excess strengthening of 7½ per hundred. Punished connections two steps and 5 or more seconds away from a rewarded connection are influenced favorably by it.[3]

The proof that a satisfying after-effect strengthens directly the connection producing it, and also other connections in close proximity to it, is important, because it explains selective modifiability. It solves many problems for which the forces of frequency, recency and intensity are inadequate. It accounts for the true contentions of purposivism without recourse to mystical agencies.

The physiological explanation of the influence of a satisfying after-effect is as yet unknown, just as the physiological explanation of the influence of mere repetition of a connection is unknown. But we can now proceed to find out facts about the former which may lead us to a physiological explanation of it, and which are valuable in any case.

Thus, Dr. Rock has measured the effect of differences in the intensity of the reward. I have measured, though as yet very imperfectly, the effect of differences in the time-interval between the connection and its reward. I have measured the effect of differences in the relevance of the reward. Dr. Lorge is proceeding to measure the influence of an occurrence that is neither rewarded nor punished, so that we may compare the strengthening by it with the strengthening by various after-effects.

I can already frame a physiological explanation which demands little more from the nervous system than any doctrine of facilitation demands. And I venture to prophesy that the physiology of strengthening by the after-effects of a connection will be understood sooner than the physiology of strengthening by its sheer repetition.

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IS MALIGNANCY DUE TO A PROCESS ANALOGOUS TO SOMATIC MUTATION?

MALIGNANT tumors develop in the walls of parasitic cysts of *Cysticercus fasciolaris,* the larval stage of *Taenia taeniaeformis* (*crassicollis*), the common tapeworm of the cat. Tumors have been produced experimentally by feeding rats *Taenia* eggs derived from cat feces. The shells of these eggs are digested off in the rat's intestine, and the oncospheres attach themselves to the wall of the intestine, work their way into the blood vessels of the gut wall and are carried to the liver by the portal circulation. They are strained out in the liver capillaries and grow rapidly forming clear vesicles, which about the seventh day become visible to the unaided eye.

At this stage some of the larvae have been transplanted to the subcutaneous tissues of other rats, but for the most part they have been allowed to continue their development in the liver. In either locality the growing larvae initiate considerable proliferative activity in the surrounding tissues which results in the formation of fibrous cyst walls. After from 8 to 27 months the cells of these cysts may show active and often atypical proliferation and may undergo malignant changes.

Most of the tumors produced have been polymorphous cell sarcomata, spindle cell sarcomata or a mixture of the two. The rarer tumors were of the following types: fibroma, chondroma, osteochondroma, chondrosarcoma, osteochondrosarcoma, fibrosarcoma, liposarcoma, adenoma and carcino-osteochondrosarcoma.

At the beginning of the present analysis (June, 1932) 52,223 rats from completed pedigreed matings had been autopsied. Of these 26,172 were infested with the parasite, 13,120 had survived the infestation for at least eight months (the minimum period of infestation observed in the case of a bearer of a *Cysticercus* sarcoma) and 3,285 had *Cysticercus* sarcoma. Besides these, 68 purchased animals and 316 of the unpedigreed descendants of purchased animals had the malignant complication of the *Cysticercus* disease.

Taenia eggs from cats obtained from various parts of the city and suburbs and others infested in the laboratory were equally effective in producing the disease and the associated malignant tumor, but rats showed marked strain and family differences in the proportion of individuals which developed both the disease and the complication.

Early in the experiments it was noted that the duration of the irritation (that is, the residence of the parasite in the liver) before the appearance of the malignant phase of the *Cysticercus* disease varied over a period of 19 months, which is half the maximum life span of our laboratory rats. Furthermore, the proportion of tumor bearers increased directly from the eighth to the twentieth month of infestation. It was also noted that usually only one cyst and in some of the early tumors only a small area of the cyst wall showed the malignant transformation, although the host might have had one to one hundred other cysts which were benign. Occasionally two or more apparently independent *Cysticercus* tumors occurred in the same host.

The clue to the explanation of the strain and family differences and to the variations in the duration of infestation appeared in the present analysis, when it was observed that in the 3,669 bearers of

[3] The detailed results for all the experiments will be published at an early date.

Cysticercus sarcoma there was a significant negative correlation ($-.527 \pm .008$) between the number of cysts in the liver and the duration of infestation with the parasite. It follows that if the bearers of *Cysticercus* sarcoma are distributed according to the number of parasitic cysts, a general decrease in the duration of infestation is observed with each successive increase in the number of cysts. Also the mean age at autopsy of these tumor bearers is parallel to the duration of infestation and in each case exceeds it by approximately two months, the average age at which the rats were infested. For each number of cysts the mean duration of infestation and mean age are slightly higher for females than for males, but in many cases the differences are not statistically significant. The essential factor is the duration of the irritation and not the actual age of the rat. This is shown when the tumor bearers are classified according to the age at which they were infested, for the mean age at autopsy rises proportionately with the age at which they were fed *Taenia* eggs; but the duration of infestation remains constant instead of decreasing directly with the age fed, as would be expected if age were the important factor. The mean duration of infestation not only became shorter but also became less variable with the increase in the number of *Cysticercus* cysts. This is shown by a gradual decrease in the standard deviations of the duration of infestation.

If the frequencies of rats infested with successive numbers of cysts are cut off at the mean period of infestation for tumor hosts with the corresponding numbers of cysts, and the percentage of tumor bearers among these is calculated, it is observed that the proportion of tumor bearers increases almost directly from 31.5 per cent. of the individuals with one cyst to 85.7 per cent. of those with 50 cysts. Above 50 cysts the number of rats in each group is small, since such large numbers of parasites are detrimental to the host. Nevertheless, in general the proportion of tumor bearers continues to increase with increase in numbers of cysts, and in several cases reaches 100 per cent. of the survivors of the *minimum* period of infestation. The males show a tendency to a slightly higher percentage of tumor bearers than the females, but in most cases the difference is not statistically significant.

If the different strains are considered separately, it appears that they all show the same general tendency to an increase in proportion of tumors with an increase in the numbers of parasites, but in some the increase is more rapid than in others. Furthermore, if in each strain the number of infested rats which reached the mean period of infestation for tumor bearers with the corresponding number of cysts is summed for the successive numbers of cysts, and the percentage of these which were tumor bearers is calculated, a marked difference is observed between certain strains. It can be demonstrated that this difference is determined by two factors, relative longevity and susceptibility to *Cysticercus* disease. That is, those strains which show a low proportion of tumor bearers show a low average length of life and a marked resistance to the *Cysticercus* disease, while the strains with a high proportion of tumor bearers show either a long average life span or a high degree of susceptibility to the disease.

Since an increase in the number of cysts, that is, an increase in the surface exposed to the irritant, decreases directly the time interval necessary for the onset of the malignant process and increases directly the probability of its occurrence until it becomes inevitable, it is apparent that *chance* is an important factor in the change of a normal to a *cancer* cell. Further, in the case of *Cysticercus* sarcoma hereditary factors influence the occurrence of malignancy only as they influence susceptibility of the individual to *Cysticercus* disease and longevity. Possibly when more is known about the etiology of other tumors for which there appears to be an inherited susceptibility and when the expression of genetic factors in the cells and tissues is better understood, it will be found that in the case of all neoplasms in all species the initial cell change occurs by a process analogous to somatic mutation and that hereditary factors determine this change only in so far as they influence longevity and the susceptibility of an individual to some specific irritant or condition which is favorable to mutation.

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