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## HISTORY OF SCIENCE

### CONTRIBUTIONS OF PIERRE PAUL BROCA TO CANCER GENETICS

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Pierre P. Broca was born in a small town near Bordeaux, France, June 28, 1824, the son of a Huguenot physician. After graduation from a local college, he entered medical school at the University of Paris at the age of 17, was graduated in three years. Five years later he received the M.D. degree, having special interests in pathology, anatomy, and surgery. In 1853 he was appointed assistant professor at the Faculty of Medicine and surgeon of the "Central Bureau." Broca made significant scientific and clinical contributions in all of the above fields as well as in anthropology. He founded the Anthropological Society in France.

In 1866 Broca published an outstanding two-volume treatise entitled *Traité des Tumeurs*. Although he did not use the word "metastasis," Broca distinguished between primary and secondary cancers. He noted the disparity in the sites of these two kinds of cancer in humans. Using his wife's family as an example, Broca noted that a daughter may be born long before her mother and maternal grandmother develop breast cancer, the daughter to develop it, herself, many years later. This was his proof that cancer is hereditary, present in a latent state until it appears later in life and progresses in a "malignant" fashion.

Broca was a diligent worker and took on many responsibilities both in his field of medicine and in politics. He died of a heart attack on July 8, 1880, at the age of 56.

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#### BIOGRAPHY

Pierre Paul Broca was born in Sainte Foy-la-Grande near Bordeaux, France, on June 28, 1824, the son of a Huguenot physician, Benjamin Broca (Fig. 1). His mother was the daughter of a Protestant minister. After receiving a Bachelor of Letters degree in mathematics and physical sciences at a local college, he was admitted to the University of Paris medical school in 1841 at the age of 17. He became an externe in 1843, an interne in 1844, prosector of anatomy in 1848; he received his M.D. degree in 1849, having special interests in pathology, anatomy, and surgery. In 1853 he was appointed assistant professor at the Faculty of Medicine and surgeon of the Central Bureau. Dr. Broca made significant scientific and

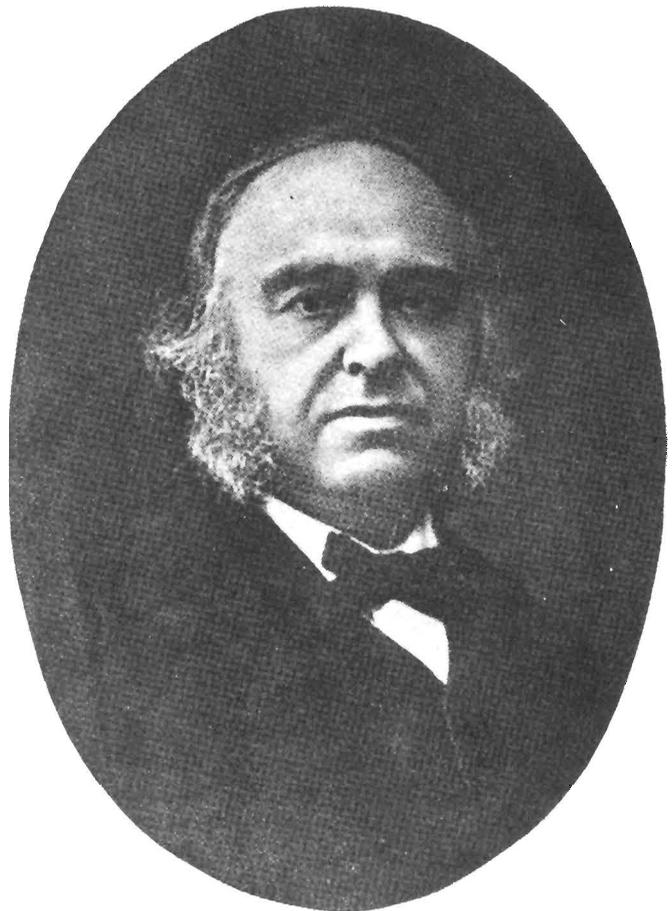


Figure 1. Pierre Paul Broca (1824-80).

clinical contributions in all of the above fields as well as in physical anthropology. He was the founder of the Anthropological Society in France.

From 1853 to 1867 Dr. Broca held important posts in the hospitals of Paris, finally serving as surgeon to the Necker Hospital (Clarke, 1970). In 1867 he was elected to the chair of "Pathologie externe" at the Faculty of Medicine, and in 1868 he became professor of clinical surgery. In January, 1880, he was elected a life member of the French Senate, representing Science. At the time of his death from a heart attack at age 56 on July 8, 1880, he was vice president of the French Academy of Medicine in Paris.

Dr. Broca's wife was the daughter of a Paris physician named Lugol. It is quite possible that Dr. Broca's awareness of the history of carcinoma of the breast, stomach, and endometrium in his wife's ancestry piqued his interest in causes of cancer and caused him to believe that in certain rare instances, cancer can be inherited.

### DEFINITIONS OF TUMORS

Before relating his thoughts about cancer in his wife's family in his two-volume treatise entitled *Traité des Tumeurs* (1866), Broca reviewed the history of medical ideas about tumors and cancer as follows.

During the Renaissance (seventeenth and eighteenth centuries) tumors were separated into three large groups: (1) *Tumores secundam naturam*, tumors that produce something in a natural physiological way such as pregnancy and milk in mammary glands; (2) *Tumores supra naturam*, in which the natural parts are displaced, such as in a fracture; and (3) *Tumores praeter naturam*, or those produced by unnatural parts, such as new tissues, accumulation of "humors" etc.

In the seventeenth century, Marc-Aurèle Séverin described all tumors as "abscesses."

Earlier Galen had described four kinds of tumors: (1) phlegmons, (2) érysipèles, (3) oedèmes, and (4) squirrhes (hard), and mixtures of all of them.

Late in the seventeenth century, it was thought that tumors were due to the extravasation of lymph. Later, benign and malignant tumors were noted. Benign tumors were considered inoffensive and did not change in volume; whereas, malignant tumors grew indefinitely, became ulcerous, and most often killed the affected person. It was later thought that benign tumors could become malignant by the action of lymph. Galenists followed the idea of "melancholy" and tumors; Cartesians followed the idea of lymph. Both views survived for a long time. Later, Broussais attributed cancer to an inflammation or the result of an organic irritation.

Early in the nineteenth century in England, Abernethy defined a tumor as "a new production which is not a part of the original structure of the body. Therefore it is hypertrophic" (Broca, 1866). He noted that the word "sarcoma"

originated in Greece and meant "having a firm and flesh feel." He described eight kinds of sarcoma as vascular, adipose, pancreatic, cystic, mammary, tuberculous, pulpy or medullary, and carcinomatous.

A cellular theory of the origin of tumors was disclosed by Dr. M. Raspail in France in 1825 by means of the microscope. This was confirmed by Hippolyte Royer-Collard in 1828.

Dr. Broca, himself, thought that malignant tumors metastasize through the lymphatics and that metastatic tumors were more malignant than those which did not spread (Broca, 1866).

### INHERITANCE OF TUMORS

Dr. Broca wrote about the diathesis of tumors defining this as "unknown dispositions of the body which precede the first appearance of certain tumors, particularly cancerous tumors" (Broca, 1866). He stated further that these diatheses do not reveal themselves by any observable symptom, but one must admit their existence by induction in order to explain two phenomena: heredity, and recurrence of tumors.

Whatever the name one wishes to call it, this deadly predisposition, impossible to foretell, impossible to escape, inaccessible to surgery, and until now even inaccessible to internal or medical treatment, is an indication of a general state which precedes each local manifestation which persists after surgery, and which determines a recurrence in the same way that it produces the first tumor. When one looks beyond, in certain cases this predisposition transmits itself by heredity through several generations (Broca, 1866).

Broca noted that many scientists disagreed with his idea of a diathesis, explaining that instead of hereditary, it was simply coincidences, and instead of a recurrence of cancer it was merely a continuation of an illness. He stated that there were, therefore, two hypotheses for the cause of cancer: infection and diathesis. He thought that the cause might lie somewhere in between the two, and said, "It is impossible to deny diathesis and difficult to negate the reality of infection. He hypothesized, then: (1) diathesis produces the first cancer, (2) cancer produces infection, and (3) infection produces secondary multiple tumors, cachexia, and death (Broca, 1866).

Broca (1866) explained further:

... diathesis is not an illness. It is only one cause of an illness. It is a theory and not an observed fact. It has no function; it does not manifest itself by symptoms; it cannot be seen nor can it be demonstrated directly.

On the other hand, the infection of cancer is characterized by producing a disturbance in the entire body, and always ends

death. It is revealed by serious symptoms, alteration in the blood, and changes in bodily functions.

A tumor may develop and be present sometimes several years before it can be detected in the body. Local evolution of a cancerous tumor is obligatory before the onset of symptoms of the infection.

Broca (1866) then stated:

... a person in whom are assembled unknown conditions, which expose him to later become cancerous, can transmit to his posterity this group of conditions before they have even manifested themselves in him. Also, having received the diathesis from one of his forebears, he may escape, during a long and healthy life, the consequences of that hereditary state, and may pass on to his children the disease from which he was spared.

He called this "atavism."

### THE FAMILY OF MRS. Z (Fig. 2)

#### *Generation I:*

Mrs. Z died of breast cancer in 1788 at about age 60. Several of her children had died at young ages, but she left four daughters, all of whom married (Mrs. A, Mrs. B, Mrs. C, and Mrs. D).

#### *Generation II:*

Mrs. A (Fig. 2, II-2), born in 1758, died of cancer of the "liver" in 1820 at age 62.

Mrs. B (Fig. 2, II-4), born 1762, died of cancer of the "liver" in 1805 at age 43.

Mrs. C (Fig. 2, II-6), born 1763, died of breast cancer in 1814 at age 51.

Mrs. D (Fig. 2, II-8), born 1773, died of breast cancer in 1827 at age 54.

#### *Generation III:*

Mrs. B had five daughters and two sons:

Son 1 (Fig. 2, III-4) died at age 28, not of cancer; he had no children.

Son 2 (Fig. 2, III-5) died at age 61 of cancer of the stomach; he had no children.

Daughter 1 (Fig. 2, III-5) died at age 35 of breast cancer, following surgery and recurrence; she had no children.

Daughter 2 (Fig. 2, III-7) died between age 35 and 45 of breast cancer; she had not undergone surgery; she had no children.

Daughter 3 (Fig. 2, III-8) died between age 35 and 45 of breast cancer; she had no children.

Daughter 4 (Fig. 2, III-9) died between age 35 and 45 of

cancer of the liver; she had no children.

Daughter 5 (Fig. 2, III-10) died at age 60 in 1858; she was married; she had no children and apparently had no tumors.

Mrs. C had five daughters and two sons.

Son 1 (Fig. 2, III-11) died in the Army; he had no children.

Son 2 (Fig. 2, III-12) was well at age 72 when the pedigree was drawn up. He was married and had three children.

Daughter 1 (Fig. 2, III-15) died at age 37 in 1817 of breast cancer; she was married and had two sons and three daughters.

Daughter 2 (Fig. 2, III-17) died at age 40 in 1822 of breast cancer; she was married and had one son.

Daughter 3 (Fig. 2, III-18) died at age 47 in 1837 of cancer of the uterus; she was not married.

Daughter 4 (Fig. 2, III-20) died at age 55 in 1848 of breast cancer; she was married and had two sons.

Daughter 5 (Fig. 2, III-21) died at age 61 in 1856 of cancer of the liver (or abdomen); she was not married.

Mrs. D had only one son, who, when the pedigree was constructed, was almost 70 years old and well (Fig. 2, III-22); he had no children.

#### *Generation IV:*

Children of son 2:

Son 1 (Fig. 2, IV-1) died at age 18, a paraplegic.

Daughter 1 (Fig. 2, IV-2) was 24 in 1856, well, and not married.

Son 2 (Fig. 2, IV-3) died "at a young age."

Daughter 1 had five children:

Son 1 (Fig. 2, IV-4) age 58 and well; he had three sons.

Son 2 (Fig. 2, IV-6) died young, in the colonies; he had no children.

Daughter 1 (Fig. 2, IV-8) died between age 27 and 30 in childbirth.

Daughter 2 (Fig. 2, IV-10) died in 1834 at age 49 of breast cancer; she was married and had two daughters. She had one son (Fig. 2, IV-12) who was healthy at the time the pedigree was constructed.

Daughter 3 (Fig. 1, IV-11) died at age 41 of tuberculosis.

Daughter 4 had two sons, both of whom were described as healthy in 1856.

#### *Generation V:*

The first son of Mrs. C's first daughter had three sons:

Son 1 (Fig. 2, V-1) age 30 and well.

Sons 2 and 3 were also healthy in 1856.

The second daughter of Mrs. C's first daughter had two daughters; one was age 22 and healthy in 1856. The second daughter was also healthy.

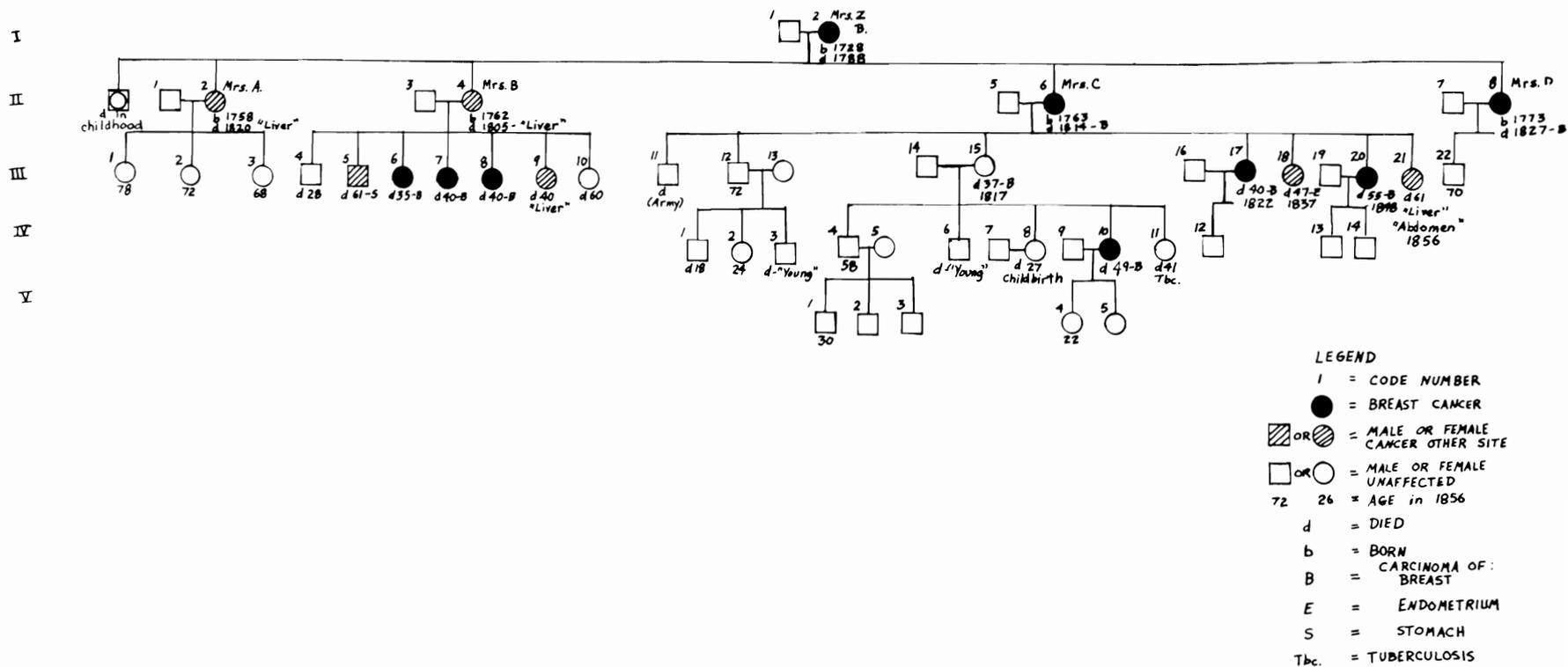


Figure 2. Pedigree of the family of Mrs. Z.

Note, then, that between 1788 and 1856 there were sixteen deaths from cancer in the family of Mrs. Z. Dr. Broca felt that this constituted proof of the inheritance of cancer.

Ignoring those family members who died before age 30 and those who were still under age 30 at the time the pedigree was drawn in 1856, twenty-six members passed the age of 30 thus reaching the age when cancer might occur. Of these twenty-six, fifteen developed cancer (Broca, 1866).

In France, at that time, the rate of cancer incidence above age 30 was 30/1,000 (or 3/100). In Mrs. Z's family, then, the hereditary influence increased the risk for cancer fifteen times over the rate in the general population. All the cancers except one were in women in this family, making the ratio 1 in 7 in men and 14 in 19 in the women.

Broca felt, however, that hereditary cancer was a rare occurrence, possibly occurring in only one out of seven cases. He quoted Dr. Lebert, who, in 102 cancer observations, had found only fourteen in which antecedents in the family had had cancer.

Broca had also noted, "a remarkable fact about the inheritance of cancer is the perfect health which is enjoyed for many years by persons who carry the 'germ' of this illness." He said that many of his patients had told him that they had never been ill before. In Mrs. Z's family the mean age at death was 49. The mean age in France in 1850 was 35; in 1800 it was 29!

Another notable fact was that the four daughters of Mrs. Z, all of whom later died of cancer, were born at least fifteen years, and one of them thirty years, before cancer overtook their mother. Broca felt that the answer may be that the disease was dormant and not revealed until a given moment. He felt that it was not the disease itself that was dormant, but that a cause of the disease remained inactive in the body for an indefinite time in an undefined state—a predisposition toward the disease.

Finally, Broca wondered why or how the dormant condition could last from fifty to sixty years and then "explode" and kill the person within one to two years. He felt that this was an impossible phenomenon to explain. And in 1978 there are many questions still unanswered concerning the etiology of polyps, tumors, and cancer!

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