THE EFFECTIVENESS OF OVARIAN AND HYPOPHYSIAL GRAFTS IN THE PRODUCTION OF MAMMARY CARCINOMA IN MICE[1]

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Two methods are available for the determination of the effects of internal secretions: (1) A diminution or elimination of the function of the organ in which certain hormones are produced should lead to a quantitatively corresponding diminution in the structural or functional effects of these hormones. (2) An increase in the quantity of the hormones should be followed by an increase in their effects. By a quantitatively graded diminution of the time during which the ovaries gave off hormones which stimulate the activities of the mammary gland, it was first shown that there exists a quantitative relation between the origin of mammary carcinoma in mice and the cancerigenic action of ovarian hormones on the mammary gland in mice.[2] This represented also the first demonstration that hormones may cause the development of cancer and that substances normally produced in the body in the usual quantity may be responsible for the initiation of cancer; it was pointed out that presumably also other hormones may have cancerigenic effects in the organs and tissues on which they act specifically and that it appears probable that with the cooperation of hereditary conditions all those internal secretions, which initiate or sustain continuous or periodic growth processes, are factors in the origin of cancer.[3] The hormones interact with genetic-hereditary (constitutional) factors in a quantitative manner approximately in accordance with the equation S (hormonal stimulation) $\times$ H (hereditary-genetic factors) = C (Cancer).[2] This equation applies also to other types of cancer, and a similar equation applies even to other biological phenomena. More recently it has been shown by Bittner[4] that in addition to these two factors a substance present in the milk, as well as in certain organs of the mother and transmitted to the sucking child, may play a part in the origin of mammary carcinoma, although not of cancer in general. It seems probable that this factor acts in a way similar to that in which genetic factors act, namely, by determining the degree of responsiveness (sensitization) of the tissues to the stimulation by ovarian hormones.

After the proof had thus been given by means of the first method that endogenous hormones may cause the development of cancer, the attempt was made to supplement this proof by increasing the incidence of mammary cancer and accelerating the time of its appearance by increasing the quantity of ovarian hormones in accordance with the second method. This was first attempted by the transplantation of ovaries from sisters to castrated brothers in as yet incompletely inbred strains of mice. These first attempts failed, probably because an insufficient similarity between the individuality differentials of host and donor of the transplants prevented a satisfactory functioning of the grafts.[5] In subsequent similar experiments in a more closely inbred strain Murray was able to observe the formation of mammary tumors in about 7 per cent. of castrated male mice;[6] and more recently de Jongh and Korteweg[7] obtained positive results in a higher percentage of animals. Development of mammary tumors in male mice was induced also by Lacassagne by means of injections of very large doses of estrogen over long periods of time.[8] Several years ago it could be shown moreover that implantation of anterior lobes of the hypophysis into virgin females of strain A, which had been closely inbred by L. C. Strong, raised the incidence of mammary carcinoma in these mice to approximately 42 per cent. from about 4 per cent. in controls, while in low mammary tumor rate strains merely increased proliferative and secretory processes in the mammary gland could be obtained. However, positive effects of the anterior pituitary grafts were noted only if ovaries were present in the hosts; in ovariectomized females and in males the results were negative.[9]

We now wish to report on new experiments on 427 mice, which had received transplants of ovaries or anterior pituitaries or a combination of both, as well as on the findings in 504 control mice which had not

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[2] A. E. C. Lathrop and Leo Loeb, *Jour. Cancer Res.*, 1: 1, 1916; L. Loeb, *Jour. Med. Res.*, 40: 477, 1919; SCIENCE, 43: 293, 1916; *Am. Jour. Med. Sciences*, 19: 781, 1920; *Jour. Cancer Res.*, 2: 135, 1917; 8: 274, 1924; *Report Internat. Conference on Cancer, London*, p. 84, 1928; C. F. Cori, *Jour. Exp. Med.*, 45: 983, 1927; L. Loeb, *Acta Union Internat. Contre Cancer*, 2: 148, 1937; *Jour. Nat. Cancer Inst.*, 1: 169, 1940.

[3] L. Loeb, SCIENCE, 42: 912, 1915.

[4] J. J. Bittner, SCIENCE, 84: 162, 1936; *Am. Jour. Cancer*, 30: 530, 1937.

[5] L. Loeb, *Jour. Med. Res.*, 40: 477, 1919.

[6] William Murray, *Jour. Cancer Res.*, 12: 8, 1928.

[7] L. E. de Jongh u. R. Korteweg, *Act. Brev. Neerland.*, 5: 126, 1935.

[8] A. Lacassagne, *C. R. Acad. d. Sci.*, 195: 630, 1932.

[9] L. Loeb and Marian Moskop Kirtz, *Am. Jour. Cancer*, 36: 56, 1939.

received transplants of ovaries or lobes of the hypophysis. The organs and grafts were examined microscopically partly by means of serial sections. Usually from two to four anterior pituitaries or ovaries or a combination of both these organs were transplanted into each of the 427 mice. Somewhat more than one half of these experiments were carried out in strain A mice which are most suitable for investigations in transplantation; the remaining mice belonged to the high tumor rate strains C3H and D, to the medium tumor rate strain New Buffalo and to the low tumor rate strains C57, CBA, Old Buffalo and AKA. Some of the earlier experiments are included in this report. It may be stated that in male mice mammary gland carcinoma hardly ever occurs spontaneously in any strain, nor was mammary gland carcinoma observed in the strain A virgin females which served as controls.

Our principal observations and conclusions are as follows: (1) After transplantation of ovaries into castrated male mice the cancer rate and proliferative as well as secretory activities of the mammary gland were greater than after transplantation of these organs into normal female mice. Transplantation of ovaries into normal female mice led to the development of tumors only in strains C3H and D in which the mammary gland is most strongly sensitized to stimulation by hormones; negative results were obtained with our strain A mice which are less strongly sensitized. (2) Transplantation of anterior pituitaries, obtained in the majority of experiments from brothers or sisters, into normal female mice is at least as effective as transplantations of ovaries into castrated male mice; it is much more effective than transplantation of ovaries into normal female mice. (3) Transplantation of a combination of ovaries and anterior pituitaries into normal female mice is as effective as transplantation of anterior pituitaries alone into the same kind of hosts, or it may perhaps be somewhat more effective. These combined transplants were very active in castrated male mice in strain A in which they produced a cancer rate of 92 per cent. (4) In low tumor rate strains these various kinds of grafts, which in high tumor rate strains caused the development of cancer, induced merely an increase in proliferative processes, often associated with secretory activities in the mammary gland. (5) The greatest intensity of cancer development, and as a rule also of preparatory activities of the mammary gland, was obtained only in mice which belonged to the highest weight classes in conformity with our earlier observations.[10] There existed a certain parallelism between the weight of the mice and the effectiveness of these hormones. (6) By means of a single transplantation of glands, which produce mammary gland-stimulating hormones, as marked a development of mammary cancer in castrated male mice may be initiated, without otherwise pathological effects being noticeable, as by injections of very large amounts of estrogen continued over long periods of time. A mammary cancer rate in castrated male mice may thus be obtained which far exceeds the cancer rate of normal virgin female mice. (7) After transplantation of anterior pituitaries into ovariectomized mice, growth response and tumor formation in the mammary gland were either diminished or entirely prevented. Likewise transplantation of ovaries alone or together with pituitaries into normal male mice did not stimulate the growth of the mammary gland nor cause formation of mammary carcinoma. The anterior hypophysis transplants seem to exert their effects on the mammary gland by way of the ovaries which, under the influence of this additional stimulus, in all probability produce larger amounts of estrogenic hormones than they would otherwise do. Ovariectomy has therefore an effect which greatly differs from that of castration in male mice, which latter enhances the cancerigenic action of ovarian transplants. (8) The development of cancer was observed in these experiments as a rule only after the transplants had been active in the host for a period of about from 6 to 7 months to 12 months, so that the age of the mice at the time of examination ranged approximately between 9 and 14 months. If the examination of the organs took place earlier, the proliferative activities in the mammary gland, often coupled with secretory processes, had not as yet progressed to cancer formation; the latter represents the last stage reached after the tissue has passed through the preliminary or preparatory growth processes in which sensitization of growth stimuli may take place. It has been suggested that at the end of this period an autocatalytically propagating growth substance has developed in the cells as the result of the preceding long-continued stimulation, a substance which would thus be directly responsible for the ensuing cancerous growth.[11] The facts established in the present investigation are in harmony with this interpretation. Within the last twenty-five years a number of investigators have carried out experiments concerning the action of ovarian and pituitary hormones on growth and secretion in the mammary gland.[12] While in some respects the results

[10] L. Loeb, V. Suntzeff, H. T. Blumenthal and M. Moskop Kirtz, *Arch. Path.*, 33: 845, 1942.

[11] L. Loeb, SCIENCE, 43: 293, 1916.

[12] C. R. Moore, SCIENCE, 52: 179, 1920; *Jour. Exp. Zool.*, 33: 129, 1921; C. R. Moore and D. Price, *Am. Jour. Anat.*, 50: 13, 1932; A. Lipschütz and collaborators, *Pflüger's Arch.*, 211: 206, 305 and 697, 1926; E. T. Engle, *Proc. Soc. Exp. Biol. and Med.*, 25: 83, 1927–28; 25: 715, 1927–28; G. K. Smelser, *Physiol. Zoology*, 6: 396, 1933; W. U. Gardner, *Endocrinology*, 19: 656, 1935; C. E. Lane, *Am. Jour. Physiol.*, 110: 681, 1935; A. A. Lewis and C.

obtained in these various investigations appear contradictory to one another, on the whole the conclusions of the majority of these investigations agree with our observations concerning the processes taking place during the preliminary growth period. (9) There are two principal conditions which inhibit or prevent the development of mammary cancer by ovarian or anterior pituitary transplants: (a) The genetic constitution of the animals or a deficiency in the amount of available milk factor may cause an insufficient degree of sensitization and responsiveness of the mammary gland tissue to the specific hormones (Strains C57, CBA and Old Buffalo). (b) Lack of a sufficient similarity between the individuality differentials in host and donor of the transplants may prevent the survival and function of the grafts for sufficiently long periods of time (strains AKA and also New Buffalo). As pointed out previously, even long-continued close inbreeding of strains of animals does not seem to lead to a completely homozygous condition, owing probably to mutations which occur in these inbred individuals[13] and this applies also to all the closely inbred strains of mice so far tested by us. (10) It has been shown that not only ovarian hormones but also pituitary hormones may be involved in the development of mammary carcinoma in mice and presumably also in other species, in accordance with the conclusion that all those hormones or other factors which stimulate growth processes in an organ or tissue may thereby also affect the production of cancer.

THE CONTRIBUTION OF JAMES McKEEN CATTELL TO AMERICAN ANTHROPOLOGY

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PROFESSOR JAMES MCKEEN CATTELL died on January 20, 1944. He was widely known as a psychologist and editor of scientific journals, but his contribution to the development of anthropology in the United States seems to have been forgotten. That he played an important role in the history of anthropological teaching may be suspected when we note that for the academic years 1896–1902 he was head of a department of anthropology and psychology at Columbia University. To most anthropologists of the present generation, this may appear as a surprising statement, so, as an outline of the history of anthropology at Columbia University, we submit the following chronological data:

1891. J. McKeen Cattell appointed professor of psychology at Columbia; previous position in University of Pennsylvania.
1893. Livingston Farrand appointed instructor in psychology at Columbia; began giving a course in anthropology also.
1896. Cattell listed as head of the department of anthropology and psychology; Farrand still giving anthropology courses and Franz Boas listed as lecturer.
1901. Farrand listed as professor of psychology, but continues to give courses in anthropology.
1902. Anthropology listed as a separate department, Boas as head, Farrand as a professor of anthropology. Cattell now head of department of psychology.

The interest of Cattell is clearly indicated; he wished to provide for the teaching of anthropology, encouraged Farrand to give courses, later brought Boas into the picture and at the opportune time saw to it that a separate department of anthropology was created. Boas came to New York in 1895 as assistant curator at the American Museum of Natural History under F. W. Putnam; Cattell added Boas to his staff in 1896. Cattell seems to have been acquainted with Boas at Clark University through the work of the latter on the growth of children. Cattell studied with Galton and Pearson in England, where he acquired a deep and lasting interest in anthropometry, so it is to be expected that Boas would come to his notice when he began to write on anthropometry in 1891. It is plain, however, that Cattell was committed to the promotion of anthropology before Boas came into the New York picture.

At Columbia the writer was assistant in psychology, 1899–1900; university fellow in psychology, 1900–1901; assistant and eventually lecturer in anthropology, 1903–1909. These facts are cited to indicate his personal contact with the situation beginning with 1899.

The writer first saw Cattell at a meeting of the American Association for the Advancement of Science in the summer of 1899 at Columbus, Ohio. He participated in the program of Section H, with other psychologists, demonstrating a few testing instruments. incidentally he made a direct appeal to anthropologists to make measurements on Indians and Negroes to secure comparative data. F. W. Putnam was present, speaking enthusiastically in support of the idea. It was clear that a mutual feeling existed in the minds

W. Turner, *Mo. Agr. Exp. Sta. Research Bull.*, No. 310, 1939; A. A. Lewis, C. W. Turner and E. T. Gomez, *Endocrinology*, 24: 157, 1939; J. P. Mixner and C. W. Turner, *Endocrinology*, 30: 591, 1942.

[13] L. Loeb, H. D. King and H. T. Blumenthal, *Biol. Bull.*, 84: 1, 1943.