

The symptoms of atonia, depression, diarrhea and dyspnea are readily induced by large doses of this extract.

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Effect of controlled conditions of illumination upon malignancy of transplantable neoplasm.

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Periodic variations in the malignancy of a transplantable neoplasm of the rabbit, which have been studied during the last four years, have been correlated with certain meteorological conditions and especially with the actual hours of sunshine. It has been found that periods of maximum and minimum sunlight corresponding with summer and winter were periods of relatively low malignancy; while the periods of greatest malignancy occurred at times of abrupt and rapid changes in the hours of sunshine corresponding roughly with spring and autumn.^{1, 2} The influence of these factors has been interpreted as operating upon or affecting animal economy, while susceptibility or resistance to disease is considered as a function of the animal organism. This conception is supported by analogous variations in experimental syphilis of the rabbit, and the observation that in normal rabbits rhythmic changes in the mass relationship of practically all organs of the body have been found which have a definite relationship to seasonal changes and prevailing meteorological conditions.³ While a variety of factors are probably involved in the production of these fluctuations, there appears to be a close relationship with sunlight and, in particular, first with the amount

¹ Brown, W. H., Pearce, L., and Van Allen, C. M., *PROC. SOC. EXP. BIOL. AND MED.*, 1924, xxi, 371.

² Brown, W. H., Pearce, L., and Van Allen, C. M., *Tr. A. Am. Phys.*, 1924, xxxix, 466.

³ Brown, W. H., Pearce, L., and Van Allen, C. M., *PROC. SOC. EXP. BIOL. AND MED.*, 1924, xxi, 373.

of sunlight as represented by the actual hours of sunshine and, second, with the rate and extent of change in the curve of sunshine. Furthermore, it is of considerable interest that these biological variations take place in the usual animal room with its illumination determined, in the first instance, by prevailing weather conditions and, in the second, by the interposition of window glass through which passes all or most of the sunlight.

In order to test this conception of the relationship between sunlight, and the physical state and functional activities of the animal, experiments were undertaken in which conditions of illumination could be controlled. The particular points studied in our first experiments were the effects induced by a constant illumination of the maximum intensity practicable with simple equipment, and a constant absence of illumination for stated periods of time upon the normal rabbit and upon the course of the disease produced by the malignant tumor. These conditions were controlled in each instance by parallel series of rabbits kept in an ordinary animal room. The investigation has yielded some striking results, and those obtained in the case of the tumor are briefly summarized in the present report.

Experimental: A constant source of light was furnished by twelve 1,000 watt Mazda lamps and three Cooper-Hewitt 50 inch low pressure mercury arcs, Type P, in crown glass, installed in a room measuring 19 x 9.5 x 10.25 feet or 1850 cubic feet, and from which all other light was excluded. It was realized that the quantity and quality of light employed differed in many respects from the diffused light of the laboratory. However, our main object was the maintenance of a constant source of maximum illumination together with the exclusion of the shorter ultra-violet rays such as are filtered out by ordinary glass. The spectrogram of the Cooper-Hewitt mercury arc shows that the crown glass absorbs all light below a wave length of 3022-28 Augström units, while the light of the Mazda lamps is cut off at about 3,100 Augström units. Three superimposed horizontal rows, $2\frac{1}{2}$ feet apart, each consisting of four Mazda lamps and one mercury arc, were arranged in the center of the room, $3\frac{1}{4}$ feet equidistant from the animal cages placed on either side. It was determined that the intensity of light reaching the cages averaged 425 foot-candles. Ventilation and the maintenance of a satisfactory temperature level were obtained by an electric fan intake of outside air.

A second room was arranged so that all light was constantly excluded except during the time the animals were fed or examined, when a single 30 watt Mazda lamp was employed. This light was not used for more than one hour per day. A third group of rabbits, as controls, was kept in an unaltered animal room which has a southern exposure and is lighted by two large windows. Recording thermometers were installed in each of the three rooms, and recording barometers in the light and control rooms.

The animals employed were male rabbits approximately one year old, and were carefully matched as to breed. They were kept in individual cages and fed the standard diet of oats, hay, and cabbage. Ten rabbits were placed in each of the three rooms on January 16, 1925 where they remained for the duration of the experiment. On February 16th, one month after they had been under the condition of constant illumination, constant darkness, or the variable diffuse sunlight of the laboratory, each rabbit was inoculated in the right testicle with the tumor. The experiment was terminated on April 15th, two months after inoculation, at which time all surviving animals were killed by an injection of air into the marginal ear vein. Detailed records of frequent clinical examinations were kept, and a complete post-mortem examination was made in each instance, special attention being directed to the presence or absence of metastases, the number and distribution of metastases together with an estimation of organ involvement and the state of the growth.

Results: The results of the experiment have been analyzed, as described in previous papers,^{4, 5} upon a basis of (1) the general course of the disease including the type of growth of the primary tumor, the appearance of metastases detected clinically, the physical state of the animal and the mortality rate, and (2) the incidence of metastases and the number, distribution, and state of these growths as found at autopsy. In this report, certain of the outstanding differences in the behavior of the tumor in the three groups of animals will be briefly summarized.

The malignancy of the disease in the control group was on a comparatively high level. The primary tumor grew rapidly and extensively during the first three weeks, after which time regres-

⁴ Pearce, L., and Brown, W. H., *J. Exp. Med.*, 1923, xxxviii, 347.

⁵ Brown, W. H., Pearce, L., and Van Allen, C. M., *J. Exp. Med.*, 1924, xl, 583.

sion took place in the 5 rabbits which survived to the end of the experiment, and in 3 of these complete absorption with healing occurred; in the 4 rabbits dying from the tumor, the primary growth was largely living. Ten superficial metastases were detected clinically in 4 animals. There was one death from an intercurrent infection, but the mortality rate for the series due to the tumor was 44 per cent, 4 rabbits succumbing four to five weeks after inoculation. The animal incidence of metastases as found at autopsy was 56 per cent, and there was a total of 73 metastatic foci in the entire group distributed as follows: 27, 15, 14, 13, and 4; while no metastases were found in four rabbits.

A definitely less malignant disease developed in the rabbits in the dark room. The group almost immediately became divided in two parts: In 3 rabbits the primary tumor grew very rapidly, and these were the animals which succumbed to the disease $3\frac{1}{2}$ and 4 weeks after inoculation. In 7 animals the primary tumor grew more slowly, and ultimately regressed. In 4 rabbits, 7 metastases were found clinically, while the mortality rate of the group was 30 per cent. The animal incidence of metastases was 40 per cent, with a total of 65 foci of secondary growths distributed as follows: 25, 23, 16, 1; and none in six rabbits.

In the light room, however, the malignancy of the disease dropped to a very low level. The initial growth of the primary tumor in the majority of the animals was unusually rapid and extensive, but in 9 rabbits it eventually became entirely necrotic or was completely healed. In addition, 6 metastases were found clinically in only 2 animals. In one of them the metastatic growth in the iris of both eyes became completely healed—an unusual occurrence; while in the second rabbit there were 4 superficial lymph node metastases which developed later than is ordinarily seen, and $6\frac{1}{2}$ weeks after inoculation the animal was killed because of a slowly developing cachexia, partial paralysis of the hind quarters, and the occurrence of convulsions. The mortality rate was only 10 per cent, as contrasted with 30 per cent in the dark and 56 per cent in the control groups. Postmortem examination showed that in 5 animals there were 24 foci of metastases distributed as follows: 19, 2, 3, with 1 each, and none in 5 rabbits, but in the animal with two, and in one of those with one metastasis, these growths were small and entirely necrotic. It is certain that none of the surviving 9 rabbits would have died from the effects of the tumor.

Conclusions: It is evident that under the conditions of the experiment the establishment of practically constant darkness produced a slight but definite influence upon the course and malignancy of this tumor so that those animals which possessed a high resistance to the tumor, either natural or acquired, were enabled to exercise this effect more efficaciously. But such an influence was not sufficient to enable less resistant animals to cope successfully with the disease. On the other hand, with the conditions of constant light, even without the short ultra-violet rays to which marked physiological effects have been ascribed, the disease assumed an extremely mild form—only one animal in the group dying from its effects, and this occurred later than the 3 deaths in the dark group or the 4 among the control rabbits. It would appear, therefore, that in this environment of artificial light a restraining or inhibitory action upon this disease was developed.

The results of this experiment furnish confirmatory evidence to the conception already referred to that there is a correlation or relationship between the light environment surrounding the rabbit and the course and malignancy of this neoplasm. We interpret these effects of controlled conditions of illumination as being developed and exercised through the operation of the factors of resistance of the host which were evidently more potent or efficacious than was the case under the controlled conditions of the diffuse sunlight of the laboratory.

Finally, it may be mentioned that no demonstrable ill effects of a general nature developed in the tumor animals of this experiment or in a large number of normal rabbits caged in the same rooms. Very definite changes, however, occurred in the mass relationships of various organs of the normal rabbit, and these will be presented in a subsequent communication.