THIRTEEN CASES
OF
PAGET'S DISEASE OF THE NIPPLE,
WITH
SPECIAL REFERENCE TO THE CAUSATION OF
THE MALADY BY PSOROSPERMS.

BY
ANTHONY A. BOWLBY, F.R.C.S.,
SURGICAL REGISTRAR AND DEMONSTRATOR OF PRACTICAL AND OPERATIVE
SURGERY AND OF SURGICAL PATHOLOGY AT ST. BARTHOLOMEW'S
HOSPITAL; SENIOR ASSISTANT SURGEON TO THE
METROPOLITAN HOSPITAL.

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It is now fifteen years since specimens of Paget's disease of the nipple were first shown at a meeting of the Royal Medical and Chirurgical Society by Mr. Butlin, and on subsequent occasions this surgeon, Mr. Henry Morris, and Dr. Thin have given details of additional cases. For the past ten years, however, the subject has not been again brought before this Society, although illustrative cases have been published elsewhere; and as it is one which has recently attracted considerable attention, I have thought the present a favorable time to again bring the matter forward. I am the more disposed to ask

the attention of Fellows because when this disease was last discussed there was some difference of opinion as to its pathology, and the nature of the morbid processes involved ; and because, although much additional information has been obtained of late years, the total number of recorded cases is yet small, and the records of additional examples may prove of value.

For the following thirteen cases I am indebted to the Surgical Staff of St. Bartholomew's Hospital, where most of the patients have been under treatment, and to my friends Mr. Everley Taylor of Scarborough, and Dr. Stowers and Dr. E. S. Tait of London. In all cases the whole of the parts removed have been placed in my hands for purposes of examination, and in almost all of them I have had the opportunity of examining the patients before operation.

CASE 1.—J. B—, æt. 53, came under the care of my friend Mr. Everley Taylor, of Scarborough, in March, 1882. She was a married woman, but had never borne children, and had had no trouble with her breasts. Three years before coming under notice a chronic irritation of the nipple and areola commenced, which she thought was caused by the friction of her stays. Eighteen months later this began to spread more quickly and to supply more exudation than formerly. After a further interval of six months she first noticed a lump in the breast.

On examination the nipple was found to be much retracted, and was surrounded by a raw, red, excoriated surface covered with thin scales. Beneath the nipple and continuous with it was an irregular, hard, and lumpy tumour. The axilla was free.

On March 6th the breast was amputated, and on section was found to be occupied by a typical scirrhus growth. The patient made a good recovery, and five years later remained quite well.

CASE 2.—M. B—, æt. 36, was admitted into St. Bartho-

lomey's Hospital under the care of Mr. Cripps on May 20th, 1882. She was a married woman and had borne five children. She had suffered from cracked nipples whilst suckling, but these had always healed after weaning the children. Otherwise she had enjoyed good health, and came of a healthy family, but her mother's sister had died of cancer of the stomach.

Her history was that a year before admission, and without apparent cause, her right nipple became cracked and sore, and never healed in spite of treatment. Six months later she noticed a lump in the breast.

On admission it was found that the right nipple was retracted and excoriated. Around it for a distance of three quarters of an inch was a ring of bright red ulceration. The edge of this ulcer was not sharply defined, but faded into eczematous skin with crusts and scales. Above the nipple, but situated in the upper part of the breast close to its edge, was a hard nodular growth the size of a chestnut, and in the axilla was one enlarged and hard gland. On May 24th the breast and the enlarged gland were removed. A section of the former showed a typical scirrhus carcinoma at the upper margin of the breast, and separated from the nipple by apparently healthy tissue. The gland also was cancerous.

CASE 3.—E. W—, æt. 52, a married woman, came under the care of Dr. Stowers in July, 1882.

Her left breast had been removed for cancer three years previously, and the right nipple had been sore and excoriated for two years, and had steadily got worse.

The right nipple and areola were a bright red. At Dr. Stowers' request I removed the nipple and about half an inch of the adjacent skin for microscopical purposes, and then Dr. Stowers destroyed the remainder of the affected area with Vienna paste. After that time I lost sight of the patient for a year and a half, at the end of which period she came to St. Bartholomew's Hospital, and remained under treatment by Mr. Cripps for some time.

She was then suffering from an enormous fungating tumour situated over the sternum, and apparently extending through that bone from the mediastinum. The right breast was quite healthy, and the scar left by the Vienna paste was quite sound. The operation scar in the left breast was also sound.

CASE 4.—H. K— was admitted into St. Bartholomew's Hospital on May 1st, 1883.

She was a healthy woman, æt. 45. She had had four children, and since the birth of the third child, seven years previously, the left nipple had been sore. The last child refused to take the breast, and for the past two years the soreness of the nipple had spread over the areola, and had caused her a good deal of burning pain. Four months before admission the patient first noticed a tumour in the lower part of the left breast at some distance from the nipple. She had previously enjoyed good health, and there was no family history of cancer.

An examination of the breast showed that the nipple and the areola were bright red and congested. The epidermis was partly destroyed, and a red, raw surface was exposed exuding some blood-stained serous fluid. In the lower part of the breast and quite separate from the nipple was an irregular, lumpy, hard tumour, about half the size of an egg, and in the axilla was a large hard gland.

On May 2nd Mr. Smith removed the breast and the axillary gland; each was found to be occupied by a typical scirrhus growth.

CASE 5.—L. S—, æt. 51, was admitted into St. Bartholomew's Hospital under the care of Mr. Smith on June 23rd, 1883. She was a healthy married woman who had borne and suckled nine children, and had never had whilst suckling, any trouble with the breasts. She said that three years before coming to the hospital the right nipple began to be chapped and sore, and that the

skin around it was red and irritable. This soreness continued in spite of treatment until the time of her admission, and four months before she came under notice she first discovered a lump in the breast.

An examination showed that the nipple had been almost entirely destroyed by ulceration, and that the skin around it was red, raw, and moist for a distance of about an inch. The affected skin was bright red and papillated, and was separated from the healthy skin by a definite sharp margin. Immediately beneath the nipple, and adherent to it, was a hard, irregular, lumpy tumour, rather larger than a walnut and tender to the touch. The axilla contained several enlarged and hard glands.

On June 20th the breast and the glands were removed, and were found on examination to be occupied by typical scirrhus growths, that in the breast involving the base of the nipple. The patient did well after operation.

CASE 6.—E. K— was admitted into Lucas Ward, St. Bartholomew's Hospital, under the care of Mr. Savory on December 2nd, 1883. She was a healthy-looking woman, æt. 51.

For two years she had noticed the left nipple sore and "chapped," and for nine months had known of a tumour in the breast.

The nipple was found to be red, raw, and discharging; the areola was similarly red and raw in some parts, and covered with scales and crusts in others. Beneath the nipple was a tumour the size of an orange, very hard and adherent to the skin. In the axilla were several large, hard glands.

On December 22nd Mr. Savory removed the breast and the axillary glands, and found a mass of scirrhus cancer in each.

CASE 7.—H. B—, æt. 44, was admitted into St. Bartholomew's Hospital under the care of Mr. Smith on June 1st, 1885. She said that she had first had trouble with her

left breast ten years previously whilst suckling, and that an abscess had then formed. From this trouble she quite recovered, but five years later, whilst suckling the last child she had borne, the nipple again became cracked and sore, and since then had never got quite well. Two years before admission the soreness of the nipple became worse, and after that time a lump appeared in the breast. The patient had had seven children, and had otherwise been healthy. There was no family history of cancer.

On admission the place of the areola and a large extent of the skin around it were replaced by an irregular ulcer two inches and a half long and an inch and a half wide. The nipple had been destroyed, and the site of the nipple and the areola was occupied by a red, papillated, granular surface with sharply defined margins. In the breast beneath was a large, hard tumour, which was not adherent to the nipple or the ulcerated skin. There were several hard and enlarged glands in the axilla.

On June 3rd the breast and the glands were removed. The tumour was a typical scirrhus cancer, and the lymphatic glands were occupied by a similar growth.

CASE 8.—S. A—, æt. 41, was admitted into St. Bartholomew's Hospital under the care of Mr. Cripps on March 8th, 1886. She was a healthy married woman, with seven children, and had never had any previous trouble with her breasts. She said that eighteen months before she came to the hospital she had suffered from soreness, which began around the left nipple and subsequently spread to the nipple itself. This got worse in spite of treatment, and after about a year's interval she first noticed a lump in the breast.

An examination showed that the left nipple had been to a great extent destroyed by ulceration. It was raw and ulcerated, and surrounded by a circle of granulation tissue discharging pus. Separated from the nipple and areola and situated in the inner half of the breast was an

irregular and ill-defined tumour as large as a walnut, and in the axilla were some slightly enlarged glands.

On March 16th the breast and glands were removed. A section of the former showed a typical scirrhus carcinoma situated at a little distance from the nipple, but the glands did not contain any growth.

In June, 1888, the patient came back to the hospital with a small recurrence in the scar, but no sign of eczema or of enlarged glands. The growth was successfully removed.

CASE 9.—P. C—, æt. 64, was admitted into President Ward in St. Bartholomew's Hospital under the care of Mr. Smith in December, 1887. She was an unmarried woman, and had suffered from soreness of the left nipple, without apparent cause, for six months. Two months later a lump appeared in the breast. Her family and personal history was good.

On admission the nipple was found depressed and raw, whilst the skin around it was red and weeping, and covered in patches with epithelial scales and crusts. There was no ulceration. Immediately beneath the nipple, and attached to it, was a hard tumour as large as a walnut, and with very irregular and knotty outline. The axilla contained one enlarged and hard gland.

On January 1st, 1888, the breast was amputated, and the enlarged gland was removed from the axilla. A section of the breast showed a typical scirrhus carcinoma involving the base of the nipple; the gland also was cancerous. The patient made a good recovery.

CASE 10.—A. P—, æt. 57, was admitted into Lucas Ward under the care of Mr. Howard Marsh on June 13th, 1889. She said that two years and a half previously the right nipple began to be chapped and sore, and that this was accompanied by redness and a watery discharge from the skin of the areola. After this the nipple was

gradually eaten away by ulceration. Two years after the nipple began to be sore she noticed a lump in the breast. Her personal and family history was good, and she could not attribute the disease to any cause.

An examination showed that the right nipple had been completely destroyed by ulceration, and that the skin for an inch around had shared in the destructive process. The result was an irregularly circular ulcer with rather hard edges and base, and slight excoriation of the cuticle immediately around. To the right of the ulcer, and at a slightly higher level, was a tumour the size of a walnut, very hard, a little tender, and fixed to the superjacent skin. The axilla was free. On June 19th the whole breast was removed, and on section the growth was found to be a typical scirrhus carcinoma extending to the skin on the outer side of the breast, but not being continuous with the ulcer which occupied the position of the nipple. The patient made a satisfactory recovery.

CASE 11.—H. C—, æt. 63, an unmarried woman, was admitted into St. Bartholomew's Hospital under the care of Mr. Morratt Baker on November 14th, 1890. She said that she had had a sore nipple for five years, and that within the last six months the areola also had become raw and sore. Two months before admission she first noticed a lump in the breast below the nipple. There was no family history of cancer or of injury.

She was a thin, healthy woman. The nipple was found to be partly destroyed by ulceration, and was much retracted. Its surface was red, raw, and granular. Around it the areola was red and congested, although not to any considerable extent. Here and there were small crusts, and in places the epithelium had been destroyed and a raw excoriated surface was exposed. There was a good deal of watery discharge, some burning pain, but no considerable irritation. The diseased area felt stiff and a little indurated on the surface. Below the nipple a tumour the size of a walnut could be

felt in the breast, and a hard and enlarged gland lay in the axilla.

The whole breast and the axillary glands were removed by Mr. Baker. The tumour was a typical scirrhus carcinoma, and the gland was similarly diseased.

CASE 12.—An unmarried lady, æt. 60, came under the care of Dr. E. S. Tait and Mr. T. Smith in January, 1890.

She said that she had first noticed a soreness of the nipple five years previously, and that in spite of various treatment this had gradually got worse. Mr. Smith informed me that the nipple and areola presented the appearance typical of Paget's disease, but that no tumour could be discovered. He advised amputation of the breast, and this operation was performed on January 10th. After removal the breast tissue was found to be normal except at the orifices of the ducts, and no growth was found in any part.

CASE 13.—The specimen in this case was sent to the museum at St. Bartholomew's with a statement that the eczema of the nipple had existed for some years, and that a growth in the breast had been noticed six months.

The tumour was found to be a scirrhus carcinoma, the areola was excoriated, and the nipple partly destroyed by ulceration. The growth in the breast was placed at some distance from the nipple.

Before venturing upon any remarks which the foregoing cases suggest it appears to be advisable to allude very briefly to the cases published by other writers in order to form some estimate of the available information.

I find that at the present time eleven cases have been recorded in England, two in Scotland, six in France, four in America, and one in Germany. With the exception of the last, clinical details are given as well as accounts of the morbid anatomy of the disease. It thus appears

that, although no records of cases occurred out of England for several years subsequent to Sir James Paget's paper on the subject, the disease is nevertheless widely distributed, and it is certain that it is much more common than these figures might lead us to think—a fact which is emphasized by the consideration that the cases I bring forward to-night are as numerous as all the other English cases hitherto recorded.

The whole literature of the subject has been so lately reviewed by Dr. L. Wickham¹ in an admirable monograph to which I shall again allude, that there does not appear to me to be any necessity for describing in detail cases already published. I am, however, indebted to Dr. Wickham's book for many references, and for a detailed account of the cases hitherto observed in France by himself and M. Darier.

From a study of the published cases the following deductions may be drawn. With regard to the *sex* of the patients, all the examples of the disease occurred in females, with one exception, that of a man aged 66, recorded by Forrest.

As to the age of the females *when they came under notice*, 3 were between thirty and forty, 5 between forty and fifty, 9 between fifty and sixty, 4 between sixty and seventy, 1 between seventy and eighty. Total 22.

The youngest patient was aged thirty-three, and the oldest seventy-two, and in the former the disease of the nipple commenced at the age of twenty-eight.

In nine cases there was no tumour in the breast. In the remaining fourteen the mamma was the seat of cancerous growth.

The duration of the disease of the nipple in the nine cases where there was no tumour was in one six months, in one two and a half years, in one three years, in one five years, in one nine years, in one ten years, in one eleven years, in one twenty years, in one a doubtful period.

In the fourteen cases where the disease of the nipple

¹ 'Maladie de la peau, dite maladie de Paget,' par le Dr. Louis Wickham.

was complicated by a tumour in the breast, the duration of the disease of the nipple *before operation* was in one case fifteen days, in two cases six months (one a male), in two cases one year, in one case one and a half years, in three cases three years, in one case four years, in three cases six years, in one case twelve years.

In eight cases there was *ulceration* and destruction of a part or the whole of the nipple as well as of the skin of the areola, and of that in its neighbourhood to a varying extent.

A similar analysis of the cases recorded by myself shows the following results.

Age when seen by surgeon, 1 between thirty and forty, 3 between forty and fifty, 5 between fifty and sixty, 3 between sixty and seventy. The youngest patient was aged thirty-six and the oldest sixty-four. The earliest age at which the disease *commenced* was thirty-five.

In two cases there was no tumour in the breast. In the remaining eleven the mamma was the seat of cancerous growth.

The duration of the disease of the nipple in the two cases where there was no tumour was in one three years and in the other five years.

In the eleven cases where the disease of the nipple was complicated by a tumour in the breast, the duration of the disease of the nipple *before operation* was in one case six months, in one case one year, in one case one year and a half, in one case two years, in one case two years and a half, in three cases three years, in two cases five years, in one case seven years.

In seven cases there was no ulceration, whilst in the six others more or less of the nipple and of the areola had been destroyed.

It is further to be noticed that in none of the cases recorded by myself or by other writers (with one exception) was the soreness of the nipple the result of lactation or its attendant troubles. In most cases the mamma had not been used for suckling for many years, whilst several of

the patients were single women who had never been pregnant. There was seldom any history of injury or of cancerous tumours in other members of the family.

With regard to the appearance of the diseased nipple and areola, it is clear that the lesions are not those of simple eczema. It is true that in the earliest stages of the disease there may be appearances which cannot be certainly differentiated from those of eczema, but as the process extends certain definite distinctions can be established.

At first there is a branny desquamation, with slight watery discharge which may be noticed either on the nipple itself or else on the areola. After a variable time small scales and crusts form, and when these are cast off a raw and excoriated surface may be exposed, which may again be covered by a scab. As the disease spreads it does so in a definitely eccentric fashion, so that the nipple remains throughout the centre of the affected area. In all recorded cases there has been no formation of vesicles or pustules, and the margin of the diseased tissues is sharply defined. Although commencing in, and at first confined to the nipple and areola, the morbid process may extend to and involve a considerable area of the skin covering the breast. In all cases there is slight stiffness and induration of the affected parts, so that the skin cannot easily be pinched up or thrown into folds.

In the later stages of the disease the nipple becomes retracted, and may be withdrawn to such an extent that its summit becomes depressed below the level of the surrounding integument. The surface is not equally denuded of epithelium, and small particles of the latter may remain as islands in the area of excoriation.

In most of the advanced and chronic cases the surface of the nipple becomes ulcerated, and this ulceration extends to the areola, and thence to the skin around it. As a result of this the whole nipple may be destroyed, and a large circular or oval ulcer with a definitely papillated surface may occupy the site of the areola. From

the commencement of the disease the affected parts are much more red and congested than are eczematous tissues, and the redness becomes more marked in the later stages of the affection. Most patients complain much of continued burning pain, but not of severe itching. In many cases the disease, after being comparatively quiescent for a long time, spreads with greatly increased rapidity. This is especially the case before the development of a cancerous tumour in the breast.

In all the cases in which a cancerous tumour of the breast has succeeded to the disease of the nipple and areola, the new growth has run the usual course of a scirrhus carcinoma, and has been found on clinical examination to present the usual characters of this form of tumour.

Histology.—The microscopical anatomy of Paget's disease was first described by Mr. Butlin,¹ and his descriptions have been confirmed by most other investigators. The lesions are essentially inflammatory in their nature, and differ in degree and extent according to the duration of the morbid process.

Mr. Butlin sums up his observations with the following conclusions as to the conditions found :

- (a) Proliferation with thickening of epithelium.
- (b) Infiltration of subcutaneous tissues.
- (c) Filling up of ducts, and infiltration of leucocytes around.

- (d) Acini enlarged and filled with epithelium.

Dr. Thin says,² "It is in this weaker layer of the connective tissue of the cutis (pars papillaris) that the changes take place which produce the disease of the nipple and areola which I am discussing. These changes consist in a complete destruction of the connective tissue of the layer, the space which is occupied being filled with a dense mass of exudation cells. The persistence of the epidermis in a more or less complete state distinguishes

¹ 'Med.-Chir. Trans.,' vols. lix and lx.

² 'Brit. Med. Journ.,' 1881, vol. i, pp. 760 and 798.

the condition from that of ulceration. . . . The affection of the nipple is neither eczema nor any known specific skin disease, but a destructive dermatitis of the papillary layer."

Messrs. Duhring and Wild¹ describe similar changes, and lay stress on the fact that the process appears to be most intense in the papillary layer of the skin, whence it spreads into the breast tissue and towards the surface.

Various other authors have described similar appearances, and Butlin and Thin have further figured and described certain peculiar appearances in the surface epithelium which they believed were due to endogenous cell formation.

The conclusions of these observers as to the inflammatory nature of the process have lately been confirmed by Darier and Wickham, but the observations of these authors which are of the most interest at present have reference to the presence of parasites in the affected parts. The parasites in question were first described by Mr. Darier, and in six other cases have been demonstrated by Mr. Wickham. These gentlemen are of the opinion that the vacuolated cells described by Butlin and Thin are really psorosperms, and have figured these parasites in the epithelial cells of the diseased tissues.

Mr. Wickham says that the parasites are always enclosed in epithelial cells, and present under various forms. In many cells there are only irregular protoplasmic nodules, which cannot be certainly proved to be psorosperms.

In a further stage of development the psorosperm distends the cell in which it is placed, and thrusts the nucleus to one side. It then presents itself as an oval or round body with a definite envelope, sometimes containing several nuclei. In many specimens the protoplasm of the parasite is shrunken and retracted, so that it does not fill its capsule, and leaves a clear space or vacuole. The contracted protoplasm usually occupies the centre of the capsule; in other cells the protoplasm is collected to

¹ 'Amer. Journ. of Med. Sci.,' July, 1884.

one side of the capsule. At a later stage of development it appears that the capsule bursts and discharges its contents. The capsule in its typical form has a double contour.

With regard to the condition of the breast tissue and of the cancerous growth, all observers, with the exception of Dr. Thin, describe the tumours found as "scirrhus cancers" or "spheroidal-celled carcinomas." Dr. Thin considers that the specimens examined by him were examples of duct cancer.

Mr. Wickham describes in two of his cases ingrowth of the interpapillary processes, and the presence of epithelial nests in some sections, and considers that in these specimens there was a commencing epithelioma. Inasmuch, however, as these cases did not clinically present the usual appearances of epithelioma, and did not in any way run the course of this disease, I do not think the evidence adduced justifies the conclusion arrived at. I am all the more inclined to this opinion because it is well known to all pathologists that at the edge of any old ulcer the interpapillary processes are large and branching, and are frequently mistaken by inexperienced observers for the typical ingrowth of an epithelioma.

The changes seen in breasts which have not become cancerous may be briefly summed up as inflammatory in their nature. They consist in—

(a) Proliferation of the epithelium of the ducts and acini, the cells of which may fill the tubes.

(b) Cell infiltration of the connective tissue, and subsequent formation of fibrous tissue, first around the ducts, and subsequently deeper in the breast.

With regard to the cases I have myself recorded, I would say that, from an examination of a very large number of sections, I am of the opinion there is little to add to the generally accepted descriptions of the affected tissues.

I have found in the earliest cases an infiltration of the papillary layer of the skin with leucocytes, and in many

specimens I have found the blood-vessels most unusually large and numerous. In such specimens the surface epithelium is in places thickened and desquamating, whilst the interpapillary processes are large, and penetrate deeper than is usual into the skin. The sebaceous and sweat glands do not show any change.

At a later period the epidermis becomes gradually thinned away, in proportion as the derma beneath is destroyed by the small cell-growth, and in the final stages of the process the whole epidermal layer is destroyed, and a granulating surface is exposed. In some specimens there is a definite papillary growth, caused apparently by a swelling and increase in size of the papillæ of the derma, which are covered at first by thickened epithelium.

As to the presence of psorosperms, I would first of all premise that in all my cases except the last one my original sections had not been specially stained or prepared with a view to the discovery of these parasites, the presence of which has only been described very recently. After reading Mr. Wickham's work, however, I prepared a very large number of sections taken from the breast removed by Mr. Baker in Case 11. I had also fortunately kept portions of tissue from six others of my cases, and these were again cut and re-examined. I shall allude later to the methods of preparation employed, but must take the present opportunity of expressing my indebtedness to Mr. Miller, one of my clerks, for the great skill and care exhibited by him in the preparation and mounting of many of the sections.

Considering first of all the specimens obtained from Case 11, I was at once struck by their similarity to the drawings made by Mr. Wickham. Indeed, so close was the resemblance that some of his drawings might well have been made from sections taken from this case. It was evident on even the most superficial observation that the bodies he had described as parasites were to be found in very large numbers in these specimens.

Under a half-inch objective the epidermis was seen to

contain innumerable oval or rounded bodies twice or three times as large as an epithelial cell. Many other smaller, but evidently similar, bodies could be seen in neighbouring cells, and it was noticeable that almost all the oval-shaped bodies were arranged with their long axes at right angles to the free surface. These bodies were confined to the epidermis, and were nowhere seen in the cutis vera. They were more numerous and well marked in the deeper parts of the epidermis and in the interpapillary processes than in the more horny layers, and some of them, though very few, were to be seen at the orifices of the milk-ducts, though not in the deeper parts of these tubes.

The bodies in question consisted apparently of a well-defined wall bounding a central clear cavity or cyst, in which lay protoplasmic granules and nuclei. In some of the cysts there were several nuclei which almost or quite filled the cavity, but in the majority the protoplasmic contents were scanty, and either occupied a small area in the centre or were collected to one side of the space.

Under a higher magnifying power it was seen that many of the smaller of the bodies mentioned could not be certainly distinguished from the surrounding protoplasm of the cells within which they lay. The larger bodies looked at first more like vacuoles in the epithelial cells than like psorosperms, yet it was evident that they were not merely vacuoles and nothing else. The regularity of their distribution in the deeper epithelial cells, the presence of several granular nuclei inside them, their presence in the areola in almost all the cases examined, and their absence from the surrounding skin convinced me that they could not be accounted for merely by a process of vacuolation.

On the other hand, after examining a series of psorosperms from the livers of rabbits it was evident that these bodies were not typical psorosperms, for in hardly any of them could I distinguish the envelope with a double contour which characterises these parasites, and upon which much stress is laid by Wickham.

It appears to me, after a very careful examination of some hundred sections, that it is impossible to affirm with absolute certainty that the bodies described by Wickham and myself are clearly psorosperms, and I think that the matter is one on which there may well be legitimate differences of opinion. My own opinion is that these bodies are probably psorosperms, and I am naturally influenced in arriving at this conclusion by the fact that in no other pathological process affecting an epithelial covered surface have I ever seen anything which in any way resembles the appearance presented by the innumerable bodies I have described as lying in swarms in the epithelial cells. It is certain that such bodies as these are not to be found in cases of simple eczema, and they are certainly not present in cases of real eczema of the nipple, as I have had an opportunity of proving by the examination of a breast which was removed for eczema and suppuration following on lactation. The appearances presented in a typical case of Paget's disease are in fact so striking that, when once familiar with the appearance under the microscope, no observer could fail to recognise other specimens of the disease, and could not mistake the sections for those of simple eczema or ulceration.

In no case have the psorosperms in a case of Paget's disease been successfully transplanted into animals, but it should also be remembered that experiments with undoubted psorosperms from rabbits have similarly failed.

With regard to the proportion of cases in which the psorosperms were found, I may say that in all cases where many sections were made the appearances I have described were to be seen, although some sections showed no evidence of parasitic growth, whilst others taken from the same breast showed many; the total number of barren sections was, however, very few. In the seven breasts, in each of which I had but four or five sections preserved, and of which I had no more material for further examination, I found the parasites in greater or less numbers, although in two cases they were so few as to require a

long search to establish their presence with certainty. In these cases also it should be remembered that no special staining methods had been employed.

There is but little to describe further as to the microscopical appearance of the breast tissue itself in these cases. I have in most found evidence of proliferation of the duct epithelium, although in some cases it was but slight, and in most breasts where there has been a tumour the remainder of the mammary secreting tissue has been normal. In those cases where the tumour has been developed in a part of the breast far removed from the nipple, I have generally found no change in the intermediate mammary tissue, and such changes as have been noticed have been limited to catarrh of the ducts. In many specimens I have found much small-cell infiltration around the inflamed ducts, and in some cases this cell-growth was replaced by fibrous tissue.

In all the cases I have examined the tumour was a typical spheroidal-celled alveolar carcinoma, evidently originating in the epithelium of the acini, and when the lymphatic glands were involved they contained similar growth. In none of the many sections examined did I find any evidence of psorosperms in the cancerous growth either in the breast or in the lymphatic glands, although careful search was made in order to confirm this observation.

In staining my sections I used hæmatoxylin, osmic acid, methylen blue and rubin, eosin and picro-carmin.

The true pathology of "Paget's disease of the nipple" is a matter of considerable importance if the disease is to be treated rationally, and if the cancerous growth which so often ensues is to be obviated.

Sir James Paget, Mr. Butlin, Dr. Goodhart, and others of the earliest observers did not make any suggestions as to the cause of the disease of the nipple, and it was left to Dr. Thin to be the first to formulate a theory as to its causation. This observer suggested that the disease of the nipple was not itself primary, but that it was the

result of a cancerous growth originating in the ducts, and was caused by the irritation of the discharge set up by the tumour ; or, as Dr. Thin puts it, "the hypothesis is that a change takes place in the columnar epithelium at or near the mouths of the ducts, which exerts a destructive influence on the adjacent connective tissue, and is in reality the first stage of cancer." As already stated, Dr. Thin considered that the tumours in the breast were "duct cancers."

It is now many years since Dr. Thin first propounded these views, and I do not know whether he still holds the same opinions. I think, nevertheless, it as well to point out that the observations published since his papers do not lend any support to his views, and I would submit the following arguments against their acceptance.

1st. There is no evidence in any recorded case that such a discharge from the nipple as is supposed to occur has ever been seen ; and although it was carefully inquired for in all my cases, in none of them was any discharge present.

2nd. Duct cancers are soft, vascular, and friable growths, whilst in all the recorded cases of Paget's disease, as well as in those I have seen, the tumours have been hard and scirrhous. Duct cancers are much less liable to affect the glands and to disseminate than were the tumours described by other authors or seen by myself.

3rd. In a recent volume of 'St. Bartholomew's Hospital Reports'¹ I have described a series of six cases of "duct cancer," and have collected the reports of other published cases. In almost all of them there was discharge of much blood-stained fluid from the nipple, but in not one of them was there any "Paget's disease."

4th. The histories of undoubted cases of duct cancer are very different from those of Paget's disease, and it is not possible to believe that in cases where this condition of the nipple has lasted for as long as nine, ten, or even twenty years without the development of any tumour,

¹ Vol. xxvi, p. 263.

there has been nevertheless a cancerous growth during the whole of such a period.

5th. In cases where the mamma has been removed before the development of any evident tumour (with the exception of one case of Dr. Thin's), no cancer has been found on subsequent examination of the breast, and such patients have remained subsequently free from tumour growth. On the other hand, when definite tumours have been present the course of the case has been that which is common in other examples of scirrhus carcinoma.

It is then evident that some other origin must be sought for a disease which is so evidently *sui generis*, and I have already pointed out that the cause is not to be found in the inflammatory lesions of lactation, nor in any antecedent condition of the breasts such as chronic mastitis.

Accepting, therefore, that the morbid condition of the nipple precedes any morbid change in the mamma, it is evident that the cause of a lesion so persistent and chronic must itself be of the same nature. It is certain that no transient cause could account for so long lasting a disease. Further, but very little consideration is required to negative the suggestion that the cause is a constitutional one, for the patients whose breasts are affected are otherwise healthy, there is in almost all no family history of cancer, and the fact that the area of skin involved is so small a part of the whole body surface, added to the equally important fact that but one nipple is commonly attacked, indicates that the origin of the affection is not to be sought in any constitutional predisposition.

Quite lately, however, Drs. Darier and Wickham have attributed the disease to the presence of the psorosperms in the diseased skin already alluded to, and their observations have been confirmed by Mr. Jonathan Hutchinson, jun., in a case recorded by him in the last volume of the 'Transactions of the Pathological Society.' I have already expressed my opinion on the presence of psorosperms in my own sections.

With regard to the parasites themselves, it may be said

that psorosperms are found under very different forms, and for full details of their mode of growth and their varieties I would refer to the admirable paper by Dr. Delépine published in vol. xli of the 'Transactions of the Pathological Society.' From the observations of this author, who studied the parasites in the livers of rabbits, it would appear that psorosperms may be found—

1st. "As small, round, oval or elongated, structureless masses, mixed with a number of granules, which are of smaller size, and possibly indifferent." These bodies, when inside epithelial cells, cannot be differentiated from protoplasmic granules.

2nd. "After a short time, however, bodies looking very much like nuclei appear in various parts of the [epithelial] cells. The cells containing these bodies are larger than the normal ones. These nuclear-looking bodies are probably nothing more than small protoplasmic masses contained in a large vacuole-like cavity; when the small mass is slightly contracted a space remains between it and the walls of the cavity, and this space looks like a membrane with double contour."

3rd. "The body now assumes distinctive features, which render its recognition easy. The small amœboid mass contains a nucleus-like body, which itself encloses one large nucleolus or several rounded granules. The protoplasm surrounding the nucleus is coarsely granular, and many of the granules stain black with osmic acid, and brown with iodine."

4th. "The parasite assumes a distinct ellipsoidal shape, and becomes larger than an ordinary epithelial cell, and distends the enlarged cell in which it is lodged. An external layer (ectosarc) is at this stage distinct from the granular endosarc; the granules are large, and distributed equally all over the body of the organism: the nucleus is indistinct, and seems to be replaced by a large mass of highly refractive granules, which stain quite black with osmic acid and dark brown with iodine. A nucleus may, however, be demonstrated at this stage by staining the

specimen with rubin and double staining with methylen blue. . . . The organism is distinctly contractile, and may assume a nearly globular shape, or an elongated, almost vermiform appearance. It is often irregular, being, for instance, flat on one side and convex on the other. The mass may also contract within the cavity containing it, so as to leave a space between itself and the protoplasma of the cell. . . . They measure from 30 to 35 mm. in length by 15 to 20 mm. in width."

The parasite may escape from the cell containing it, or its capsule may burst and allow of the escape of the protoplasmic contents.

Psorosperms are widely distributed in the animal kingdom, and are found in amphibians, fishes, birds, and mammals. In fish they are found in all the organs ; in the higher Vertebrata chiefly in the alimentary canal and the liver. In rabbits they are especially common in the latter organ, and according to Dr. Delépine occur in 92 per cent. of all animals examined.

The next point for consideration is the part played by the parasite in causing the diseased conditions amongst which they are found ; for, assuming that they really occur in all cases of Paget's disease, it by no means follows that they cause all the lesions associated therewith.

Three theories may be formulated.

1st. The parasites may be implanted in the diseased skin, and may grow on a surface the cells of which are already damaged.

2nd. The parasites may cause the disease of the nipple.

3rd. The parasites may be the direct cause of the cancerous tumours.

With regard to the first suggestion I would say at once that I do not consider the presence of the parasites to be merely fortuitous. Considering that they have been found in all the cases examined in France, in most of the specimens prepared by myself, and that earlier writers have described appearances which might well be due to the presence of psorosperms, I am myself of the opinion

that these facts alone are sufficient to negative the theory that their presence is merely a matter of chance. It is further certain that psorosperms are not to be found in ulcerated or raw surfaces as a rule, and I have myself failed to find them in any other tissues or diseased organs I have examined.

With regard to the causation of cancer by psorosperms Dr. Wickham appears to me to hold opinions which are not in any way supported by facts. He says that he considers the parasites to be the *direct* and specific cause of the cancer, and in support of his contention states that he has found the parasites in the cells of the new growth. If, however, Dr. Wickham's work be carefully examined, it will be seen that he merely depicts the presence of the psorosperms in the cells of what he describes as "epithelioma," and not in the cells of any definite tumour found in the breast. As I have already stated that there is no good reason for believing that epithelioma really existed in his cases, it is nearly certain that the cells in which the parasites were seen belonged to interpapillary processes.

I am the more strongly of the opinion that the psorosperms have no specific influence on the causation of the cancer for the additional reasons that out of many hundred sections examined none of these parasites were found in any part of a scirrhus tumour ensuing upon Paget's disease, nor did I find any traces of them in the secondary growths in the lymphatic glands.

As additional arguments against the theory that the psorosperms are the direct and specific cause of the cancer, it may fairly be urged—

1st. That, in numerous cases where the disease of the nipple was of long standing, they have probably existed for many years in the nipple and the areola, and have yet caused no cancer, whereas if they possess some definite specific influence this could scarcely be the case.

2nd. That in the many animals in which they exist they are not associated with tumour growth.

3rd. That in the vast majority of cases of cancer in

the human subject psorosperms are certainly not present.

4th. That when they have been found in the human subject, apart from cases of Paget's disease, *e. g.* in the liver, the ureter, &c., they have not been associated with cancer.

I have, therefore, no hesitation in concluding that the problem of the etiology of cancer has not been solved by the discovery of these parasites in the nipple, and that they have no specific influence in causing cancerous growth.

The facts, as far as we know them at present, rather seem to me to point to the conclusion that the disease of the nipple is the direct result of the presence of psorosperms, and that the raw and irritated surface bears the same relation to the development of cancer subsequently as does an old ulcer of the leg or of the tongue to an epithelioma.

A further problem to be solved is how the parasites obtain a footing in the areola, and why they should attack this portion of epidermis. To this, I think, we have at present no satisfactory answer. It is, of course, reasonable to suggest that the skin of the areola probably shares with the mammary tissue in the degenerative changes which occur late in life, and thus becomes predisposed to morbid processes, and less able to resist parasitic growth.

But if this theory be accepted it must still be explained why more evidently damaged skin in other parts of the body is not attacked in a similar way, for it is certain that portions of eczematous or ulcerated skin are not commonly attacked by psorosperms. The mode of infection of the breast is again a matter in which as yet no evidence is forthcoming, and no good reason has yet been assigned for the depth beneath the areola at which the cancerous growth is sometimes placed.

The development of a tumour at some distance from the irritation which is supposed to cause it is not paralleled by the known histories of growths in other parts of the body.

DESCRIPTION OF PLATE VI.

Thirteen Cases of Paget's Disease of the Nipple (ANTHONY A. BOWLBY).

FIG. 1.—Section of the skin of the areola from a case of Paget's disease. The section is taken from a part beyond the area of excoriation, and shows in the midst of the normal epithelial cells numerous oval or rounded spaces with well-defined margins. Some of these spaces are occupied by nuclei, others are empty ($\frac{1}{8}$ inch Crouch).

FIG. 2.—Section through the same area of skin under a higher power ($\frac{1}{8}$ inch Crouch). It shows one of the rounded spaces occupied in part by a granular mass of protoplasm with a nucleus. The space has been formed by the distension of an epithelial cell, and the nucleus of the cell can be seen at the lower part of the space and a little to the left of it.

FIG. 3.—Section showing a cavity occupied by three oval granular masses surrounded by protoplasm (Crouch $\frac{1}{8}$ inch).

FIG. 4.—Section of an empty vacuolated cell, greatly flattened, the nucleus of which may be seen to the left of the space.

Fig 1.

Fig 2.

Fig 3.

Fig 4.