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THE PATHOLOGY OF THE SKIN FROM THE EYELIDS AND THE NASO-FACIAL GROOVES.

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It must have struck many how frequently new growths of the face have occurred in the oculo-facial and naso-facial folds. There is scarcely a human being whose skin below the lower eyelid or at the junction of the nose and the cheeks, when carefully examined, does not reveal the appearance of several small glands, some of which may be so enlarged as to be pathological.

The mere looseness of the skin over this area making the underlying structures more apparent will not account for the phenomenon, the explanation only being forthcoming when the same regions in the lower mammalia are studied.

If a microscopical examination of the skin at the base of the lower eyelid is made it will reveal in almost every individual specialised embryonic epithelial structures, as lanugo hair-follicles, sweat, and sebaceous glands.

On a larger scale they may be considered pathological, and when the growth is limited to the lanugo hair-follicles the term "tricho-epithelioma" may be applied, when to sebaceous glands, sebaceous adenoma, and when to sweat glands, syringoma.

The tumour may consist of any one of these alone or mixed, and when mixed the different types may be present in the same area, or a type may be found pure in one part of the section and another type pure in another part of the section.

None of these types increase in size, ulcerate, or become malignant,

for the simple reason that they consist of nearly mature epithelial cells, or perhaps it would be better to say cells which cannot wander from a special form, because they have arrived at that stage when a function has been appointed them, and because they occur in tissue in which they normally would be, viz. corium. This is not the case with rare tumours, which when present are common in the situations under discussion, viz. epithelioma adenoides cysticum, and multiple rodent ulcers. The swellings not only increase in size up to a certain point, they also ulcerate, but without extending further or giving rise to metastases. The cells of the tumours are epithelial in origin, but whether of the type destined to be hair-follicles or sweat-glands, etc., although probably the former, cannot always be ascertained, since in some cases the cells have not arrived at the stage when they are to serve a purpose, *i. e.* they are more embryonic than the cells of the tricho-epithelioma, syringoma, etc. Still more is this the case with a tumour which is most commonly situated in the orbito-facial and nasofacial folds, and which, once it has ulcerated, tends to spread and destroy all the structures in the neighbourhood, but without giving rise to metastases or glandular enlargements—the so-called rodent ulcer. The controversy as to the origin of a rodent ulcer, whether it arises from the inner root sheath of the hair-follicle or at the point of exit of the sebaceous gland into the hair-follicle, because the cells are spindle in form, seems so much waste of energy, as the cells constituting a rodent ulcer are embryonic epithelial cells of a very early type, when the spindle shape is the rule rather than the exception; the cells being laid down at a time when hair-follicles and sebaceous glands, etc., are unthought of. When development takes place in an area in which the structures have matured, and in tissue in which they are not wont to occur, the cells grow in a peculiar way, and so constitute what we call a malignant growth.

A rodent ulcer is the tumour *par excellence* of the Cohnheim theory, and when we know a little more about carcinoma and sarcoma I should not be surprised to find that they are caused by a specific agent (non-bacterial), which would separate them distinctly from innocent tumours and rodent ulcer, both of which will lend more and more support to the Cohnheim theory of embryonic rests. But, on the other hand, malignancy may be determined by the depth in the corium at which the tumour arises, by the position in which it

takes origin, as some places are richer in lymphatics than others; so that metastases are of easier production. Also by the degree of reactionary inflammation around the growth, inhibiting cellular transmigration. Also by the resisting powers of the host in terms of antibodies, etc. The lowering of the surface tension in a mixture of malignant serum and malignant antigen, as evidenced in the meiostagmine reaction lends support to the last suggestion. The whole question is at present shrouded in mystery.

The presence of cell nests in a rodent ulcer have raised many difficulties both as regards the diagnosis between a rodent ulcer and

squamous-celled epithelioma, and the origin of the former; but quite unnecessarily.

Characters typical of an epithelioma may be found alongside a rodent ulcer, but not *vice versâ*, and the explanation is no doubt due to the fact that the rodent ulcer acts as an irritant and so causes an abnormal epithelial growth with cell-nests, as occurs in a skin exposed to the sun's rays or X-rays. Again, small horny nests may be found in the rodent ulcer tissue itself, but it will be noticed that the cells around are cubicle, more like the normal rete cells than the typical spindle cells. The epidermis primarily consists of one layer of spindle cells, and from this layer other cells cubicle in form arise, and these in turn become transformed into horny tissue at quite an early stage in embryonic existence, before hair-follicles and other

specialised epithelial structures are considered. Then is it not possible that such rodent ulcers arise from rests of a later date when the cells have already learnt the transformation into horny tissue? Possibly it would be better to limit the term "malignant" to carcinoma and sarcoma, calling the rodent ulcer an ulcerating nævus, which in point of fact it really is.

A concomitant feature in nearly all cases of growths from these regions is the presence of milia (Fig. 1). How these tiny round hard white swellings—which shell out on incising the skin over, and

FIG. 1.

which under the microscope appear as cysts filled with some homogeneous substance—are formed, opinions differ widely. No doubt they are formed in various ways: (1) From a dilated lanugo hair-follicle. Fig. 2 shows this admirably. A case of a rodent ulcer, in the surrounding inflammatory tissue of which is seen a typical milium, to which is attached part of a sebaceous gland, and below is the hair-root with its papilla. (2) From a dilated sweat-duct: Schidachi was able to produce sweat-gland cysts by shaving off a piece of skin from the pad of a cat's foot parallel to the surface, stretching the same and then laying it back to let it grow. As the sweat-ducts did not overlap, cysts were produced. (3) From an epidermic inclusion, which has become cystic, since they occur in skin which has

FIG. 2.

Sebaceous adenoma.

Rodent ulcer tissue : milium.

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formed over a burn, in the new skin which develops after a bulla in pemphigus, Epidermolysis bullosa, etc.

I will now mention a typical case of each type of epithelial growth referred to above.

CASE 1.—*Tricho-epithelioma papulosum*.—E. D—, aged 48 years, housewife, came up to St. Bartholomew's Hospital complaining of a scaly eruption on her right shin. She was also noticed to have some pale, slightly raised nodules on her face. When attention was drawn to these the patient said that they were of no moment, gave rise to no inconvenience, and that she had had them for years.

These nodules were about the size of a lentil, about ten in number,

and situated on the lower border of the lower eyelid, and extending from the inner to near the outer canthus, where they somewhat decreased in number and size.

Both sides of the face were equally affected. One or two nodules were found on the upper eyelid, and at the outer canthus there were a few milia. Each lesion was about the size of a lentil, circular, very slightly raised above the level of the skin, flat on surface, and the skin over was paler than elsewhere.

They felt hard, did not disappear on pressure, but became quite white. Patient said she had had them as long as she could remember, but believed they first appeared when she was fourteen or fifteen years of age.

The mother and one sister had the same condition. Three other sisters were free.

There was no history of any male member of the family being affected.

A nodule was excised for microscopical examination (Fig. 3).

The epidermis is flattened, all papillary arrangement has disappeared.

The number of layers of the epidermis is somewhat smaller than normal, but the gradual transition from the basal cell layer to the stratum corneum remains intact.

FIG. 3.

The basal cell layer is pigmented more than usual.

Along the epidermis, processes are to be seen dipping down into the corium; each process is cystic, the space being filled with horny material, in the centre of which lies a lanugo hair. Oddly enough in some of the cysts acne bacilli are to be seen. These have probably penetrated from the surface and might have had something to do with stimulating the growth formation. Notice the age at which the tumours occurred, the age when acne most commonly commences.

In places where the lanugo hair has been able to penetrate the epidermis it is surrounded with several layers of horny material,

having an arrangement as seen in a transverse section of an onion through its middle. Around these epidermal processes there is no cellular infiltration (inflammation). In the corium are numerous hair-follicles, all of which are cystic.

The walls show the transition stages from the stratum spinosum to the stratum corneum, as is seen in the epidermis, with the only difference that the basal cell layer remains quite free from pigment.

In the centre is a mass of horny material; distinct cells are to be seen containing eleidin granules.

In the centre of each horny cyst a lanugo hair is to be found.

Only here and there are any of the hair-follicles surrounded by or have sebaceous gland elements in their neighbourhood.

Around each hair-follicle is well organised connective tissue, arranged circularly, and consisting of spindle-cells with well-stained elongated nuclei.

The vessels running in this connective tissue are dilated and the walls are thickened.

Also surrounding the hair-follicles, especially marked at the base and sides, is a dense cellular infiltration. This cellular infiltration consists largely of plasma-cells and small round-cells.

The marked feature of this cellular infiltration is the abundance of mast-cells, many of which, as usual, stain red with polychrome methylene-blue, but the protoplasm is homogeneous, mucinous in appearance, non-granular, a type of mast-cell which Unna described in *Molluscum fibrosum*.

In the centre of the tumour is a large horny cyst surrounded by epithelium which branches in a few places.

Towards the centre of these branches the cells become larger, stain less distinctly, and the spongioplasm becomes divided up into loculi—in short, the cell becomes a sebaceous gland-cell.

The transformation is not quite complete, since there is not that well-marked differentiation of the cells and the clear well-stained nucleus and network-like protoplasm seen, as in normal secreting sebaceous gland tissue.

These cells obviously are embryonic and functionless.

In other places scarcely any transition can be made out; the epithelial cells have simply become swollen, refuse the stain, have lost their nuclei and are degenerated cells.

The collagenous bundles are broken up and are not found in the new growth.

The elastic tissue has in part disappeared and nowhere shows its fine fibrillary character, being instead broken up and occurring in clumps or masses.

In no part of this section are there any traces of either sweat-glands or sweat-ducts.

One of the cysts in the section shows an intra-cystic epithelial growth. In this cyst there is no lanugo hair and no horny material; the cells of the wall not so well differentiated as elsewhere, the cellular infiltration around is very much more marked, and no doubt the cells constituting this cyst are of an earlier date than the rest.

CASE 2: *Syringoma*.—A girl, aged 12 years, came up to hospital complaining of some spots on her chest. According to the mother's history the spots appeared when the child was one year old. No other member of the family was affected.

The lesions were very faint yellowish-white, raised above the surface of the skin, and varied in size from that of a pin's head to a lentil. The lesions were smooth on the surface and embedded in the corium, so that the skin was not movable over them; they were sharply circumscribed, although the bigger ones were not invariably regular in outline. The lesions gave rise to no subjective symptoms. The area most affected was the chest over the sternum and beneath the clavicles, and in these situations the largest lesions were to be found. The neck was also involved, lower eyelid on left side, lateral walls of thorax and abdomen, and inner sides of thighs.

Histology (Figs. 4, 5, and 6).—The epidermis over the new growth, which is situated in the upper portion of the corium, is unaltered. The corium itself is unchanged, except for the presence of the epithelial elements, from which the new growth arises, and also for a slight increase in the fixed connective-tissue cells.

The new growth consists of the following structures:

(1) Solid cords and nests of epithelial cells.

(2) Cords and nests of epithelial cells which are hollowed out in the centre, the walls of the former being made up of two layers of epithelial cells, the latter of several layers with the central cells degenerated and staining badly. The hollow cords resemble in every way the normal sweat-ducts.

FIG. 4.

FIG. 5.

(3) Small cystic spaces with a colloid content. The walls are made up of one or two layers of epithelial cells; in parts the cells are indistinct, and the nuclei, when present, are elongated. The colloid material is most marked in those the cells in the walls of which have degenerated, and appears to be a degeneration product of those cells.

Although the case just mentioned is one in which the lesions are widely distributed over the body, the lesions on the left lower eyelid

FIG. 6.

are identical with those seen so commonly only in these situations, and which cannot be distinguished from a tricho-epithelioma or a sebaceous adenoma until a biopsy has been made. This is the condition first described and christened by Kaposi and Biesadecki as *Lymphangioma tuberosum multiplex*. The few cases described of hyaline degeneration of the skin—a painting of a case with a microscopic section is to be seen in Morgan Dockrell's atlas—are nothing more or less than typical cases of *syringomata*.

CASE 3, *sebaceous adenoma*, was a man, aged 43 years, who had had flat whitish lesions in his oculo-facial folds as long as he could remember. The lesions were sharply circumscribed and about the size of lentils. The only difference clinically that I could ascertain between this condition and those already described was that each papule seemed to be divided up into loculi, not unlike a wasp's nest, and the loculi were slightly more transparent than usual.

FIG. 7.

Histologically the corium was filled with sebaceous gland tissue, either fully formed or in parts partly transformed from the epithelial cells, from which the gland-cells took their origin (Fig. 7).

CASE 4: *Mixed tumour*.—A woman, aged 36 years, had noticed some "white spots" beneath her lower eyelids since she reached the age of puberty. The lesions were round, white, smooth on the surface, slightly raised, and clinically quite indistinguishable from any we have already described.

A histological examination of this mixed tumour showed the following points (Fig. 8, Plate) :

FIG. 8.

Syringoma.

Sebaceous adenoma.

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In the left-hand part of the section beneath some lanugo hair-follicles (tricho-epithelioma) are some small cysts, below which again are some solid cords of epithelial cells, both constituting a syringoma.

The lanugo hair-follicles persist in all parts of the section, but in the right-hand side is seen a typical sebaceous adenoma. Some of the cells are well formed sebaceous gland-cells, while others have not yet been formed from the epithelial cells destined for the purpose.

Another type of tumour occurring in these situations is the Epithelioma adenoides cysticum of Brooke. The lesions are more widely spread on the face than in the cases just described, are rather larger, more elevated, and not so flat on the surface. The condition occurs in women, and the lesions appear in childhood. The marked feature about the disease is the strong hereditary element, mother and daughter being usually affected. Histologically the lesions consist of masses of epithelial cells which are highly branched; in the centre of the masses there may be a cyst in which lies a lanugo hair, or the cyst is filled wholly or in part with some homogeneous substance as is found in a milium.

Another condition found also in the same regions, the earlier lesions of which are indistinguishable from the case just described, is the multiple rodent ulcer.

CASE 5 (reported by Dr. H. G. Adamson in the *Lancet*, October 17th, 1908, p. 1133): "*Mr. W. Bruce Clark's case*.—(This case was demonstrated by Mr. Bruce Clarke at a meeting of the Clinical Society of London on April 24th, 1903, and the following report of the case is printed in the *Transactions of the Clinical Society*, vol. xxxvi, 1903, p. 271) (Fig. 1).

"*Daniel C—, aged 37 years. History of condition*: Two and a half years ago he first noticed a small red spot near the outer canthus of the left eye, which gradually grew in size. Seven months later a second spot occurred near the outer canthus of the right eye and increased slowly in size. At about the same time another ulcer appeared on the forehead above the right eyebrow. This one has healed of its own accord, but has left a scar exactly similar to the scarring which has occurred round the ulcer underneath the eye. There is another ulcer on the inner side of his nose, and one on the under lip and another on the side of his neck, but he cannot give

any accurate account of the dates at which these appeared. *Present condition* : In addition to these six patches which have been already described, there are numerous pimples on his face. They vary from the size of a millet-seed to that of a split-pea. As many as twenty or thirty of these can easily be counted. Were it not for the fact that he states that the ulcerated patches all began with simple pimples, they would perhaps barely deserve attention, as they have the appearance of small sebaceous glands in which the ducts are blocked. Two of these pimples have been excised and examined microscopically, as well as pieces from the six ulcerated patches above alluded to. They one and all exhibit the microscopical appearance of typical rodent ulcers, as are displayed under the microscope. The patient is now undergoing electrical treatment with X-rays four times a week, and is deriving considerable benefit from it. The ulcers are healing rapidly. *N.B.* : The patient remained in hospital about six weeks after he was shown, during which time the ulcers completely healed; but the pimples, though they improved and diminished in size, and in some instances entirely disappeared, had not altogether vanished. The patient declined to remain any longer.'

"Later the patient was again in the hospital, and many of the lesions were excised and others were scraped. In 1907, by the kindness of Mr. Bruce Clarke, I (Dr. Adamson) had an opportunity of seeing this patient. There were then altogether seventeen lesions upon the face, varying in size from small nodules of the dimensions of a pin's head up to ulcerated lesions of $1\frac{1}{2}$ in. in diameter. There were also scars marking the excision or scraping of former lesions. For purposes of description the lesions then present may be divided into groups as follows :

"(1) Six nodules, reddish in colour and semi-translucent, of the size of a large pin's head to that of a millet-seed, and distributed over the left cheek and the forehead.

"(2) Nodules of the size of a millet-seed to that of a split-pea, dull red in colour, raised, but flat on their surface, firm and semi-translucent; a group of three upon the right temple at the outer angle of the orbit, two just below the left ala of the nose, one on the left upper eyelid, and one on the left brow.

"(3) Larger lesions, which have undergone treatment on a former occasion; two on the forehead, one on the left ala of the nose.

These were from $\frac{1}{4}$ in. to $\frac{1}{2}$ in. in diameter, with a central scar and a marginal rolled edge. (The photograph was taken before these had recurred, and shows scars only at these points.)

"(4) An irregularly shaped lesion, partly scarred, partly ulcerating, and partly crusted, extending from the inner canthus of the right eye on the right cheek, here and there showing a raised nodular edge. This lesion measures $1\frac{3}{4}$ in. in length by $\frac{3}{4}$ in. in diameter.

"(5) A similar ulcer, 1 in. by $1\frac{1}{2}$ in., involving the inner canthus on the left side, the lower lid, and the left cheek.

"(6) About the forehead and cheeks there are scattered a few milia, but there are none on the lesions themselves."

Histology (from sections kindly given to me by Mr. Onslow Ford).—Beneath the ulcerating surface is a new growth of spindle cells; the cellular masses are irregular in outline, and in many places branch—features typical of a rodent ulcer.

Only here and there are cysts to be found in the spindle-celled masses, but not of the type found in those cases described by Jarisch. Those present in this section are empty and probably spurious. Around the new growth is a dense cellular infiltration, consisting of polymorphonuclear leucocytes, plasma-cells, and lymphocytes.

The most interesting part of the section is the occurrence of a true Adenoma sebaceum in the healthy corium surrounding the new growth, and also masses of epithelial cells not quite mature, on their way to form sebaceous gland-tissue. It is not uncommon to find a tricho-epithelioma and a sebaceous adenoma in the same section as a rodent ulcer (see Fig. 2 Plate), although the simultaneous occurrence has, as far as I know, not been described. The combined growth undoubtedly speaks largely in favour of a rodent ulcer being a nævus, and having its origin in epithelial cells which are not mature enough to form any specialised epithelial structure.

Although I have described only one case of each type, it is only with the idea of giving the main clinical and histological features thereof, since if several cases are microscopically examined, although the clinical aspect of all may be the same, extraordinary variations are to be met with.

For instance, in the so-called Epithelioma adenoides cysticum—a bad name, as it gives no clue to the adenoid tissue affected—one may find lesions more closely resembling the Tricho-epithelioma papulosum

as described in Case 1, while, on the other hand, the origin of the epithelial masses from the lanugo hair-follicles may be so difficult to make out, because of the more embryonic nature of the cells, that the condition becomes more like that seen in multiple rodent ulcer.

Take multiple rodent ulcer; in some cases cysts are evident, hence the name multiple benign cystic epithelioma. The walls of the cysts consist of cubicle cells almost indistinguishable from mature rete cells, so that the epithelial masses in which the cysts occur suggest an origin from the lanugo hair-follicles. In other cases, again, the epithelial masses consist of spindle cells only, and a diagnosis could not be made from an ordinary rodent ulcer.

See again how the common single rodent ulcer itself varies. Some consist of pure spindle cells, while in others cubicle cells are found with horny matter in the centre.

These variations are links in one pathological chain, and entirely depend upon the time the cells forming the tumour were laid down in their embryonic life.

The most mature are the true adenomata, viz. tricho-epithelioma, sebaceous adenoma and syringoma. Going back we meet with a condition which can be said to arise from lanugo hair-follicles—a tricho-epithelioma, but at a period when sebaceous gland and sweat-gland tissue has not been organised, as seen in Brooke's type, which would be better called *Tricho-epithelioma papulosum* (Brooke). Still further receding we reach the condition when the origin of the epithelial masses from the lanugo hair-follicles is by no means clear, although suggested. As such lesions in which this condition histologically is found clinically ulcerate, they should be called *Tricho-epithelioma papulosum ulcerans*.

Lastly, in those cases in which the cells are too embryonic when the epithelial masses are formed from the primary epithelial cells before hair-follicles are even conceived, the term "rodent ulcer," be they single or multiple, should stand.

What is the reason for the frequency of these growths in this neighbourhood? Generally speaking cutaneous new growths, which are usually of epithelial origin, are more common in man than in the rest of the mammalia, and new growths are more likely to occur in situations which once served a purpose. Most mammals have specialised hairs in the orbito-facial fold corresponding to the supra-

orbital eyebrows and no doubt serving the same purpose; further important glands occur in both the orbito-facial and naso-facial folds of many animals.

Owing to a more or less uniform distribution of sebaceous and sweat-glands, man stands in no need of those facial glands so characteristic of many antelopes.

The commonest epithelial growth is in connection with the lanugo hair-follicles—tricho-epithelioma—growths which are usually limited to the face, and which in my opinion arise in those lanugo hair-follicles which are atavistic of the lower eyebrows. Lanugo hair is embryonic, is atavistic, and a remnant of the complete body covering with hair, which is typical of most of the mammals.

The adult members of the orders Sirenia and Cetacea, though hairless, have their young in the case of the former covered with hair, and in the latter with hair limited to the face. The only exceptions are the Beluga or white whale and the monodon or narwhal. Young elephants have lanugo hair like the human. The lanugo hair-follicles soon disappear, but some on the face remain, and they are those which are atavistic of the specialised hairs which ought to have formed the lower eyebrows.

Syringoma is, again, a common new growth.

In man the sweat-glands are uniformly distributed over the body, but in many animals they are localised—for instance to the soles of the feet in some of the rodentia—or they may be completely absent as in the Sirenia and Cetacea.

In animals most of the sweat-glands open into the hair-follicles, but some have their own point of exit in the epidermis, the latter being the case in adult life only.

As in man the sebaceous glands in animals are usually associated with the hair-follicles, but can be found alone, viz. peri-anal glands, Tyson's glands, etc., but these are probably specialised glands.

So closely are the sebaceous glands connected with the hair-follicles that when the hair of the Cetaceæ disappears the sebaceous glands vanish also.

Like the sweat-glands, the sebaceous glands are in some animals localised, for instance, to the snout and anus in the manis or scaly ant-eater, or they may be absent altogether, although the animal be well covered with hair, viz. *Cholæpus* and *Chrysochloris*.

The specialised skin-glands, of which man possesses none, perhaps, with the exception of Tyson's glands, so characteristic in other mammals, are made up of either sweat- or sebaceous glands, or a mixture of the two. They are situated in different parts of the body in the various orders, the face glands being typical of the artiodactyla and so on.

Of the face glands there are two kinds :

(a) Supra-orbital as in *oryx beisa*.

(b) Sub-orbital or ante-orbital.

The second group is typical of certain deer, and in most cases designated by a fold of skin or pocket, the edges of which are sometimes inverted; these are the so-called tear grooves—*folliculi lacrymales*.

In my opinion the small tumours so frequent below the lower eyelid, which may be made up of lanugo hair-follicles and often of sebaceous and sweat-gland tissue, are reversions to the face glands of deer.

The tumours are often mixed, which is another point in favour, since the anti-orbital gland of the gnu is made up of both sebaceous and sweat-glands, which may open separately in the epidermis or direct into the hair-follicles.

If the sebaceous gland type of tumour be carefully examined it is often found with remains of a lanugo hair-follicle in the centre. Human beings are not only those affected with epithelial growths below the lower eyelid; I have seen the same in monkeys.

Summary.—Tumours affecting the orbito-facial and naso-facial grooves are of epithelial origin and atavistic of both the lower eyebrows and the specialised glands found in these regions in many of the mammalia. There is probably not an individual which will not show some trace of epithelial embryonic tissue (*nævus*) when a section is made from the skin of these grooves.

All the tumours, from a simple lanugo hair-follicle growth to a rodent ulcer, are links in one chain, the former being the head or most mature, the latter the tail or most embryonic. As they are all links the histological differences of one clinical entity is at once explained.

Bullous transformation of vesicular Dermatitis herpetiformis.