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SPONTANEOUS TUMORS IN TWO COLONIES OF RATS OF THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY *

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The Wistar Institute maintains two colonies of albino rats, the Experimental Colony Strain and the Wistar Stock Colony, from which animals may be supplied to other laboratories. On occasion these have been used in research on neoplastic diseases. It seems desirable, therefore, that records of spontaneous tumors in animals of these colonies be made available.

The material to be presented was collected over a 5 year period, during which animals that developed abnormal swellings of any part of the body were submitted for study. The personnel in charge of the colonies selected these while making routine inspections of the stock.

Depending on their condition when received, the rats were either killed for immediate autopsy, or held for observation and experiment. All tumors were examined microscopically, tissues being prepared according to standard methods, and classified according to sites of origin and histological make-up. Interpretations of their actual or potential nature were based on accepted criteria, but doubtful cases will be described in some detail.

Of 468 animals selected for examination, 393 (295 females and

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98 males, or about 5 per cent of all animals dying in the group during the period) were from the Experimental Colony Strain. The remainder, 44 females and 31 males, also about 5 per cent of the animals dying in the group, were from the Wistar Stock Colony. From the entire series, 273 tumor-bearers were obtained, these being divided between the two colonies as follows: Experimental Colony Strain, 207 females and 37 males; and Wistar Stock Colony, 24 females and 5 males (see Table I).

Age Distribution and Types of Tumors

The ages of the tumor-bearing rats varied from 120 to 1020 days. The distribution of neoplasms, according to age, is shown for both colonies in Table I, cases being arranged into age groups that are separated by an arbitrary interval of 90 days.

Table I

Age Distribution at 90 Day Intervals in all Tumor-Bearing Rats

Age classes	Experimental Colony Strain		Wistar Stock Colony	
	Females	Males	Females	Males
days				
91–180	1	1	..	..
181–270	4	3	2	1
271–360	12	..	..	..
361–450	21	..	2	..
451–540	26	2	7	..
541–630	23	7	..	2
631–720	49	6	4	1
721–810	33	8	2	1
811–900	30	9	5	..
901–990	7	1	2	..
991–1080	1	..	..	..
Total tumor-bearers	207	37	24	5

In the first column of the table female rats of the Experimental Colony Strain have been listed. The actual range in age was 120–1020 days, the average age being 680 days. The age distribution followed fairly well a normal curve and irregularities probably would have been less with a larger series. Age distribution of tumor-bearing males of this colony was much less regular than for the females but the number of cases was too small for satisfactory comparison. The average age of these animals was 690 days.

The number of cases from the Wistar Stock Colony also was too

small for comparison, but the range in age corresponded fairly well with that of the 1st group, and in each group more than 75 per cent of all animals developed tumors between 451 and 900 days. The average age of females of the Wistar Stock Colony was 670 days, and of the males of this colony, 580 days.

Types of Tumors: Because of the manner in which the animals were selected for examination it was to be expected that surface tumors would predominate in the series, and this was true. However, a number of growths of internal organs were encountered also.

In Table II the neoplasms have been grouped according to their place of origin in the body and the cases have been arranged to show for both colonies, number, sex and average age of animals developing various types of neoplasms, and the histological make-up of the lesions. Indicated also are my opinions of the actual or potential growth characteristics of the tumors.

Listed in Table II are 302 neoplasms in 273 rats, 25 animals each having 2, and 2 others, 3 independent growths. For convenience of presentation, tumors of the mammary gland, although comprising the bulk of the material, have been placed last in this section.

Skin and Subcutis: Listed in this section of Table II are 22 tumors. With two exceptions, these were all of fibrous tissue origin. Tumors from females of the Experimental Colony were: 3 fibrosarcomas, 1 myxosarcoma and 1 lipoma. In males from this colony there were: 1 papilloma of the foot pad, 7 fibrosarcomas and 6 fibromas. The neoplasms from females of the Wistar Stock Colony were: 1 myxosarcoma and 1 fibroma. One male of this colony developed a carcinoma of the skin at the tip of the snout. Secondary tumors were found in the lungs in this animal. One other tumor of this group, a fibrosarcoma of the subcutis of the thorax in an Experimental Colony male, also gave rise to secondary growths in the lungs.

The average age of all animals with tumors of the skin and subcutis was 780 days, and the range in age was from 520 to 950 days. The average age of the rats that developed malignant subcutaneous neoplasms was 710 days, and again ages ranged from 520 to 950 days.

These subcutaneous tumors were located at various points on

TABLE II

Number of Tumors, Tissues Involved, Ages of Tumor-Bearers and Histological Characteristics of Tumors

Location of tumors	Experimental Colony Strain								Wistar Stock Colony							
	Cases ♀	Average age	Number of tumors E*	F**	Cases ♂	Average age	Number of tumors E	F	Cases ♀	Average age	Number of tumors E	F	Cases ♂	Average age	Number of tumors E	F
		days				*days*				*days*				*days*		
SKIN AND SUBCUTIS	5	600	..	5	14	750	1	13	2	790	..	2	1	..	1	..
Malignant tumors	4	610	..	4	7	780	..	7	1	690	..	1	1	630	1	..
GENITO-URINARY	17	720	9	8	5	430	..	..	..	..	..	..	2	430	..	..
Vagina																
Benign tumors	2	660	..	2	..	..	..	..	..	..	..	..	..	..	..	..
Malignant tumors	2	500	1	1	..	..	..	..	..	..	..	..	..	..	..	..
Uterus																
Benign tumors	3	880	..	3	..	..	..	..	..	..	..	..	..	..	..	..
Malignant tumors	7	780	5	2	..	..	..	..	..	..	..	..	..	..	..	..
Ovary																
Malignant tumors	3	500	3	..	..	..	..	..	..	..	..	..	..	..	..	..
Testes																
Malignant tumors	..	..	..	..	1	730	..	1	..	..	..	..	1	600	..	1
Kidney																
Malignant tumors	..	..	..	..	1	850	..	1	..	..	..	..	..	..	..	..
Embryonal tumors	..	..	..	..	3	200	Mixed tumors		..	..	..	..	1	270	Mixed tumor	
DIGESTIVE TRACT																
Malignant tumors	1	420	1	..	1	900	..	1	1	240	1	..	..	..	..	..
MEDIASTINUM																
Malignant tumors	..	..	..	..	1	250	..	1	1	390	..	1	..	..	..	..
THYMUS																
Malignant tumors	1	720	1	..	1	810	1	..	1	870	..	1	..	..	..	..
OTHER LYMPHOID TISSUES																
Malignant tumors	..	..	..	..	1	780	..	1	..	..	..	..	1	690	..	1
ADRENAL	1	690	1	..	..	..	..	..	..	..	..	..	..	..	..	..
SKELETON																
Malignant tumors	2	850	..	2	3	560	..	3	1	870	..	1	..	..	..	..
MAMMARY GLAND	187	650	203	3	..	..	..	..	..	..	..	..	..	..	..	..
Single tumors	168	650	165	3	13	650	5	8	19	640	18	1	1	750	..	1
Multiple tumors	19	680	38	..	..	..	..	..	..	..	..	..	..	..	..	..
Malignant tumors	13	470	11	2	..	..	..	..	1	690	1	..	..	..	..	..
Tumors of mammary gland and of other tissues	6	780	10	4	2	540	2	2	1	870	..	2	..	..	..	..

* E = Epithelial tumors.
** F = Fibrous tissue tumors.

the body from the head to the base of the tail, no one part being distinctly favored. The fibromas presented nothing unusual in their make-up, all being small, spherical, circumscribed nodules composed of dense tissue. The fibrosarcomas varied considerably in consistence. All were locally invasive, infiltrating skin and muscles. In section they varied from richly cellular tissues with many mitoses to relatively acellular structures in which abundant collagen was formed. Two of the more cellular tumors underwent central necrosis, forming large cystic spaces filled with serosanguineous fluid. Both of these tumors were easily transplanted, being carried through 4 series of animals. Other sarcomas were not subjected to this test.

Genito-Urinary Organs: Neoplasms of various parts of the genito-urinary system developed in 24 animals.

The ages of females, all of the Experimental Colony, ranged from 360 to 940 days. The average age of those having carcinomas was 690 days and the range in age was the same as for the whole group. The average age of females with tumors of fibrous tissue equalled that of the group and ranged from 540 to 930 days.

Four of the tumors in females originated in the vagina. Two of these were fibromas, 1 occurring within the vaginal canal as a pedunculated growth, the other as a nodular mass on the serous surface. A 3rd growth also formed within the vagina as a soft body which expanded the tube and infiltrated a wide section of the wall. This was classified as a myxosarcoma. The final tumor was a squamous cell carcinoma, developing at the mucocutaneous junction of the genital tract.

Of tumors of the uterus, 2 were soft pedunculated masses of fibrous tissue attached to the endometrium, and 1 a large irregular growth of soft tissue arising from the serosa of one uterine horn and adhering lightly to the intestines. This was composed of myxomatous tissue which did not appear to be malignant. Two other tumors of fibrous tissue origin involved large segments of a uterine horn. Both were locally invasive, replacing wide areas in the wall. One was a fibrosarcoma and 1 a myxosarcoma.

Epithelial tumors of the uterus were all malignant and have been classified as adenocarcinoma, and in each case secondary growths developed within the peritoneal cavity.

The other 3 neoplasms of the genital tracts of females involved

the ovary. These were carcinomas and all were essentially alike grossly, as well as in histological make-up. Two of these gave rise to secondary growths on peritoneal surfaces.

Tumors of the genito-urinary organs of male rats may be considered together, although both colonies were represented. Two of these growths involved the scrotal tissues of the host, 1 from each colony. Both were fibrosarcomas, which were locally destructive and extended into the peritoneal cavity as well.

Five other neoplasms involved a kidney in each host, completely replacing the organ. Four of these animals were from the Experimental Colony and, except for 1, were under 1 year of age at death. The male from the Wistar Stock Colony also was under 1 year of age. Four of the tumors were essentially similar in histological make-up, being composed of imperfectly formed epithelial structures and blood vessels which simulated nephrons and which were supported by abundant, richly cellular stroma. These growths were confined to the organ in which they developed and apparently were embryonal tumors.

The last of the renal neoplasms also replaced one kidney but, in sections, was composed of a dense mass of spindle cells which, in some areas, were arranged about an osteoid matrix. Metastases were found in the omentum. This tumor seems to have been a fibrosarcoma. The animal in which it occurred was the oldest of the group — 850 days. The average age of the other 4 was 210 days, the youngest 130 and the eldest 270 days.

Digestive Tract: Three tumors occurred in tissues of the digestive tract. One was an adamantinoma of the lower jaw in a female of the Experimental Colony. This invaded local tissues and was successfully transplanted into 2 animals. A 2nd was a fibroma of the serosa of the small intestine of a male from the same colony. The 3rd was a carcinoma of the salivary gland of a female from the Wistar Stock Colony.

Mediastinum: One male of the Experimental Colony developed a fibrosarcoma of the lower anterior mediastinal tissues and 1 female of the Wistar Stock Colony had a lymphoblastoma of this region. Extensive secondary growths were found in both animals.

Thymus: Neoplasms of this tissue developed in 3 animals. The tumors in 2 of the rats from the Experimental Colony were composed chiefly of epithelial elements of the thymic tissues, while

that of the 3rd animal was made up of small lymphoid cells. In each instance secondary growths developed in the lungs.

Other Lymphoid Tissues: Lymphosarcoma of the mesenteric lymph nodes developed in 1 male rat from each of the colonies.

Adrenal: A relatively large adenoma of cortical cells arranged as irregular cords and masses into which hemorrhages had occurred was found in a female of the Experimental Colony. This animal also had 2 other tumors.

Skeleton: Neoplasms of skeletal tissues developed in 6 animals. One of these arose at the costochondral junction, 2 involved the left femur arising near the distal end, and 1 the right femur. A 5th developed at the proximal end of the tibia, and the last involved the humerus. Only 1 of these tumors gave rise to a secondary growth, and this in the ovary. The gross characteristics and histological make-up of the growths permit their classification as osteogenic sarcoma.

The average age of animals that developed this form of neoplasm was 690 days and ages ranged from 490 to 870 days. The females were all over 800 days of age; the males were much younger, the average age being 560 days.

Mammary Glands: The mammary gland was a prolific source of tumors in animals of both strains, 77 per cent of all tumor-bearers having a growth at this site. In 207 tumor-bearing females from the Experimental Colony, this tissue produced 206 neoplasms. These developed in 187 animals, 19 of which bore 2 mammary tumors each. Of these growths, 203 were composed either of glandular and ductal epithelium, or of ductal epithelium alone, with variable amounts of fibrous tissue. Three of the growths, each occurring in separate hosts, did not contain epithelium; 2 were fibromas and 1 a lipoma.

The histological appearance of 13 tumors suggested malignancy, 11 of these being interpreted as carcinomas and 2 as sarcomas.

In 6 females of the Experimental Colony, tumors of the mammary gland were associated with growths in other organs. In 2 of these animals, 1 with 2 mammary tumors, fibromas of the uterine wall were found. The mammary tumor of the 3rd female was undergoing sarcomatous change and was accompanied by a carcinoma of the uterus. The 4th animal developed a carcinoma of the mammary gland, a fibrosarcoma of the subcutis, and a cortical

adenoma of the adrenal. In the 5th animal the accompanying tumor originated in the thymus. In the 6th there was an osteogenic sarcoma of the femur.

Thirteen males from the Experimental Colony also developed tumors of the mammary area of the subcutis. Five of these growths contained epithelium and were identical with the fibroepithelial tumors of female rats. Five others were similar to these grossly but on section proved to be fibromas. The remaining tumors were lipomas. In 2 males with fibroepithelial tumors of the mammary gland there were also malignant growths of other tissues. One had a sarcoma of the mediastinum and the other a sarcoma of the subcutis.

The females of the Wistar Stock Colony developed only single tumors of the mammary gland, all fibroepithelial except 1, a lipoma. The animal in which this last occurred also had a malignant tumor of the thymus. Histological make-up of 1 mammary tumor of this group suggested carcinoma. A lipoma was found in the mammary area of 1 male from the Wistar Stock Colony.

Thus, the great majority of tumors of the mammary glands of animals of both strains were the benign fibroepithelial growths which are known by a variety of names. For present purposes these have been called fibroadenoma.

In location these growths were distributed about equally among the right and left inguinal and axillary groups of mammae. In size, shape, consistence, color, rate of growth and histological appearance they differed widely. In size these tumors varied from multiple small nodules 1 to 2 mm. in diameter to large spheroid or discoid masses of 6 to 8 cm. Generally they were sharply outlined in the subcutis with or without the attached or adjacent mammary tissue being hyperplastic. Incision into the tumors usually exposed nodules or lobules of various size, consistence and color, more or less firmly embedded and irregularly spaced in a less dense tissue matrix. Occasional growths were uniformly firm and tough without definite subdivisions. Others were soft and spongy and often contained milk-like fluid in single or multiple cysts.

Although variation was considerable, the histological make-up of fibroadenomas from females of this series seemed to follow a basic pattern, the essential elements of which were variable amounts of ductal and acinar epithelium arranged into fairly defi-

nite lobules and distributed in stroma which also varied in amount, density and maturity. The amount of glandular tissue ranged from a few scattered hypoplastic ducts to well formed areas of apparently actively secreting acini. Usually the condition of the glandular tissue was fairly uniform throughout a tumor, but occasionally hypoplastic lobules lay adjacent to hyperplastic lobules. The extremes of variation in amounts of epithelium have been illustrated in Figures 1 and 2 which, for convenience, were taken from tumors that developed in male rats.

The microscopic appearance of fibroadenomas developing in the mammary glands of male rats did not differ essentially from that of the tumors found in females. Four of the 5 tumors contained only ductal epithelium enclosed in dense fibrous tissue. In the other tumor, both ducts and acini had formed (Figs. 1 and 2) and secretion was abundant.

The gross and microscopic features of the fibroadenomas from animals, each of which developed 2 of these tumors, differed from case to case. Often too, growths on a given animal were unequal in size and consistence, but with one exception each pair was similar histologically. Of the growths in this animal, 1 was an ordinary fibroadenoma while the other was an adenocarcinoma.

Fibroadenomas varied widely in their rate of growth. By measurements at 30 day intervals on 20 tumors, 11 of them were found to have increased from 2 to 10 times their original volume during a period of 90 days. The remainder were unchanged. As a rule tumors that were less than 2 cm. in diameter when the hosts were received grew most rapidly, but rate of growth did not seem to be correlated with the condition of the host or the histological make-up of the neoplasms. For example, 1 of the tumors that proved to be a carcinoma increased in average diameter from 1.5 to 2.7 cm., while 2 fibroadenomas grew from 2 to 4.5 cm. and 3.5 to 6.5 cm. respectively during the same period. The carcinoma developed in a rat 120 days of age.

Surgical removal of the major portion of the fibroadenomas, without disrupting the blood supply, did not cause appreciable change in 10 instances. The remnants of the tumors had not increased in size when the animals were killed 3 to 5 months after the operation.

Complete removal of the fibroadenomas from 10 rats also was

without result after 4 to 7 months, except in 1 animal. In this rat the mammary gland about the site of the original tumor underwent hyperplasia so that 30 days after the operation its outlines could be palpated. It remained in this condition for about 2 months, during which time a 2nd fibroadenoma developed in another group of mammary glands.

The malignant tumors of the mammary gland were recognized only by microscopic examination. All were taken to be fibroadenoma grossly. Secondary tumors were found only in 1 animal, and these in the lung. In the whole series of rats 12 carcinomas of the mammary gland were encountered. These seemed to be of two types. The first included 9 specimens. These have been classified as adenocarcinoma and, histologically, were characterized by dense masses of pseudoglandular tissue with relatively scanty but cellular stroma. All infiltrated adjacent structures and mammary tissue of the involved gland was hyperplastic (Fig. 3). One of this group of tumors developed in an animal that also had a fibrosarcoma of the subcutis and a cortical adenoma of the adrenal.

The second type was represented by 3 tumors from females of the Experimental Colony. In these growths the microscopic appearance suggested that a carcinoma had developed in a fibroadenoma, filling spaces formerly occupied by ducts and glands with masses or strands of cells. In 1 of these tumors glandular epithelium was undergoing squamous metaplasia (Fig. 4).

The 2 fibroadenomas in which sarcomas developed were not unusual otherwise. In both tumors portions apparently were being replaced by a richly cellular tissue composed of spindle cells arranged in irregular strands and whorls. One of the animals in which this occurred also had a carcinoma of the uterus.

Age Distribution of Mammary Tumors: The ages of the animals developing tumors of the mammary gland varied widely. Age distribution for both colonies is shown in Table III, cases being grouped into classes that increase throughout the range by an arbitrary interval of 90 days.

In the first column of this table mammary tumors in females of the Experimental Colony are arranged according to age groups. The ages ranged from 120 to 1020 days, and the frequency of tumors increased with age up to 720 days, approximately 80 per cent developing between 451 and 900 days. In the second column

of the table carcinomas of the mammary glands of females of this colony are arranged according to age. Seven of these occurred between the ages of 90 and 450 days; actually the youngest animal was 120 days of age, and 4 carcinomas developed between 631 and 810 days. In the third column mammary tumors of males of the Experimental Colony Strain are arranged according to age groups. In this series, as well as that shown in the fourth column,

TABLE III

Age Distribution at 90 Day Intervals in Rats Developing Tumors of the Mammary Gland

	Experimental Colony Strain			Wistar Stock Colony	
Age classes	All cases ♀	Carcinoma ♀	All cases ♂	All cases ♀	Carcinoma ♀
days					
91–180	1	1	..	..	..
181–270	4	2	1	1	..
271–360	11	2	..	..	..
361–450	20	2	..	1	..
451–540	21	..	..	5	..
541–630	21	..	4	2	..
631–720	44	2	5	3	1
721–810	31	2	2	2	..
811–900	27	..	1	3	..
901–990	6	..	..	2	..
991–1080	1	..	..	..	..
Total	187	11	13	19	1

mammary tumors of females of the Wistar Stock Colony, age distribution tends to parallel that in the first column which reproduces fairly well a normal curve.

Incidence of Tumors: The colonies of rats from which this material was drawn differ from the usual population groups in which incidence of neoplastic disease has been studied in that they are essentially breeding stocks. A variable fraction of their number is disposed of each year. These are of all ages.

From available records it is impossible to determine the average age of the colonies from year to year or the proportion of males to females. The census merely indicated the number of animals present at a given time.

For each year of this study the census, *i.e.* animals present at the end of the year, the numbers sold, dying and bearing tumors

during the year, and the incidence of neoplasms, both as a percentage of population and of deaths, has been given for each colony in Table IV. Colony population for each year is the sum of census, sales and deaths. Only the number of deaths and of tumor-bearers may be divided according to sex. Since all records, except number and sex of tumor-bearers, are available only by calendar years and the work was begun and ended in September,

TABLE IV

Census, Sales, Deaths, Tumor-Bearers and Incidence of Tumors as a Percentage of Population and of Deaths in Two Colonies of Rats of the Wistar Institute of Anatomy for a Period of Six Years *

Year	Census	Sales	Deaths ♀	Deaths ♂	Tumors ♀	Tumors ♂	Percentage incidence of tumors: Population	Percentage incidence of tumors: Deaths ♀	Percentage incidence of tumors: Deaths ♂
Experimental Colony Strain									
1	2579	2177	548	714	8	5	0.86	6.68	2.24
2	2789	1206	531	720	37	4	0.78	6.96	0.55
3	2316	1291	625	788	74	16	1.79	11.84	2.03
4	2124	1097	510	896	21	5	0.46	4.11	0.55
5	2479	666	682	760	28	4	0.69	4.10	0.52
6	1715	711	613	643	39	3	1.52	8.48	0.62
Wistar Stock Colony									
1	796	391	178	233	1	0	0.25	2.24	0.00
2	1040	286	240	331	9	0	0.47	3.75	0.00
3	626	74	297	421	8	1	0.64	2.69	0.23
4	290	9	204	198	5	2	0.99	2.45	1.01
5	258	50	105	147	1	1	0.36	0.95	0.67
6	178	2	81	111	0	1	0.37	0.00	0.90

* Incidence of tumors for the 1st and last years are estimated because the study was begun and ended in September. Under the column entitled "Tumors" is given the actual number of tumor-bearers.

Table IV was arranged to accommodate for this by dividing the totals according to calendar year and estimating the number of cases for the 1st and last years in terms of actual number of tumors obtained during the portion of the year covered by the study. These totals were used only to compute incidence. In the column "Tumors" is given the actual number of cases.

The census of both colonies, the sales and the tumor-bearers varied irregularly from year to year. At the same time the annual death rate also varied, from 20 to 35 per cent of the population in the Experimental Colony and from 25 to 51 per cent in the

Wistar Stock Colony. The incidence of neoplasms shows little relation to the death rate and, both as a percentage of population and of deaths, changed from year to year in the two colonies.

The proportion of tumor-bearers to total population of the Experimental Colony Strain was less than 1 per 100 during 4 of the 6 years and was never higher than 1.79 per cent. In animals of the Wistar Stock Colony the yearly incidence of tumors also was less than 1 per cent and except for 1 year was lower than in the other group.

When divided according to sex and expressed as a percentage of deaths (see last column, Table IV) the incidence of tumors was much higher in females of the Experimental Strain than in the other groups. Females of the Wistar Stock Colony were next in order of frequency, except for 1 year when no neoplasms were found, followed by males of the Experimental Strain. Males of the Wistar Stock Colony developed very few tumors but, for the last 3 years of the study, there were proportionately more cases among them than in males of the other group.

Using the estimated total number of tumor-bearers, since losses by death for the actual period of the study are not available, the incidence of neoplastic disease for all deaths in both colonies was 3.1 per cent; for all females 5.7 per cent, and for all males 1 per cent. Again using the estimated number of tumor-bearers, the ratio of neoplasms to deaths in the Experimental Colony was 6.7 per cent for females and 1.2 for males, and in the Wistar Stock Colony 2.4 per cent for females and 0.4 per cent for males.

With this material it must be remembered that animals were selected for examination by the personnel in charge of the colonies. Thus, growths of surface tissues should, as they do, predominate, and these percentages apply chiefly to external tumors.

As pointed out before, most of the surface growths (77 per cent) involved the mammary gland. The incidence of mammary tumors for all female deaths in the Experimental Colony was 5.4 per cent, and in the Wistar Colony 1.7 per cent. When taken for each of 4 yearly periods for which returns are complete, frequency of growths of the mammary gland varied from 3.9 to 11 per cent of deaths among females of the Experimental Colony, and from 0.95 to 2.5 per cent in the other group.

Malignant tumors of the mammary glands of females were

relatively uncommon. For the Experimental Colony the percentage of carcinomas was 0.31 and for fibroadenomas undergoing sarcomatous change 0.06. In the Wistar Colony 1 carcinoma occurred in 1105 female deaths.

Fibroepithelial tumors of the mammary glands of males were found only in animals of the Experimental Colony, there being 5 cases, or about 1 per 1000 deaths.

With the exception of the skin, subcutis, skeleton and genitourinary organs, all of which were the sites of relatively few neoplasms, records for other tissues probably do not represent completely their susceptibility. However, it should be noted that tumors of genital organs developed in approximately 0.6 per cent of female rats dying in the Experimental Strain, but did not occur in females of the Wistar Stock Colony.

Discussion

In considering the types of tumors found in rats of these two colonies, together with their frequency and location in the body, it must be emphasized again that all animals received for examination were selected by the personnel in charge of the colonies. Thus, in comparing these strains of rats with others, some degree of bias in favor of tumors of surface tissues must be taken into account. Perhaps very few growths developing in abdominal organs were missed because of the ease with which small abnormal masses may be palpated in this section of the body cavity of the rat. But very probably a high percentage of thoracic neoplasms was not detected.

Material drawn from each of the two colonies undoubtedly was subject equally to selection. Therefore, differences shown by the two strains in incidence of tumors generally, as well as in relative frequency of growths in the mammary glands and genital organs of females, may be of importance for those using these animals for experimental studies of neoplasms. Often rats obtained from the Wistar Institute for such investigations have not been assigned a definite colony origin in reports of the work.

On the whole, the incidence of neoplasms, expressed as percentages of deaths by sexes for the combined material, compares favorably with that given by Curtis, Bullock and Dunning [1] for a more extensive series of autopsies on rats which were derived

from several strains. But incidence of growths of the mammary gland in both sexes of the present series, as well as frequency of sarcoma of bone, was considerably higher than they reported.

Tumors of the mammary glands of rats, particularly fibroadenomas, have been studied for a considerable period.[2] As illustrated further by the present material, frequency of the spontaneous tumors varies widely in females of different strains, from less than 1 per cent up to 30 per cent or more having been reported.[3]

Prolonged subcutaneous injection of estrogenic substances,[4] as well as direct application of mixtures of ovarian and pituitary hormones to the mammary glands of rats,[5] has been found to increase the incidence of neoplasms of this tissue. And the pituitaries of male and female rats that carried spontaneous, induced or transplanted fibroadenomas have shown increased numbers of chromophobe and degranulated cells and decreased acidophilic cells.[6] Similar changes in the pituitaries, associated with irregularities of estrous cycles, have been reported in females of the Albany Strain of rats of which more than 30 per cent developed fibroadenomas.[3]

Unfortunately estrous cycles and endocrine glands were not studied in any of the animals of the present series, but in the pituitaries of females of the Experimental Colony Strain examined elsewhere abnormal cell ratios were reported in 15 of 26 animals.[7] In 2 rats chromophobe adenomas had developed. These animals were 632 days of age, about the center of the age groups in which fibroadenomas were most common in this strain, and this tumor occurred in 3 of them.

These abnormalities of the pituitary body correspond to those reported to be due to prolonged stimulation by estrogenic hormones.[8] Thus, available evidence supports the suggestion [3] that fibroadenomas and adenomas, and possibly other tumors of the mammary glands of female rats, are due to prolonged, recurrent abnormal stimulation of mammary tissue by ovarian and pituitary hormones.

Increased frequency of fibroadenoma, adenoma and carcinoma of the mammary glands of female rats (obtained from the Wistar Institute, but colony origin not stated) has been reported following forced breeding [9]; that is, breeding as frequently as possible without allowing young to be suckled. In this study, functional

activity of the mammary tissue and retained milk were stressed as factors in tumor growth.

The presence of milk within acini, ducts and cysts of fibroadenomas may be part of the response to internal secretion (pseudopregnancy). And, if it be granted that rapidly recurring pregnancies permitted more intense hormonal stimulation of mammary tissue than would have occurred normally, then the results of forced breeding are in keeping with other studies that have been discussed.

The mammary gland of the male rat normally develops an extensive system of ducts.[10] Opinions differ as to the source of the stimulus for growth of this tissue in the male, it being claimed that the testes do and also do not exert an influence, and that theelin is effective if the hypophysis be intact.[11, 12, 13]

Four of the fibroadenomas that developed in males of the Experimental Colony Strain may be regarded as fibromas in which normal mammary ducts were included as the tumors grew. Thus, these lesions would be essentially similar to simple fibrous tissue tumors of the mammary areas of males, 8 of which were found. But in the 1 remaining fibroadenoma, well developed glandular structures were formed and lactation had occurred.

If the testes have an influence in mammary development of rats, perhaps fibroadenomas of the mammary glands of males are analogous to gynecomastia in man, which develops when the testes undergo atrophy.[14] But if pituitary disorders be regarded as a factor in the development of fibroadenomas of female rats, it may be that there is a strain susceptibility to pituitary disfunction which could account for the appearances of these tumors in males, for although the mammary gland of the male rat does not respond to implantation of normal rat hypophyses,[15] it is stimulated to hyperplasia by extract of pituitaries of pregnant animals.[16] And as evidence that theelin is not a factor in the appearance of fibroadenomas of male rats, is the report that this substance does not prevent fibrosis of transplanted fibroadenoma in males or affect the rate of growth of the tumors.[17]

Summary

During a 5 year period, rats from two colonies of the Wistar Institute of Anatomy were submitted for examination whenever

spontaneous tumors were suspected, the animals being selected by the personnel in charge of the colonies.

Due probably to this means of selection a majority of the neoplasms were found to have developed in surface tissues, the mammary gland being the important focus. Much less prolific sources were other tissues of the skin and subcutis, various divisions of the genito-urinary system, and the skeleton.

Frequency of tumors in terms of deaths was approximately 3.1 per cent for all animals, and 5.7 for females and 1 per cent for males. Separated for the two colonies the percentages were 3.03 of one (6.7 per cent of females, and 1.2 per cent of males) and 1.1 (2.4 per cent of females and 0.4 per cent of males) of the other. The material has been analyzed to show age distribution and type of tumors for the colony groups.

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DESCRIPTION OF PLATE

PLATE 62

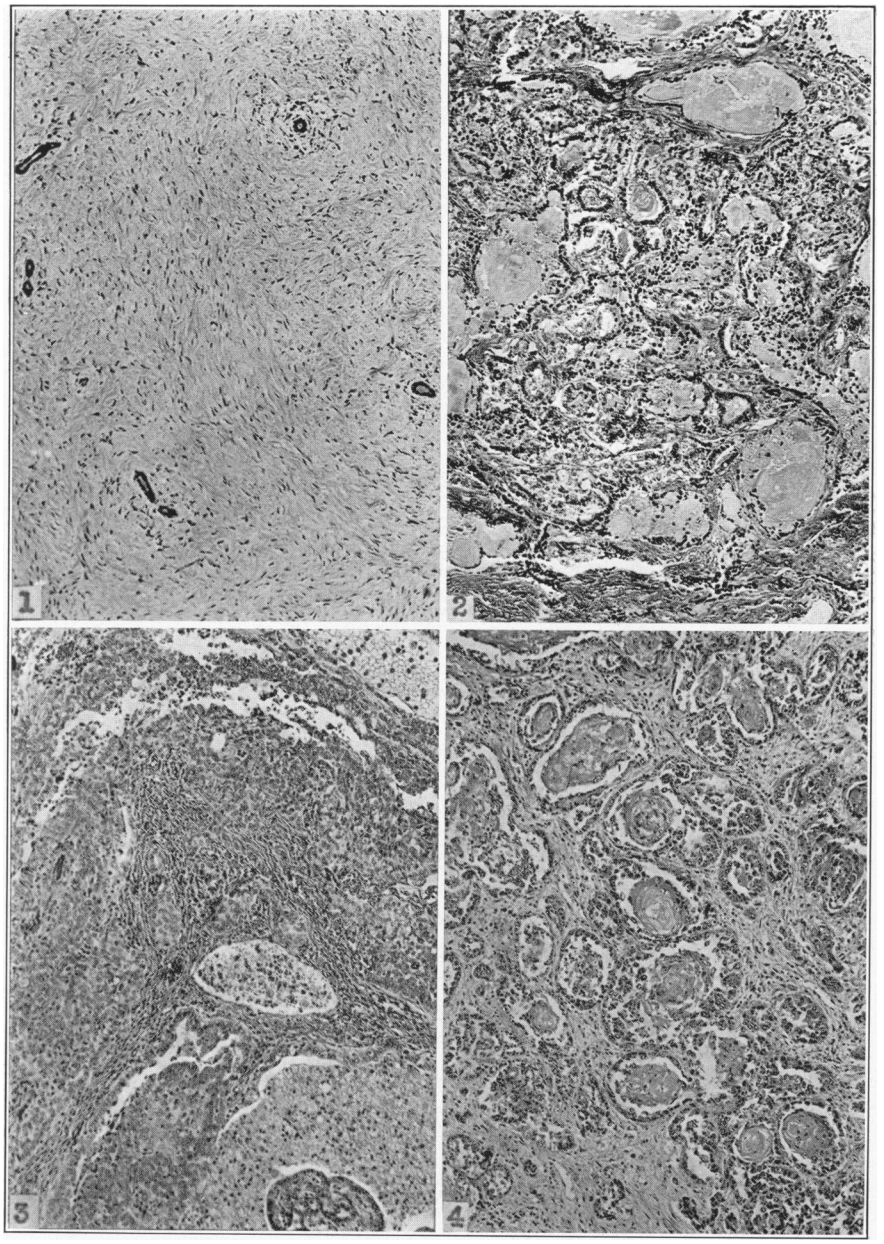
FIG. 1. Rat 855, ♂, 840 days. Fibroadenoma of mammary gland. Scattered ducts lined by cuboidal cells are enclosed in a dense stroma. × 90.

FIG. 2. Rat 749, ♂, 250 days. Fibroadenoma of mammary gland. A lobule of glandular tissue bordered by dense bands of fibrous tissue is composed of indistinctly formed acini and ducts, the latter distended with secretion. × 90.

Figures 1 and 2 represent the extremes in glandular tissue content in fibroadenomas of all animals of the series.

FIG. 3. Rat 535, ♀, 680 days. Carcinoma of mammary gland. × 90.

FIG. 4. Rat 578, ♀, 380 days. Mammary gland, the appearance of which suggests that squamous carcinoma had developed in a fibroadenoma. × 90.



Ratcliffe

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