perimental errors having a random distribution. To test this hypothesis the values of x^2/m (square of departures divided by expectations) were calculated and presented at the right of the table. Chi-square was 49.49, which with the degrees of freedom equal to 48 was found not to exceed what might have been expected from the foregoing assumptions ($\sqrt{2x^2} - \sqrt{2n-1} = 0.202$). It is even suggestive that the experimental error is unusually small; were it not for the values for the spleen the 2 series could be said to consist of a pattern of 2 highly correlated variables with a minimum of experimental error. The coefficient of correlation on the 2 distributions was $+0.922$ ($n = 46$, $P = 0.001-$, significant) and the regression line is linear. The only significant departure from the regression line is in the value for the spleen, in which more metastases were found among treated animals than was to have been expected. It is our belief that the original observations were not correct, and that the error occurred because animals receiving homologous material frequently had massive metastases involving the omentum and often the capsule of the spleen by extension. Such extensions probably should not be considered true metastases to the spleen. When they are eliminated, the data indicate the expected involvement for the spleen. Furthermore, when homologous material was administered to animals which were later inoculated intracutaneously in another series of experiments, no significant preponderance of splenic metastases was noted.

It is therefore concluded that injection of rabbits with an homologous material from the Brown-Pearce tumor does not affect the relative distribution of metastases following transplantation. The constancy and character of the relative distribution of metastases in this tumor is thus confirmed for the third time.[5, 6]

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Distribution of Metastases in the Brown-Pearce Tumor. IV. Effects of Site of Inoculation.*

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It has been shown that the distribution of metastatic foci in the

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Brown-Pearce tumor of the rabbit (a) is not disturbed by the breed of animal used for transplantation,[1] (b) has remained constant over a period of 15 years of transplantation,[2] and (c) is not affected by treating the animal with an homologous material.[3] All the inoculations in the 3 series were intratesticular and unilateral.

The present paper concerns the possible effect of intracutaneous inoculation upon this constant and characteristic distribution of metastases. To determine this effect a comparison was made of the distribution of metastatic foci in rabbits injected intracutaneously with the same distribution in rabbits injected intratesticularly.[3]

Observations were made upon 469 rabbits. Thirty-two rabbits 8 to 18 weeks old were injected intracutaneously over the right scapula, first with 0.3 cc of an homologous material, and 2 weeks later with 0.3 cc of a saline emulsion of Brown-Pearce tumor (Table I). Four hundred thirty-seven young adult rabbits were injected intratesticularly with 0.3 cc of a saline emulsion of Brown-Pearce tumor; 44 of this group also received homologous material.[3] An additional num-

TABLE I.
Metastases from Primary Tumor Growth in Skin Over Scapula in Rabbits Treated with an Homologous Tumor Material.

Site	Metastasis	Site	Metastasis
Extension	12	Skin	3
Interscapular space	8	L eye	4
R axillary node	13	R eye	5
L axillary "	2	Ant. portion thigh muscles	5
R inguinal "	3	Thyroid	1
L inguinal "	0	Mandible	7
R kidney	16	Teeth	3
L "	15	Muscles, thorax and abdomen	9
Lungs and pleura	10	Heart	2
Omentum and ligaments	2	Muscles of mastication	8
Liver	9	Femora	3
Intestine	5	Tibiæ	3
R adrenal	5	Spleen	2
L "	5	Diaphragm	3
Muscles of scapula	8	Pericardium	1
Retroperitoneal space	6	R spermatic cord	1
Bladder and pelvis	7	L " "	0
L perirenal area	7	Pancreas	1
R " "	5	Parathyroid	0
Serosa	6	Brain and dura	4
Stomach	3	Hypophysis	2
Superior mediastinum	5	Muscles of tongue	3
Posterior "	3	R testicle	2
Posterior cervical region	4	L "	1
Anterior " "	4	Spinal canal	1
Pericranium	1	L fallopian tube	1
Nose and nasal sinuses	3	Parietal peritoneum	1

[1] Casey, PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 223.
[2] Casey, PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 228.
[3] Casey, PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 230.

TABLE II.

Comparison of Metastatic Foci from Testicular and Intracutaneous Inoculation of the Brown-Pearce Tumor.

Site	Actual values		Expected Values			x^2/m		
	Testis	Skin	Testis	Skin	Total	Testis	Skin	Totals
Extension and Lymphatic Spread.								
Primary spermatic cord extension	169	1	159.86	10.14	170	—	—	8.86
Retroperitoneal tissues	178	6	173.03	10.97	184	—	—	2.48
Opposite spermatic cord	70	0	65.83	4.17	70	—	—	4.49
Parietal peritoneum	66	1	63.00	4.00	67	—	—	2.43
Omentum	123	2	117.55	7.45	125	—	—	4.32
Primary skin extension, right shoulder	0	12	11.28	.72	12	—	—	188.04
Right axillary nodes	45	13	54.54	3.46	58	—	—	27.57
Subtotals						14.34	223.85	238.19
						n = 6, P = 0.001—		
Hematogenous Spread.								
Kidneys	212	17	215.33	13.67	229	.05	.74	.79
Lungs	142	10	142.94	9.06	152	.01	.08	.09
Suprarenals	132	7	130.71	8.29	139	.01	.22	.23
Liver	105	9	107.20	6.80	114	.04	.66	.70
Eyes	61	6	63.00	4.00	67	.06	.94	1.00
Hypophysis	46	2	45.14	2.86	48	.02	.27	.29
Skin	41	3	41.38	2.62	44	.00	.05	.05
Heart	38	2	37.61	2.39	40	.00	.07	.07
Uninoculated testis	18	1	17.87	1.13	19	.00	.01	.01
Thyroid	17	1	16.93	1.07	18	.00	.01	.01
Parathyroids	15	0	14.11	0.89	15	.06	.89	.95
Spleen	18	2	18.81	1.19	20	.03	.53	.56
Brain	2	0	1.88	0.12	2	.00	.18	.18
Subtotals						0.38	4.65	4.93
						n = 13, P = 0.98		
Totals	1498	98	1498.00	95.00	1593			

ber of rabbits injected intracutaneously with the tumor alone are not included in this analysis because no visceral metastases were observed. (Table I.)

Many sites had too few metastatic foci for adequate statistical analysis and are therefore excluded from this comparison. The sites affected were arranged in 2 groups (Table II), according to whether spread seemed to have occurred by tissue spaces and lymphatic channels or was hematogenous. There were 7 sites in the former and 13 in the latter group. Both the actual and the expected values are presented, with their totals. To test the significance of the differences between actual and expected values, the figures x^2/m were calculated.[4] The method of calculating this value has been explained previously.[5] These values are summarized as subtotals for each group of sites.

In the group of sites in which spread seemed to have occurred by tissue spaces and lymphatic channels, the metastatic foci are predominantly concentrated near the sites of inoculation, and obviously differ according to whether inoculation was intracutaneous or intratesticular, as shown by the first subtotal values at the right of the table (chi-square = 238.19, n = 6, P = 0.00001–). This is in contrast with the results reported in the preceding papers in which the distribution of metastatic foci was constant in this group of sites when the same site of inoculation was employed.

In the group of sites in which metastasis seemed to have occurred by the hematogenous route, the actual and expected values for intratesticular and intracutaneous inoculations show so little variation that almost no experimental error need be assumed (chi-square = 4.93, n = 12, P = 0.98).† The coefficient of correlation calculated upon these variables was found to be +0.9716, a value having a linear regression line and indicating a high and significant relationship (n = 11, P = 0.001–).

It was therefore concluded (a) that the relative distribution of distant metastases in the Brown-Pearce tumor is constant and characteristic, follows a definite pattern, and is independent of the site of inoculation, and (b) that spread by tissue spaces and lymphatic channels is determined by the site of inoculation.

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[4] Fisher, *Statistical Methods for Research Workers*, 4th ed., Oliver & Boyd, London, 1932.

† While not all the categories have the recommended number of items, the value of P indicates so clearly a difference which is not significant, that this departure from the recommended minimum probably does not vitiate the conclusions.