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A CASE OF PAGET'S DISEASE OF THE NIPPLE.*

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THE unreliability of statistics is well shown by a glance at the statistical returns of the American Dermatological Association. In the combined returns from 1877 to 1893 no mention of Paget's disease is made either under the commonly used title I have chosen for this paper, or under any other name suggested for it. These statistics cover 204,866 cases. Doubtless some cases are hidden from sight, or, better, buried forever under the title of epithelioma or carcinoma. In 1894, among 24,321 cases we find one case of the disease reported from New York. So far as I know there are no statistics so complete as ours are, yet how shall we regard the disease as to frequency of occurrence? Our statistics would say once in 229,187 cases, but not one of us would accept that as true. At any rate it is a rare disease. It so happened that in the autumn of 1895 I saw two cases of Paget's disease, one in my service at the Woman's Medical College of the New York Infirmary, and one in the practice of Dr. B. Farquhar Curtis, of New York, who kindly sent the patient to me for confirmation of his diagnosis and opinion as to the advisability of operation.

I would briefly report my own case. I would say that it was seen by Dr. George H. Fox and by Dr. B. Farquhar Curtis. The latter operated upon it, and by both of these gentlemen the diagnosis was confirmed.

Matilda K., aged fifty-two years, born in Germany; married. The family history is unimportant. The patient gives a history of having had rheumatic fever when she was sixteen and when she was

* Read at the Twentieth Annual Meeting of the American Dermatological Association, September 8, 1896.

twenty years of age. She was married when she was forty years old, and had two children. The youngest child was born ten years before the trouble with the breast. She suckled both her children, the last one for eighteen months. She never had any disease of the breast during lactation. She has always menstruated regularly, and does so still. She enjoyed good health up to December, 1894, when she had a slight stroke of apoplexy followed by paralysis, that in course of time lessened. The patient came to the dispensary in the fall of 1894 for an inflammation about the right nipple. I did not see her then. Apparently it was taken for a simple inflammation and treated with simple remedies. These seem to have relieved her for a time.

I saw her for the first time in May, 1895. At that time she presented herself on account of a return of the inflammation of the nipple. She said that the first thing she noticed was that there was itching about the nipple, and that the areola became red and looked angry. When I saw her in May the appearances were those of a chronic eczema, some crusting, and an eroded surface. There was then no pain complained of. On account of the markedly circumscribed character of the patch, its limitation to the nipple and areola, and the slight amount of induration of the lesion, together with some hardness of the breast, I made a tentative diagnosis of Paget's disease, and directed that she be kept under observation and the lesion treated as an eczema.

About the middle of September, 1895, she came again to my clinic. Since last seeing her a marked change had taken place. The nipple had become very much depressed. The whole areola was very much indurated. The site of the nipple and areola was occupied by an eroded, red, irregular-shaped patch. It was perfectly dry and looked raw. Outside of this there was a narrow line of apparently normal skin, and outside of all, extending nearly around the whole diseased patch, there was a light brown, infiltrated, slightly elevated ridge. There were no dilated blood-vessels. The patient complained of a good deal of itching and of sharp, sticking pains in the breast. The breast felt hard, and the axillary glands of both sides were enlarged. There now being no doubt of the nature of the trouble, amputation was advised.

On October 16, 1895, Professor B. Farquhar Curtis amputated the diseased breast in the New York Infirmary, and removed the enlarged glands from the right axilla. The patient made a good recovery, and was discharged from the Infirmary on October 30, 1895.

I saw the patient again on June 17, 1896. The scar from the operation was perfect. There was no sign of a return of the disease. There were no enlarged glands in the right axilla. The patient stated that she had been entirely free from pain since the operation. She had a second attack of paralysis in December, 1895. In the left breast there was a hard, circumscribed, nodular mass. She said that she had had this lump in the breast for years, and that it gave her no pain.

We have here an instance of the development of what seemed to be a simple eczema into a well-marked case of Paget's disease within about ten or eleven months. The clinical diagnosis was confirmed by the microscope. The pathological examination was made for me by my friend Dr. John Slade Ely, Professor of Histology and Pathological Anatomy in the Woman's Medical College of the New York Infirmary, and Assistant in Pathology in the Medical Department of Columbia University. His report upon the findings in the case is as follows:

Professor John Slade Ely's Report.

The specimen is a breast which has been removed by operation and comprises the entire mammary gland, a considerable piece of the skin covering it, and surrounding fat and pectoral muscle.

The skin appears normal except where it covers the nipple and its areola, where it is somewhat coarsely seamed and appears to be thickened. Surrounding the areola there is a circumvallate depression, in places as much as two millimetres and a half in depth, which separates the thickened tissue of the areola from the normal surrounding skin. Just within this depression there is a zone of hyperæmia about two millimetres in breadth. Though coarsely seamed, as above mentioned, the skin covering the nipple and areola is in general smooth, showing neither ulceration nor crust formation. The nipple is not sunken or noticeably retracted, though it projects very little above the level of the surrounding skin.

Median section through the nipple, its areola, and the entire breast shows the skin covering the nipple and areola to be distinctly thickened and the site of the mammary gland to be occupied by a large, dense tumor. This tumor measures $8.1 \times 7.6 \times 4.7$ centimetres. It is quite sharply circumscribed, though not distinctly encapsulated, and, except where it is connected with the nipple by the lactiferous canals and their supporting connective tissue, it is completely sur-

rounded by fat. The substance composing the tumor is extremely dense, resembling in appearance the tissue of dense fibroma. It shows no distinct lobulation, but is somewhat mottled in places, as the result, apparently, of the presence of small, more or less circular areas of somewhat less dense tissue of a slightly yellowish color. A few small cysts are evident, the largest not more than three millimetres in diameter, and containing clear or only slightly cloudy liquid material. The blood supply of the tumor appears to be meager.

The fat tissue surrounding the tumor appears normal, as does also the portion of pectoral muscle attached to the specimen.

Microscopic examination confirms the impressions obtained from gross inspection of the specimen.

The skin covering the nipple and areola is much thickened. This is chiefly the result of a very considerable development of connective tissue in the corium and of an inflammatory infiltration of its papillary layer, though the epidermis is also thicker than normal. These changes are evident everywhere in the skin covering the nipple and areola, but are more intense in that of the areola, and the details of the changes about to be described are those which have been observed in that region more particularly.

The corium here is upward of four millimetres in thickness. Its deeper layer consists of bundles of dense connective tissue surrounding masses of unstriped muscle. It is poorly supplied with blood-vessels, but where these are visible they are often surrounded by collections of cells, for the most part of the small spheroidal type and mononuclear. This cellular infiltration about the blood-vessels increases toward the more superficial layers of the corium, becoming very intense in the papillary portion, where it is not limited to the immediate proximity of the blood-vessels, but is quite general throughout the tissue. The cells here are also in great part of the small spheroidal variety and mononuclear, but there are also many larger spheroidal, polyhedral, and spindle cells. These cells all lie in a reticulum of fibrous connective tissue which is finer in the more superficial parts, coarser below. The cells and fibrous reticulum of the papillary layer are often not in close juxtaposition, but are separated by clear spaces such as are observed in tissues which have been the seat of œdema. This change is very marked. In the papillary layer, also, are many thin-walled blood-vessels, whose endothelium is swollen and whose lumina contain variable numbers of polynuclear leucocytes. The majority of these blood-vessels would appear to have been con-

siderably congested. A few polynuclear leucocytes are also observed in the tissue outside the blood-vessels.

The changes in the epidermis are even more pronounced than those in the corium. All the layers of the epidermis are thickened. In the rete Malpighii the cells of the deepest layer appear to have undergone a more rapid multiplication than normal, being very closely packed together and rather small. More superficially the cells are seen to be passing through the various transitions characteristic of the rete mucosum, but in the majority more or less abnormity is discernible. This appears to be due in most instances to swelling of the cell bodies, which are more spheroidal than normal and consist of rather coarsely granular protoplasm. Many of the cells also inclose clear, more or less globular spaces, now apparently empty. These spaces often occupy the greater part of the cell body, leaving only the nucleus intact, but usually a small amount of finely granular protoplasm surrounds the space, or is visible at one side of the cell surrounding the nucleus. At times these spaces appear to surround the nucleus in a ring, giving it a vacuolated appearance, and under these circumstances there is usually visible a distinct zone of protoplasm about the vacuoli. The outlines of these peculiar cells are, as a rule, very distinct, though they can not be said to have a definite wall. In many instances the cells immediately adjacent to these swollen cells appear to have been compressed by their enlarged neighbors, at times presenting in section a distinctly crescentic appearance, the vacuolated cell occupying the concavity. The nuclei of the cells are for the most part well preserved, though occasionally somewhat distorted in the vacuolated cells; their chromatin stains well with the ordinary nuclear dyes.

In addition to the changes in shape and appearance of the cells of the rete Malpighii, there is also noticeable an increase in the intercellular spaces, which are distinctly broader than usual. This is particularly evident in the region of the spine cells, where the channels separating the adjacent cells are very wide. These intercellular spaces now appear to be empty.

The changes above described are everywhere evident, but are so intense in places as to completely destroy the regular stratification of the rete Malpighii and to give it the appearance of a confused mass of swollen epithelial cells loosely and indiscriminately thrown together.

The stratum granulosum of the epidermis is much thickened where

the changes in the rete are pronounced, and the cells composing it are very granular and are larger than usual. The stratum lucidum is also much increased in thickness in places, apparently as the result of excessive swelling of its component cells, which are often almost spherical in shape. These swollen cells of the stratum lucidum show little besides the cell outline and a small faint nucleus, the entire cell body having been occupied by some substance which has disappeared in the process of preparation of the specimen, the space formerly occupied by it showing now only as a hollow cavity. The same separation of the cells noticed in the rete Malpighii is also observable here.

The stratum corneum is also greatly thickened. In its deeper layers the cells are much swollen, presenting a similar appearance to those of the stratum lucidum, and throughout its entire thickness the intercellular spaces are markedly increased, forming irregular cavities, often of considerable size, now destitute of contents.

The changes in the skin above described are sharply limited by the circumvallate depression surrounding the areola, the skin beyond this point showing no pathological change other than a moderate infiltration of the perivascular spaces of the corium by small spheroidal cells, even this slight change quickly disappearing as the distance from the areola is increased.

The lactiferous canals in the nipple and just beneath it are irregularly dilated, and are everywhere filled with desquamated, swollen, and degenerated epithelium and polynuclear leucocytes. In many of the epithelial cells distinct vacuoles are visible similar to those observed in the cells of the rete Malpighii, though this change is never so intense as in the skin. The connective tissue surrounding the lactiferous canals is moderately infiltrated with small spheroidal cells. No marked congestion of the blood-vessels about these canals is observed.

The tumor, occupying the mammary gland, is composed for the most part of extremely dense, white fibrous tissue disposed in bundles of various sizes, often distinctly wavy and quite lawless in arrangement, many of which show evidence of hyaline degeneration. This connective tissue occupies the spaces between the lobules of the gland, separating them widely from one another, and penetrates the individual lobules. Immediately about the acini of the lobules it is less dense and appears younger, connective-tissue cells being relatively more abundant. The network of fibers is here also very much more open than in the interlobular regions, disclosing many open spaces

between the fibrils and presenting the apppearance often met with in œdematous tissues. The acini inclosed by this tissue are often widely separated by it, and show more or less abnormity of size and shape. Some degeneration of their lining epithelium is also noticeable, but this is far less striking than in the epithelium of the lactiferous ducts. Though in some instances the acini of the lobules branch somewhat irregularly, the impression conveyed is rather that of inflammatory hyperplasia than of adenoma.

In places in the dense fibrous tissue of the tumor there are collections of small spheroidal cells, mononuclear, and resembling very young connective-tissue cells. These are interpreted as marking the site of active development of the connective tissue at the time of removal of the mass.

Near the center of the tumor there are a number of small cysts, lined with cuboidal or irregular epithelium, and containing loose granular material and desquamated cells. A few of these cysts are regular in outline, but the majority of them are irregular, showing what appear to be papillary ingrowths of connective tissue into their lumina. These ingrowths consist of connective tissue of the same characters as that found about the acini of the lobules, and are covered with epithelium similar to that lining the rest of the cyst wall. The picture in these cases is very suggestive of that presented by the papillary ingrowths observed in the early stages of intracanalicular fibroma of the breast and in papillary cyst-adenomata of the ovary.

Though numerous specimens have been stained for bacteria and for parasites of the sporozoa type, none have been found.

The changes above described are substantially those which have existed in all the cases of Paget's disease which have been subjected to careful pathological study.

Consideration of the significance of these changes leads to the conclusion that the lesion in the skin is essentially of an inflammatory nature. And they furthermore suggest that the inflammation which gave rise to them was of slow progress, was primarily and pre-eminently a change of the corium, and was of such a nature as to cause a very considerable connective-tissue development, and, by interference with the nutrition of the skin, to lead to an intensely œdematous condition of the epidermis and of the papillary layer of the corium.

The tumor of the mammary gland may be regarded as fibroma durum or as the result of long-continued interstitial mastitis, the lines separating these two conditions being at the present time exceedingly

vague. For my part, I would prefer to consider the present growth as fibroma of the so-called "pericanalicular" variety, basing this opinion chiefly on the lawlessness of the fibers composing it. It is certainly neither adenoma nor carcinoma.

That the two conditions here met with should be associated appears most natural when we remember the close similarity in the lesions (both consisting chiefly of connective-tissue development) and the intimate topographical and genetic relationship of the skin of the nipple and areola with the glandular element of the breast. The determination of the precise chronological sequence of the two conditions, however, presents some difficulty. In a large majority of the cases of Paget's disease thus far studied, the attention of the patient has been attracted first to the lesion of the skin, and the mammary tumor has remained undetected until it has attained to a very considerable size or has been noticed by the physician in his examination. This has led to a widespread belief, expressed also by Paget in his first description of the condition, that the change in the skin antedates the lesion of the gland and is in some remote way its cause. In the present case I am loath to regard the lesion in the skin as primary, basing this opinion on the large size of the tumor, on the extreme density of the tissue composing it suggesting its long duration, on the nature and relatively slight intensity of the skin lesion, on the frequency of occurrence of fibrous growths in the breast independently of any pre-existing skin lesion, and on the absence of any evident ætiological factor in connection with the skin lesion other than the large fibrous tumor closely underlying it.

In the description of the changes in the epidermis and in the lactiferous ducts mention has been made of certain spheroidal, clear spaces or vacuoles commonly met with in the epithelial cells. These have been described by Darier, Wickham, and others as psorospermæ, and have been regarded by them as the primary ætiological factor in the induction of the disease. A careful study of these "bodies" in the present case has produced a strong belief that they are in reality not psorospermæ but spaces in the cells, and they have accordingly been described as such, spaces which have formed as the result of an accumulation of clear liquid within the cell bodies, such as is seen in extreme dropsy of cells or in hydropic degeneration, as it is characterized by Ziegler. This change is relatively frequent in the inflamed skin covering superficial tumors—I have met with it in much greater intensity than in the present case in the epidermis covering

a melano-sarcoma of the heel—and I have seen nothing in the present case which is not abundantly explained on the supposition that the condition is here one of extreme inflammatory œdema of the cells. And in this connection it may be stated that I have seen appearances apparently identical with all those pictured by Wickham in his elaborate study and interpreted by him as indicative of the presence of psorospermæ. And, finally, the sharp limitation of the supposed psorospermæ to the epithelium seems to be inconsistent with any conception of them as parasites responsible for the genesis of a distant neoplasm in which they are not found.

In conclusion, then, I find it much more consistent to consider the lesion of the skin as a secondary inflammatory process resulting in some way from the large underlying tumor of the mammary gland, and to admit that in the present state of our knowledge the precise exciting cause of the tumor and the exact manner in which its presence induces the inflammation of the skin must be regarded as uncertain.

After seeing my patient in June of this year (1896) I wrote to Dr. Ely, telling him that I found a tumor in the other breast. Replying to my letter, he said: "Its contents is an extremely interesting corroboration clinically of the findings of the report, both as to the nature of the tumor and as to the priority in time of the tumor to the skin lesion. Such fibrous growths as the tumor in the present case are very apt indeed to affect both breasts, while adenoma, carcinoma, etc., very rarely affect both. I think that you may be sure that the mass in the other breast is not carcinoma, but fibroma or interstitial mastitis."

It would a waste of time for me to dilate upon the symptoms of Paget's disease of the nipple before such an audience. Dr. Ely has begun a critical study of its pathology which he hopes to publish in a short time. In writing this paper I had two objects in view—namely, to put on record another case of this rare disease, as it seems to me to be the duty of every one to report every case of a rare disease, and to elicit from you a discussion upon its treatment, as it is to such bodies as we are that the profession looks for guidance in the treatment of rare diseases.

In looking over Wickham's admirable treatise upon Paget's disease * you will find a record of some eighteen cases. Paget reported

* Maladie de la peau dite maladie de Paget, Paris, 1890.

fifteen cases not abstracted by Wickham. Besides these, Elliot reported one case; * Jamieson reported in his Treatise on Skin Diseases two cases; † Audry, one case; ‡ Fleming, one case; # Anderson, one case; ‖ Lewis, one case; ^ and Duhring, three cases. I do not offer this as a complete list of the cases reported, but they are unselected and enough for my present purpose. With the case now reported we have forty-five cases. Of these it is said that in twenty-four cases carcinoma developed in the breast which was the site of Paget's disease; in four of them the breast is said to have felt hard; and in one of them, my case, a fibroma was found as the cause of the hardness of the breast. That is, in twenty-nine out of the forty-five cases there was some disease of the gland in connection with the disease of the nipple. Only one of the forty-five cases is reported as cured by treatment addressed to the skin. The history of the vast majority of them is that they grew steadily worse under treatment, no matter whether mild or most energetic with powerful caustics or the curette. On the other hand, in the cases operated on most did well, though in three of them a general carcinosis developed, and in one death resulted from a secondary deposit in the brain.

We learn from this that the tendency of the disease is to the development of carcinoma. Moreover, we find that it is eminently refractory to treatment addressed to the skin lesion. It is possible, as the histories show, to produce an amelioration. It is doubtful if a lasting cure can be obtained after the disease has plainly declared itself. We also find that we have reason to expect good results from amputation of the breast.

When we consider the malignant tendency of the disease and its obstinacy to treatment, it seems to me that it is our duty in all cases to advise amputation of the breast just as soon as we are sure of our diagnosis. Of course, as long as there is any possibility of the trouble being a chronic eczema or a dermatitis of simple character, operative interference is not to be thought of. Usually it will not take one who is at all expert in dermatology very long to assure himself, one way or the other, of the nature of the case. As most of the women

* Journal of Genito-Urinary and Skin Diseases, 1892, vol. x, p. 272.

† Annal. de dermat. et syph., 1896, t. vii, p. 644.

‡ British Medical Journal, 1891, vol. i, p. 846.

Glasgow Medical Journal, 1892, vol. xxxvii, p. 138.

‖ Glasgow Medical Journal, 1892, vol. xxxviii, p. 132.

^ Medical Record, 1887, vol. xxxi, p. 641.

are past the childbearing age, and the breast is useless so far as any function of the organ is concerned, and as the mortality of breast amputations is very slight (Dr. B. Farquhar Curtis informs me that it is from one to four per cent), we can advise operation as a preventive of future trouble with good grace. Of course, when there are signs of involvement of the breast, no one would hesitate to insist upon amputation of the gland. It is true that in my case my pathologist reports that the tumor of the breast was not malignant. But the clinical signs of carcinoma were present, and it would have been impossible, probably, to determine the nature of the tumor without amputation. I feel that I was justified in advising amputation even in this case, and in the absence of malignancy of the tumor, as the patient, by the comparatively trivial operation, was promptly cured of an otherwise practicably incurable disease, and at once freed from all pain and annoyance.