows a clearly defined division into three periods, and each period of increase lies within and parallel with the curve of general distribution. The notable differences between the two curves are at those points where liver metastases were at their lowest level, indicating that the liver contributed very little to the general picture of the disease at these times. The periods of greatest frequency of liver metastases were again periods of widespread systemic involvement. The terminal rise might appear to contradict this statement, but the animals responsible for this feature of the curve all came from early generations, as was noted with the lungs.

In contrast with pulmonary metastases, those of the liver were much larger, and more numerous, suggesting that opportunities for growth were better than in the lungs but that the organ was in general less accessible to tumor cells and hence was involved only at times when cell distribution was at its optimum.

Kidneys.—The kidneys were not only the most frequent sites of metastases but they also showed the greatest degree of involvement. As a rule, both kidneys were affected, and while in some instances there were only a few large or small nodules, comparable in all respects to those of the liver, the surface of the organ was more often completely obscured by an irregular nodular mass of tumor growth (Figs.
Metastases were located primarily in the cortex and in the subcapsular tissues; a few lesions developed in the pelvis of the kidney, but the medulla was practically free, except as it became involved by extension of the growth from other parts of the kidney or from surrounding tissues. As a rule, the growth developed in the outer portions of the cortex and extended outward rather than inward.

In instances of slowly progressive disease, the individual lesions were usually large, and not infrequently there was a marked thickening of the capsule. In more rapidly progressing cases, the lesions were smaller but still numerous. These lesions were frequently hemorrhagic in character and gave rise to profuse subcapsular hemorrhages.

Encapsulated, necrotic, and completely healed metastases were found in a considerable number of animals. In these cases, there were usually only a few lesions, but one animal was encountered with almost complete healing of what appeared to have been an extensive involvement of both kidneys.

The form of the curve of renal metastases (Text-fig. 5) is different from that of either the lungs or the liver. During the earlier phases, it conforms more nearly to that of general metastatic involvement than does the curve of any other organ. This might be expected on account of the high incidence of renal metastases, but it is important to note that the maximum incidence is not reached until the 9th week, or at a time when metastases in most organs have begun to decline or have already reached a low level. Moreover, a high incidence of renal metastasis was maintained during the first 12 weeks, the curve from the 8th to the 12th weeks exceeding but conforming to that of distribution, indicating that a large proportion of the metastases found during this period was referable to the kidneys. At the 14th week, the curve reaches the base line but again rises with the distribution curve. This final rise, as with the two preceding groups of metastases, was due largely to animals from early generations.
The most significant feature of the curve of renal metastases is its sustained elevation and in this respect it resembles the curve of pulmonary metastasis. Its trend is upward, however, at a time when pulmonary lesions are diminishing, and this difference is even more striking in comparison with the course of events in the liver. These characteristics of the curve, together with the extensive growth of renal metastases, suggest two things: first, accessibility to tumor cells, and second, adaptation to the growth of metastases, or its converse, low resistance to tumor growth.

Heart.—Comparatively few animals showed metastases in the heart. The lesions were located chiefly in the tissues about the coronary sinuses and vessels or were distributed diffusely through the myocardium. In a few instances, masses of tumor cells were found in the right auricle or ventricle, apparently free or attached to the walls of the heart by a slender pedicle.

The metastases comprising this group varied from minute points to nodules measuring as much as 1 cm. in diameter. The majority of the metastases in the myocardium and many of those along the course of the coronary vessels were extremely small, semitranslucent masses of a firm consistency and showed no gross evidence of hemorrhage or necrosis, and apparently none of them underwent spontaneous resolution.

The larger nodules, on the other hand, were of a medullary character and showed extensive retrogressive changes. Metastases of this type were confined to the epicardial tissues about the base of the heart and apparently represented lesions of a different order from those in the myocardium. In one instance, a lesion of this character was found in the parietal pericardium.

The extent of the cardiac involvement was usually slight, but in a few animals with an unusually malignant disease, there were innumerable foci of tumor growth distributed through all parts of the heart.

The most significant feature of the occurrence of cardiac metastases was that they were confined almost exclusively to animals with extremely malignant growths. This is indicated by the relatively high point reached in the curve of incidence at 4 weeks and the absence of cardiac metastases after the 7th week (Text-fig. 6). In fact, the cases of most extreme cardiac involvement occurred in animals that showed marked debility 4 weeks after inoculation. The liver shown in Fig. 6 came from one of these animals and metastases were almost as numerous in the myocardium. The few exceptions to this rule occurred in animals with marked mediastinal involvement, and the cardiac lesions present were of the same general character as those in the mediastinum and were confined to the epicardial tissues about the base of the heart. A few lesions of this kind were found in animals autopsied several months after inoculation.

Suprarenals.—Metastases in the suprarenals were of frequent occurrence. Of the 114 animals showing metastases, 37 showed metastatic growths in the suprarenals. In 10 instances, both suprarenals were involved, while the right was affected in 12 and the left in 15 animals.
The growth usually arose in the cortex at one or several foci. These tended to coalesce, forming a single mass which occupied the center of the gland and was usually surrounded by a narrow rim of cortex.

The metastases varied in size from a few millimeters to more than 2 cm. in diameter. The growth was of a grayish white or reddish gray color and usually rather translucent. The lesions were always soft, and while they were frequently hemorrhagic, they showed comparatively little tendency to mass necrosis.

The mode of growth was peculiar in that it produced a comparatively uniform expansion of the gland with gradual obliteration of both cortex and medulla but showed little or no tendency to invade the surrounding tissues. On the other hand as long as the growth was confined to the substance of the gland, there was practically no reaction of any kind about the tumor cells and none in the surrounding tissues. When the capsule became involved, however, there was a slight granulomatous reaction but still no encapsulation of the tumor mass such as occurred at times in all other organs with the exception of the hypophysis. In like manner, no cases of regressing or healed metastases were found.

The circumstances associated with the occurrence of suprarenal metastases were also unusual. In the first place, they developed early in the course of the disease, the period of maximum incidence being fully a week in advance of that shown by even such organs as the lungs, while a second peculiarity was the maintenance of a practically constant and comparatively high level of incidence from the 7th week onward (Text-fig. 7). Translating these facts into clinical terms, it may be said that suprarenal metastases occurred chiefly in two groups of animals: first, in cases of fulminating malignancy, and second, in animals that showed few or no lesions elsewhere. Some of these had definitely recovered from a more extensive involvement, while others gave no evidence of preexisting metastases in other organs. In brief, when both suprarenals were involved, death occurred,
but when only one was involved, there was no serious impairment of vitality on
this account, and since suprarenal metastases did not undergo spontaneous
resolution, a comparatively high level of incidence was maintained throughout
the period of observation. The condition presented by many of these animals
was that of an apparent immunity in the presence of an actively growing metas-
tasis in one suprarenal.

Nowhere else was there an exact parallel of the conditions described and they
are worthy of especial emphasis on account of their bearing upon phenomena of
tumor growth and upon animal resistance.

**Eyes.**—Eye metastases may be considered to advantage in connection with the
suprarenals since they presented some of the same peculiarities that were noted
with metastases in those organs and possessed the additional advantage of per-
mitting a correlation between clinical and pathological observations which is
helpful in their interpretation.

![Text-Fig. 7. Relative incidence of suprarenal metastases.](image)

Metastatic growths were noted in the eyes of fourteen animals during life, and
a few additional lesions were encountered at autopsy. The right eye alone was
involved twelve times, the left twice, while in four animals, metastases developed
in both eyes. In one or two instances, the growth was located in the choroid, but,
as a rule, it arose from the iris or ciliary body and with few exceptions extended
forward through the iris into the anterior chamber.

The presence of these metastases was first indicated by a focal or complete
pericorneal injection or by the occurrence of hemorrhage into the anterior chamber
associated with an irregular prominence in some part of the iris, usually towards the
upper or outer margin. The growth of these tumors was very rapid and they
presented the same general appearance as primary tumors in this location.

There was one peculiarity of these lesions which may be referred to briefly. In
most instances, the cornea remained clear or showed only a slight clouding at the
outer margins, and this usually occurred very early and without reference to the extent of the growth. In exceptional instances, however, the entire cornea became very much clouded with an apparent roughening and dryness of the surface which reminded one of the condition described as xerophthalmia. Again, there was no constant relationship between the development of this condition and the extent of the tumor growth. Moreover, the change was not entirely permanent but cleared to some extent in animals in which the tumor regressed.

Eye metastases, as in the case of primary tumors, showed clearly defined periods of progression and regression followed by relapse. In some animals, the growth completely disappeared, leaving only a small fibrous scar, while in others the tumor remained active with no tendency to heal during a period of 3 to 4 months.

As in the case of the suprarenals, eye metastases occurred in two very different classes of animals: first, in animals with highly malignant tumors, and second, in animals with few or no secondary lesions in other parts of the body. These facts are represented in the curve showing the presence of eye lesions at different times as determined by postmortem examination (Text-fig. 8). The curve shows a rapid rise during the 4th to the 6th weeks with a more gradual decline and a second elevation of equal extent during the later periods of observation. This final rise is artificial and is due to the fact that a number of animals with eye metastases were held under observation in order to determine what the outcome in these cases might be. If the existence of these lesions had not been known, this group of animals would probably have been distributed over the periods from the 7th week onward giving a curve not unlike that of the suprarenal metastases.

The curve of actual incidence (Text-fig. 8) assumes much this form. That is, if the time of clinical record be substituted for the record of postmortem examination, it will be seen that the majority of eye metastases occurred about 4 weeks
after inoculation and that there was a slight secondary increase during the 7th and 8th weeks. In brief, 80 per cent of the lesions occurred during the first 8 weeks.

This comparison of clinical and pathological data, when taken in conjunction with the history, is helpful in interpreting the results obtained in other organs where the curve of incidence indicates the operation of a similar group of factors.

Hypophysis.—Metastases in the hypophysis also presented a picture closely related to that of suprarenal metastases both as regards the character of the growth and the conditions under which they occurred.

As far as could be determined, the tumors arose from either the anterior or middle lobe and were identical in character with those in the suprarenals. They were usually small and, with one exception, were confined within the sella which showed a varying degree of enlargement, depending upon the size of the tumor. In one instance, the growth involved both the infundibular stalk and the entire area of the tuber cinereum, forming a mass in the base of the brain which was more than a centimeter in diameter.

As in the case of suprarenal metastases, there was practically no reaction about the growth in the hypophysis and there was no evidence that these lesions underwent spontaneous resolution.

There were two features of interest in the occurrence of hypophyseal tumors. The curve of incidence (Text-fig. 9) brings out in typical form the three waves of diminishing frequency which correspond with similar waves in the curves of many other organs. In fact, this group of lesions was confined almost exclusively to animals with widespread metastases. The exceptions occurred in animals with combined suprarenal and hypophyseal involvement in which few metastases had developed elsewhere or in which preexisting lesions in other organs had healed. In this respect, there was close agreement between the conditions under which metastases occurred in the suprarenals and hypophysis, indicating comparable
resistance to tumor growth. There were wide differences, however, in the curves of incidence which may be attributable on the one hand to differences of accessibility to tumor cells and on the other hand, to the fact that hypophyseal involvement almost inevitably caused death.

In the present paper, a description is given of secondary growths arising from direct extension of the primary tumor and from the implantation of cells on serous surfaces, together with metastases in the lungs, the liver, the kidneys, the heart, the suprarenals, the eyes, and the hypophysis. Metastases in other organs and tissues will be described in Part 2 of this paper.

BIBLIOGRAPHY.


EXPLANATION OF PLATES.

The illustrations are reproductions of photographs which have not been retouched. Statements of time are from the date of inoculation.

PLATE 25.

FIG. 1. 52 days. Physical condition of animal fair; beginning weakness and slight loss of weight; loss of bladder control. Killed. The most striking features of the condition presented by this animal were the extension of the growth upward in the retroperitoneal tissues to the base of the neck and the formation of a profusion of implantation metastases some of which were extremely large and actively growing with little or no necrosis anywhere. The serous cavities were all filled with a blood-stained fluid. There were comparatively few metastases outside the abdominal and thoracic cavities. Note the well nourished condition of the animal, which may be contrasted with Fig. 3. $\times \frac{4}{9}$.

PLATE 26.

FIG. 2. 49 days. Extreme weakness; moderate loss of weight. Killed. This photograph shows a comparatively small primary tumor in the right testicle which has invaded the tunics and extended along the retroperitoneal lymphatics to the lumbar and perirenal regions. There is a small metastatic nodule in the left testicle, and there are a few lesions in the liver, but the growth is most marked in the kidneys. Many of the lesions show a hemorrhagic tendency, and there is a diffuse subcapsular hemorrhage in the left kidney. There were numerous metastases in other parts of the body. Natural size.
PLATE 27.

Fig. 3. 49 days. Extreme weakness and emaciation. Killed. This animal is intended primarily to illustrate the condition present in fulminating malignancy, although the progress of the disease was not so rapid as is sometimes seen. There were metastases in all the abdominal and thoracic viscera, including the spleen, and in the cerebral meninges, the hypophysis, the eyes, and widespread lesions in the skin and subcutaneous tissues, the deep and superficial lymph nodes, the muscles, and the bones. Many of these metastases are marked by arrows to facilitate identification. This photograph should be examined in connection with Fig. 4 which shows the lesions over the back of the same animal. The lesions of especial interest which may be seen are those in the heart, the skin and subcutaneous tissues, superficial lymph nodes, the muscles (thigh and jaw), the bones of the jaw, and the extensive hemorrhage in the right kidney. The animal also shows a wasting of the fat and of the muscles, especially noticeable in the lumbar region. About \( \frac{3}{4} \).

PLATE 28.

Fig. 4. The same animal as in Fig. 3. Note the number and size of the cutaneous and subcutaneous metastases and the prominence of the right shoulder, which was due to a growth in the muscle which possibly arose from the scapula. Natural size.

PLATE 29.

Figs. 5 and 6. The animal whose liver is shown in Fig. 5 died 82 days after inoculation; that from which the liver in Fig. 6 was taken showed an extremely rapid development of skin and bone metastases during the 4th week after inoculation with progressive weakness and emaciation and was killed on the 29th day. Natural size.

The metastases in these two livers illustrate a difference in the character of the lesions seen in cases of rather slowly progressive malignancy and in those that are truly fulminating. The difference in the lesions and the associated change in the organ are typical of the conditions presented by all other organs under similar circumstances and show to what extent the number and character of the lesions present can be taken as an index of malignancy or more properly of animal resistance, since varying degrees of the condition illustrated may be seen in different animals of the same series.
(Pearce and Brown: Malignant tumor of the rabbit. V.)