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Present day clinicians usually rely upon the most recent medical literature to assist them with the diagnosis and treatment of diseases in their patients. The historian, on the other hand, delves into the past and is often rewarded by finding detailed and meticulous descriptions of diseases in the older medical literature. This is especially true of the medical writings of the 19th century before the development of mechanical devices (such as the stethoscope and the electrocardiograph) and modern laboratory tests.

Many conditions and diseases have been named for scientists who were supposed either to have discovered them or initially described them. Historians sometimes find that the conditions were actually described earlier by other investigators, but because their findings were published in obscure journals or in a different language they were not given the proper credit. Such was the case with Sir James Paget, a British surgeon who lived in the 19th century (1814-1899), and whose contemporaries included M. K. Kaposi (Austria), von Recklinghausen, R. Virchow, and J. C. Warren (Germany), and P. Broca, A. Velpeau, and M. Lebert (France) – all physicians who observed and described many different diseases and conditions of man, including cancer and its etiology.

Sir James Paget was a renowned surgical pathologist.[1] He is best known for his descriptions of eczema of the nipple with subsequent mammary cancer (1874) (Paget's disease of the nipple) and osteitis deformans (1877) which may develop into osteogenic sarcoma (Paget's disease of the bone). Paget was also known as a keen clinical observer.

The following conditions were all described by Sir James Paget, for only two of which he has been given credit in the medical literature.

NEUROFIBROMATOSIS

Neurofibromatosis is a genetic tumor predominantly of the nervous system and inherited as an autosomal dominant. The only consistent features are cafe-au-lait spots, fibromatous skin tumors and palpable tumors of nerve trunks. Many other less frequently occurring features may be present indicative of the broad range of the phenotypic expressivity in this disease.[2]

Although von Recklinghausen was said to be the first person to describe neurofibromatosis in 1882 in a paper entitled "Uber die multiplen Fibrome der Haut and Ihre Beziehung zu den multiplen Neuromen,"[3] Paget's description of neurofibromatosis was published in his book entitled "Lectures on Tumors" in 1851.[4] Among the topics discussed in his lectures were two types of neuromas. He distinguished between these

two types, the chief distinction being that the neuromas of neurofibromatosis were not painful while those of the second type (later known as Dercum's disease) *were* painful.

DERCUM'S DISEASE (ADIPOSIS DOLOROSA)

The most recent description of Dercum's disease is that of Lynch and Harlan:[5] It is a condition in which the chief clinical manifestations are obesity and painful subcutaneous lipomata. There may be variability in the expressivity of the dominant gene which causes this condition. Lynch and Harlan[5] described two families in which members of three generations in one family and two generations in another were affected with this condition. The nodules of this condition are more prominently distributed over the extremities and gluteal region. From the literature, it is noted that this disease is more frequent in females than in males. Obesity is more often associated with this condition in affected women than in affected men.

Dercum first described adiposis dolorosa at a meeting of the American Neurological Association in Washington, D.C., in 1888.[6]

Dercum felt that this was probably a connective tissue dytrophy, a fatty metamorphosis associated with irritation of nerve trunks. Since fatty swelling and pain are the two most prominent features, he called it adiposis dolorosa.

In 1851, Paget also presented a description of painful subcutaneous tumors[7] as being formed of either the looser fibrocellular or more dense fibrous form of connective tissue, in either a rudimentary or a perfect state.

"The characteristic of all these tumors in their pain; pain which may precede all notice of the tumor or may not commence until much later, or may be contemporary with it, but which, once it has set in, may give rise to agony such as I suppose is not equalled by any other morbid growth."

PAGET'S DISEASE OF BONE
(Osteitis Deforman) Osteogenic Sarcoma.

Paget's disease occurs in about 3% of all persons over age 40.[8] Males are affected more frequently than females. Bones involved include sacrum, femur, and vertebrae, as well as skull. Marked deformity may occur, enlargement of skull, and bowing of the legs.

Statistics suggest that an individual with Paget's disease is thirty times more likely to develop osteogenic sarcoma than a person in the general population.

The occurrence of malignant neoplastic processes in "pagetoid" bone was first reported by Sir James Paget in 1876[9] as follows:

"The primary tumor consists chiefly of bone but has on its surface and interstices of its osseous parts, an unossified fibrous constituent as firm as fibrous cartilage; after a time, similar growths ensue in parts distant from the seat of the first-formed, and not on bones alone, but in the areolar tissue, serous membranes, lungs, lymphatics, etc. This is also known as fibrous osteo-sarcoma or osteoid cancer. It has the characteristics of cancer disease. It has hereditary characteristics.

"The primary seat of osteoid cancer is usually some bone but it is not limited to bones."

PAGET'S DISEASE OF THE NIPPLE

Fibro-sarcoma of the breast or Paget's disease of the nipple is described as a weeping, eczematoid lesion involving the nipple areola, and occasionally a large area of contiguous skin carcinoma is found directly beneath the nipple. The mass is hard because

of increased connective tissue. It has chalky, yellow streaks and is usually confined to the ducts.

Between 0.5 and 3% of all malignant tumors of the breast are this type and it occurs predominantly in the fifth decade of life.[10]

In 1851 Paget[4] described this mammary tumor as follows:

"The nipple and the skin or other tissues of the mammary gland are peculiarly affected.

"Commonly the hard cancer extends from the mammary gland to the nipple and areola involving these as it may any other adjacent part. When seated at or near the center of the gland, it commonly draws down the nipple which descends as it were into a round pit sunk below the general level of the breast. As it extends, also, the cancer structures deposited in the nipple make it hard, or very firm, inelastic, inflexible, and comparatively immovable but the changes which thus usually occur later or in a less degree than those in the gland may commence or predominate in the nipple or the areola. The former may be found quite hard and rigid, or in the place of the latter. There may be a thin layer of hard cancerous substance with a superficial ulcer like an irregular excoriation, while the structures of the gland itself are yet healthy."

HEREDITARY MULTIPLE EXOSTOSIS

Hereditary multiple exostosis is a disorder affecting the skeleton during the period of growth; "it is characterized by thickening and deformity of the growing bone with the formation of numerous cartilage-capped exostoses clustered around the areas of most active growth. There is a shortness of stature, asymmetry of the pelvic and pectoral girdles, bowing of the forearm with ulnar deviation of the wrist . . . and deformities of the knees and ankles."[11]

A certain proportion of cases (1 to 25 per cent) undergo malignant change to chondrosarcoma.

The earliest description of multiple exostosis occurring in several members of the same family was that of Boyer in 1814. As the disease became more generally recognized, a fairly constant hereditary pattern emerged. By 1925, Stocks and Barrington[12] were able to collect 1124 case histories from the medical literature of which family history of the disease was noted in 163 families (727 cases). Although Paget was not the first to describe hereditary multiple exostoses, still, his contribution to the description of this disease has never been recognized.

He wrote[4] in 1851:

"In certain instances, a large number of the bones bear outgrowths which at least in the external shape are like tumors. They are commonly regarded as of constitutional origin. Some, indeed, appear to be so in the sense of constitutional disease which implies a local manifestation of some morbid condition of the blood; but others can be so called only in that sense by which we intend some original and *inborn error* of the formative tendency in certain tissues or organs.

"Of these last, we may especially observe that the tendency to osseous over-growths is often hereditary, and that its result is asymmetrical deformity. A boy 6 years old was in St. Bartholomew's Hospital several years ago who had symmetrical tumors on the lower ends of his radii, on his humeri, his scapulae, his fifth and sixth ribs, his fibulae and internal malleoli. On each of these bones, on each side, he had one tumor; and the only deviations from symmetry were that he had an unmatched tumor on the ulnar side of the first phalanx of his right forefinger . . .

"I saw this child's father, a healthy laboring man, 40 years old who had as many or

even more tumors of the same kind as his son's but only a few of them were in the same positions. All these tumors had existed from his earliest childhood; they were symmetrically placed and ceased to grow when he attained his full stature; since that time, they had undergone no apparent change. None of this man's direct ancestors nor any other of his children had similar growths; but four cousins, one female and three male children of his mother's sisters had as many of them as himself."

VIRUSES, IN RELATION TO CANCER SUSCEPTIBILITY, AND CANCER RESISTANCE

Paget compared the viruses which cause cancer with those which cause galls or tumorous growths on plants and which are deposited on plants by insects.[13] He said, "each virus requires a susceptible and fitting place and substance; and this is a fact confirming what we believe is the case in many diseases and, I venture to say, in cancers, the two conditions must co-exist – 1) the specific material, microbe, virus, or whatever we may name it in the blood which will carry it to every part, and 2) the one appropriate part, texture, or place in which this material can produce the disease . . . If there be in the body a part, however small, which is susceptible to cancer, this may become cancerous; but we may fully believe that if this one part had been as *insusceptible* as all the rest (of the body), the morbid material would have remained in the blood harmless and unobserved.

"I could indeed imagine that in the hereditary transmission of cancer, there might be transmitted such a tendency to likeness to that part of a parent or ancestor which was cancerous that the same part in the offspring might of itself become cancerous but even if this were sure, it would not explain the numerous cases in which the cancer in the offspring is not in the same part as it was in the progenitor, or those in which many members of one family have cancer in many different parts."

From the above description, it is impossible to state exactly what Paget meant by "virus," since he seemed to equate a virus with a microbe, or specific material. He placed this material "in the bloodstream" and thought that it was transmitted via the blood to various parts of the body. It is possible that Paget *was* the first to describe a virus as a specific agent in cancerigenesis.

Thus, we see that, like his contemporaries, Paget was interested in many phases of medicine. He made significant contributions to cancer genetics, some of which have *not* been recognized in the medical literature. Therefore, it behooves us to study some of these early writings more carefully. Perhaps it would then not be necessary to repeat some studies which have already been performed!

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