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PRACTICAL HANDBOOK

OF THE

PATHOLOGY OF THE SKIN.

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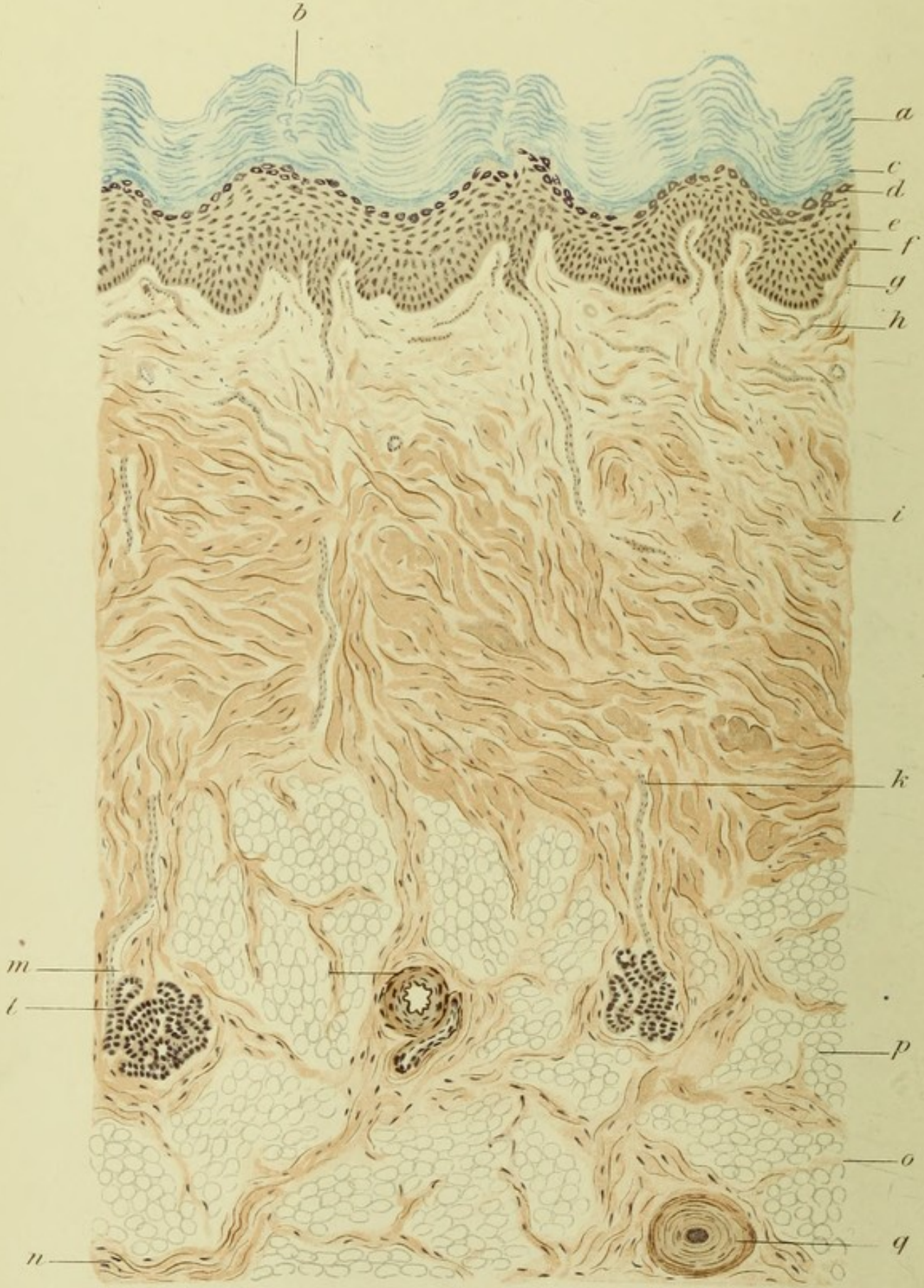

J.M.H.M. del.

PLATE I.

DRAWING FROM A SERIES OF SECTIONS OF THE SKIN OF THE PALM OF THE HAND. (× about 150.)

Stained with polychrome methylene blue and neutral orcein.

a. Stratum corneum.
b. Sweat-pore.
c. Stratum lucidum.
d. Stratum granulosum.
e. Stratum Malpighii.
f. Stratum germinativum.
g. Papilla of the papillary layer.
h. Blood-vessel.
i. Corium and fibrous bundles; some cut across.
k. Sweat-duct.
l. Sweat-coil.
m. Artery and vein.
n. Trabecula between fat-lobes.
o. Septum between lobules.
p. Fat-cells.
q. Pacinian body.

PRACTICAL HANDBOOK

OF THE

PATHOLOGY OF THE SKIN

AN INTRODUCTION TO THE HISTOLOGY, PATHOLOGY, AND BACTERIOLOGY OF THE SKIN, WITH SPECIAL REFERENCE TO TECHNIQUE.

BY

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WITH EIGHT COLOURED AND THIRTY-TWO BLACK AND WHITE PLATES

LONDON

H. K. LEWIS, 136, GOWER STREET

1903

TO

THE MEMORY OF

MY FATHER.

PREFACE.

THIS handbook is intended primarily for students of dermatology, and is based on a series of demonstrations given by me in the Dermatological Laboratory of Charing Cross Hospital.

The sub-title, "An Introduction to the Anatomy, Pathology, and Bacteriology of the Skin, with Special Reference to Technique," indicates more precisely than does its title the object of this book, which is to place before the student a compact handbook in which are described the histology of the skin, the pathological changes which may affect its various elements, its bacteriological flora, and the technical methods applicable to its study.

But although the changes affecting the elements of the skin in disease are described in detail, and the more important morbid states are referred to in which these changes are found, the book does not profess to be a complete treatise on the pathology of the skin, but rather a practical introduction to the subject.

There is no work on similar lines in this or, as far as I am aware, in any other language, and its arrangement is, I venture to hope, the one best adapted to simplify the subject to the student.

The skin is one of the few organs which can be seen and felt, and consequently it affords a peculiar opportunity for the study of the histological changes in relation to the multiform naked-eye appearances which they produce. By considering skin-lesions from the anatomo-pathological

basis, much of the confusion which at present embarrasses dermatology, especially with regard to nomenclature, might be avoided ; and this is the natural line of advance in the future.

As it is impossible to appreciate the finer points in the pathology of the skin without a thorough knowledge of its minute structure in health, and without some acquaintance with its development, I have deemed it advisable to devote a considerable part of the letterpress to these elementary subjects.

The book is the outcome of a number of years of research ; but in it I have also drawn freely from the accumulated knowledge of recent years scattered so widely over the various text-books and journals. I trust I have duly acknowledged such sources of information in the text ; but should any have been inadvertently omitted, I crave forbearance for the oversight.

The majority of the illustrations are drawn from my own specimens, a few are from preparations kindly lent to me for the purpose, and several are reproductions. In making these drawings I have attempted to combine accuracy with clearness, and as far as possible have avoided the reproduction of the irrelevant detail which renders so many photo-micrographs of comparatively little value from the teaching point of view.

No one could be more sensible of the imperfections of the book than the writer ; but whatever its shortcomings may be, and doubtless they are many, I would fain hope that it will be accepted in the spirit in which it was written—and if it be the means of stimulating further research towards the elucidation of this important branch of medicine, its existence will have been more than justified.

It now remains for me to express my debt of gratitude to my various masters in dermatology—to the late Professor Kaposi, Professor Ehrmann, Professor Cæsar Boeck, and

especially to Dr. P. G. Unna, to whom I am indebted more than I can adequately express for his teaching while I was a pupil in his laboratory in Hamburg, and for his well-known writings on the pathology of the skin. I must also thank the many friends who have so generously assisted me by their valuable advice and warm encouragement. Among these I must specially mention Dr. T. Colcott Fox and my senior colleague, Dr. James Galloway. For kindly criticism and valuable assistance while this book was going through the press I have to thank Dr. E. Graham Little and Mr. H. J. Curtis; and for much help in the correction of the proofs, Dr. Cecil Bosanquet.

In conclusion, it is my pleasant duty to thank my publishers for their great generosity with regard to illustrations, and their invariable kindness and courtesy.

J. M. H. MACLEOD.

HARLEY STREET, W.
December, 1902.

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THE PATHOLOGY OF THE SKIN.

CHAPTER I.

THE APPARATUS REQUISITE FOR THE HISTOLOGICAL TECHNIQUE OF THE SKIN.

The Microscope.—In order to study and appreciate thoroughly the finer details in the structure of the skin in health and in disease, and to detect the micro-organisms which may be present in it, the student must be equipped with a reliable microscope. For such purposes only a first-grade instrument will be found to be adequate. It should have a solid, heavy stand, a hinged condenser such as Abbé's, concave and flat mirrors, an iris-diaphragm, a triple nose-piece, and a fine adjustment. A movable stage, though not absolutely essential, is a great convenience.

The Lenses.—Of the various lenses which may be employed in dermato-histology the following will be found to be adequate:

1. *Objectives.*—3, 6, and $\frac{1}{12}$ oil-immersion (Leitz); 8 (Reichert).

Instead of these, A, D, and $\frac{1}{12}$ oil-immersion (Zeiss), or corresponding lenses by other makers may be employed.

2. *Oculars.*—I., III., and IV. (Leitz), or corresponding lenses.

The nose-piece screws of the better microscopes have as a rule a universal thread, so that objectives by different makers may be fitted on the same stand; in the same way, the diameters of the upper opening of the tube being constant, the various oculars are interchangeable. To obtain the best advantage from the different combinations of objectives and oculars, it may be necessary to elongate the tube according to the directions issued with the microscope. The magnifying power of combinations of the lenses is generally printed on a

card, which it is customary to fix on the inside of the door of the microscope-box.

The following table shows the magnifying power of the combinations of the Leitz lenses mentioned above:

Tube 170 *mm. in length.*

Objective.	Ocular.		
	I.	III.	IV.
3	60	85	105
6	275	390	480
Oil-immersion $\frac{1}{12}$	570	800	1000

The Essential Characters of a Good Lens are: (1) A clear definition, peripheral as well as central; and (2) an absence of chromatic aberration. The higher the powers of magnification the more difficult is it to obtain these qualities. Special apochromatic lenses are made by which chromatic aberration is completely eliminated, but the price of such a lens is as a rule prohibitive. In a good lens, however, the chromatic aberration may be so slight as to be negligible.

After acquiring a reliable microscope it is equally important to be able to make the best possible use of it. This obvious axiom is far too often ignored. It is presumed that the student is already familiar with the general technique of the microscope, but it may not be out of place to emphasise here a few details which are apt to be neglected.

The Light.—For all kinds of histological work by far the best illuminant is daylight—not brilliant sunlight, but white diffuse light. For bacteriological purposes brighter artificial light, such as may be obtained from an incandescent lamp, is superior to daylight. When artificial light is employed, the yellowish rays should be eliminated by causing the light to pass through a disc of blue glass placed upon the diaphragm.

The Use of the Condenser and Iris-Diaphragm.—The purpose of the condenser is to concentrate and intensify the light, while that of the diaphragm is to increase the definition of the object by cutting off the diffuse peripheral rays.

(*a*) When the condenser is employed, the flat mirror should always be used.

(*b*) In examining unstained or faintly stained specimens, the iris-diaphragm should have a small aperture.

(*c*) In examining stained sections, where a general coloured picture is desired, the diaphragm should have a wide opening.

(*d*) In examining with strong artificial light specimens stained for micro-organisms, the diaphragm should be kept wide open and the condenser carefully focussed.

The Oil-Immersion Lens.—When rays of light are reflected by the mirror through the condenser and the preparation, the central rays pass up through the objective, while, owing to the difference in the refractive indices of glass and air, many of the peripheral rays become spread outwards and are lost. The smaller the objective the greater is the loss of the peripheral rays and the less the illumination. Cedar-wood oil has a refractive index much more nearly approaching that of crown glass than of air, and the interposition of a film of this oil between the cover-glass and the objective conserves numerous peripheral rays—which would otherwise have been deflected—and greatly increases the illumination. For this reason a droplet of cedar-wood oil is placed on the cover-glass, and the objective lowered by the coarse adjustment till it touches the oil, the focussing of the object being then done by the fine adjustment.

After use, the lens should be wiped with a piece of filter-paper or clean wash-leather, and any trace of oil removed by xylol or benzene. On no account should alcohol be used for this purpose, as it more readily dissolves the Canada balsam by which the lens is fixed in its metal casing.

Cedar-wood oil, when not in use, should be kept in the dark, as in the light it tends to become thick and opaque.

The Measurement of Objects.—By the constant use of a microscope and a familiarity with the appearances produced by the different combinations of lenses, slight variations in the size of objects become easily appreciated, and with practice the student is able to judge fairly accurately the relative size of the objects he is examining. Special instruments, known as *micrometers*, are frequently employed for this purpose; for a description of them and of the method of using them, the reader is referred to the various text-books on microscopy.

Microscope-Slides and Cover-Glasses.—The *slides* should be of good, clear glass, and the usual size is 3 in. by 1 in. The *cover-glasses* may be round or square, the latter being

preferable, as they are more easily taken hold of. For ordinary work cover-glasses of $\frac{5}{8}$ in. sides are recommended; but occasionally larger ones may be necessary. Where the oil-immersion lens is to be employed, No. 1 cover-glasses are essential; they are about 0·12 mm. in thickness. Where it is desired to use only the low powers of the microscope, No. 2 (0·18 mm.) cover-glasses will serve the purpose.

Cleaning.—It is important that both slides and cover-glasses should be clean. New slides and cover-glasses require as a rule only to be rinsed in alcohol (90 per cent.), and rubbed dry before use with a clean linen rag or a piece of butter-muslin. When cover-glasses have been used for specimens mounted in Canada balsam, the following procedure for cleaning them is recommended:

The slides are heated over a flame to melt the balsam and to enable the cover-glasses to be slipped off. These should then be dropped one by one into boiling chromic acid (10 per cent.),[1] allowed to remain there for half an hour, afterwards washed under a tap of running water till no acid reaction remains, rinsed in methylated spirit, then in ether, and stored in a small capsule containing alcohol. The same process may be employed to clean the slides; but it is simpler and sufficiently effective to steep them for a few days in a strong solution of lysol in water, and then to wash and dry them thoroughly.

Slides and cover-glasses are known to be clean when, after they have been breathed upon, condensation rapidly occurs.

Other Apparatus.—Small porcelain dishes for staining sections, water-bottles, glass rods, handled needles, section-lifters, forceps, and the various appliances requisite in the technique of histology are doubtless so familiar to the student that no special reference to them is required.

Drawing.—A camera lucida, such as that of Abbé, is a most useful accessory to the above equipment, and by means of it with comparatively little practice the outline of objects under the microscope can be accurately drawn. When the student is an expert draughtsman this instrument may readily be dispensed with. However feeble the attempt may be, the art of drawing should be assiduously practised, for it increases the powers of observation and compels a careful study of the

[1] Boiling nitric acid is sometimes employed for this purpose; but it has no advantages, and has the distinct disadvantage of causing offensive fumes, which are avoided by the use of chromic acid.

objects under examination, both of which are peculiarly essential to the dermatologist.

Microtomes.—Every histologist has his favourite microtome. For the cutting of a hard tissue such as the skin a good microtome and a sharp knife are indispensable. As it is sometimes advisable to cut sections in celloidin, and at other times in paraffin, two microtomes are recommended, one for each purpose. Microtomes which cut both celloidin and paraffin sections may be obtained, but in my experience they are not satisfactory.

For celloidin sections, sliding microtomes are best. In them the object is fixed and the knife is made to slide and cut obliquely through the tissue. The models by Jung of Heidelberg and Reichert of Vienna are both reliable.

For paraffin sections I prefer a rocking microtome, such as the "Cambridge rocker."[1] In it the knife is fixed horizontally, and the tissue rocks down upon it.

The more complicated Reinhold-Giltay model is unsurpassed for cutting serial paraffin sections.

It is occasionally desirable to cut skin by a freezing microtome, for when the skin is specially hard from having a thickened stratum corneum, the thinnest sections of it may be cut by this means. There are several freezing microtomes to be had; but by the aid of a special fitting, such as that supplied by Reichert, a sliding microtome can be utilised for the purpose.

[1] It is sometimes objected that the sections cut by the "Cambridge rocker" are not absolutely plane sections, but are really segments of a cylinder. This is an objection of little practical importance, as the deviation from the plane is extremely slight. An instrument can, however, be obtained which cuts sections which are perfectly plane; but it is much more costly.

CHAPTER II.

BIOPSIES.

By a *biopsy* is meant the excision of a piece of tissue from the living subject for the purpose of microscopical or bacteriological examination. The skin is the organ, above all others, which is best adapted for the study of histological changes in association with the clinical appearances which they produce. If we wait till after death has ensued before making a microscopical examination of the lesions of the skin, the result will, in many cases, be unsatisfactory; for just as the clinical appearances are altered by death so are the histological details. In children who have died during the eruptive stage of malignant scarlet fever, the skin, an hour after death, except for a few hæmorrhages, shows little sign of the extensive dermatitis which previously affected it. In the same manner skin-lesions of the type of those of psoriasis lose their vivid colour after death and appear only as so much scaliness. By means of biopsies, however, and the immediate fixation of the tissue excised, we are able to study and appreciate the condition of the blood-vessels, the extravasation and migration of leucocytes, the state of the nuclei of the cells, and a number of other details which could otherwise have been only imperfectly detected. Besides their importance in the study of the inflammatory and suppurative lesions of the skin, biopsies are of the greatest value for diagnostic purposes, especially in the case of the cutaneous neoplasms.

As the operation is of the simplest nature, and if carefully and expeditiously carried out need cause neither pain nor discomfort, and as it is generally in the interest of the patients, there is, as a rule, no great difficulty in obtaining their consent.

In choosing the lesion for excision, a recent one should always be selected, in which the original characters have not been altered by secondary changes. In the case of an ulcer or a neoplasm it is advisable to excise the spreading edge.

A small piece of tissue not much larger than a lentil will usually be found to be sufficient.

The Operation.—The skin of the region where the biopsy is to be made should be cleansed thoroughly, boric lotion or some other antiseptic applied to it, and the whole procedure should be regarded in the light of a minor surgical operation.

The Anæsthesia.—A local anæsthetic should be employed, and for this purpose freezing by ethyl chloride or the injection of cocaine or eucaine may be resorted to.

1. **The Congelation Method by Ethyl Chloride.**—This method is occasionally employed in the case of small papules where the tissue to be removed is not larger than a split-pea. Ethyl chloride is supplied in glass tubes, with a fine opening at one end covered by a spring-stop. The tube is held in the hand, the spring-stop opened by the thumb, and the heat of the hand causes the freezing fluid to come out in the form of a fine spray. The spray is allowed to play on the part to be excised till the skin becomes white and anæmic; and at the moment when the white tint begins to go the excision should be performed.

The method has several serious disadvantages, on account of which it is falling into disuse:

(1) By it the colour of the skin is so altered that at the time of the excision it is extremely difficult to recognise the limits of the lesion, and in consequence it is advisable to map out beforehand with an anilin pencil the exact area to be excised.

(2) It is followed by a reaction in the form of congestion, on account of which it is sometimes difficult to stop the bleeding.

(3) It does not produce a constant degree of anæsthesia; and some patients—who did not seem to be neurotic—have assured me that they felt the excision to be intensely painful, in spite of the fact that the tissues were almost white when the operation was performed. The actual freezing and thawing of the tissue are also painful.

(4) It should never be used for the skin of the face, as the vapour is extremely irritating to the mucous membrane of the nose and the conjunctivæ.

(5) It renders the skin so tough that where the epidermis is thick, as in the sole of the foot, the palm of the hand, and the scalp, it is difficult to cut it after it has been frozen.

2. **The Injection Method by Cocaine or Eucaine.**—Injection of cocaine or eucaine is the most reliable method of producing local anæsthesia. By it a local anæsthesia can be rapidly obtained, which is perfect, lasts about twenty minutes, and has not the disadvantage of altering the colour and consistence of the skin, and is not followed by congestion. Much larger areas can be anæsthetised by this method than by the spray.

Eucaine has been proved to be as efficacious as cocaine. It is a more stable compound, and solutions of it can be boiled without causing decomposition, whereas solutions of cocaine are thereby altered. For the latter reason eucaine is recommended, and should be boiled before each operation. It is customary to employ a 2 per cent. solution of eucaine in water. Brocq advocates, instead, a freshly prepared solution of eucaine in equal parts of water of cherry laurel and water. A 1 per cent. solution of eucaine will be found to be sufficiently efficacious, and with it there is less likelihood of a syncope or any other of the grave consequences which may result from the stronger solutions of either eucaine or cocaine.

A few drops of the solution are injected, not subcutaneously but into the corium, the ordinary precaution of having a sterilised needle being adhered to. When it is desired to excise a piece of skin larger than a centimetre in diameter, a few drops from the syringe are injected into the corium, and the needle, without being withdrawn, is pushed horizontally in several directions, and the injections repeated till the whole area is anæsthetised.

The result of the injection is to produce a white œdema of the skin around the puncture, and when this has appeared it is a sign that the anæsthesia is complete. The minimum quantity of eucaine requisite to produce this result should be employed.

It has been suggested that the œdema and the hæmorrhage which may result from the puncture of the needle are serious drawbacks to this method. They certainly are disadvantages, but not sufficiently great to warrant excision without a local anæsthetic or with ethyl chloride.

The Procedure.—The instruments required for the excision are a tenatome or Graefe's knife, a pair of fine dissecting forceps, and curved scissors. An elliptical incision, to include the whole lesion, should be made in the direction of the lines of cleavage and vertical to the skin. The incision should extend down to the subcutaneous tissue. The portion

of tissue included in the incision should be raised up with the forceps, snipped through the subcutaneous tissue with the scissors, or dissected away with the tenatome.

On no account should the tissue be simply raised up by toothed forceps and snipped through with scissors or cut across by a scalpel, without a careful incision having first been made; for the tissue will be squeezed and mangled by the forceps, will include too little of the corium, and will thus be useless for histological purposes. After the excision the wound should be sponged with boric-acid lotion and the bleeding stopped by pressure. If the excision has been small it is sufficient to seal up the wound with sterilised cotton-wool and collodion; if large, a stitch or two may be required. If the incisions have been made in the direction of the lines of cleavage of the skin, and not across them, no difficulty will be experienced in closing the wound, and as a rule no scar will result. The piece of skin should be immediately transferred to a bottle containing the fixing fluid, and labelled.

Recently an instrument known as a skin-punch has been devised for performing this operation. I am indebted to Dr. Holder, of New York, for sending me one of these instruments. The punch can be obtained in several sizes, the most useful size being about $\frac{3}{8}$ in. in diameter. By a rotating movement the instrument is made to penetrate into the subcutaneous tissue, and is then withdrawn. The disc of tissue which has been cut by the punch is then raised up by forceps and snipped off with curved scissors.

But with this instrument it is more or less difficult to bring the edges together after the excision, and, as the wound has to granulate up, it generally leaves a scar. A further disadvantage in this instrument is the difficulty of keeping it sharp.

CHAPTER III.

METHODS FOR THE HISTOLOGICAL EXAMINATION OF SKIN-MATERIAL IN THE FRESH STATE.

BEFORE examining tissues histologically it is usual to fix and harden them, so that their elements may retain as far as possible the characteristics which they possessed in the living state, and may be enabled to withstand the various procedures associated with the methods of staining. For delicate histological work the fixing and hardening of tissues before cutting them is essential ; but there are a number of important facts which may be learned from the study of skin in the fresh state. Two methods may be employed for this purpose—namely, the *dissociation* of the elements of the skin by maceration, and the preparation of *sections of fresh skin.*

I. **Dissociation Methods.**—A small piece of skin may be teased out by handled needles, either in normal salt solution (·6 per cent.) or in a mixture of egg-albumen and salt solution (1 in 10). It is inadvisable to tease out the tissue in water, since it causes the elements to swell up. By means of normal salt solution the fibrous elements of the corium may be readily dissociated. But when it is desired to distinguish between the white and the elastic fibres of the corium, a 2 per cent. solution of acetic acid should be employed ; this causes the white fibres to swell, and renders them indistinct, while the elastic fibres, being unaffected by the acid, stand out more prominently.

These solutions are useless, however, for the cells of the epidermis ; for except after prolonged maceration they are incapable of separating the outer cells of the stratum corneum, and any attempt to dissociate them by needles only results in crushing or otherwise destroying them.

To separate the horn-cells[1] a 33 per cent. solution of caustic potash may be employed. Under the influence of this

[1] For further details on this subject *see* p. 76.

the horn-cells are dissociated, and though they are slightly swollen in the process, they retain to a great extent the peculiarities of their structure. After being soaked for half an hour in the potash solution, a fine film or pulp of cells may be scraped off the surface of the piece of skin, and transferred to a slide and examined in a drop of the alkaline solution. This solution is specially valuable, as it does not cause any immediate alteration in the fat or pigment which may be present in the cells. Its prolonged action causes complete disintegration. Hydrogen peroxide is sometimes used for the same purpose; but its action is much weaker, and it requires at least twenty-four hours to produce the effect caused in half an hour by the potash.

It is more difficult to separate the cells of the deeper layers of the epidermis so that their minute structure is preserved. I have attempted to do so by a number of methods, but have not succeeded in obtaining good results. The nearest approach to satisfactory preparations was obtained by shaving off the superficial horny layer from a piece of skin of the palm of the hand, soaking it in a 10 per cent. solution of alcohol for twelve hours, and then scraping the epidermal surface. In some of the cells thus separated the shape and the nuclei were well preserved, and, after specially staining them, a few broken prickles were detected.

To demonstrate the *fat* in the cells a solution of osmic acid (·1 per cent for twenty-four hours) should be employed as a dissociating fluid, for by this means the fat is stained brownish or greenish black.

NOTE.—The special methods of examining epilated hairs, scrapings of nails, scales, crusts, and the fluid from vesicles and bullæ will be described in the chapters dealing with these subjects.

II. **Sections of Fresh Skin.**—

1. The most satisfactory method of cutting sections of fresh skin-material, and that most generally adopted, is by the aid of a *freezing microtome*. The freezing is accomplished by means of an ether spray, and the tissue is frozen in a drop of gum-arabic solution (*see* p. 28). The piece of tissue to be frozen should always be small, and not longer than three-eighths of an inch.

Ramsay Smith, of Adelaide,[1] has recently suggested a simple and practical method of freezing small pieces of tissue by means of a spray of ethyl chloride. The cork of a ten-ounce

[1] *The Scot. Med. and Surg. Journ.*, January, 1902, p. 12.

bottle is split lengthwise from the broad end to near the narrow end, and into this the piece of skin is fixed so that it projects beyond the cork. The cork is placed in the clamp of a Cathcart microtome, and a fine spray of chloride of ethyl is directed against the tissue. As the tissue freezes, the screw is gradually tightened, and the block of tissue becomes hard and immovable. The cylinder with the cork is then screwed down till the top of the tissue just touches the edge of the plane-iron used for cutting. The tissues should be cut when they are just beginning to thaw. By this method it is unnecessary to imbed the tissue in gum-solution.

2. Pieces of skin which have not been hardened may be *imbedded in plaster of Paris*, and after this is allowed to set, they may be cut on a microtome by a knife moistened in alcohol or water (Schlagenhaufer[1]).

Sections cut by one or other of the above methods are transferred to a slide, and mounted and examined in a drop of glycerin. The latter renders the tissues transparent, and is in consequence an excellent medium for mounting fresh sections. It is especially useful for the study of pigment, since the latter is unaffected by glycerin. The sections may be stained rapidly in hæmatoxylin-eosin or in methylene blue, but as frozen sections are extremely brittle, it is generally necessary to harden them for about fifteen seconds in absolute alcohol or in a weak solution of formalin[2] before staining them.

[1] *Wien. klin. Wochenschr.*, 1897, p. 1127.

[2] For this purpose Pick, of Prague, recommends a 4 per cent. solution of formol.

CHAPTER IV.

METHODS OF PRESERVING SKIN-MATERIAL FOR HISTOLOGICAL EXAMINATION.

Fixing and Hardening.

By the crude methods of examining skin-material in the fresh state which were described in the last chapter it is impossible to demonstrate the finer structure of the elements of the skin; to do this it is necessary to preserve the tissues in some way, so that they will be uninjured in the processes of staining and mounting, and at the same time will retain as nearly as possible the peculiarities which they presented during life. This double purpose is attained by subjecting the tissues to the action of certain reagents which are known as fixatives and hardening fluids.

By a **fixative** is meant a reagent which will kill the histological element so rapidly that it will not lose to any extent its characteristics. Fixatives are specially indicated in the histological technique of the skin for preserving tissues which have been removed by biopsy; but they are of little value for tissues which have been excised some time after death, since the finer architecture of the cellular elements is by that time generally lost.

Hardening Fluids serve the purpose of rendering the tissue sufficiently resistant to the action of the reagents used in staining and mounting the specimens. The process of hardening is thus equally necessary whether the tissue has been removed during life or some time after death. The distinction between fixing and hardening reagents is, however, a purely arbitrary one, for the majority of the fluids in general use answer both purposes. Since certain of these are powerful fixing agents, while they are of little service in hardening the tissue and *vice versâ*, combinations of them are usually resorted to.

These reagents act chiefly by coagulating the fluid and semi-fluid elements of the tissues, and in this way render them incapable of being dissolved out in the after-treatment. At the same time the coagulation process alters the refractive indices of the various elements, so that they can be more easily distinguished. This latter effect is described by Lee as the "power of optical differentiation" of the reagent. The same author gives the following qualifications for a good fixing reagent: (1) it must preserve all the elements which it is desired to fix; (2) it should cause good optical differentiation; and (3) it should have a good power of penetration. Unfortunately no single reagent has been found to possess all three qualifications to a like extent, so that compounds are usually employed.

The following practical points should be observed in the fixing and hardening of the skin:

1. The tissue should be as fresh as possible, and should be transferred to the fixing reagent immediately after excision.
2. A reagent should be chosen suitable for the special elements which it is desired to demonstrate.
3. The amount of the reagent used should be at least ten times as great as the tissue.
4. The reagent should be employed for as short a time as is sufficient to fix and harden the tissue; if its use be prolonged, it invariably causes shrinkage, and renders the tissue brittle.
5. In hardening, it is, as a rule, advisable to begin with a weak solution of the reagent, and gradually to increase its strength.
6. The tissue should be hardened in a wide-mouthed bottle in the bottom of which is placed a small piece of cotton-wool. On this the tissue rests, and is as it were suspended in the fluid, which allows the latter to act equally all round it.

Reagents employed for Fixing and Hardening Skin-Material.—

Alcohol.—For purposes of diagnosis and for the demonstration of the general architecture of the skin, alcohol is by far the simplest and most rapid hardening reagent. Weak alcohol fixes the tissue and strong alcohol quickly hardens it. The capacity of alcohol for hardening tissues is greatly in excess of its power of fixing them. Consequently, in special researches, one or other of the more active fixatives

should first be employed, and the tissue subsequently hardened in alcohol. This combined method is necessary for the demonstration of the finer structure of cells, the karyokinetic figures in the nuclei, the cutaneous nerves and their endings, and the fat in the skin.

Method of Hardening in Alcohol.—

1. Put the piece of skin for twenty-four hours in 30 per cent. alcohol.
2. Transfer it for twenty-four hours to 70 per cent. alcohol.
3. Transfer it for twenty-four hours to 95 per cent. alcohol.
4. Then place it in absolute alcohol for forty-eight hours.

For very small pieces of tissue the times in the various solutions of alcohol may be curtailed by one-half.

Pieces of skin which have been specially fixed in some other reagent, such as Müller's fluid, should be thoroughly washed, then put in 95 per cent. alcohol or methylated spirit for two or three days, and into absolute alcohol for twenty-four hours.

Pieces of tissue which are not to be immediately cut should be preserved in 75 per cent. alcohol, and this should be changed several times till the turbidity completely disappears.

NOTE.—Absolute alcohol readily absorbs moisture from the air. To keep it absolute, a layer of copper sulphate, which has been calcined in a porcelain dish, is placed at the bottom of the bottle containing the alcohol to absorb the water. By shaking up 95 per cent. alcohol with calcined sulphate of copper the former may be rendered absolute.

Corrosive Sublimate.—Corrosive sublimate is essentially a fixing reagent, and it is one of the best of the fixatives for karyokinetic figures and for demonstrating the finer architecture of cells. As a hardening reagent it has the drawback of causing considerable shrinkage of the tissues and of rendering the specimens brittle, and consequently its prolonged use is to be avoided. The tissue should be simply fixed in corrosive sublimate and the hardening completed by alcohol.

A saturated solution of corrosive sublimate in 5 per cent. glacial acetic acid (Lee) is employed, and the tissue steeped in this for two hours. The tissue is then washed, transferred to 95 per cent. alcohol for two days, and finally to absolute alcohol for twenty-four hours. It is then found to be perfectly fixed and hardened. It is important to wash the tissue thoroughly

after removing it from the corrosive sublimate, to get rid of the mercurial precipitates which are apt to form in it. By the simple expedient of washing the tissue in equal parts of Gram's iodine solution and water, or, still better, of soaking the sections for ten minutes in Gram's solution and washing them in alcohol before staining, soluble iodide of mercury is formed and the precipitation is prevented. It is necessary to avoid the use of metal instruments in manipulating specimens in corrosive sublimate.

Bichromate of Potash.—Bichromate of potash fixes the cellular elements of the skin satisfactorily, but it has a weak power of penetration. Its action is greatly improved by the addition of glacial acetic acid, and the following formula, after Tellyesnicky, gives good results (*Archiv f. mikros. Anat.*, 1899, LII., p. 242):

Bichromate of potash	3 grms.
Glacial acetic acid	5 c.c.
Water	100 „

Place the fresh piece of skin in the above solution for two days, wash it thoroughly in water, then pass it through alcohol to complete the hardening.

Müller's Fluid is a combination of bichromate of potash and sulphate of soda, and has the following formula:

Bichromate of potash	2 parts
Sulphate of soda	1 part
Water	100 parts

It has an action similar to that of the above solution, and possesses only a slight power of penetration. The time required for fixing and hardening tissues in it, is from eight to ten weeks at an ordinary temperature, but in an incubator at 37° C. the time may be reduced to about four days. If it be used as a fixative alone, and the hardening be completed in alcohol, the results are similar to those obtained with the former bichromate solution.

Chromic Acid.—Chromic acid is a valuable fixing reagent for karyokinetic figures, nerves, and fat in the skin. It is rapid and penetrates quickly. Its value is increased by the addition of osmic acid, as in Flemming's well-known solutions, which are specially serviceable for staining the medullated nerves and the fat of the skin.

Flemming's Strong Formula (*Zeit. f. wiss. Mik.*, 1884, p. 349):

Chromic acid, 1 per cent.	15 parts
Osmic acid, 2 per cent.	4 „
Glacial acetic acid	1 part

The piece of skin is placed in this fixing solution for two days, washed in water for twenty-four hours, and hardened in alcohol.

Picric Acid.—Picric acid is one of the most penetrating of the fixatives, and is specially useful in fixing pieces of skin in which the horny layer is thickened. A saturated solution in water is employed, the tissue being immersed in this for twenty-four hours, and the hardening completed in alcohol. Tissues fixed in picric acid must not be washed in water, since the chemical combinations formed by picric acid with the tissue-elements are soluble in water.

Formalin.—A 40 per cent. solution of formalin is a useful and rapid hardening fluid, but an inferior fixative. It has no distinct advantages, and its employment is associated with irritation of the eyes and of the nasal mucous membrane of the worker. Small pieces of skin may be hardened in it in from twelve to twenty-four hours.

NOTE.—Where there is no definite indication for the employment of special fixatives, as for the demonstration of karyokinetic figures or of fat, it is better to avoid their use and simply to fix and harden in alcohol. By so doing the shrinkage and discoloration of the tissue, which are produced by reagents of the type of Flemming's solution and Müller's fluid, are avoided.

CHAPTER V.

METHODS OF IMBEDDING SKIN-MATERIAL AND OF CUTTING AND PREPARING SECTIONS FOR STAINING.

General Introduction.—In order to cut thin sections of tissues without injuring their minute structure in the process, it is necessary to permeate their interstices with some substance in a liquid form which is capable of solidifying, and by so doing of giving a sufficient power of resistance to the tissue to enable it to be cut without injury. This process is known as *imbedding* the tissue. Three substances are commonly employed for this purpose—namely, *celloidin*, *paraffin*, and *gum*. In the first method a solution of celloidin in alcohol-ether is used, and by the evaporation of the ether the requisite hardness is obtained ; in the second, melted paraffin is made to permeate the tissues, and this solidifies on cooling ; and in the third, when the tissue is impregnated with gum, the latter is solidified by freezing. These three methods are known respectively as the celloidin, paraffin, and freezing methods. All three methods are applicable in skin-histology, but each has its advantages and disadvantages. The skin, both in a normal and patholog cal state, is a peculiarly difficult tissue to cut into thin sections. There are two chief reasons for this difficulty ; first, the extreme hardness of the stratum corneum, and, second, the difference in the resistance offered respectively by the epidermis and the corium to the knife in cutting.

General Directions for cutting Sections of Skin.—

1. In cutting sections of skin by any of these methods the tissue should usually be so placed that the epidermis is towards the cutting edge of the knife. If the corium be cut first, the epidermis will generally be torn. This is not, however, an invariable rule, as when the epidermis is soft and œdematous the corium may be the harder structure, and should then be cut first.

2. In cutting celloidin sections the knife-edge should be drawn obliquely through the tissue, while in paraffin and frozen sections the knife should be made to cut straight through.

3. In order to cut successful sections the knife must be kept well sharpened. Great skill is required in sharpening the large-bladed knives supplied with several of the sliding microtomes ; unfortunately the art of setting these knives has not been acquired in this country to the same perfection as on the Continent, and consequently each worker is compelled to learn to keep his own knives in condition. There is not the same difficulty in sharpening the small knives and razors used with microtomes of the type of the "Cambridge rocker." Each knife should be fitted with a handle, so that it may be easily stropped, and a solid strop with flat surfaces should be used. The great secret of keeping a knife in good condition is to clean it with ether and alcohol, and to strop it each time after use.

The Celloidin Method.—*Celloidin* may be obtained from the makers in the form of a powder or in tough cakes not unlike gelatin in consistency ; it is cheaper in the latter form. These cakes should be pared down into small shavings, which are allowed to dry in the air into hard chips, like pieces of horn. This procedure ensures that the celloidin is thoroughly dehydrated. The chips or powdered celloidin are dissolved in equal parts of absolute alcohol and ether,[1] and two solutions are made : a thin 5 per cent. solution, which has the consistency of glycerin ; and a thick 10 per cent. solution, of the consistency of syrup. The two solutions are generally described as "thin" and "thick" celloidin. These should be kept in tightly stoppered bottles, otherwise the ether will evaporate and the celloidin solidify.

Imbedding.—Before tissues can be imbedded in celloidin they must be thoroughly dehydrated. Tissues hardened in alcohol in the manner described on page 15, should be dehydrated by being left for twenty-four hours in absolute alcohol. When other reagents have been used for hardening, the tissue should be transferred from the reagent to absolute alcohol for forty-eight hours before being put in the celloidin.

[1] Some workers prefer to put the chips of celloidin in absolute alcohol for a night, which causes them to soften and swell up, and then to add an equal volume of ether.

The following are the stages in the process of imbedding in celloidin :

(1) Thoroughly dehydrate the tissue in absolute alcohol for forty-eight hours ;

(2) Transfer it to equal parts of absolute alcohol and ether for twelve hours ;

(3) Then to thin celloidin for at least twenty-four hours, but a longer time is advisable ; and, finally,

(4) To thick celloidin for a like period.

The longer the tissue is allowed to remain in the celloidin the more completely will it be permeated. Tissues may be left in celloidin for an indefinite period without injury.

Instead of employing two solutions of celloidin, several histologists prefer to have only a thick one, which they use as follows :

After the piece of skin has been in the alcohol-ether mixture for twelve hours, a few drops of the thick celloidin are added daily till the mixture reaches the consistency of syrup. The tissue is then transferred to thick celloidin for twenty-four hours. Five days should be occupied in the process, and in this way excellent results may be obtained.

After the piece of skin has been thoroughly permeated with celloidin, it is placed on a block of wood and allowed to harden sufficiently for cutting. This part of the celloidin process is known as " blocking."

The Process of Blocking.—A small block of wood about half an inch square or larger, according to the size of the tissue, is taken, and the piece of skin is removed from the celloidin with forceps, and placed upon it with the surface which it is desired to cut uppermost. The tissue should be placed on one of the cross-grained surfaces of the block, so that the celloidin around may adhere more firmly to the wood. Thick celloidin is then poured over the tissue, and the block exposed to the air till the surface of the celloidin is hardened. It is known to be sufficiently hard when it is difficult to make an impression on it with the tip of the finger (not with the finger-nail). The block is then immersed in 80 per cent. alcohol for at least twelve hours, when it is ready for cutting. This method of drying the celloidin in the air and subsequently immersing the block in dilute alcohol is commonly employed, and is simple ; but it is liable to cause shrinkage. This defect may be obviated by one or other of the following modifications :

1. Around the block fit a stiff paper collar stretching

beyond the surface on which the tissue is to be placed so as to form a box for the tissue. After arranging the piece of skin on the floor of the box so formed, pour in sufficient thick celloidin to cover it completely. Allow this to set in a covered vessel, or, still better, in a bell-jar from which the air has been exhausted. The time occupied in setting varies from twelve to twenty-four hours. Preserve the blocks till required in 80 per cent. alcohol.

2. Another method of causing the celloidin to set without shrinkage of the tissue is to place the block in an atmosphere of chloroform. Pour chloroform over the bottom of a glass capsule, place the block in it so that the chloroform does not touch the celloidin, and put on the lid. The setting is complete in about a couple of hours, and the block is then put for twelve hours in 80 per cent. alcohol and cut.

Bubbles in the Celloidin.—It frequently happens that after the celloidin has been poured on the tissue, numerous air-bubbles appear in it. These are of no consequence unless they occur immediately around the tissue, in which case the latter is unsupported, moves in the cutting, and thin sections of it cannot be obtained. These bubbles may be removed by placing the block before hardening in an atmosphere of ether. Ether is poured on the bottom of a glass capsule, the block is placed in it, and the lid put on. The ether must on no account be allowed to come in contact with the celloidin. About an hour will usually suffice to remove the bubbles, after which the hardening is proceeded with in the manner already described.

The Cutting of Celloidin Sections.—The block is fixed in the clamp of a sliding microtome. The edge of the knife is placed obliquely to the epidermis of the piece of skin, so as to slice through the tissue. In cutting, both the knife and the surface of the celloidin must be kept wet; otherwise the sections are apt to break or curl up, and generally stick to the knife. Alcohol (80 per cent.) may be employed for this purpose, and may either be painted on with a brush or sprayed on in a fine jet from a water-bottle.

The sections are lifted by means of a camel's-hair brush into 80 per cent. alcohol contained in a glass dish. If a porcelain vessel be used, it is difficult to see them.

Before staining, the sections are immersed in water. If they are curled up and refuse to spread out in water, put them for a few minutes in 95 per cent. alcohol and then into water, when they will almost invariably uncurl.

As a rule it is unnecessary to remove the celloidin from the sections before staining them, and it is a decided advantage not to do so, as it prevents the sections from breaking. When it is desired to demonstrate finer structures, however, such as the fibrils of the epithelial cells, it is necessary to get rid of the celloidin. This is done by putting the sections into absolute alcohol for a few minutes, and for about ten minutes into equal parts of alcohol and ether, and then transferring them to water. If the sections be very friable after the celloidin has been removed, they should be soaked in absolute alcohol for a few minutes to harden them before they are put into water.

After the sections are stained they may be examined in glycerin; but if permanent preparations be desired, they should be dehydrated in absolute alcohol, cleared in bergamot oil or xylol, and mounted in Canada balsam.

Clearing.—By *clearing* a tissue is meant the removal of the alcohol to render the section transparent, and to allow the mounting fluid to penetrate. This is accomplished by several oils, such as bergamot oil, xylol, cedar-wood oil, clove oil, and origanum oil. Of these, bergamot oil acts most rapidly, and causes little, if any, shrinkage, such as is caused by several of the others. Xylol acts less strongly than bergamot oil, cedar-wood oil more slowly, and clove oil has the disadvantage of rapidly dissolving out the celloidin.

Preserving Celloidin Blocks.—Celloidin blocks may be preserved in 70 per cent. alcohol. Diluted methylated spirit must not be used for this purpose, since its impurities have a deleterious effect on the blocks. A better method is to coat the cut surface with celloidin again, and then to cover the whole with melted paraffin; in this way they may be kept dry. Before storing them, be careful to mark all the wooden blocks with the name of the tissue with an anilin pencil.

Epitome of the Celloidin Method.

1. Put the hardened piece of skin for forty-eight hours in absolute alcohol, using ten times the volume of alcohol.
2. Transfer it to equal parts of alcohol and ether for twelve hours.
3. Add a few drops of thick celloidin (10 per cent.) daily, till the consistency of the mixture nearly reaches syrup. This process should be made to occupy four or five days.
4. Transfer the tissue to thick celloidin for at least twenty-four hours.

5. Place the tissue on one of the cross-grained surfaces of a wooden block, and fit a paper collar round it. Pour sufficient celloidin into the box so made to completely cover the piece of tissue.

6. Place the block in a glass vessel with a well-fitting cover, containing only a little air, and allow the celloidin to harden till the pressure of the finger-tip does not make a deep impression on it.

7. Put the block in 80 per cent. alcohol for at least twelve hours.

8. Cut on a sliding microtome, with the knife placed obliquely to the epidermis, keeping the knife and celloidin wet with 80 per cent. alcohol.

9. Put the sections in 80 per cent. alcohol.

10. Transfer them before staining to water, in order to remove the alcohol and to cause the sections to spread out.

11. Stain.

12. Dehydrate in absolute alcohol.

13. Clear in bergamot oil.

14. Mount in Canada balsam.

Lee, in the fifth edition of the *Microtomist's Vade-Mecum* (p. 133), recommends the following rapid and simple method by which sections may be cut dry and the blocks preserved dry in a stoppered bottle:

1. Imbed the tissue in celloidin as already described.

2. Harden for an hour in the vapour of chloroform (*see* p. 21).

3. After the surface is hardened sufficiently, put the block in a mixture of equal parts of chloroform and cedar oil (Gilson's mixture); add more and more of the latter till the mixture is almost pure cedar oil. Allow the block to remain in this till it is cleared throughout. Expose it to the air, and the remainder of the chloroform will evaporate. Cut the sections dry, and preserve the blocks in stoppered bottles.

The Paraffin Method.—

The Paraffin.—Paraffins vary considerably both in quality and in their melting points. A pure paraffin is essential, and it should be obtained from a reliable firm. As a general rule paraffins having low melting-points should be employed, since the tissues are rendered brittle by the heat required to liquefy those with high melting points. A paraffin melting at about 52° C. is most generally useful. In the winter months when the room-temperature is about 16° C. a paraffin

melting at about 45° C. will suffice; but in summer a paraffin with a slightly higher melting-point is required.

The Apparatus.—A special paraffin-oven or a water-bath fitted with a gas-regulator to preserve a constant temperature is employed to keep the paraffin liquid during the process of imbedding. The oven should be kept at a temperature a few degrees above that of the melting-point of the paraffin. The paraffin is placed in small porcelain or metal dishes.

The Clearing of the Tissues before Imbedding them in Paraffin.—Before the piece of skin which has been hardened and dehydrated in alcohol can be imbedded in paraffin, it is necessary to get rid of the alcohol by the process known as "clearing." This should be done by some fluid in which paraffin is soluble, in order to allow the latter to thoroughly penetrate the tissues. Chloroform is one of the most rapid and efficient means to this end. It quickly de-alcoholises the tissues, and is a powerful solvent of paraffin. Lee strongly recommends the use of cedar oil as a clearing agent for paraffin, since it (1) penetrates rapidly, (2) is not injurious to the finer structures of tissues, and (3) does not require such careful removal as chloroform. Xylol is also extensively used.

The Method of Imbedding.—

(*a*) After the piece of skin has been fixed and hardened, it is transferred from the absolute alcohol to the clearing agent—for example, chloroform—and allowed to remain there for twenty-four hours or longer, till it sinks.

(*b*) The tissue is next put for twenty-four hours in the oven in a mixture of equal parts of chloroform and paraffin; if the tissues be put directly from the chloroform to pure melted paraffin, shrinkage is apt to occur.

(*c*) The tissue is then transferred to melted paraffin in the oven, and kept there for twenty-four hours, in which time it should have become thoroughly impregnated and the chloroform should have completely evaporated. The tissue is now ready for blocking. Tissues must never be left for an indefinite period in the oven in melted paraffin, as the heat will eventually cause marked shrinkage. Xylol or cedar oil may be employed in exactly the same manner as chloroform.

Blocking.—The dish of melted paraffin containing the tissue is now removed from the oven. Two L-shaped metal blocks are placed on a glass or porcelain plate, and are so arranged that they form a box slightly larger than the piece of tissue. Into this improvised box some of the melted

paraffin is poured, the piece of tissue is placed in it by forceps in the desired position for cutting, and the box filled up with paraffin. After the surface of the paraffin has solidified, the setting is completed in water and the L-shaped blocks removed ; the blocks easily come away without breaking the paraffin. In the case of small pieces of tissue the desired position for cutting is more readily obtained by the following procedure : instead of using the metal blocks, smear the bottom of a watch-glass or flat dish with glycerin, and pour the melted paraffin into it around the tissue. When this solidifies, remove it from the dish and pare away the superfluous paraffin.

The paraffin block is next fixed by a layer of melted paraffin on a small cube of wood or a special cylindrical holder, such as is supplied with the Cambridge rocking microtome. The more practical method, however, is the former, for by this means the tissue which remains can be cut in exactly the same plane on a subsequent occasion. If it had been fixed to the cylinder and removed after cutting a number of sections from it, when fixed again the plane of cutting would most probably be altered. The fixation is done by the aid of a flat-bladed knife heated in a flame and placed for a second on the under surface of the paraffin, to melt it, after which the melted surface is pressed against the wood. When fixed, the block is hardened for a few minutes in cold water, and is then placed in the microtome and cut.

The Cutting of Paraffin Sections.—The knife is placed so as to cut straight through the tissue, and is not made to slice obliquely, as in cutting sections in celloidin. If the knife be sharp and the microtome working easily, sections averaging 5 μ in thickness may readily be obtained. With the rocking microtome the cutting should be done rapidly, but with as little jerking as possible, and in this way ribbons of serial sections may be got. Whether serial sections are desired or not, if the sections be cut in ribbons it is a clear indication that the microtome is in good order, and the individual sections will be found to be excellent. The sections are removed from the knife by a camel's-hair brush or by an improvised lifter, made by transfixing a square inch of stiff paper with a dissecting needle. Sections, instead of adhering in ribbons, fall singly and roll up in cutting when the paraffin is too hard. By bringing a spirit lamp or a Bunsen burner near the microtome the paraffin may be slightly softened and the rolling thus prevented. It is necessary to take care

that the flame be not brought nearer to one side of the tissue than to the other, or the sections will curl up on the off-side. When the surface of the section presents a gritty appearance it is an indication that the imbedding is incomplete, in which case the process should be repeated. Curled sections can usually be flattened by being floated on water heated to about 10° below the melting point of the paraffin. This may be done by pouring from time to time a little boiling water from a kettle into a basin containing hot water till the water in the basin has a temperature of nearly 40° C. A special apparatus may be obtained for this purpose, but the above simple means will be found to answer almost as well. Certain workers prefer to unroll the sections on the slide by placing them in a drop of water or 70 per cent. alcohol and slightly heating the slide above the flame till unrolling takes place.

Fixing the Section to the Slide.—Paraffin sections are fixed on the slide during the processes of staining and mounting. The section is floated from the water on to a clean slide, and fixed there, either by some substance, such as albumen, which by coagulating causes it to adhere firmly to the slide, or by heat.

1. *Fixation by Albumen* (*Mayer, Journ. Roy. Mic. Soc.*, 1888, p. 160).—Mayer's albumen solution is very generally used for this purpose. It has the following composition :

White of egg	50 c.c.
Salicylate of soda	1 grm.
Glycerin	50 c.c.

The salicylate is dissolved in a little distilled water, the white of egg beaten up with it, then the glycerin added, and the solution carefully filtered. The presence of salicylate of soda prevents micro-organisms from growing in the solution. A small drop of the solution is placed in the centre of the slide and smeared all over it in a thin film by the finger. These prepared slides are allowed to dry for a few minutes, being covered up in the process to prevent dust collecting on them. The sections are floated from the water on to the centre of the prepared slide, and pressed down firmly with a piece of blotting-paper. The slides are placed in an incubator at 40° C. for about half an hour to complete the fixing. This method fixes the sections firmly, and is specially suitable for fixing paraffin sections of the skin, since the latter are frequently subjected to complicated methods of staining, which

are apt to loosen them. Unfortunately the coagulated albumen stains readily by protoplasmic stains, and the preparations are in consequence not infrequently defective.

2. *Fixation by Heat.*—The sections are floated on to a clean slide and all the surplus water wiped away; they are then carefully pressed dry with a piece of filter-paper, and placed for twenty-four hours on the top of the paraffin-oven or in an incubator at about 37° C. The slides should be arranged with the section downwards on a rack for the purpose, or piled in a small cardboard box, separated from each other by small pieces of matches. They must on no account be put inside the oven, or the paraffin will melt, and the sections will be certain to come off in staining.

If fixation by heat be carefully done, and care be taken not to approach too near the melting point of the paraffin, the sections will usually adhere sufficiently to the slide for staining purposes. This method has the great advantage of being free from the troublesome precipitation of coagulated albumen, which is the chief drawback to the former method.

Several histologists, instead of fixing the sections on the slides, prefer to fix them on cover-glasses, so that they may be immersed in small dishes containing the various staining fluids.

Removal of the Paraffin from the Sections before Staining.—Before staining the sections it is necessary to remove the paraffin completely. This may be done either by chloroform or xylol. Of the two, chloroform is the more rapid in its action.

After the paraffin has been dissolved out, the chloroform or xylol must in turn be removed by absolute alcohol, after which the slide is immersed in 50 per cent. alcohol, and finally in water. The section is then ready for staining.

The time occupied in the removal of the paraffin varies with the thickness of the section and with different samples of paraffin. The action of the xylol may be hastened by gently heating the slide over a flame, care being taken not to allow the xylol, which is very inflammable, to catch fire.

Clearing before Mounting.—After the section has been stained it is dehydrated by absolute alcohol, and must then be cleared before it is mounted in Canada balsam. Xylol is most generally used for this purpose. The section is known to be cleared when it is transparent and presents no whitish opaque patches (*see* Method of Clearing, p. 24).

Epitome of the Paraffin Method.

1. Place the hardened tissue in absolute alcohol for at least twenty-four hours.
2. Transfer it for twenty-four hours to a mixture of equal parts of absolute alcohol and chloroform.
3. Transfer it to pure chloroform for twenty-four hours, or till the tissue sinks.
4. Add an equal volume of paraffin to the chloroform, and put the dish containing the mixture in the paraffin-oven for at least twelve hours.
5. Transfer the piece of tissue to melted paraffin in the oven for twenty-four hours.
6. Block and cut.
7. Float the sections in water at about 40° C.
8. Fix them on slides by heat or albumen.
9. Dissolve out the paraffin by xylol, and remove the xylol by absolute alcohol.
10. Immerse the slide in 50 per cent. alcohol, and then in water.
11. Stain.
12. Dehydrate in absolute alcohol.
13. Clear in xylol.
14. Mount in Canada balsam.

Freezing Method.—When the skin is specially hard from a thickening of the horny layer, thinner sections can be obtained by freezing than by any other method.

The piece of skin after hardening should be put in running water for at least twenty-four hours, to remove the hardening reagent completely. It is then transferred to a *gum-syrup solution* for twenty-four hours or longer.

The following solution is recommended by Hamilton :

1. Make a syrup of the strength of 28·5 grm. of pure sugar to 30 cc. of water ; boil, saturate with boracic acid, and filter through muslin when cold.
2. Make a mucilage of gum acacia in cold water ; boil, saturate with boracic acid, and filter.

Take of the	syrup	. . . . .	4 parts
„	„ mucilage	. . . .	5 „
„	„ water	. . . . .	9 „

Boil, saturate with boracic acid while hot, and filter when cold.

A simpler gum-syrup may be made with five parts of gum mucilage (B.P.), four parts of syrup, and five grains of carbolic acid added to each ounce (Cole).

A little of the gum-syrup is smeared on the freezing plate of the microtome, and the tissue, impregnated with the solution, is placed on it and frozen by an ether spray. The sections, when cut, are removed from the knife into water. Care must be taken that no drops of water get on to the tissue while it is being cut, as they will freeze and make notches on the edge of the knife.

The tissue should be cut when it is on the point of thawing, and not when it is frozen hard, or it will be too brittle to cut well.

The chief disadvantage of this method is that the sections on thawing are unsupported, and are liable to break on being manipulated. To obviate this difficulty the *freezing and celloidin methods may be combined* as follows:

1. Imbed in celloidin in the manner described on page 22; transfer the piece of skin from the celloidin to a porcelain plate or to a paper box, and pour a few drops of thick celloidin over it; allow this to set for half an hour in the air, then put it in 80 per cent. alcohol for twelve hours, and finally in water for several hours.

2. Transfer the celloidin block from the water to gum-syrup for a few hours, and then place it on the freezing plate; freeze and cut.

This modification has all the advantages of the freezing method, and the sections are much less friable.

The Choice of a Method for Imbedding the Skin.—The *celloidin method* is perhaps the one which is in most common use for imbedding skin. It has the following advantages over the paraffin method:

1. It is simpler.

2. The sections do not require to be fixed on the slide during the staining process, but are stained in dishes containing the dyes. In this way the dyes penetrate more thoroughly, and the differential staining reactions are more vivid.

3. The celloidin need not, as a rule, be removed from the section before staining, and it acts as a support to the elements of the section.

By the *paraffin method*, however, thinner sections may be obtained than with celloidin. It is difficult to obtain celloidin sections thinner than 10 μ, though it must be conceded that there are several experts who can do so; but by the paraffin method sections of 5 μ can easily be cut, provided the tissue

is smaller than a centimetre square. If it be larger than a centimetre square, there is little to choose between the two methods.

For ordinary diagnostic purposes the celloidin method gives adequate results, but for the study of the finer details in the elements of the skin the paraffin method is recommended.

The *freezing method* is specially indicated when the skin is hard and the stratum corneum thickened; but unless it be combined with celloidin, as already described, the thin frozen sections are so brittle that it is almost impossible to manipulate them without damaging them. The freezing method is of service when it is desired to demonstrate fat or eleidin in the skin, since these substances are soluble in the hardening fluids used in preparing the tissues for imbedding in paraffin and celloidin.

CHAPTER VI.

GENERAL PRINCIPLES OF STAINING SKIN.

THE technique connected with the staining of the skin is now a special and complicated one, and some knowledge of it is indispensable to the student of dermatology. The dermatologist has to be able not only to distinguish minute differences in structure, but also to recognise degenerative changes in the skin and alterations in the chemical reactions of its elements, and to do this only a few of the methods of staining used in general histology are adequate.

Staining Pieces of Skin in Bulk.—Though staining in bulk is not a method to be recommended for the skin, since the results obtained by it are not sufficiently delicate, still, it may be useful when it is desired to mount rapidly a large number of sections for class-demonstrations.

The most useful stains for the purpose are *alcoholic solutions of carmine and cochineal.* Anilin dyes do not give such good results, and aqueous solutions do not penetrate sufficiently.

Beale recommends the following ammoniacal solution of carmine (*How to Work*, etc., p. 95):

Carmine	0·6 grm.
Liq. ammoniae	3·75 c.c.

Boil and add:

Glycerin	60 c.c.
Distilled water	60 „
Alcohol	15 „

Grenacher employs an alcoholic solution of borax-carmine (*Archiv f. mik. Anat.*, 1879, XVI., p. 466). "Make a concentrated solution of carmine in borax solution (2 to 3 per cent. carmine to 4 per cent. borax) by boiling for half an hour or more; dilute it with an equal volume of 70 per cent. alcohol; allow it to stand for twenty-four hours, and filter" (Lee and Mayer).

Method.—A piece of skin-material, the smaller the better, is fixed and hardened. It is then thoroughly washed, transferred to an excess of the stain, and allowed to remain there from two days to a week, according to its size. The superfluous stain is washed away, and the tissue is dehydrated in absolute alcohol, and either imbedded in celloidin or cleared and imbedded in paraffin, and sections cut and mounted in the usual manner.

Staining Sections of the Skin.—

General Remarks.—The majority of the dyes in common use in skin-histology belong to the coal-tar or anilin series; and dyes such as carmine and cochineal, which do not belong to this group, are only occasionally of service. The number of anilin dyes which have been employed in staining skin is a large one, and every year it increases. To attempt to give a complete list of those which have been used would serve no useful purpose, and only the most important of them need be mentioned.

Anilin dyes vary considerably in different samples; and since it is an advantage not only to make well-stained specimens, but also to compare them with those of others employing the same methods, it is necessary that the dyes used should all have the same standard of purity. This difficulty has, to a great extent, been solved on the Continent, since so many histologists get their stains from Grübler, of Leipzig. Grübler's stains can be obtained in this country from one or other of his agents.[1]

These stains may be obtained in solution or in powder and dissolved as required; in either case they should be carefully filtered before use.

Classes of Stains.—Stains may be divided into two classes—namely, (1) diffuse stains, and (2) selective stains.

By a *diffuse stain* is meant one which stains all the elements of a tissue with equal intensity, while a *selective stain* is one which selects or picks out certain elements in a tissue and leaves the remainder partially or wholly unstained. In all finer histological work selective stains must be employed, and the more definitely selective a stain is, the greater is its value. As examples of *selective stains* the following may be mentioned: Safranin, which is essentially a nuclear stain,

[1] Kanthack, 18, Berners Street, London, W.; Baker, 244, High Holborn, London; Townson & Mercer, 89, Bishopsgate-Street-Within, London, E.C., etc., etc.

and leaves the rest of the cell and the intercellular substance only faintly coloured ; acid orcein, which picks out the elastic tissues ; and acid fuchsin, which has a marked affinity for certain products of degeneration, such as hyalin.

Certain of the selective stains are so rapid in their action that they at once attack the particular element towards which they have an affinity, without affecting the remainder of the tissue ; and to obtain satisfactory results by these it is only necessary to understain the sections and then to dehydrate, clear, and mount them. These have been called *progressive stains*. Thionin is an example of them, and it is one of the most useful of nuclear stains.

In contradistinction to the progressive stains there is another group known as *regressive stains*, in which the selective action is obtained by overstaining the sections, and subsequently decolorising them to the required degree. The regressive method of staining gives more satisfactory results, and is the one almost invariably employed.

The Reaction of Stains.—Ehrlich[1] inaugurated a new era in the staining of sections by his elaborate work on the granules of the white blood-corpuscles. From his observations in this connection he concluded that the anilin dyes might be divided into three groups—namely, (1) acid stains, (2) basic stains, and (3) neutral stains.

Acid Stains.—An acid stain is a compound in which the staining element is an acid, while the remaining element—namely, the base—is colourless. Picrate of ammonia is a simple example of this variety. It is the picric acid which stains the protoplasm of the cells yellow, while the basic ammonia is colourless.

Basic Stains.—In the basic stains the active element of the compound is the chemical base, which is combined with a colourless acid. Fuchsin or hydrochloride of rosanilin is an example of a basic stain. The hydrochloric acid is colourless, while the rosanilin stains the nuclei red.

Neutral Stains.—A neutral stain is one in which the staining principle is neutral in reaction. Such dyes are rare.

According as the granules of the leucocytes attract one or other of these classes of stains, they are known as *acidophilic*, *basophilic*, and *neutrophilic granules*. Acidophilic granules

[1] *Verh. d. Berlin. Phys. Ges.*, May 16th, 1879 ; and *Zeit. klin. Med.*, 1880, p. 555.

attract acid stains, and in order to do so they must themselves have an opposite reaction ; hence acidophilic granules are in reality basic in reaction, and, *vice versâ*, basophilic granules are acid.

It would seem at first sight to be a simple matter to determine the reactions of the various elements of a tissue such as the skin by means of dyes which are known to belong to one or other of these groups. Unfortunately this is not the case, for in dealing with sections of a tissue the original reaction may have become completely changed by the processes of hardening, clearing, and imbedding. The reactions of tissues fixed and hardened in alcohol may persist unaltered, but where osmic acid, chromic acid, or bichromate of potash have been employed the original reactions are greatly interfered with : this is also the case when overstained sections are decolorised in acidulated alcohol.

But in spite of these difficulties, an attempt should be made to distinguish as far as possible the reactions of the elements of the skin, as much valuable information may thereby be obtained.

Note on the Reaction of the Skin in General.—The reaction of the various layers of the skin depends on the reaction of the blood and the lymph, on the one hand, and on that of the sweat, on the other. Heuss,[1] in his investigations on the reaction of the sweat, has proved that in health it is acid, but that in excessive sweating it loses much of its acidity and may at times become alkaline. The acidity of the sweat is dependent on the presence in it of carbonic acid and certain organic acids, such as acetic and butyric.

On account of the acidity of the sweat, the reaction of the epidermis, both on the surface and in the Malpighian layer, is generally acid, and the intensity of the acidity varies in different regions in proportion to the number of the sweat-glands.

The reason why the reaction of the sweat influences that of the epidermis much more than that of the corium is that the sweat-duct really ends at the epidermis, and the channel through the latter to the surface is an unlined winding passage between the epidermal cells, which freely communicates with the lymphatic spaces between the neighbouring cells.

The reaction of the corium and its fibrous elements is mainly dependent on that of the blood and lymph, and these are faintly alkaline.

[1] *Monats. f. prakt. Derm.*, 1892, XIV., p. 343.

The white fibrous bundles and the elastic fibres are both alkaline in reaction, and in consequence attract acid dyes (acidophilic); the elastic fibres have a peculiarly strong affinity for acid dyes. The nuclei of cells, whether of the epidermis or corium, are more acid in reaction than the remainder of the cell; hence the nuclei and their chromatin are basophilic, while the hyaloplasm and spongioplasm of the cells are acidophilic.

It is important to recognise these differences in reaction of the elements in health, because pathologically these reactions become altered. As a prelude to disintegration, for instance, the fibrous elements generally lose their acidophilic characters and begin to attract basic dyes; and degenerative products such as hyalin may appear in the protoplasm of the cells, which are more intensely acidophilic than the protoplasm itself.

The Process of Staining Sections in General.—From the above brief reference to the reaction of the skin it will be realised that there are two sets of stains commonly required in staining it—namely, *basic stains*, which are practically synonymous with *nuclear stains*; and *acid* or *plasma stains*, which are more diffuse and stain the protoplasm of the cells as well as the intercellular fibrous substances.

The following are the most generally employed basic or nuclear stains: methylene blue, hæmatoxylin, thionin, gentian violet, dahlia, safranin, and fuchsin; and the acid plasma stains are picric acid, orcein, orange, eosin, and water-blue.

When it is desired to demonstrate only the basophilic or the acidophilic elements of the skin, a single stain may be employed. Where all the elements are to be demonstrated, double staining is resorted to—that is, employing a dye from the first group to stain the nuclei, and one from the second to stain the protoplasm of the cells and the fibrous elements. Occasionally the two dyes are mixed together in the right proportions, and the staining done at one time; but this is rarely satisfactory. Whether the acid or the basic dye should be used first in the staining depends on the dyes which are chosen, and special directions regarding this point will be given in describing the various methods of staining.

There are certain dyes which give a double-staining effect, owing to the presence of impurities in them of the nature of by-colours; for example, if methylene blue be prepared in a certain manner, a red by-colour is formed, and this fact has been taken advantage of by Unna in preparing "polychrome

methylene blue." The formation of these by-colours is known as *metachromism.*

The Time required by the Stains.—The *time* required by the various stains to act will be given approximately in describing the special methods. It is impossible to give definite times for each of the stains, as the times vary according to the thickness of the section and the method of imbedding. But as the various methods of staining become familiar to the student a facility will be acquired in telling from the appearance of the section if the staining be sufficient.

Differentiation.—In the sections overstained by the "regressive method" it is necessary to remove the superfluous stain to define the different elements, and this process is known as *differentiation.* This is usually done by alcohol; but occasionally acidulated alcohol (absolute alcohol with 5 per cent. hydrochloric acid, or 1 per cent. acetic acid) may be required when several dyes have been employed, or when it is desired to decolorise everything except the single element towards which the dye has its peculiar affinity.

Dehydration.—Sections stained by aqueous solutions of dyes require to be dehydrated before they can be cleared and mounted. The dehydration and differentiation are generally done at one time by alcohol. For the latter purpose 95 per cent. alcohol may be employed, but absolute alcohol is more effective.

Mordants or Fixing Agents.—In the ordinary process of dyeing, certain reagents called *mordants* are employed to fix the dye, so that it will resist decoloration. In staining sections, mordants are, as a rule, unnecessary, except where a strong fixation is required. Metallic salts, such as iodide and permanganate of potassium, are generally employed for this purpose.

Clearing and Mounting.—Before mounting in Canada balsam it is necessary to clear the sections in the manner already described.

Glycerin or Farrant's solution may be substituted for Canada balsam in mounting. With them neither dehydration nor clearing is necessary; but they do not give a permanent mount unless the cover-glass is ringed afterwards with cement.

FARRANT'S SOLUTION.

Picked gum arabic	4 oz.
Water	4 „
Glycerin	2 „

To be kept in a stoppered bottle with a lump of camphor.

Epitome of the Staining and Mounting Processes.

1. Transfer the section from the water to the filtered stain.

2. Stain the sections for the requisite time; if double staining be desired, stain with the first dye, wash thoroughly, then stain with the second.

3. Wash in water.

4. Differentiate in 95 per cent. alcohol for about five minutes, till the stain ceases to come off.

5. Dehydrate in absolute alcohol for five minutes or longer, according to the thickness of the section.

6. Clear in bergamot oil, cedar-wood oil, or xylol.

7. Mount in Canada balsam. If the balsam is thick and does not spread well after the cover-glass is applied, heat the slide gently over the flame, which will cause it to spread more easily, and at the same time will remove the air-bubbles.

NOTE.—The above procedure refers to celloidin sections, which are stained in dishes and manipulated from the one to the other by a section-lifter. In the case of paraffin sections, which are fixed to the slide, the various reagents are dropped on to it, and the time taken in staining is slightly longer.

The Stains most usually employed in Skin-Histology, and the Methods of using Them.—A detailed description of the chemical composition of the various stains which are of service in the histological technique of the skin would be out of place here, and for more complete information the reader is referred to the classical text-books on the subject. to which the writer is indebted for many of the following facts. Only the general methods of using the stains will be described in this chapter, the descriptions of special methods being reserved for the chapters dealing with special subjects.

BASIC AND NUCLEAR STAINS.

Safranin.—It is employed as a 1 per cent. solution in water, or in 50 per cent. alcohol, as some samples of safranin can be dissolved in water only with difficulty. The sections are stained in the alcoholic solution for about five minutes, but in the watery solution a few minutes longer is necessary.

Safranin gives a beautiful, bright red and transparent nuclear stain, and is one of the best dyes for chromatin. It illuminates brilliantly in artificial light, and gives good results in photo-micrography.

One of its most important uses for the skin is to demonstrate mitotic figures in the cells of the epidermis and corium. By differentiating overstained sections in acidulated alcohol only the mitosing nuclei retain the safranin, while the resting nuclei become colourless. Water-blue, which is an acid dye, constitutes a good counter-stain to safranin.

Method of Double Staining with Water-Blue and Safranin.—

1. Stain for five minutes in a 0·5 per cent. solution of water-blue.
2. Wash in water.
3. Stain from five to ten minutes in a 0·5 per cent. solution of safranin in 50 per cent. alcohol.
4. Wash in water.
5. Differentiate in 95 per cent. alcohol.
6. Dehydrate in absolute alcohol.
7. Clear in bergamot oil or xylol.
8. Mount in Canada balsam.

The chromatin and nucleoli are stained a transparent red, and the protoplasm of the cell and fibrous elements blue.

NOTE.—If safranin be used first the results are not so good, and the staining is less definite.

Fuchsin or Magenta is a basic dye and a good red stain for chromatin; but the results obtained with it are not so vivid as those with safranin. It may be used in a 1 per cent. solution in water; it is chiefly employed in the carbol-fuchsin mixture of Ziehl for the staining of various bacilli and trichophytons.

Ziehl's Formula (*Zeit. f. wiss. Mik.*, 1890, p. 39).—

Fuchsin	1 grm.
Carbol. acid cryst.	5 grms.
Alcohol	10 „
Distilled water	100 „

There is also an **Acid Fuchsin** dye, but as it belongs to the group of the plasma stains the reference to it will be deferred.

Gentian Violet is one of the best bluish stains for chromatin, and may be used as a 1 per cent. solution in water or in 50 per cent. alcohol.

An alcoholic solution of gentian violet combined with anilin water is an important stain for bacteria and for the fungi of ringworm and favus. The method in which it is usually employed is known as the Ehrlich-Gram method.

Ehrlich-Gram Method.[1]—

1. Stain the sections for ten minutes in Ehrlich's solution :

Gentian violet	1 part
Anilin oil	3 parts
Alcohol	15 „
Water	80 „

2. Wash in water.

3. Fix in Gram's iodine solution for two minutes, till the sections are quite black.

Iodine	1 grm.
Iodide of potassium	2 grms.
Water	300 c.c.

4. Wash in water.
5. Differentiate and dehydrate in alcohol.
6. Clear in clove oil.
7. Mount in Canada balsam.

Nuclei, interepithelial fibres, bacteria, and the fungi of ringworm and favus are stained violet. The one disadvantage of the method is that iodine is liable to be precipitated in the sections in the form of fine granules resembling micro-organisms. This disadvantage can be minimised by using the following modified Gram's solution :

Iodine	1 part
Potassium iodide	2 parts
Glacial acetic acid	2 „
Water	300 „

Methylene Blue.—This is a useful stain for nuclei and for medullated nerves. In dermatological technique it is frequently used, either in the form of the "Polychrome methylene blue" of Unna, or the "Borax methylene blue" of Sahli and Boeck.

[1] A further reference to the Ehrlich-Gram method of staining and the modifications of it will be found on page 73.

Polychrome Methylene Blue (*Unna, Monats. f. prakt. Derm.* 1891, XII., p. 296, and 1894, XIX., p. 225).—The name originated from the fact that old samples of methylene blue and those treated with an alkali not only possessed the blue stain, but also a by-product in the nature of a reddish violet impurity. Polychrome methylene blue has been so greatly employed by Unna in his classical work on the histology of the skin that it has come to be one of the most generally used dermatological stains.

COMPOSITION OF THE DYE.

Methylene blue	1 part
Potassium carbonate	1 „
Distilled water	100 parts

Polychrome methylene blue is not only a nuclear stain, but it acts as a diffuse plasma stain. By it the chromatin is stained reddish violet, and the protoplasm of the cells blue. It is differentiated in alcohol, tannic acid, and in Grübler's glycerin-ether mixture. This dye is chiefly employed to stain the mast-cells and plasma-cells of the skin, and the methods of using it will be described later.

Borax Methylene Blue.—Boeck strongly recommends this dye for staining micro-organisms in the skin. Its composition is as follows:

Methylene blue	1 part
Borax	1 „
Water	100 parts

Thionin.—This stain should be employed as a 1 per cent. aqueous solution. In its staining reactions it closely resembles polychrome methylene blue, and, like it, has a reddish by-product, which stains nuclei and mast-cell granules red.

Hæmatoxylin is a penetrating nuclear stain which does not belong to the group of anilin dyes. It stains nuclei and keratohyalin granules a deep violet colour approaching black. It belongs to the group of Ehrlich's basic stains, but it also acts diffusely, staining the protoplasm of the cells a delicate violet tint. The active colouring principle of this important dye is a substance called *hæmatein*, which is produced by the oxidation of hæmatoxylin. Hæmatein may be obtained pure from the manufacturers. As a rule solutions of hæmatoxylin are used, and the following are the formulae of two of them:

Delafield's Hæmatoxylin (*Zeit. f. wiss. Mik.*, 1885, p. 288).—

Hæmatoxylin	4 grms.
Absolute alcohol	25 c.c.
Saturated solution of ammonia and alum	400 „

Expose the above to the air and light for several days in an unstoppered bottle, till oxidation is complete ; then add :

Glycerin	100 c.c.
Methyl alcohol	100 „

and filter. The addition of the glycerin stops oxidation and makes the solution permanent.

Unna's Hæmatoxylin (*Zeit. f. wiss. Mik.*, 1892, p. 483).—

Hæmatoxylin	1 part
Alum	10 parts
Alcohol	100 „
Water	200 „
Sublimed sulphur	2 „

This solution does not keep well, and requires to be freshly prepared every six months. The sulphur is added after several days when the mixture has become blue in tint, and it serves to stop oxidation and to render the solution constant.

For the demonstration of nuclei, sections should be stained from two to three minutes in the hæmatoxylin solution, and then washed for several hours in distilled water ; for keratohyalin twelve hours in the stain may be required.

Acid and Plasma Stains.

These dyes are much more diffuse in their action than the basic stains, and affect not only the protoplasm of the cells, but also the intercellular fibrous tissue.

Orcein.—Orcein belongs to this group, and, being one of the best stains for connective tissue, is extensively used. Unna introduced two solutions of orcein, known as "neutral orcein" and "acid orcein."

Orcein is obtained from the makers in the form of a brownish red powder.

1. *Neutral orcein* is a 1 per cent. solution of orcein in absolute alcohol. It stains white fibrous tissue reddish brown, elastin brown, and protoplasm brownish. As it is an alcoholic solution it is advisable to dry the sections as much as possible before staining them ; and since it quickly evaporates when dropped on to a paraffin section, it is an

advantage to immerse the slide in a cylindrical staining-glass containing the dye.

The time occupied in staining by neutral orcein is about fifteen minutes. It makes a most serviceable counter-stain for polychrome methylene blue.

Combined Method (*after Unna, Monats. f. prakt. Derm.*, 1894, XVIII., p. 511).—

(*a*) Stain the sections for five minutes in polychrome methylene blue.

(*b*) Wash and dry them thoroughly.

(*c*) Stain them for ten minutes in neutral orcein.

(*d*) Differentiate in absolute alcohol.

(*e*) Clear in bergamot oil.

(*f*) Mount in Canada balsam.

The nuclei and protoplasm of the cells are stained blue, the collagen and elastin reddish brown, and the mast-cell granules bright red.

A rapid and beautiful double staining is obtained by placing sections for three minutes in polychrome methylene blue, and washing and differentiating them in a watch-glass containing absolute alcohol, to which four or five drops of neutral orcein have been added. The white fibrous bundles are stained a bright red (Pl. I.).

2. *Acid orcein* is also a 1 per cent. solution of orcein in absolute alcohol, but with the addition of 1 per cent. of hydrochloric acid. It is chiefly used for staining elastin. Hæmatoxylin is one of the best counter-stains for it (*see* p. 147).

Acid Fuchsin is also a valuable plasma stain. It is generally used in the form of a 1 per cent. aqueous solution. Its chief uses in skin-histology are to detect degenerative products of the white fibrous substance in collagen, and to stain the hyalin degeneration of cell-protoplasm.

Picric Acid is a reliable plasma stain and a good counter-stain for hæmatoxylin, safranin, and gentian violet. Its employment is simple, as it only requires to be added in the strength of ·5 per cent. to the absolute alcohol used for decolorising. It stains the connective tissue and the protoplasm of the cells pale yellow.

Orange is also an excellent stain for protoplasm, and it is one of the best dyes for picking out the spongioplasm and interepithelial fibres of the prickle-cells. Sections should be

stained for fifteen minutes in a saturated aqueous solution. As a counter-stain for gentian violet or methylene blue it can be used in the same simple manner as picric acid by dissolving about 1 per cent. of it in the alcohol used for decolorising.

Orange G. (Grübler) is one of the most satisfactory of the orange stains.

Impregnation Stains.

By *impregnation stains* are meant stains which act in virtue of the colour being deposited on the elements in the tissue in the form of a fine granular precipitate. The chief impregnation stains are the metallic stains, *nitrate of silver* and *chloride of gold*; but a few other dyes, like methylene blue, are capable of staining occasionally by impregnation. A pathological instance of impregnation occurs in the slaty blue pigmentation of the skin in argyria, which is due to the deposition of fine granules of silver in the skin.

It is customary to describe two kinds of impregnation stains—namely, *negative impregnation* stains and *positive impregnation* stains. Negative impregnations are those in which the deposit takes place in the intercellular substance, while in positive impregnations it occurs in the protoplasm of the cells. This distinction is arbitrary, since the impregnation affects the intercellular substance first; and, according to Lee, the cell-protoplasm is stained only when the deposit becomes dissolved in the intercellular fluid. Impregnation stains are of service in dermatological technique in staining the epidermis and the nerve-fibrils of the skin.

In preparing this chapter I am indebted for much assistance to Lee's valuable treatise on the subject (*The Microtomist's Vade-Mecum*, 1900, 5th Edition).

CHAPTER VII.

THE CELL AND ITS MODE OF REPRODUCTION, AND THE METHOD OF STAINING THE CELL IN GENERAL.

SINCE a thorough working knowledge of the structure of the animal cell in general, and of the methods by which it reproduces itself, are essential before the student can approach the difficult problems and fine distinctions which present themselves in the study of the histology of the skin, it will be advisable to recapitulate briefly a few elementary facts in this connection (Pl. II., Figs. 1 and 2).

The basis of all living cells is the substance known as *protoplasm*, a substance which is semi-fluid, alkaline in reaction, and which swells up in water. It is composed of a proteid called plastin, albumen, water, and salts. The protoplasm of the animal cell is not structureless, but forms a fine network known as the *spongioplasm*, in the meshes of which there is a homogeneous semi-fluid substance named the *hyaloplasm* ; and the younger the cell the greater is the proportion of hyaloplasm.[1] The network of spongioplasm varies greatly in its arrangement in the cells of different tissues. In the prickle-cells of the epidermis it radiates from the nucleus to the periphery of the cells, while in the columnar cells of the basal layer its fibrils run in the long axes of the cells so as to produce elongated meshes. It may radiate beyond the cell in the form of fine fibrils, as in the prickle-cells of the epidermis, or it may stop abruptly at the periphery of the cell, and, being condensed there, may have the appearance of a cell-membrane.

Where the fibrils of the spongioplasm cross each other, small knots or nodules may be seen which give the cell, especially where the meshes are small, a distinctly granular appearance ; this is most probably merely an optical illusion.

[1] In the hyaloplasm small granules, called *microsomes*, are described ; these are absent in the peripheral zone or *exoplasm* of the cell.

PLATE II

FIG. 1. DIAGRAMMATIC SCHEME OF A CELL.

a. Exoplasm.
b. Endoplasm.
c. Network of spongioplasm.
d. Spongioplasm prolonged beyond the cell in fine fibrils (only represented in half the cell; this prolongation occurs in the prickle-cells of the epidermis).
e. Granules in the hyaloplasm.
f. Granules of some foreign substance, such as carbon.
g. Nuclear wall or membrane.
h. Nuclear network.
i. Nuclear sap or nucleoplasm.
j. Chromatin bodies.
k. Nucleolus.

FIG. 2. DILATATION OF THE SPONGIOPLASTIC NETWORK OF CELLS BY ŒDEMA.

The drawing represents the granuloma of Lupus vulgaris forty-eight hours after exposure to the rays from a Finsen lamp. It shows the "vacuolisation" or œdematous degeneration, the result of an acute inflammatory reaction, affecting chiefly the giant-cells, plasma-cells and the fibrous stroma, and demonstrates the spongioplastic network of the cells.

a. Œdematous giant-cell.
b. Œdematous plasma-cell.
c. Group of leucocytes and small round cells of doubtful origin.
d. Attenuated œdematous fibrous stroma.
e. Connective tissue nucleus.

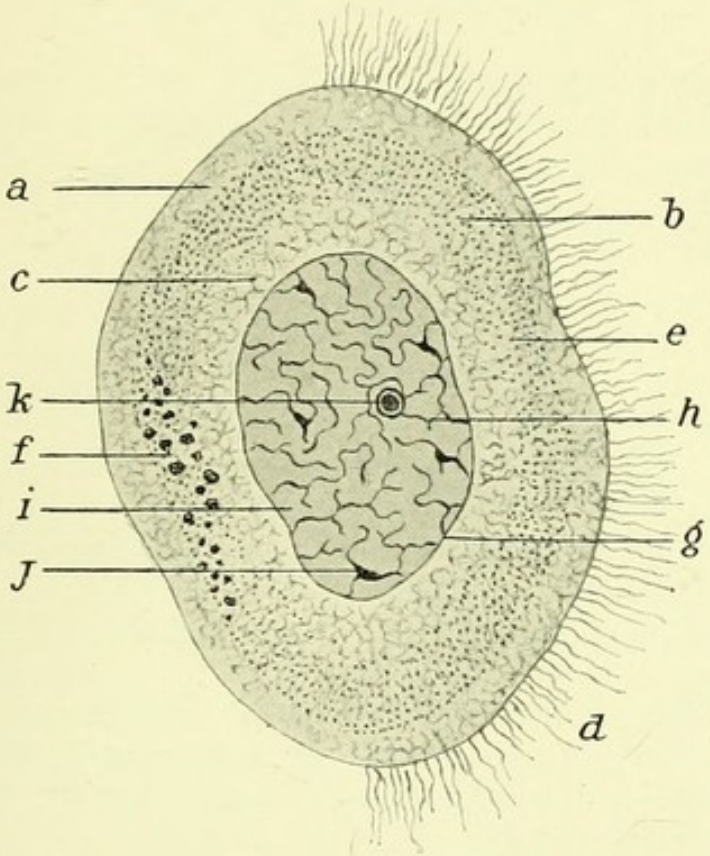

FIG. 1.

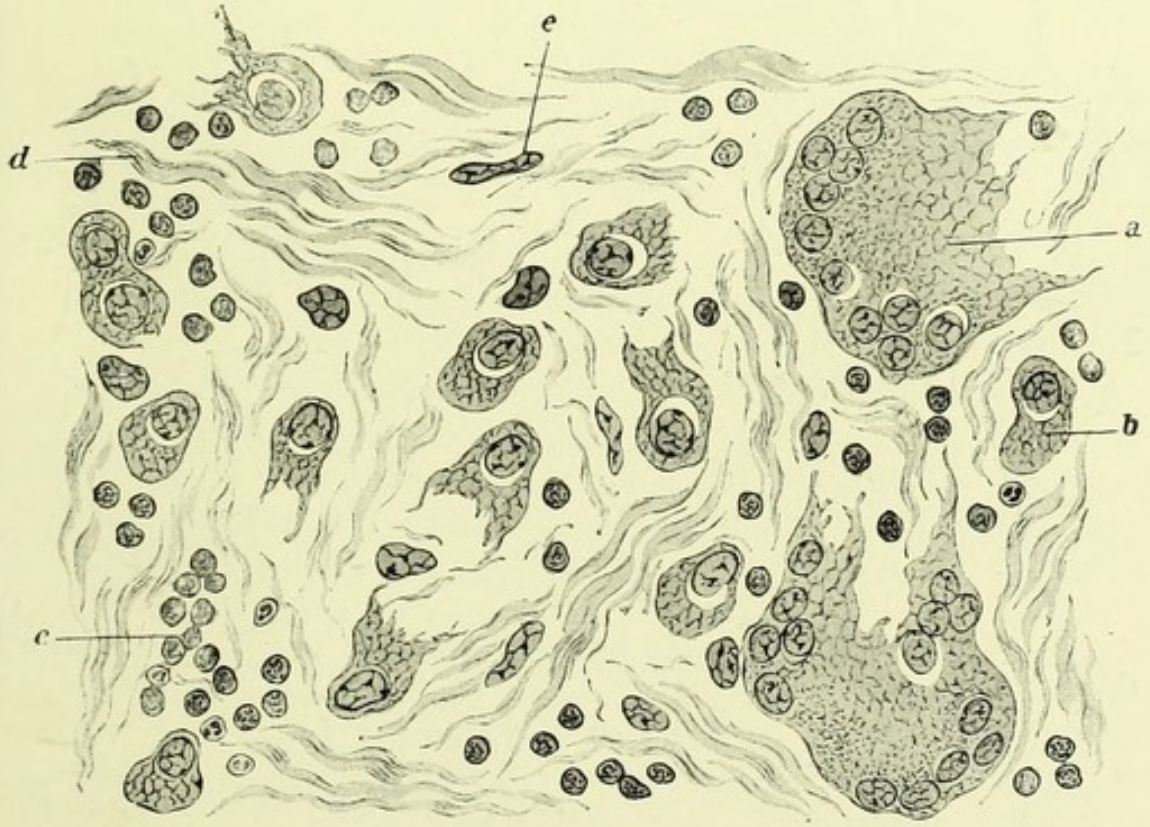

FIG. 2.

J. M. H. M., del.

Besides these hypothetical granules, real granules of various kinds may be present in the hyaloplasm of the cells. In leucocytes, for example, there are the various types of granules which Ehrlich has described according to their reactions as eosinophilic, basophilic, and neutrophilic granules. In the mast-cells of the corium coarse basophilic granules are present; in the cells of the epidermis in certain regions pigment-granules occur; and in the cells of the granular layer of the epidermis there are numerous granules of the substance known as keratohyalin.

The cell may or may not be limited by a definite cell-wall. If such be present, which is rare in the cells of higher animals, it is either the result of a secretion of the cell, or is simply due to a condensation or hardening of the peripheral protoplasm or exoplasm.

The *nucleus* is situated towards the centre of the cell. Like the protoplasm of the cell-body, it is built up of a network, in the meshes of which there is a homogeneous semi-fluid matrix, which is probably continuous through pores in the nuclear wall with the hyaloplasm of the cell. The network is composed of an easily stained substance called *chromatin* or *nuclein*, and at intervals presents angular enlargements called *karyosomes*. In the meshes one or more roundish bodies, known as *nucleoli*, are usually found; these are composed of a substance known as *pyrenin*. The chromatin network is condensed at the periphery to form a limiting membrane or *nuclear wall*.

Reproduction of Cells.—In health the cells of the skin divide by the so-called *indirect method*, known as *mitosis* or *karyokinesis*, in which the nucleus goes through the following complicated changes before the division is complete:

Stages in the Process of Mitosis.—

(*a*) In the first stage of the division of the nucleus the nucleoli and the nuclear membrane disappear, and the chromatic network becomes coarser and assumes the form of a *tangled skein*.

(*b*) The fibrils of the skein increase in thickness, the meshes become more open, and a *loose skein* is formed.

(*c*) The skein becomes rearranged by the breaking of its fibrils at the periphery so as to form a *star*. At the same time a spindle-shaped structure of achromatic fibrils may be noted passing through the star and radiating from two small bodies situated at either pole of the cell, called "*attraction spheres*."

(*d*) The star now splits at the equator into two halves, which are attracted to the poles by the attraction spheres along the achromatic fibrils, and so the *diaster stage* is reached.

(*e*) The daughter-stars rebuild through the loose skein and tangled skein till each assumes the appearance of a resting nucleus. Then the protoplasm of the body of the cell becomes constricted and gradually divides, so that two cells result, each possessing a perfect nucleus in the resting state.

Occasionally the nucleus completes its indirect division without a corresponding division occurring in the protoplasm of the cell, and in this way multinuclear cells are produced.

Direct Nuclear Division.—In certain pathological states the cells divide directly or by simple cleavage. The resting nucleus becomes constricted, assumes an hour-glass shape, and divides ; corresponding changes occur in the protoplasm of the cell. This is known as the *amitotic* form of cell-reproduction, and is associated with degenerative changes in the cells.

NOTE.—In this short chapter it is not my object to do more than refresh the memory of the student on the salient points in the morphology and reproduction of cells in so far as these are of importance in the histology of the skin ; but I would urge a careful study of this subject in one or other of the well-known text-books on histology.

THE METHOD OF STAINING THE CELL IN GENERAL.

The Methods of Staining Hyaloplasm and Spongioplasm.—

Fixing and Hardening.—For the study of the detailed structure of the cell the ordinary fixing and hardening agents have certain disadvantages. Alcohol, osmic acid, and corrosive sublimate all tend to cause changes in the protoplasm, more or less shrinkage of the nuclei, and even destruction of the chromatin. Flemming's solution (chromo-aceto-osmic acid) has none of these disadvantages, and is consequently an ideal fixing fluid for cytological work.

Staining.—One of the best stains for picking out the spongioplasm of the cell is polychrome methylene blue ; but unfortunately its finer staining properties are interfered with if the tissue has been hardened in chromic or osmic acid. On this account alcohol must be employed, in spite of the shrinkage it may cause.

The Method of Staining (*after Unna, Monats. f. prakt. Derm.*, 1894, XIX., p. 225).—

(*a*) Fix and harden in alcohol and cut in celloidin.

(*b*) Stain the sections in polychrome methylene blue for twenty-four hours.

(*c*) Wash thoroughly.

(*d*) Transfer them for one minute to the following solution :

Absolute alcohol	20 parts
Xylol	30 „

(*e*) Then to xylol for one minute.

(*f*) Then into anilin-alum mixture from five to ten minutes (saturated solution of alum in anilin oil).

(*g*) Clear in xylol.

(*h*) Mount in Canada balsam.

The spongioplasm is stained a dark, purplish blue, while the hyaloplasm has a fainter tint of the same colour.

If tissues have been fixed in Flemming's solution, *Mitrophanow's Method* (*Zeit. f. wiss. Mik.*, 1888, p. 513), staining with water-blue and safranin gives good results.

(*a*) Stain for twelve hours in a 1 per cent. solution of water-blue.

(*b*) Wash in water.

(*c*) Stain for five minutes in a 1 per cent. aqueous solution of safranin.

(*d*) Wash in water.

(*e*) Differentiate and dehydrate in alcohol.

(*f*) Clear in bergamot oil.

(*g*) Mount in Canada balsam.

The spongioplasm and hyaloplasm are stained blue, the former being of a darker tint. The chromatin is stained red.

Method of Staining the Nuclei for Mitotic Figures.—The more recent methods of studying skin-histology with the help of biopsies give us an excellent opportunity of demonstrating mitotic figures. To obtain specimens showing these delicate structures it is necessary for the tissue to be quite fresh when it is put in the fixing fluid, since the slightest decomposition invariably destroys them. The tissues where these figures can be most easily studied are commencing carcinoma of the skin and condyloma acuminatum, for in them the epithelial cells are large, and present numerous mitotic figures. Thin sections are necessary, and consequently paraffin gives the best results.

The excised tissue should be fixed in Flemming's solution

and then rapidly hardened in alcohol in the following manner:

(*a*) Put the excised tissue directly into Flemming's solution for forty-eight hours.

(*b*) Wash thoroughly in water.

(*c*) Transfer to 70 per cent. alcohol for twenty-four hours.

(*d*) „ „ 96 „ „ „ „

(*e*) „ „ 100 „ „ from twenty-four to forty-eight hours.

(*f*) Imbed in paraffin or celloidin.

Method of Staining with Safranin (after Lee, Microt. Vade-Mecum, 1900, p. 203).—

(*a*) Stain the sections for twenty-four hours in Lee's safranin solution (equal parts of a saturated solution of safranin in anilin water and absolute alcohol).

(*b*) Wash.

(*c*) Differentiate in acid alcohol.

(*d*) Clear and mount in the usual manner.

Only the mitosing nuclei and the nucleoli of the resting nuclei retain the stain, and these are stained red.

Alternative Method with Safranin, which gives good results.—

(*a*) Stain the sections for two hours or longer in a 1 per cent. safranin solution in 50 per cent. alcohol.

(*b*) Wash in water.

(*c*) Differentiate in absolute alcohol with ·5 per cent. hydrochloric acid added to it.

(*d*) Transfer to absolute alcohol.

(*e*) Clear in clove oil, as it helps to decolorise safranin.

(*f*) Mount in Canada balsam.

The mitosing nuclei and the nucleoli of resting nuclei are stained red.

Gentian Violet is also a useful stain for mitosing nuclei. The Ehrlich-Gram method (*see* p. 39) should be employed. By this method the chromatin of the mitosing nuclei is stained dark purple, while in the resting nuclei the nucleoli alone are darkly stained and the chromatin only faintly.

CHAPTER VIII.

THE SUPERFICIAL ARCHITECTURE OF THE SKIN, THE EMBRYOLOGY OF THE SKIN AS A WHOLE, AND A NOTE ON THE DEVELOPMENT OF THE EPIDERMIS.

The Superficial Architecture of the Skin.—The surface of the skin is everywhere traversed by ridges and furrows, the presence of which in great measure determines the shape of many of the elementary lesions of the skin. These ridges and furrows vary in different situations in regularity, in arrangement, and in size. Their existence is dependent on three factors: (1) the arrangement of the fibrous bundles and elastic fibres of the underlying corium; (2) the direction of the movements to which the parts are subjected; and (3) the attachment of the skin to deeper structures, such as the capsules of joints.

There are two distinct varieties of furrows—namely, *fine furrows* and *coarse furrows*.

(*a*) *Fine Furrows.*—In certain situations, such as the palms and the soles, these furrows have a regular arrangement, and tend to run parallel to one another. On the flexor aspects of the tips of the fingers (Pl. III., Fig. 3) and toes they form more or less regular patterns, which are singularly constant during life, but differ so much in each individual that they are of great value in the recognition of criminals, and impressions of them are frequently taken in the routine of prison-anthropometry. Over the rest of the body these furrows form a close network, whose meshes tend to be trapezoidal in shape, and they correspond roughly in direction with the so-called lines of cleavage of the skin (*see* p. 131).

Between the furrows, and best marked on the palms and soles, there are corresponding fine parallel ridges which are depressed at regular intervals by the sweat-pores.

(*b*) *Coarse or Deep Furrows.*—The coarse furrows of the

skin are due to the fixing down of the skin by fibrous bundles to the capsules of joints, periosteum of bones, and other underlying structures. These deep furrows are found chiefly in the neighbourhood of joints—for example, over the olecranon, and about the sacrum, iliac crest, and in the flexor aspects of the hands and feet. These furrows indicate the hinges where the skin folds in the various movements of the joints, and are liable to become the seats of the deep fissures so frequently associated with eczema and other dry thickened conditions of the skin of the palms of the hands and soles of the feet.

Folds of Emaciation.—In old age and as the result of wasting diseases, wrinkles or folds of emaciation occur in the skin. These result from the disappearance of the subcutaneous fat and of the tension kept up by it.

Note on the Embryology of the Skin as a Whole.—The human skin, considered embryologically, may be said to consist of only two layers—namely, the epidermis and the corium, which are developed respectively from the epiblastic and mesoblastic layers of the blastodermic vesicle (Pl. III., Fig. 1). The subcutaneous tissue, on account of the great difference in appearance which exists between it and the true corium, was regarded at one time as a hypoblastic structure; but most observers are now agreed that it is of mesoblastic origin, and that its peculiar appearances are simply the result of the infiltration of its cells with fat. We may then regard the corium and subcutaneous tissue as layers of a mesoblastic structure, which matures from within outwards, and increases not by a deposition of new cells on its surface, but rather by cell-division, the formation of new fibrous bundles, and the deposition of fat in its deepest layer. The epidermis and its appendages, the hairs, skin-glands, and nails are thus clearly differentiated from the underlying corium, since they are developed from a different embryological layer.

NOTE.—I have thought it advisable to add from time to time short notes on the embryology of the skin, since even a comparatively slight knowledge of its development greatly facilitates the understanding not only of its histology, but also of many of the pathological anomalies which may affect it.

Note on the Development of the Human Epidermis.—In its primitive condition in the blastodermic vesicle the epidermis consists of a layer of polygonal nucleated cells, known as

PLATE III.

FIG. 1. EPIDERMIS OF RAT EMBRYO OF FIFTEEN DAYS. (× 800.)

a. Epitrichial layer of flat cells.
b. Layer of palisade cells with large nuclei.
c. Connective tissue cell.
d. Nucleus undergoing division by mitosis.

FIG. 2. THE EPITRICHIAL LAYER OF A HUMAN EMBRYO OF FOUR AND A HALF MONTHS (SEMI-DIAGRAMMATIC).

The drawing represents the superficial layer of cells of a thin film of the epidermis torn from the scalp of an embryo of four and a half months, and macerated in normal salt solution. It shows large polygonal swollen cells with a clear periphery and granular matter collected around the nuclei.

FIG. 3. RIDGES AND FURROWS FROM THE SURFACE OF THE FINGER-TIP (SEMI-DIAGRAMMATIC).

a. Ridges parallel to each other; beneath each ridge there are generally two rows of papillae.
b. Furrows between the ridges.
c. Depressions on the ridges giving the appearance of a transverse striation, caused by the openings of the sweat-ducts.

FIG. 4. THIN TRANSVERSE SECTION OF THE STRATUM CORNEUM OF THE SOLE OF THE FOOT DIGESTED IN PEPSIN-HYDROCHLORIC ACID.

The drawing shows the delicate keratin network.

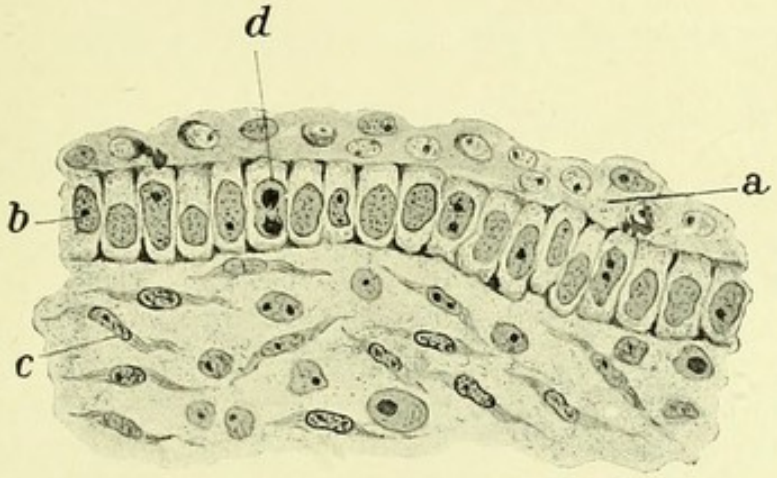

FIG. 1.

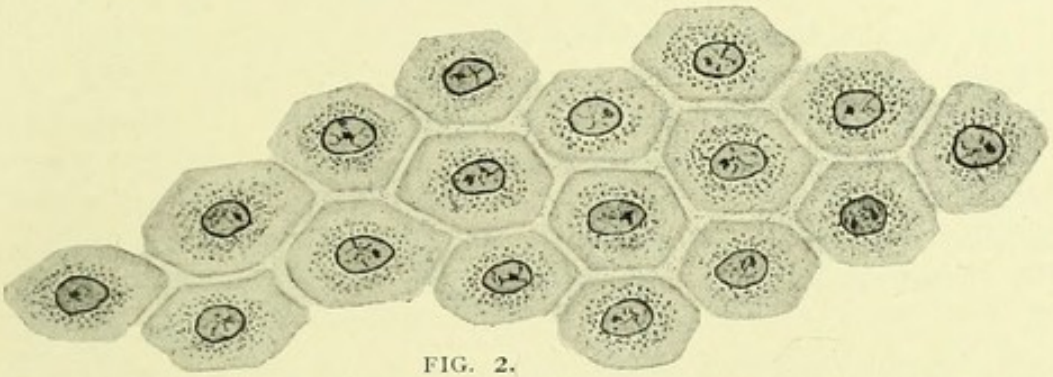

FIG. 2.

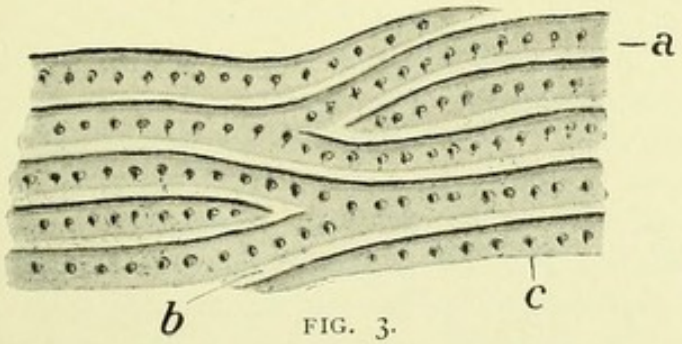

FIG. 3.

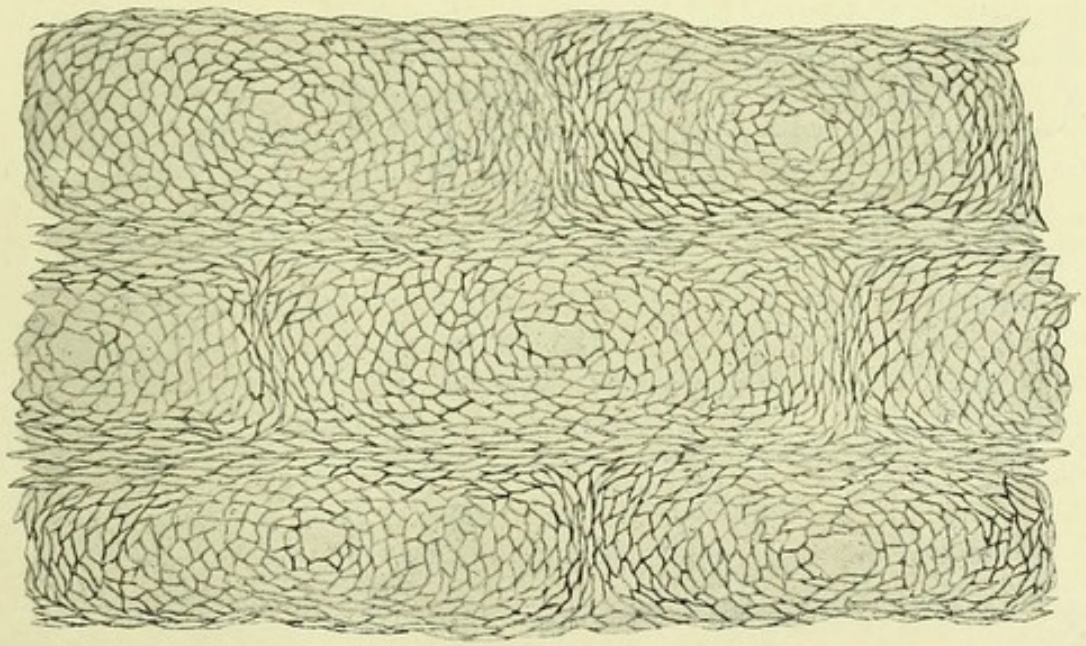

FIG. 4.

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Rauber's Layer, and beneath it a layer of cubical cells with large round nuclei.

Between the first and second months of embryonic life three layers of cells are present: the superficial Rauber's layer, the cells of which have become flattened; and two layers of cubical or columnar cells. Towards the end of the second month certain of the cells of Rauber's layer about the tips of the fingers and toes become swollen to form the so-called "Bladder cells" of Zander.[1] Bowen[2] described these "bladder cells" as dome-shaped polygonal cells of ·02 mm. in diameter, with nuclei of ·008 mm. and granular contents. In the embryos of several of the lower animals there occurs a superficial layer of large oval cells, which covers the developing epidermal appendages. Welcker discovered this membrane in the embryo of the sloth, and called it the "epitrichial layer." The superficial layer in the human epidermis with its swollen "bladder cells" corresponds with the epitrichial layer or epitrichium in animals, and Unna[3] has named the part of it which covers the developing nails the "eponychium."

The Superficial Layer or Human Epitrichium may be demonstrated in the following manner: Macerate small pieces of skin from a human embryo of about four months in normal salt solution, to which a few drops of thymol have been added. The superficial layer or layers of the epidermis can then be detached in from twenty-four to forty-eight hours in the form of a thin film. Transfer the film to a slide, and stain it with methylene blue or picro-carmine. On examination, the stained specimen is found to consist of a superficial layer of large polygonal cells, which fit together like the cells of a pavement epithelium. These cells have a clear peripheral zone and a granular, darkly stained central zone surrounding the nucleus. Beneath this layer smaller cells may here and there be noted (Pl. III., Fig. 2). Bowen suggests that the epitrichium may be the direct cause of the formation of the vernix caseosa, since in early embryonal life the epitrichium forms a continuous membrane over the surface of the skin, and retains the fatty secretions of the glands of the skin. Against this hypothesis are the facts that the epitrichium disappears, except in the flexor aspects of the fingers and toes, before the end of the eighth month, and that the vernix caseosa more or less completely covers the fœtus at birth.

[1] *Archiv f. Anat. u. Phys.*, 1886, p. 273.

[2] *Anat. Anzeiger*, 1889, p. 441, and *Journ. of Cut. and Gen.-Urin. Dis.*, 1895, p. 485.

[3] Ziemssen, *Handbook of Skin Disease*, 1885, p. 23.

By the end of the fourth month the epidermis consists of five or six rows of cells, a superficial row of flattened cells, a deep layer of columnar cells, and several intervening rows of cells, which are polygonal in shape. In the nuclei of the cells of the deepest layer mitotic figures can be detected.

By the sixth month a marked proliferation has taken place in the epidermis, and the epitrichium has disappeared, except in the fingers and toes and over the developing nails. The increased vascularity of the underlying corium and the pressure exerted by the superficial blood-vessels have caused the formation of the papillae and forced the proliferating epidermis to grow down between them to form the interpapillary processes. By the seventh month the polygonal cells of the epidermis have become differentiated, and present all the characteristics of "prickle-cells" (p. 55). About the eighth month two or three rows of cells near the surface of the epidermis become granular in appearance, owing to the presence in them of variously sized irregular granules of a substance named "keratohyalin." These granules are chiefly grouped around the nucleus, and are accessory to the process of cornification. The most superficial cells of the epidermis have been transformed by this time into cornified cells or *horn-cells*, and these form a layer known as the stratum corneum.

CHAPTER IX.

THE EPIDERMIS, THE BASAL AND PRICKLE-CELL LAYERS, STAINING OF THE PRICKLE-CELLS, HERXHEIMER'S SPIRALS.

THE fully developed human epidermis is generally divided for descriptive purposes into five layers, which are named, from within outwards, (1) the Basal Layer, or Stratum Germinativum ; (2) the Prickle-Cell Layer, or Stratum Malpighii ; (3) the Stratum Granulosum ; (4) the Stratum Lucidum ; and (5) the Stratum Corneum. Such a division as this is useful, but it is somewhat arbitrary, as these layers are ill-defined, and should be considered not so much as special layers as stages in the gradual evolution of the basal columnar cells, till they become cornified squames.

THE BASAL AND MALPIGHIAN LAYERS.

This portion of the epidermis is next the corium, and dips down between the papillae to form the interpapillary processes ; consequently the line of demarcation between the epidermis and the corium in vertical sections of the skin presents a wavy appearance. The Malpighian layer varies greatly in thickness in different regions of the skin and in different individuals. As a rule it is thickest on the soles of the feet and on the palms of the hands, and thinnest about the elbows, forehead, and cheeks. The variations in thickness are so great in different individuals that tables giving average thicknesses of this layer in different situations are of comparatively little value.

The Basal Layer, or Stratum Germinativum, is the deepest layer of the epidermis, and consists of a row of regular columnar cells, with oval nuclei. These cells are arranged vertically to the wavy line between the epidermis and the corium. Occasionally two rows of these cells may be

present, but more usually there is only a single one. Here and there between the cells smaller oval daughter-cells may be seen. The cells of this layer are united together by fine protoplasmic threads, which pass from cell to cell across the interepithelial spaces. Towards the corium the protoplasmic fibres are collected into tufts, which give a denticulate appearance to the line of demarcation between the two layers. It used generally to be taught that the cells of the basal layer were situated on a homogeneous basement membrane, and that they were held together by an albuminous cement-substance; but the most recent researches on this subject have thrown considerable doubt on the existence of either of these, and several well-known histologists regard them as purely hypothetical. The interepithelial protoplasmic fibrils of the epidermis bind the cells together sufficiently firmly to render the existence of a basement membrane, as a means of support, wholly unnecessary. As its synonym denotes, the germinal layer is the one from which the whole of the epidermis is developed. Its cells are constantly dividing, indirectly by mitosis, and their whole function is that of proliferation. They have been called the mother-cells of the epidermis. Their daughter-cells do not divide in the normal state, but are simply pushed towards the surface by new layers of cells forming beneath them, and as they approach the surface they become more and more differentiated till they eventually evolve into horn-cells. In the pigmented regions in white races, and throughout the skin in dark races, the cells of the basal layer contain numerous brownish pigment-granules scattered around their nuclei.

The Prickle-Cell Layer, or Stratum Malpighii.—Above the basal layer the cells are polygonal in shape, and, instead of being arranged in rows, tend rather to be built up in the form of a mosaic (Pl. IV., Fig. 1). Towards the surface they become more and more flattened. Their nuclei are roundish in shape in the centre of the layer, and oval as it merges into the granular layer; they have a well-marked chromatin network and one or more nucleoli. Much has been written regarding the structure of the cells of this part of the epidermis. They conform to the cell-type already described (p. 44), but are peculiar in that their network of spongioplasm stretches beyond the cells in the form of fine radiating protoplasmic threads, which pass across the intercellular spaces, to be continuous with the spongioplasm of neighbouring cells. The whole of the cells of this layer are consequently in organic

PLATE IV.

FIG. 1. GROUP OF PRICKLE-CELLS (SEMI-DIAGRAMMATIC). (× about 1000.)

Stained with gentian-violet by the Unna-Kromayer method.

a. Large nucleus in the cell with an intranuclear network and three chromatin bodies.
b. Cell in which the surface is in focus, and the prickles being seen in "relief" appear as fine specks.
c. The "exoplasm" of the cell, showing the protoplasmic fibres over it.
d. The lighter "endoplasm," with only a few fibres present.
e. Small nodules on the protoplasmic threads.
f. Nuclear space.

FIG. 2. CELLS OF THE STRATUM GRANULOSUM, WITH KERATOHYALIN GRANULES, FROM THE SOLE OF THE FOOT OF AN ADULT MALE. (× about 1000.)

Stained with hæmatoxylin and polychrome methylene blue.

It shows shrivelled nuclei lying in spaces in the cells, and the keratohyalin granules most dense around the nuclei.

FIG. 3. STRATUM LUCIDUM AND ELEIDIN. (× about 800.)

Stained with nigrosin.

a. Eleidin in lakes or puddles around and within the cells, stained blue.
b. Protoplasm of the cells, faintly blue.
c. Remains of nucleus.

FIG. 4. HORIZONTAL SECTION THROUGH THE STRATUM CORNEUM OF THE SOLE OF THE FOOT FROM A MAN OF THIRTY-FIVE YEARS OF AGE. (× about 60.)

Stained by polychrome methylene blue (Rausch's method).

a. Sweat-pore more or less filled up by unstained or faintly stained cells.
b. Cells concentrically grouped round the sweat-pore. These cells appear to be reddish purple in colour at the periphery, and blue towards the centre of the group.
c. Interlinear furrows of the skin.
d. Transverse lines where two systems of these concentrically grouped horn-cells meet one another.

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PLATE IV. *(continued).*

FIG. 5. HORN-CELLS FROM THE SOLE OF THE FOOT. (× about 1000.)

Macerated for twelve hours in hydrogen peroxide and 1 per cent. thymol. Stained by polychrome methylene-blue method (Rausch).

a. Blue-stained cell showing fine intracellular network and no prickles.
b. Reddish-purple stained cell covered with fine purple prickle-points on the surface, and purple prickles stretching out from the periphery.
c. Blue-stained cell partly covered with coarse dark granulations, and with fine purple prickle-points at the opposite end.
d. Blue-stained cell covered at the lower end by reddish purple prickle-points, and on the surface with small granulations.
e. Unstained cell mapped out in coarse purple granulations.
f. Blue-stained cell covered with coarse purple granulations.

FIG. 6. HORN-CELLS FROM THE SOLE OF THE FOOT. (× about 1000.)

Macerated for twelve hours in hydrogen peroxide and 1 per cent. thymol. Stained by Gram's method.

a. Violet-stained horn-cells with their facets marked out in darker violet, and covered on the surface with violet prickle-points.
b. Two such cells not separated by the maceration, and showing the reduced prickles between them.
c. Shrunken prickles around the horn-cell.
d. Cell showing fine prickle-points and coarser granulations.
e. Cell with no prickles visible on the surface, but showing a fine intracellular network.

FIGS. 7, 8, 9. THE EVOLUTION OF THE "MOLLUSCUM BODY." (× about 1000.)

FIG. 7. I. PRICKLE-CELL UNDERGOING HYALIN DEGENERATION.

Stained by acid fuchsin and hæmatoxylin.

Nucleus pressed to one side; two hyalin masses in the protoplasm.

FIG. 8. II. CELLS OF STRATUM GRANULOSUM.

Stained by acid fuchsin and hæmatoxylin.

Nuc ei shrivelled; hyalin masses and globules.

FIG. 9. III. HORN-CELL WHICH HAS UNDERGONE HYALIN DEGENERATION.

Stained by polychrome methylene blue and acid fuchsin.

Keratised capsule and flattened shrivelled nucleus stained violet; central hyalin mass stained pinkish.

FIG. 10. PSEUDO-PSOROSPERMS FROM THE EPIDERMIS OF A SECTION OF PAGET'S DISEASE. (× about 1000.)

Stained with safranin and water-blue-tannin solution.

a. Double-contoured membrane.
b. Nucleus pushed aside.
c. Central homogeneous mass of degenerated protoplasm.

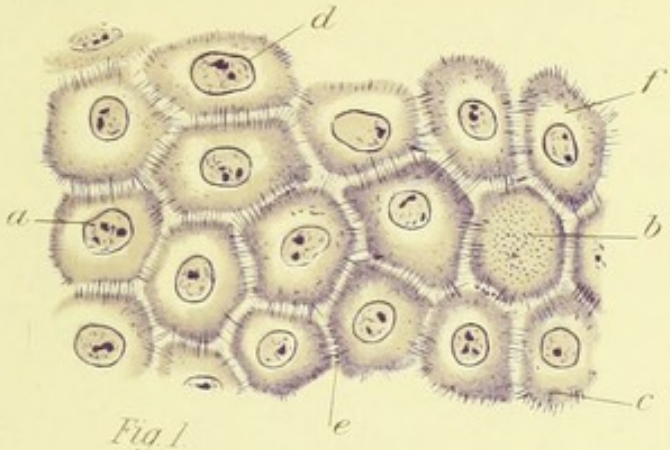

Fig. 1

Fig. 3

Fig. 8.

Fig. 2.

Fig. 7

Fig. 9.

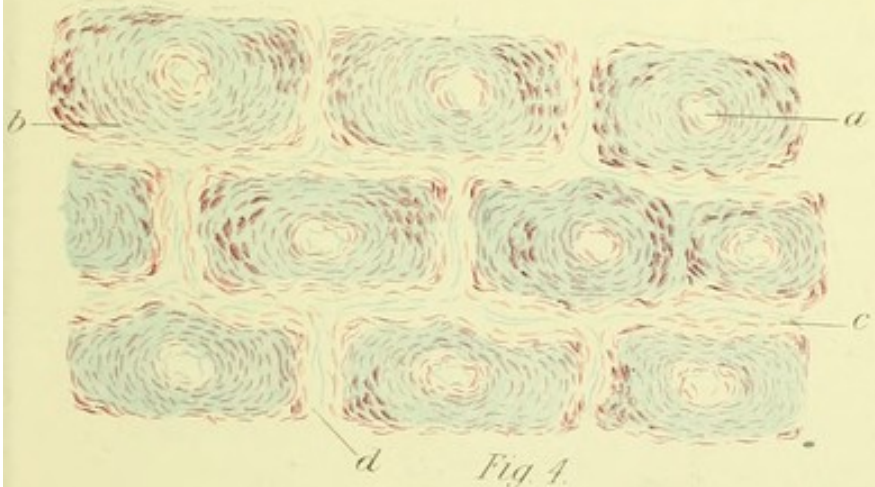

Fig. 4.

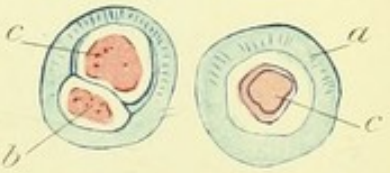

Fig. 10.

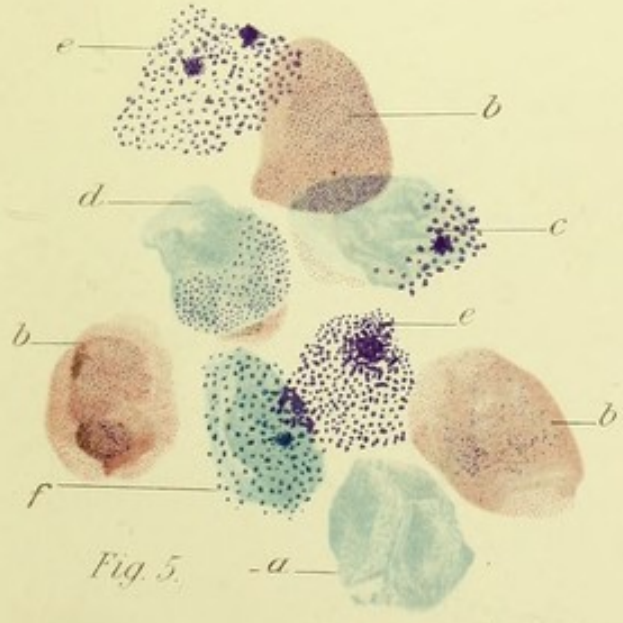

Fig. 5.

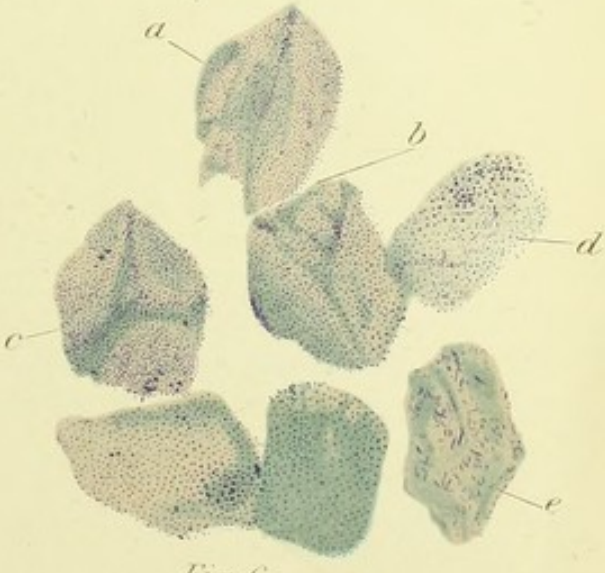

Fig 6.

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connection with one another, and so much is this the case that Ranvier has compared the layer to one vast cell with numerous nuclei. At one time it was believed that each of these cells was surrounded by a set of protoplasmic spicules, like the prickles on a prickly pear, and on this account the cells were named "prickle-cells" by Max Schultze, and still retain the name. Some observers believed that these prickles met corresponding prickles of neighbouring cells, and so united the cells; while others asserted that the prickles alternated like the teeth of cogged wheels. These views are no longer sustained. The protoplasmic fibres are simply the prolongations of the intracellular spongioplasm, which pass from cell to cell without breaking, and may even pass over a cell to one beyond. Occasionally small nodules have been noted on these intercellular fibrous bridges. These have been variously explained, (1) as nodules of a cement-substance, uniting prickles of adjoining cells; (2) as elastic nodules, which disappear when the cells become separated by œdema; (3) and as the result of an optical illusion similar to that which occurs in striped muscle-fibres forming Dobie's line.

It has been suggested that the organic connection of the cells of this layer by protoplasmic fibrils is necessary for the vitality of the cells. Unna has shown, however, that these cells may have their connections ruptured by intercellular œdema, and yet retain their vitality.

In spite of their delicate appearance, the protoplasmic threads are comparatively resistant structures. They are unaffected by boiling water, and weak acids only make them swell up. Alkalies readily cause them to disintegrate, and they are easily digested in pepsin.

As in the basal layer, an intercellular albuminous cement-substance used to be described, but it is now regarded as hypothetical. Instead of there being a homogeneous substance between the prickle-cells, there are in reality lymphatic spaces which are bridged over by the protoplasmic fibres.

A peculiar appearance is presented by the prickle-cells in sections of the epidermis when the surface of the cells is intact and is seen from above. Here the prickles are seen "in relief" in the form of fine dots, which become spicular in shape towards the periphery of the cell. These give to the cell a finely granular appearance, and they have been mistaken for actual granules within the cells.

Staining of the Prickle-Cells.—The following are the most

practical methods for demonstrating the epithelial fibres or prickles:

Fix a piece of skin from a commencing carcinoma or a condyloma acuminatum—in both of which the prickles are unusually large—in Flemming's solution or in some other chromo-aceto-osmic mixture; harden rapidly in alcohol, and imbed and cut either in celloidin or paraffin. The sections must be thin, as clear differentiation of the prickles cannot be obtained in sections more than 10 μ in thickness. Before staining celloidin sections for prickles, the celloidin must be removed.

I. *Kromayer's Method* (*Archiv f. mikr. Anat.*, 1892, XXXIX., p. 41).—

(*a*) Cut sections in paraffin.

(*b*) Stain for five minutes in a mixture of equal parts of a saturated solution of anilin oil in water and a concentrated watery solution of methyl violet.

(*c*) Wash in water.

(*d*) Drop on Gram's iodine solution till the section becomes blackish blue.

(*e*) Wash and dry with filter-paper.

(*f*) Differentiate in anilin-xylol mixture (1 to 2), controlling under the microscope.

(*g*) Clear in xylol and mount in Canada balsam.

The prickles are stained bluish.

NOTE.—Gentian violet may be substituted for methyl violet in this method of staining. The sections may be previously counter-stained with alum-carmine to stain the nuclei, as recommended by Joseph and Loewenbach.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 5).—

(*a*) Imbed in celloidin and remove the latter before staining.

(*b*) Stain from half an hour to twelve hours in the following solution:

ALUM-HÆMATOXYLIN SOLUTION.

Hæmatoxylin	0·5 part
Spirit	10 parts
Hydrogen peroxide	10 „
Glycerin	10 „
Soda	0·1 part
Alum	2·5 parts
Water	100 „

(Delafield's hæmatoxylin solution may be employed instead of the above.)

(*c*) Wash in water.

(*d*) Differentiate in a concentrated aqueous solution of picric acid for half an hour.

(*e*) Transfer for the same time to a ·5 per cent. alcoholic solution of picric acid.

(*f*) Dehydrate in absolute alcohol.

(*g*) Clear in bergamot oil and mount in Canada balsam.

The nuclei are stained dark blue, the mitosing nuclei being specially darkly stained. The epithelial protoplasm has a brownish purple tinge, and the protoplasmic fibres are stained slightly darker in tint.

NOTE.—This method stains very deeply, and I have found it difficult to obtain satisfactory results by it.

III. *After Kromayer-Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 2).—

(*a*) Imbed in celloidin, and remove the latter before staining.

(*b*) Stain from fifteen minutes to an hour in alum-gentian-violet mixture :

Gentian violet	1·5 parts
Alum	10 „
Distilled water	100 „

(*c*) Wash in water.

(*d*) Transfer to a 5 per cent. solution of potassium iodide, to which a crystal of iodine has been added, and allow the section to remain in it till it becomes bluish black.

(*e*) Wash in water and dry with filter-paper.

(*f*) Put it for a minute in anilin-xylol (1 to 4).

(*g*) Transfer to anilin-xylol (1 to 1).

(*h*) Clear in xylol and mount in Canada balsam.

This is a thoroughly satisfactory method, and by it not only the interepithelial fibres are demonstrated, but also the intracellular spongioplasm.

Unna maintains that this method is more certain than Kromayer's original method, and that it is simpler, since the manipulation is carried out in dishes and not on the slide. He recommends that the sections be stained first with carmine, in which case the epithelial fibres will stain blue, the cell-protoplasm violet, and the nuclei red.

IV. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 280) : *Water-Blue and Orcein.*—

(*a*) Stain for ten minutes in a 1 per cent. water-blue solution.

(*b*) Wash in water and dry with filter-paper.
(*c*) Stain for fifteen minutes in neutral orcein.
(*d*) Differentiate in absolute alcohol.
(*e*) Clear in bergamot oil and mount in Canada balsam.

The spongioplasm and prickles are stained reddish, the hyaloplasm blue.

V. *After Unna: Polychrome Methylene Blue and Tannin-Orange.*—
(*a*) Stain for ten minutes in polychrome methylene blue.
(*b*) Wash in water.
(*c*) Differentiate in orange-tannin solution (Grübler) for ten minutes.
(*d*) Wash in water.
(*e*) Differentiate and dehydrate in absolute alcohol.
(*f*) Clear in bergamot oil and mount in Canada balsam.

The nuclei are stained purple, and the intercellular fibres and spongioplasm have a greenish tinge.

VI. *After Rausch* (*Monats. f. prakt. Derm.*, 1897, XXIV., p. 65).—
(*a*) Cut in celloidin and remove the celloidin before staining.
(*b*) Stain for five minutes in polychrome methylene blue.
(*c*) Wash in acidulated water (1 per cent. hydrochloric acid).
(*d*) Transfer for one minute to a 1 per cent. aqueous solution of potassium ferricyanide.
(*e*) Wash in water.
(*f*) Differentiate and dehydrate in absolute alcohol.
(*g*) Clear in bergamot oil or xylol, and mount in Canada balsam.

The prickles, spongioplasm, and nuclei are stained reddish purple; the hyaloplasm is stained pale blue.

NOTE.—Rausch employed this method for the staining of horn-cells, but it is also a useful method for the prickle-cells.

Maceration of the Prickle-Cells.—The separation of the prickle-cells by maceration without destroying them is exceedingly difficult. I have only occasionally succeeded in obtaining specimens, and these were not very satisfactory. They were got by hardening pieces of condyloma acuminatum in alcohol, cutting them horizontally through about the middle of the epidermis, and macerating the pieces for twenty-four hours or longer in 50 per cent. alcohol. A film of cells could then be scraped off, fixed on the slide by heat, and stained

as described in Method VI. Philippson recommends ⅓ per cent. acetic acid for this purpose, and Loewy[1] suggests macerating for twenty-four hours in 6 per cent. pyro-ligneous acid at a temperature of 40° C.

Herxheimer's Spirals.

At the first Congress of the German Dermatological Society held at Prague in 1889, Herxheimer[2] described "peculiar spiral fibres between the cells of the stratum Malpighii and basal layer." They appeared as corkscrew-like fibres between the cells, and were chiefly parallel to the long axes of the cells. Similar spirals were also detected occasionally between the cells of the granular and horny layers and between the cells of the inner root-sheath of the hair-follicle. Besides the spiral type of fibrils, Herxheimer has also described a form in which the fibres are arranged in bunches or brushes around the prickle-cells ("Buschelform").

The true nature of the Herxheimer spirals has been much disputed. It is generally admitted that the second type (Buschelform) are simply the protoplasmic fibres or prickles of the prickle-cells. With regard to the spirals, several explanations have been put forward. It has been suggested that they are artificially produced by Weigert's method of staining which is employed for their demonstration, and also that they are the result of the penetration of elastic fibres between the epidermal cells. Since the spiral fibrils of the basal layer are continuous with an irregular network of fibrin which lies in the lymphatic spaces of the corium, it seems extremely probable that they are really spirals of fibrin. Jadassohn and Ehrmann[3] regard this explanation as adequate, because these spirals are increased in number and size in inflammatory conditions where the lymphatic spaces are dilated and the deposition of fibrin is excessive, and since they are found to vary directly in size with that of the interepithelial lymphatic spaces.

Other observers deny the fibrin explanation, and assert that they are epithelial fibres which, instead of uniting adjacent cells, pass across these to join the cells of a more remote layer.

[1] *Archiv f. mikros. Anat.*, 1891, XXXVII., p. 159.

[2] *Archiv f. Derm. u. Syph.*, 1889, p. 645; *ibid.*, 1896, p. 93; and *Archiv f. mikros. Anat.*, 1899, p. 510.

[3] *Archiv f. Derm. u. Syph.*, 1892, *Ergänzungsheft*, I., p. 307, and *Monats. f. prakt. Derm.*, 1897, XXIV., p. 549.

The Method of Demonstrating Herxheimer's Spirals.—The spirals may be demonstrated by staining with Gram's method, but they are more satisfactorily brought out by the following modification of Weigert's stain for neuroglia:

After Herxheimer.—

(*a*) Harden small pieces of skin [1] for four days in formol (40 per cent. solution of formaldehyde in water).

(*b*) Further fix and harden for four days in an incubator at about 37° C. in the following solution:

Neutral acetate of copper	5 parts
Acetic acid	5 „
Chrome alum	2·5 „
Water	187·5 „

Add the alum to the water, raise to the boiling point, then add the acetate and the acetic acid.

(*c*) Wash, dehydrate in alcohol, imbed in celloidin, and cut thin sections.

(*d*) Transfer the sections for five minutes to a solution of ·1 per cent. potassium permanganate till they are brown and the copper is reduced.

(*e*) Transfer to chromogen solution for at least one hour.

Chromogen (a compound of naphthalin)	5 parts
Formic acid	5 „
Water	90 „

Filter and add 90 c.c. of the filtrate to 10 c.c. of a 10 per cent. solution of sodium sulphite.

(*f*) Stain in the following modification of Weigert's fibrin stain from three to four minutes.

Methyl-violet solution, 5 per cent.	88 parts
Alcohol, 96 per cent.	12 „
Anilin oil	2 „

(*g*) Wash, transfer to Lugol's solution (iodine, 4; iodide of potassium, 6; water, 100 parts).

(*h*) Dry with a filter-paper, treat with anilin-xylol (equal parts), then xylol, and mount in Canada balsam.

The cells are stained dark blue; the nuclei, intercellular fibrils, and spirals are stained lighter blue.

[1] Pieces of commencing carcinoma or condyloma acuminatum are very good for this purpose.

CHAPTER X.

THE EPIDERMIS (Continued)—THE STRATUM GRANULOSUM AND KERATOHYALIN—THE STRATUM LUCIDUM AND ELEIDIN—THE STRATUM CORNEUM AND KERATIN — THE PROCESS OF CORNIFICATION.

THE STRATUM GRANULOSUM AND KERATOHYALIN.

TOWARDS the surface the prickle-cell layer of the epidermis merges into a layer consisting of two or three rows of flattened cells containing numerous granules, which is known as the **Granular Layer** (Pl. IV., Fig. 2). These cells lie more closely together than the prickle-cells of the Malpighian layer, their prickles are shrunken, and their nuclei are shrivelled and mulberry-shaped, and appear to have shrunk away from the protoplasm of the cell so as to leave a nuclear space.

The *granules* of the cells are densest in the protoplasm near the nuclear space, and are more sparse at the periphery of the cell; a few may be present in the nuclear space itself. They vary considerably in shape and size, from small roundish specks peppered throughout the cell-protoplasm, to irregular coarse angular lumps. They are strongly light-refractive, and help to give the white colour to the skin. A few of these granules may be detected in the underlying prickle-cells as far down as the middle of the Malpighian layer.

The granular layer is present in every part of the skin at birth, except in the red portion of the lips and the nail-bed. It is this layer which forms the whitish halo or bloom around a healing granulating wound when the epidermis begins to grow inwards. Similar granules are also present in the mother-cells of the medulla and inner root-sheath of the hair. The nature and origin of these granules has been, and is still, a favourite subject for controversy among histologists. It was Langerhans[1] who first carefully described them, though

[1] *Beiträge z. Anat. u. Embryol.*, 1882.

they had also been observed by Kölliker.[1] Ranvier,[2] too, described them, and believed that they consisted of a fluid substance which, from its fancied resemblance to oil, he christened *éléidine*. For certain chemical reasons, and chief of these because it swelled up under the influence of weak alkalies, it was evident that the substance was at least semi-solid, and Ranvier's view was superseded by that of Waldeyer. The latter observer believed that the substance had a close affinity to "hyalin" (*see* p. 172), and since Unna had pointed out that it had a constant relation to the process of cornification, he named it *keratohyalin*. As it has been shown recently that this substance has no connection with keratin, though its affinity to hyalin may be conceded, the term "keratohyalin" is almost as unfortunate as that of "éléidine." To avoid the multiplication of terms, however, the name "keratohyalin" is generally retained for these granules, while the name "eleidin" is applied to an oily fluid substance which occurs in and between the cells of the stratum lucidum. It is not improbable that keratohyalin and eleidin are not two different substances, but different physical states of one substance.

Keratohyalin is most probably a separation product of the protoplasm of the cell. It was generally believed to be a degenerative product derived from the breaking up of the nucleus, spongioplasm, and prickles of the cell; but as granules occur in the protoplasm of prickle-cells in which the nuclei have not begun to shrink, and in which both the spongioplasm and prickles are perfect, this view cannot be accepted.

The Chemical Nature of Keratohyalin.—Keratohyalin is a solid or semi-solid substance which is insoluble in alcohol, ether, chloroform, weak acids, and weak alkalies. It is destroyed by strong acids and strong alkalies, and is easily digestible in pepsin and hydrochloric acid. Glacial acetic acid at first renders it more visible, as it destroys the other granules in the protoplasm of the cells; but, like other strong acids, it eventually causes the keratohyalin to swell up and disintegrate. It is not stained by osmic acid or iodine, which shows that it is neither a fatty substance nor glycogen; and the fact that it is digestible in pepsin and soluble in strong acids differentiates it from keratin.

[1] *Entwicklungs-Geschichte des Menschen*, 1879, p. 770.
[2] *Archiv de Physiol.*, 1884, p. 125.

The Methods of Staining Keratohyalin Granules.—Keratohyalin granules can be stained by numerous dyes, such as polychrome methylene blue, gentian violet, safranin, carbol-fuchsin, picro-carmine, picro-cochineal, and others, all of which stain the granules in their respective colours. The most satisfactory stain for these granules is hæmatoxylin.

I. The following is a simple and reliable method of staining them :

(*a*) Stain the sections in Delafield's hæmatoxylin for half an hour.

(*b*) Wash in acidulated water (1 per cent. of hydrochloric acid).

(*c*) Rinse in water.

(*d*) Dehydrate in absolute alcohol.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The keratohyalin granules are stained dark violet, the nuclei pale violet, and the stratum corneum brownish.

The sections may be counter-stained before dehydrating in a 1 per cent. aqueous solution of eosin.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1895, XX., p. 69).—Harden in alcohol, and cut in celloidin.

(*a*) Overstain the section in hæmatoxylin, leaving it for about twelve hours in a strong solution of the dye.

(*b*) Wash in water.

(*c*) Decolorise for about ten seconds in a 1 to 2000 solution in water of potassium permanganate.

(*d*) Further decolorise and dehydrate in absolute alcohol.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The keratohyalin granules are stained violet, and the rest of the section a brownish red.

NOTE.—If there be any difficulty in decolorising, the section may be put for ten minutes into a 33 per cent. solution of sulphate of iron, instead of into the potassium permanganate solution.

III. *Van Gieson-Ernst* (*Virchow's Archiv*, 1892, CXXX., p. 279).—To distinguish keratohyalin from hyalin.

Harden in alcohol or Müller's fluid.

(*a*) Stain the sections for half an hour in Delafield's hæmatoxylin.

(*b*) Wash in water.

(*c*) Stain from three to four minutes in the following solution : To a saturated aqueous solution of picric acid add

sufficient of a saturated aqueous solution of acid fuchsin to give the mixture a deep red colour.

(*d*) Wash in water.

(*e*) Differentiate and dehydrate in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The keratohyalin granules are stained dark brown, the hyalin orange.

NOTE.—This method of staining is simple to do, and gives a good contrast stain between hyalin and keratohyalin.

A similar contrast may be obtained by staining in water-blue and then in neutral orcein, when the keratohyalin is stained by the water-blue, and the hyalin by the orcein.

IV. *After Rausch* (*Monats. f. prakt. Derm.*, 1897, XXIV., p. 65).—Stained by Method VI., on page 58.

The keratohyalin granules are stained purple.

NOTE.—This method is as rapid as it is simple, and gives excellent results.

THE STRATUM LUCIDUM AND ELEIDIN.

Between the granular layer and the stratum corneum there is a thin intermediate layer of cells which is known as the **Stratum Lucidum of Oehl** (Pl. IV., Fig. 3), because in unstained fresh or slightly hardened sections of the skin of the sole of the foot, where this layer is particularly well developed, the layer may be seen as a semi-transparent line across the section, resembling a narrow oily streak across a sheet of paper. The cells of this layer are larger and more irregular in shape than those of the stratum granulosum, their prickles are more shrunken, and their nuclei have still further shrivelled, and may sometimes be represented only by a mass of *débris* in the nuclear spaces. The keratohyalin granules have now disappeared and been replaced by a homogeneous oily-looking substance, known as *eleidin*, which is present not only within but between the cells, and which is the chief characteristic of this layer. It rarely, if ever, completely fills the cells, but generally occurs as variously sized droplets or globules, which tend to run together to form "puddles or lakes."

There is considerable confusion, especially in the French literature, with regard to the use of the term eleidin, since Ranvier applied it also to the granules of the granular layer. It is becoming more and more customary to restrict its use

to the oily substance in the stratum lucidum, and to draw a clear distinction between it and keratohyalin. This custom is warranted, since keratohyalin and eleidin differ not only with regard to their physical states, but also in their staining reactions, though, as has already been observed, it is not improbable that the one may be an antecedent of the other.

The Chemical Nature of Eleidin.—Eleidin is slightly soluble in alcohol, insoluble in ether, easily digested in pepsin-hydrochloric acid, and quickly dissolved in acids and alkalies. It is not stained with osmic acid, and hence it is not fat. The cells of the stratum lucidum, however, stain with osmic acid, showing that they contain fat as well as eleidin.

The Staining Methods for Eleidin.—The staining of eleidin requires a difficult and delicate technique.

Since eleidin is slightly soluble in alcohol and rapidly destroyed by formalin and sublimate, these fluids are contra-indicated to harden tissues for the demonstration of eleidin. For this reason the tissues should be cut by the freezing method. Alcohol does not, however, dissolve eleidin to such an extent that its use is absolutely prohibited, and it may be used when it is specially desired to imbed the tissues in celloidin or paraffin.

I. *After Frickenhaus* (*Monats. f. prakt. Derm.*, 1896, XXIII., p. 64).—Harden the tissue in alcohol and imbed in celloidin.

(*a*) Remove the sections directly from the knife into a 1 to 1000 aqueous solution of water-blue or alkali blue (Grübler), and stain them from five to ten minutes.

(*b*) Wash in water.

(*c*) Counter-stain from fifteen to twenty minutes in picro-cochineal (Grübler).

(*d*) Wash for twelve hours in water.

(*e*) Differentiate for a few seconds in acidulated alcohol (1 per cent. hydrochloric acid).

(*f*) Wash in water.

(*g*) Dehydrate in absolute alcohol.

(*h*) Clear in bergamot oil and mount in Canada balsam.

The eleidin is stained dark blue, the nuclei red, and the hyaloplasm of the cells yellowish.

NOTE.—If in place of picro-cochineal, Unna's alum-

hæmatoxylin[1] solution be employed, the keratohyalin granules of the stratum granulosum are stained a dark violet tint, and they can then be compared with the blue-stained eleidin droplets.

II. *After Buzzi* (*Monats. f. prakt. Derm.*, 1896, XXIII., p. 54).—Harden the tissue rapidly in alcohol or cut it fresh.

(*a*) Stain the section for a few minutes in a weak solution of congo-red (two or three drops of a 1 per cent. aqueous solution of congo-red added to a watch-glass of water).

(*b*) Float the section on to a slide and examine it. The section will be stained a rose-red tint, and the eleidin an intense red.

(*c*) Add a drop of a 1 per cent. hydrochloric acid solution, and the section becomes a slaty blue colour and the eleidin a darker blue.

NOTE.—This method is somewhat unsatisfactory, as it depends on differences in tint which are often so slight as to be indistinguishable.

III. *After Dreysel and Oppler* (*Archiv f. Derm. u. Syph.*, 1895, XXX., p. 63).—To demonstrate both eleidin and keratohyalin. Harden for two days in absolute alcohol, imbed in paraffin, and cut with a dry knife.

(*a*) Stain for one minute in ammonio-picro-carmine (carmine, picric acid, and liquor ammoniae, of each 1 ; distilled water, 100).

(*b*) Wash in water.

(*c*) Stain for twenty-four hours in alum-hæmatoxylin solution.

(*d*) Wash in water.

(*e*) Dehydrate in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The eleidin is stained reddish yellow, the nuclei violet, and the keratohyalin dark violet.

THE STRATUM CORNEUM AND KERATIN.

The **Stratum Corneum** is the most superficial layer of the skin (Pl. IV., Fig. 4). It is the layer which we see and touch, and the study of its minute structure is of the greatest importance, since it is this layer which gives to the skin its power of resisting the entrance of toxins and

[1] Hæmatoxylin, 1, dissolved in 95 per cent. alcohol, 100 ; alum, 1, dissolved in water, 300 ; hydrogen peroxide, 15.

PLATE V.

FIG. 1. VERTICAL SECTION OF THE SKIN OF THE SOLE OF THE FOOT. (× about 150.)

a. "Fine furrow" corresponding in position to an interpapillary process.
b. Sweat-pore.
c. Ridge corresponding in position to two papillae.
d. Stratum corneum, showing stratification, and its great thickness in this situation
e. Granular layer.
f. Ma.pighian layer.
g. Germinal or basal layer.
h. Interpapillary process.
i. Papilla.

FIG. 2. HORIZONTAL SECTION OF THE PLANTA PEDIS NEAR THE APICES OF THE PAPILLAE (SEMI-DIAGRAMMATIC). (× about 500.)

a. Papilla in transverse section, showing a few bundles of fibrous tissue, and in two instances capillaries in section.
b. Cylindrical prickle-cells surrounding the cut papilla.
c. Prickle-cells of an interpapillary process.

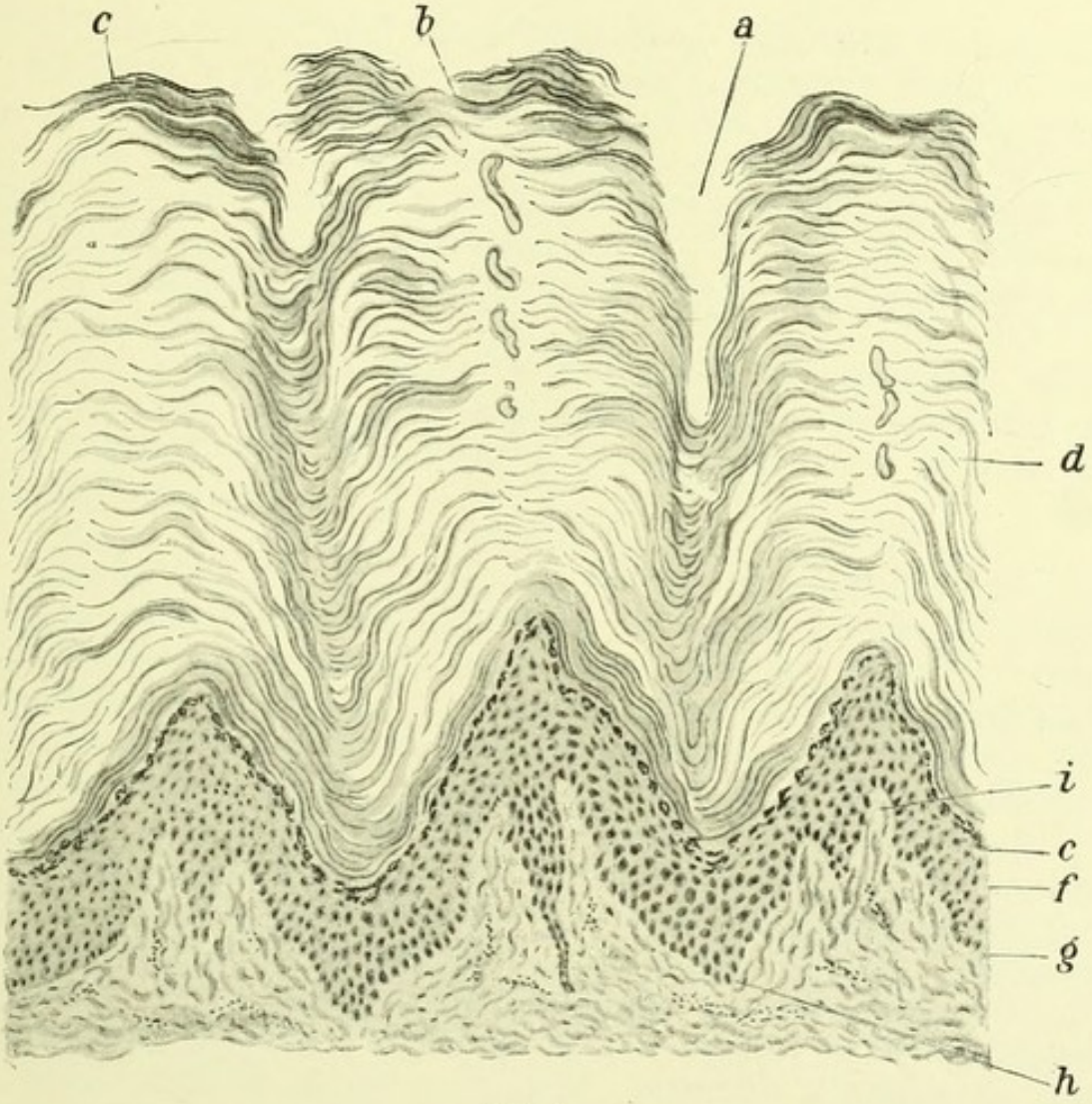

FIG. 1.

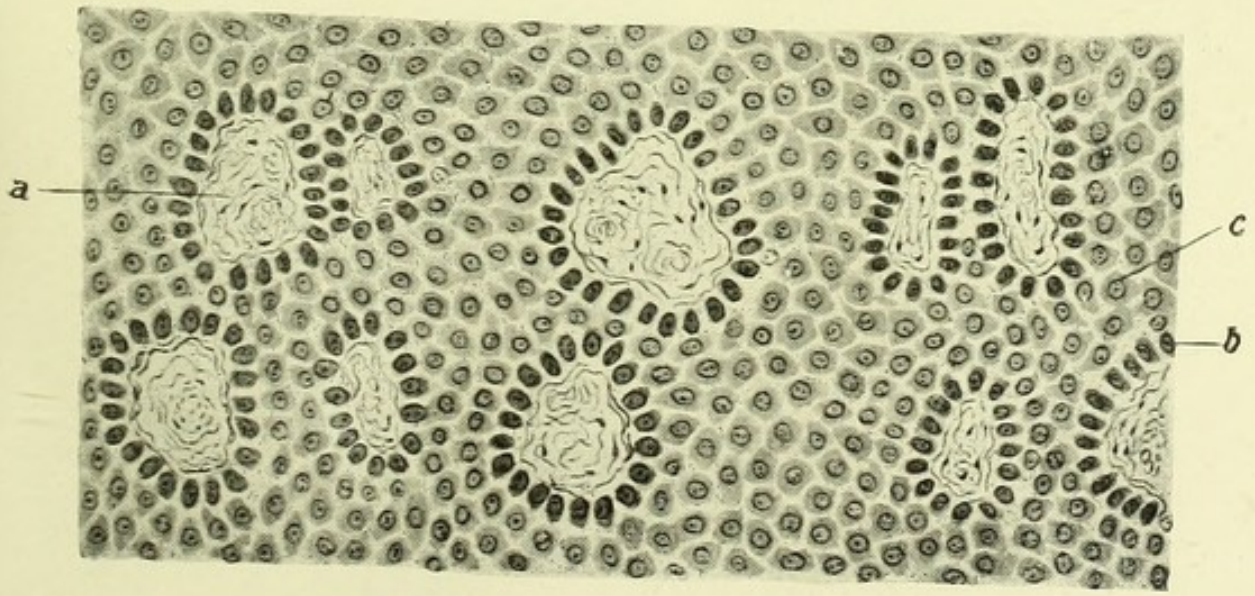

FIG. 2.

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micro-organisms, and of withstanding mechanical injuries. This layer varies greatly in thickness in different parts of the skin. It is thickest on the soles of the feet, where it may reach 5 to 6 mm., and on the palms of the hands, where it averages 4 mm. It is especially thin on the face and on the flexor aspects of the extremities. On the flexor surface of the forearm, for example, it has an average thickness of about ·02 mm.

The stratum corneum is composed of epidermal cells which have undergone the process of cornification or "keratinisation." The individual cells are now known as "horn-cells."

Horn-Cells (Pl. IV., Figs. 5, 6) vary considerably in size and shape, according to their situation. The most perfect horn-cell is situated immediately above the stratum lucidum, while towards the surface of the body alterations from drying and pressure produce the flattened degenerate type of horn-cell known as the "squame," which is rubbed off constantly by the friction to which the skin is subjected.

The perfect horn-cell, such as occurs in the layer next the stratum lucidum, is not a degenerate cell, but rather the most highly evolved cell of the epidermis, which has become specially differentiated for purposes of protection. It is polygonal in shape, facetted on the surface from pressure against neighbouring cells, and presents a space in the centre from which the nucleus has completely disappeared. The cells are now so closely packed together that no inter-epithelial spaces exist between them. The eleidin and hyaloplasm of the cell have given place to a fatty or waxy substance, and the peripheral portion of the spongioplasm has become transformed into a highly resistant substance called *keratin*. The epithelial fibres or prickles persist as dried shrunken spicules, having also become changed into keratin. It is generally taught that the horn-cells are held together by a more or less dried-up intercellular substance; thin sections of this layer disprove the existence of this hypothetical substance, and it is necessary to seek another explanation for the close union of the cells of the stratum corneum. The explanation of this union I believe to be found in the persistence of the epithelial fibres and their transformation into keratin. These, as it were, suture the cells of this layer together and explain its extraordinary toughness, the initial difficulty of piercing the skin with a hypodermic needle, the raising up and stretching out of the layer without

its rupturing in the formation of vesicles and bullae, and the many other instances of its power of resistance. If, on the other hand, cornification be imperfect, and the intercellular bridges do not become transformed into keratin, the defective horn-cells become separated, air appears between them, and they desquamate in variously sized scales.

The existence within the horn-cells of the fat, which Ranvier has compared to beeswax, makes the stratum corneum a waterproof coating to the body, acting, as it were, as an impermeable varnish over the skin, and preventing the absorption of water and substances dissolved or suspended in it.

The Arrangement of the Horn-Cells in the Stratum Corneum.—To study the arrangement of these cells it is necessary to cut and stain both vertical and horizontal sections.

The most noticeable feature in *vertical sections* of the horny layer is the presence of a more or less regular stratification, which is most marked in situations like the sole of the foot, where the epidermis is subjected to pressure (Pl. V., Fig. 1). It is due chiefly to the intermittent pressure from without, combined with the continuous addition of new rows of cells from beneath. In this way layers of flattened cells frequently alternate with layers of cells in which the flattening is less marked. The stratification is also made evident by differences in the staining capacity of the various strata, since lightly stained strata alternate with others which are more deeply stained.[1]

On account of certain staining peculiarities, Unna[2] divided the stratum corneum into four layers. He stained vertical sections with picro-carmine, osmic acid, and hæmatoxylin, and differentiated the following strata :

1. A basal layer, corresponding to the stratum lucidum, the cells of which are densely packed together. This stratum is stained yellow with picro-carmine, and the upper half of it is darkened by osmic acid.

2. A super-basal layer composed of densely packed cells, which are stained dark red by picro-carmine, but are not darkened by osmic acid.

[1] The reason of the difference in the staining-reactions of the individual horn-cells is not fully understood. It does not seem likely that it is due to there being several types of horn-cells, or that the differences indicate stages in the process of cornification ; it is more probably due to a difference in the reaction of the cells, and possibly to the fact that some of them are in section, while others are intact.

[2] Ziemssen's *Handbook of Skin Disease*, 1885, p. 20.

3. A middle layer, whose cells are loosely arranged, stain red with picro-carmine, and are not blackened by osmic acid.

4. A superficial layer in which the cells are densely packed together, are stained yellowish with picro-carmine, and are darkened by osmic acid.

The differences in staining by which Unna claims to have separated these layers have not, in the hands of other observers, been sufficiently constant to warrant this hard and fast division.

The remarkably regular arrangement of the horn-cells can be most clearly demonstrated by cutting *horizontal sections* of this layer. The appearances produced by such sections are puzzling to those who are unfamiliar with them. In Fig. 4, Pl. IV., a horizontal section of the skin of the sole of the foot is represented. In this section a number of parallel bands, composed of elongated horn-cells closely packed together, are seen. These bands correspond to the fine furrows on the surface of the skin. Between the bands, small spaces indicating the sweat-pores are present at regular intervals. On careful staining it can be demonstrated that these spaces are almost completely filled with cells which do not stain readily. Around the pores the horn-cells are arranged concentrically, and form oblong or rounded areas of cells. This regularity of arrangement is not so well marked in situations other than the palms of the hands; but the tendency to a concentric arrangement of the horn-cells around the sweat-pores is everywhere evident. In this way the horn-cells form in the soles of the feet a regular mosaic, whose elements are closely facetted together. This mosaic is rendered more distinct by the fact that when the sections are doubly stained, or stained with compound dyes such as polychrome methylene blue, the individual cells assume different tints.

Keratin or Horn-Substance is chemically, as well as physically, a highly resistant substance. It can withstand 50 per cent. mineral acids for a prolonged period. It is indigestible in pepsin-hydrochloric acid solution, and so differs from keratohyalin and eleidin. It is soluble, however, in weak solutions of potash and other alkalies.

The Persistence of Prickles and their Transformation to Keratin.—The fact that the prickles persist in the horn-cells seems to be very generally, though not universally, accepted by histologists. The chief reason for the existence of a doubt concerning the fact is the difficulty of demonstrating the

prickles. Recently a series of papers on horn-cells have been published which have an important bearing on the subject. Rausch[1] in 1897 described the appearances produced in horn-cells separated by maceration and stained with polychrome methylene blue. He noted that many of the cells had a finely granular look, which he considered might be due to the prickles persisting on the horn-cells and being seen "in relief." Intact prickle-cells of the stratum Malpighii present a very similar granular appearance (Pl. IV., Fig. 1) when stained by the same dye. By staining sections of the stratum corneum with Gram's method, Ernst[2] also showed that the cornified cells had a granular appearance, but it seemed to him that the granules resembled fine keratohyalin granules, and were inside the cells.

He considered that they were granules of keratin, and that they originated from the breaking up of the spongioplasm of the cell. Kromayer,[3] in a critical paper on Ernst's results, put forward the view that these granules were artificial products which resulted from Gram's method of staining.

In a series of experiments carried out in Unna's laboratory I found that the granules described by Rausch and Ernst appeared to be identical; that they had the chemical reactions of keratin; that they did not seem to be due to the method of staining;[4] and that they appeared to be situated on the surface of the cells. From these observations I concluded that they were most probably shrivelled prickles.[5]

The Process of Cornification and the Relation to it of Keratohyalin and Eleidin.—By the process of cornification is meant that by which an epidermal cell is converted into a resistant horn-cell. This transformation is found not only in the

[1] *Monats. f. prakt. Derm.*, 1897, XXIV., p. 65.
[2] *Beiträge z. path. Anat. u. z. allg. Path.*, 1897, XXI., p. 438.
[3] *Centralbl. f. Path. u. path. Anat.*, 1898, p. 439.
[4] These granules did not seem to me to be products of staining, but prickles in relief, for the following reasons:

1. By the special modification of Gram's method employed there was comparatively little, if any, precipitation (*see* p. 74). Precipitates, if present, were much more irregular than the granules, and not so evenly distributed.

2. The granules were grouped as though they belonged to individual cells, while the precipitate was spread irregularly over the specimen.

3. Prickle-cells of the stratum Malpighii, if uncut, presented a similar granular appearance when stained by the same method, while connective-tissue cells did not do so.

4. Some of the granules presented a distinctly spicular appearance, especially those situated towards the periphery of the cells.

[5] For further information on this subject see *Monats. f. prakt Derm.*, 1899, XXVIII., p. 1, and *Brit. Journ. of Derm.*, 1899, p. 137.

epidermis, but also in the hairs and nails; but as the details of the process differ somewhat in the latter appendages, it will be advisable to refer here only to the epidermis.

There is at present no unanimity among histologists with regard to the process of cornification, and one of the most important problems in the histology of the skin remains yet to be solved. Within recent years, however, marked advances have been made towards its solution. It was at one time believed that the whole contents of the epidermal cell became solidified, and that keratohyalin was simply a "drop-like" condition of keratin (Zander,[1] Zabludowsky[2]). This view was modified by Cajal,[3] who suggested that only the spongioplasm of the cell became converted into keratin. The principal opposing view to this was that keratohyalin united with the protoplasm of the cell to form keratin, either directly (Waldeyer[4]) or indirectly, through the formation of an intermediate substance called "prokeratin" (Reinke[5]).

By the publication of Unna's[6] "digestion experiments" on the stratum corneum and the horn-cells, and the corroboration of them by subsequent observers, a distinct advance was made in our knowledge of this subject. By treating sections of the stratum corneum with pepsin-hydrochloric acid solution it is evident that only the outer zone or "mantle" of the cell is indigestible and has become keratin, while all within the mantle is not implicated in the cornification process. If the still more recent view be correct, that the prickles become converted to keratin, then the appearance of a cornified cell-mantle is in reality the result of the close apposition of numerous keratinised fibres and spicules derived from the transformation of the intercellular fibres and the outer portion of the spongioplasm of the cells into keratin.

The Relation of Keratohyalin and Eleidin to Cornification.—The transitional layers, though usually present, do not seem to be essential to the process of cornification. In certain pathological conditions—for example, in tuberculosis verrucosa cutis—the transitional layers may be hypertrophied, and in places may even be several times thicker than in the healthy skin, while the overlying stratum corneum may show no

[1] *Archiv f. Anat. u. Phys.*, 1888, p. 51.
[2] *Mitth. a. d. embryol. Instit. Wien*, 1880, II., p. 1.
[3] *Monats. f. prakt. Derm.*, 1897, XXIV., p. 3 (quoted by Unna).
[4] *Beiträge z. Anat. u. Embryol.*, Bonn, 1882.
[5] *Archiv f. mikr. Anat.*, XXX., p. 198.
[6] *Monats. f. prakt. Derm.*, 1897, XXIV., p. 1.

distinct increase in thickness. On the other hand, it is not uncommon to find a marked thickening of the stratum corneum without a corresponding increase in the transitional layers, though as a rule hyperkeratosis is accompanied by a thickening of these layers. At the mucous orifices, such as the red portions of the lips, the keratohyalin gradually disappears, although a horny layer is present. Still, the absence of the transitional layers is associated with defective cornification, in which the nuclei of the horn-cells do not completely disappear, which shows that these layers have an intimate connection with the process.

Instead of regarding keratohyalin and eleidin as essential for the formation of keratin, it is probably more correct to look upon them as accessory phenomena which occur during the process of cornification, and which are invariably present when perfect cornification takes place.

Keratohyalin is probably a separation-product of the protoplasm of the cell, which appears as the vitality of the cell is diminishing; eleidin, a further product of the same substance; and the ultimate product of both is probably the fatty or waxy substance which is present in the horn-cells.

Keratohyalin, eleidin, and the fat of the horn-cells would thus have no connection with keratin, but would subserve the purposes of causing the cells of the stratum lucidum to swell up and so become more closely packed together, and of rendering the stratum corneum a waterproof coating to the skin.

The intercellular bridges or prickles would, according to this hypothesis, become hardened into keratin by an inherent power of their own, in much the same way as the fibrovascular system of a leaf at the fall of the year becomes hardened into a brittle leaf-skeleton.

Technique for the Study of the Stratum Corneum, Horn-Cells, and the Process of Cornification.

The Cutting of Sections of the Stratum Corneum.—To cut sections of the horny layer the freezing method is the most serviceable, and by it thinner sections can be obtained than with celloidin or paraffin. The horny layer is always difficult to cut, and when it is thickened pathologically, or when pieces of skin are specially chosen where the layer is naturally thick, this difficulty is so greatly increased that it becomes practically impossible to obtain thin sections by any other method. Freezing alters the horn-cells to some

extent, so it is advisable not to freeze the tissues fresh, but to harden them rapidly in alcohol before freezing. This may be sufficiently done by putting the piece of skin for twenty-four hours in 95 per cent. alcohol, and then into absolute alcohol for forty-eight hours. It is then necessary to soak the tissue for twenty-four hours in water to remove all trace of the alcohol, or freezing will not take place. The piece of skin is then saturated with the gum-syrup solution and frozen. Vertical, horizontal, and oblique sections should be cut.

Oblique sections are particularly useful, as by means of them a large area of the individual cells can be demonstrated. The method of cutting oblique sections is simple: A piece of skin about threequarters of an inch square is cut; the subcutaneous tissue is shaved off; the tissue is then folded so as to leave the horny layer outwards, and the skin is tied or stitched in this position; it is then hardened, washed, impregnated with gum-syrup, and frozen, and cut with the edge of the knife parallel to the fold of the skin. The first few sections contain only stratum corneum; but as the cutting is proceeded with, sections are obtained in which the stratum corneum, transitional layers, and the remainder of the epidermis are present on each side of the section.

The Staining of Sections of the Stratum Corneum.—The stratum corneum is the most readily stained of all the layers of the skin, and the more complete the cornification the deeper the staining. It may be stained by any of the anilin dyes, but unless special methods are adopted the whole stratum is apt to be so darkly coloured that no differentiation into cells can be detected. Keratin is stained dark violet by Gram's method, pink by safranin, deep blue by methylene blue, red by carbol fuchsin, and picro-carmine stains it in layers which vary in tint from yellow to red. By all these stains, when they are washed out sufficiently, a differentiation into strata may be detected.

Methods of Demonstrating the Granular Appearance of the Horn-Cells which some Observers regard as due to Keratin Prickles.—

Modified Ehrlich-Gram Method (*Brit. Journ. of Derm.*, 1899, XI., p. 137).—

(*a*) Stain the sections for ten minutes in freshly prepared anilin gentian violet solution:

Gentian violet	1 part
Anilin oil	3 parts
Alcohol	15 ,,
Water	80 ,,

(*b*) Wash in water.

(*c*) Fix the stain for five minutes in iodine solution:

Iodine	1 part
Iodide of Potassium	2 parts
Water	100 „

(*d*) Wash out the iodine solution in water.

(*e*) Differentiate and dehydrate in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The horn-cells are stained violet, and present a fine intracellular network (spongioplasm). The keratin prickles are stained a deeper violet.

NOTE.—Occasionally by this method slight precipitation, due to free iodine granules, may be encountered. To obviate this the following iodine solution may be employed:

Iodine	1 part
Pot. iodi	2 parts
Glacial acetic acid.	2 „
Water	300 „

Modified Kromayer-Weigert Method (*Ibid.*).—

(*a*) Stain the sections for a minute in a concentrated anilin methyl violet solution.

(*b*) Wash in water.

(*c*) Fix the stain in the iodine solution or the above modification of it for one minute.

(*d*) Wash in water and dry on the spatula with a piece of filter-paper.

(*e*) Decolorise in anilin-xylol.

(*f*) Clear in xylol and mount in Canada balsam.

The horn-cells are stained a reddish violet and the "granules" a deeper tint of the same colour.

After Rausch (*Monats. f. prakt. Derm.*, 1897, XXIV., p. 65).—

(*a*) Stain from one to two minutes in polychrome methylene blue solution (*see* p. 40).

(*b*) Wash in slightly acidulated water (add a drop of hydrochloric acid to a watch-glass of water).

(*c*) Fix the stain for five minutes in a 1 per cent. aqueous solution of potassium ferricyanide.

(*d*) Wash in acid water.

(*e*) Differentiate and decolorise in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The horn-cells are stained either pale blue or reddish purple, or exhibit shades of colour intermediate between

these two extremes. The reddish purple cells show keratin prickles stained a deeper purple. Some cells are unstained, but present granules stained purplish. This is an instance of metachromism.

After the Writer (*Brit. Jour. of Derm.*, 1899, XI., p. 137).—

(*a*) Stain the sections for thirty minutes in a 1 per cent. aqueous solution of safranin.

(*b*) Wash in water with 1 per cent. tannic acid.

(*c*) Fix for five minutes in a 1 per cent. solution of potassium ferricyanide.

(*d*) Wash again in the tannin-water.

(*e*) Differentiate and decolorise in alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The horn-cells are stained either a pale rose pink or an orange colour, and many of them exhibit orange-coloured keratin prickles.

After the Writer (*Ibid.*).—

(*a*) Stain the sections for five minutes in Delafield's hæmatoxylin solution.

(*b*) Wash in water.

(*c*) Stain them for two minutes in Gram's gentian violet solution, as in the modified Gram-Ehrlich method.

(*d*) Wash in water.

(*e*) Fix the stain in the modified iodine solution (*see* p. 74).

(*f*) Wash thoroughly in water.

(*g*) Dehydrate in absolute alcohol.

(*h*) Clear in bergamot oil and mount in Canada balsam.

The object of this stain is to bring out the keratohyalin granules so as to compare them with the fine keratin prickles. The keratohyalin granules of the stratum granulosum are stained a brownish purple colour, and are irregular in shape and size; while the keratin prickles of the horn-cells are stained a dark violet, and are small and regular in shape.[1]

[1] By combining hæmatoxylin with the polychrome methylene blue method a similar comparison may be obtained.

1. Polychrome methylene blue, 1 minute.
2. Acidulated water.
3. 1 per cent. ferricyanide of potassium, 1 minute.
4. Acidulated water.
5. Decolorise in alcohol.
6. Water.
7. Hæmatoxylin (Delafield's), 2 minutes.
8. Alcohol.
9. Bergamot oil and Canada balsam.

The Digestion of Sections of the Stratum Corneum.—*After Unna* (*Monats. f. prakt. Derm.*, 1897, XXIV., p. 1).—Place sections not thicker than 5 μ in the following pepsin solution for twelve hours at a temperature of 40° C.:

Pepsin	0·5 part
Hydrochloric acid	1 „
Water	100 parts

The section on removal is found to consist of a fine keratin network like a honeycomb, and its cell-contents have disappeared (Pl. III., Fig. 4).

Stain the digested section by the Rausch method or the modified Gram-Ehrlich method, when it will be found that the prickles can still be stained, showing that they have resisted digestion. The digested sections should then be placed for twenty-four hours in 50 per cent. hydrochloric acid, and then stained to demonstrate the resisting power of the keratin to strong acids. Alkalies may then be employed, when it will be noted that even in weak alkaline solutions the keratin quickly swells up and disintegrates—a fact which is of great practical importance as suggesting a method of destroying horny growths.

The Maceration of the Horn-Cells in Order to Study the Individual Cells.—The *macerating fluids* which are of most service in separating the horn-cells are concentrated salicylic acid, glacial acetic acid, and hydrogen peroxide. Any of the mineral acids will serve the purpose also. Alkalies, even in weak solutions, have the disadvantage of acting too rapidly and of tending to destroy the cells.

Small pieces of skin from different parts of the body should be placed in one or other of the above-mentioned fluids from twelve to twenty-four hours at a temperature of 40° C. In order to prevent micro-organisms from contaminating the preparations, 1 per cent. of thymol should be added to the macerating fluid, since, if some antiseptic be not employed, the preparations will become covered with cocci and bacilli, which are often very difficult to distinguish from the keratin prickles. After lying for twelve hours in the acid fluid, it is easy to scrape off a fine pulp of horn-cells from the macerated epidermis. The scraping should be done with a sharp-edged piece of glass, as the use of metal on tissues saturated with strong acids must be avoided. A small quantity of the scraped-off pulp is then thinly spread on a clean slide, and if necessary a drop of distilled water may be added

to it if there be any difficulty in spreading the pulp. The slide should then be dried under a glass cover to prevent dust from settling on it, and the film of horn-cells should be fixed by passing the slide ten times over the flame. The slide should on no account be passed through the flame, as the heat will cause the horn-cells to shrivel. By this means the pulp is sufficiently adherent to the slide to permit of the process of staining.

Staining of Films of Horn-Cells.—The methods for staining films are identical with those described for sections of the stratum corneum. The most serviceable of these are the modified Gram-Ehrlich method, Rausch's method, and the safranin method. The time required with the various reagents is, however, considerably shorter than that which is necessary for the sections.

After Rausch (*Monats. f. prakt. Derm.*, 1897, XXIV., p. 65).—

(*a*) Drop on to the film a few drops of polychrome methylene blue, and pass the slide three or four times over the flame.

(*b*) Wash off the superfluous stain with acidulated water.

(*c*) Fix for one minute with a few drops of a 1 per cent. potassium ferricyanide solution.

(*d*) Wash in acidulated water.

(*e*) Dehydrate and decolorise in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The horn-cells will be found to present all shades of colour, from pink, through purple to blue; and in many of them reddish-purple granules or spicules may be detected, the granular appearance being due to the prickles being seen in relief. In the cells coloured blue the prickles are not visible, though the intracellular spongioplasm may be distinct. The reason for this is difficult to explain, unless it be due to the reaction of these cells, which, being more basic than that of the others, causes them to repel basic dyes; or that the surface which appears to attract basic dyes is destroyed, and the contents of the cell, being exposed, have the opposite reaction.

A striking feature in the macerated horn-cells is their size. They are large cells in comparison with those of the Malpighian layer. Their flat shape is not always apparent when they are macerated, but their peculiar facetted appearance may be easily recognised.

A Useful Alternative Method for Staining the Films is the following:

(*a*) Stain the film with a few drops of a 5 per cent. solution of water-blue for two minutes.

(*b*) Wash with water to which 1 per cent. of sodium bicarbonate has been added.

(*c*) Stain in a 1 per cent. aqueous solution of safranin for twenty minutes.

(*d*) Wash off the superfluous counter-stain in water with 1 per cent. tannic acid.

(*e*) Fix for five minutes in a 1 per cent. solution of potassium ferricyanide.

(*f*) Wash in water.

(*g*) Dehydrate and decolorise in absolute alcohol.

(*h*) Clear in bergamot oil and mount in Canada balsam.

The horn-cells are by this means stained a bluish to an orange colour, and the keratin spicules are stained a darker tint. The orange-coloured cells correspond to the reddish purple cells in the last method, while the bluish cells correspond to those of a somewhat similar tint.

CHAPTER XI.

PATHOLOGICAL CHANGES INVOLVING PRIMARILY THE EPIDERMIS.

ACQUIRED CONDITIONS AFFECTING CHIEFLY THE HORNY AND TRANSITIONAL LAYERS.

I. **The Hyperkeratoses.**—By *hyperkeratosis* is meant an excessive growth or true hypertrophy of the stratum corneum in which the layer may be simply thickened by an increase in the number of its component cells, or, in severe cases, may be transformed into a hard, horny mass. Hypertrophy of this layer is invariably associated with a stronger power of cohesion of the individual horn-cells. In mild examples of hyperkeratosis the stratum corneum presents a comparatively even surface; but where the thickening is pronounced the surface becomes broken up by deep furrows into irregular areas, which are frequently surmounted by grotesque horny protuberances. When sections of the affected skin are digested in pepsin-hydrochloric acid solution or subjected to the various macerating reagents, it is found that the cells are more resistant than those of the normal stratum corneum, and separation of them occupies a longer time than ordinarily, taking almost a week instead of a night. This is the result of an excessive production of keratin. The transitional layers, though generally thickened in association with hyperkeratosis, are not necessarily so, and in some instances they may even be diminished. The underlying prickle-cell layer frequently exhibits no corresponding hypertrophy, and it would seem that hyperkeratosis is independent of proliferative changes either in the prickle-cell layer or in the transitional layers.

Hyperkeratosis may be either diffuse or circumscribed, and may affect almost the whole cutaneous envelope, or be confined to clearly demarcated areas.

1. **Diffuse Hyperkeratosis.** — A primary non-congenital diffuse hyperkeratosis rarely, if ever, occurs. Certain writers

maintain that the diffuse dry scaly conditions of the skin which are grouped under the term *Ichthyosis* are not congenital; and if their view be accepted, the ichthyosis group would belong to this category. On the other hand, they assert that a congenital diffuse hyperkeratosis, which is not a variety of ichthyosis, does occur in the rare affection of the skin popularly known as *Harlequin fœtus*, and named by Unna[1] *Hyperkeratosis universalis congenita.*

Since this belief is not universally accepted, I will provisionally class ichthyosis and harlequin fœtus under the heading of the congenital anomalies of cornification.

As an example of an acquired hyperkeratosis which may become diffuse, there is, however, the disease of the skin known as *Pityriasis rubra pilaris* (Pl. VI., Fig. 1). Although the hyperkeratosis seems at first to affect chiefly the openings of the pilo-sebaceous follicles, it is by no means confined to these structures, and the intervening stratum corneum is generally found to be affected to a greater or less extent. Clinically, the skin may be almost universally covered with small reddish brown, rounded, or acuminate papules, about the size of a millet seed, and generally pierced by a hair. These papules are frequently scaly, and tend to coalesce to form raised scaly patches.

2. **Circumscribed Hyperkeratoses.** — The circumscribed hyperkeratoses form the majority of the instances of hypertrophy of the horny layer. These localised hyperkeratoses are frequently grouped under the heading of *keratomata*; but as this name has gradually become specially associated with certain skin-diseases, such as the *angiokeratomata*, it is less confusing to restrict its use to them. The circumscribed hyperkeratoses may be classified in the following manner[2]:

(*a*) *Simple Traumatic Hyperkeratoses.*—Localised areas of hyperkeratosis are frequently caused by intermittent pressure. They occur in the situations where the skin is most liable to be subjected to pressure, such as the palmar and plantar regions. *Corns* and *callosities* of various kinds belong to this category. In these, intermittent pressure or irritation has caused a hyperplasia of the horny layer limited to the region affected. In the centre of the thickened horny layer a conical plug or core usually forms, and this, by pressing on the

[1] *Histo-Pathology*, Walker's Trans., 1896, p. 1154.

[2] The classification here adopted follows, with certain modifications that of Dubreuilh (*Ann. de Derm. et de Syph.*, 1896, VII., p. 1158).

PLATE VI.

FIG. 1. HYPERKERATOSIS AFFECTING CHIEFLY THE MOUTH OF THE FOLLICLES. ACUMINATE PAPULE OF PITYRIASIS RUBRA PILARIS PIERCED BY A HAIR. (× about 100.)

a. Horny plug filling the funnel of the follicle.
b. Slight hyperkeratosis between the papules.
c. Malpighian layer, not thickened.
d. Lanugo hair-follicle.

FIG. 2. CIRCUMSCRIBED HYPERKERATOSIS AFFECTING THE HAIR-FOLLICLE. COMEDO. (× about 100.)

a. Comedo consisting of an oat-shaped horny mass filling the dilated funnel of the pilo-sebaceous follicle.
b. Outer third of the plug darkened by diffuse horn-pigment.
c. Sebaceous material.
d. Sebaceous gland.

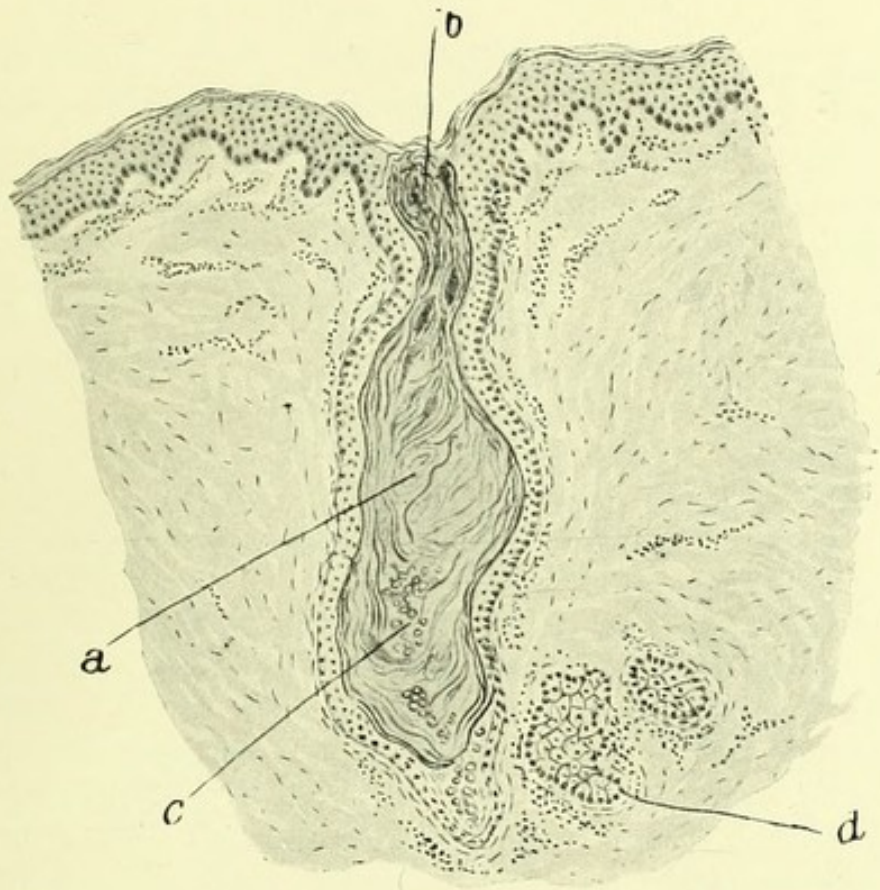

FIG. 2.

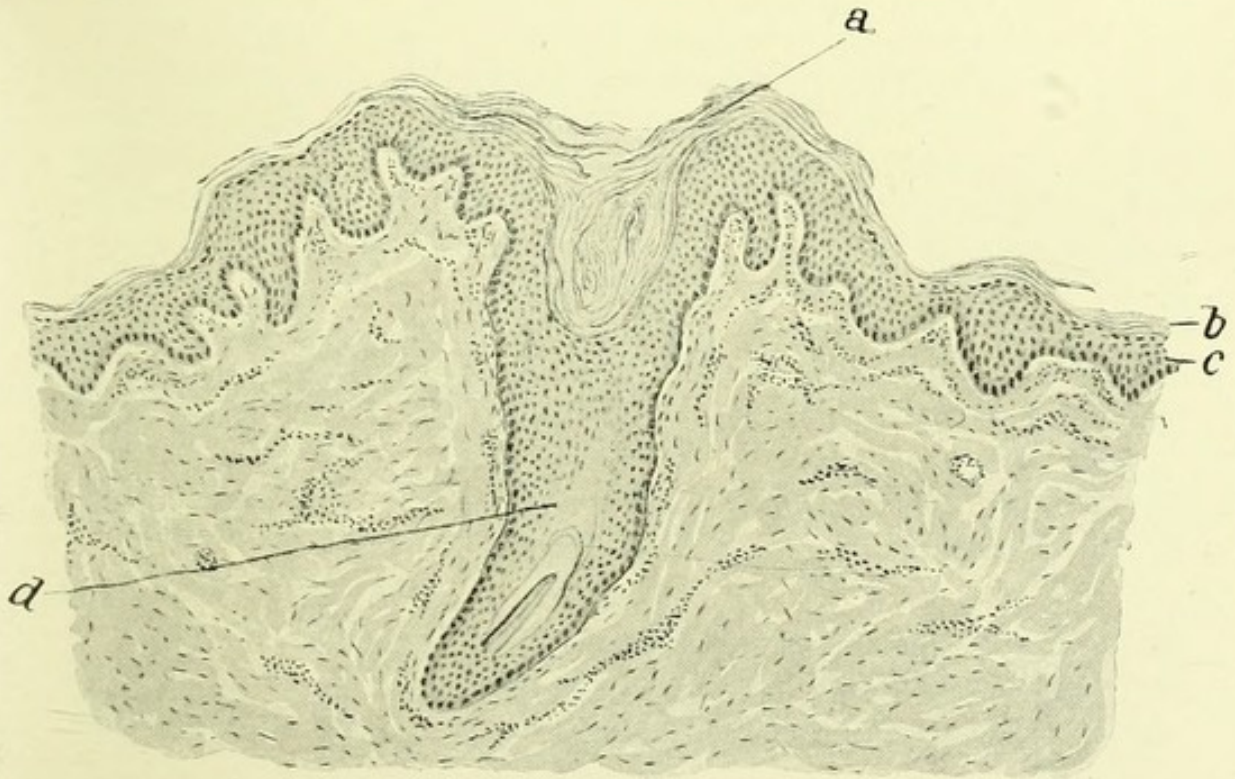

FIG. 1.

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underlying sensitive corium, occasions the boring pain which is associated with the presence of corns (Pl. VII., Fig. 1).

(*b*) *Circumscribed Hyperkeratoses associated with Dilatation of the Vessels of the Corium.*—Dubreuilh has called the papillary layer of the corium the "vascular foundation of the epidermis or the interstitial tissue of an organ of which the epidermis is the parenchyma." The association of dilatation of the vessels of the papillary layer with marked hyperkeratosis is not unusual, and the *angiokeratomata* are examples of it. In much the same way a dilatation of the lymphatic vessels may be associated with a hypertrophy of the fibrous elements of the corium and a hyperplasia of the epidermis, as in elephantiasis. Clinically, the angiokeratomata appear as horny excrescences situated on an erythematous base. They are localised to the palms of the hands and soles of the feet, and vary in size from a pin's head to a split-pea. Occasionally larger patches occur, which are simply exaggerated instances of the same pathological condition. These were described by Brooke[1] under the heading of *Erythema keratodes.* In this affection patches may occur which occupy the whole of the palmar and plantar regions. These patches are covered with a thickened transparent horny layer, and their margins are well demarcated by a narrow zone of hyperæmia. In both the small papular variety and the latter patchy type the initial change is a dilatation of the blood-vessels, for the lesions commence as simple erythematous macules, and the hyperkeratosis follows as a result of the vascular stasis. But the reason why hyperkeratosis should occur here, while the more pronounced dilatation of the vessels in psoriasis is associated instead with defective cornification and the formation of scales, has yet to be explained. There is, as a rule, no marked alteration in either the prickle-cell layer or the transitional layers. A slight proliferation of the former has been described by Pringle,[2] and a widening of the latter by Mibelli.[3] Conditions such as these are generally symmetrical, and occur, as a rule, in young people with weak circulations, and not infrequently in those who are subject to chilblains.

(*c*) *Circumscribed Hyperkeratoses especially affecting the Hair-Follicles and the Orifices of the Sweat-Ducts.*—There are numerous examples of this variety of hyperkeratosis; a few

[1] *Brit. Journ. of Derm.*, 1891, Vol. III., p. 335.
[2] *Ibid.*, 1891, Vol. III., p 237.
[3] *Giorn. Ital. d. Mal. Ven. e d. Pelle.*, 1889, XXIV., p. 285.

of these will serve to illustrate the group. The most familiar instance of it is the common *comedo-plug* (Pl. VI., Fig. 2), which is a hyperkeratosis affecting the outer third or funnel of a pilo-sebaceous follicle. It is an oat-shaped body, composed of concentrically arranged horny layers, enclosing a mass of sebaceous material and twisted up lanugo-hairs. The outer portion of the plug is dark in colour from excessive cornification and the formation of diffuse horn-pigment.[1]

By the action of some external irritant, such as the pressure of the growing hair at puberty, a hyperkeratosis of the funnel of the follicle is caused, and this results in the formation of the comedo.

In the face, where comedones usually occur, the sebaceous gland, instead of being a small appendage to the hair-follicle, is the larger structure of the two, and consequently sebaceous material enters very largely into the formation of the plug. By the growth of micro-organisms in the pent-up sebum, *acne* is liable to supervene.

A somewhat allied hyperkeratosis, but one which affects the funnel of the follicle chiefly, and the sebaceous gland to a less extent than in the comedo, has been described by Brooke [2] with the title of *Keratosis follicularis contagiosa.* In this the plugs consist almost entirely of horny material, and are like small "spikes of mortar." It occurs chiefly in children, and is possibly contagious. The clinical picture presented by this form of hyperkeratosis is peculiarly striking. The affected parts—chiefly the extensor aspects of the limbs, the neck, and the side of the face—are covered with black or brownish specks and papules. From the centre of many of these papules small spikes project, which are sometimes so large as to merit the name of bristles. The process is essentially "a hyperplastic growth of the epithelial cells, with a modification of the horny process, which allows them to retain their vitality for a longer period than usual, and permits of their permanent adhesion." In addition to this somewhat rare variety, all degrees of hyperkeratosis may affect the hair-follicle, from a simple blocking of the orifice to a deep plugging, which results in atrophy. Clinically, this plugging is made evident by the production of acuminate or spiny papules generally confined to the extensor aspects of the extremities, which

[1] The horn-pigment is a diffuse blackish pigment, and is independent of dirt-granules. It is gradually dissolved by chlorine water, hydrogen peroxide, concentrated nitric and acetic acids. These reagents do not completely destroy particles of carbon (Unna).

[2] *Int. Atlas*, 1892, No. 7, XXII.

give rise in mild cases to a permanent condition resembling goose-skin, and in the severer forms to a harsh spiny surface like a nutmeg-grater. Unna[1] has termed the mild and severer types respectively *Keratosis suprafollicularis* and *Keratosis follicularis*. They have been designated also as *Lichen pilaris* (Bazin), *Keratosis pilaris* (Brocq), and *Lichen spinulosus* (Devergie), and by several other names. It is less confusing to restrict the term "Lichen" for the *Lichen planus* group, and Unna's name has the additional advantage of describing the pathological change which is present.

Hyperkeratosis has also been described as specially affecting the orifices of the sweat-ducts. Mibelli[2] has drawn attention to a rare affection of the skin, which he named *Porokeratosis*, in which the hyperkeratosis appeared to be localised at the sweat-orifices. It begins as flat horny excrescences, which spread eccentrically, leaving a slightly atrophic centre surrounded by a hard and horny ridge. Histologically, the ridge is the clinical evidence of a thickening of the epidermis and a hyperkeratosis. According to Mibelli, the funnel[3] of the sweat-duct is chiefly involved, and there is a hypertrophy of the interpapillary process through which the duct passes, and an increase of pigmentation. The connection of this hyperkeratosis with the sweat-orifices has been doubted by subsequent observers, and the disease has been re-named by Respighi[4] *Hyperkeratosis eccentrica*.

(*d*) *Localised Hyperkeratosis associated with Excessive Sweating*.—Circumscribed thickening of the horny layer of the palms and soles in association with hyperidrosis is familiar to all who have the opportunity of seeing even a limited number of skin-diseases. Like the hyperkeratosis accompanying stasis of the blood, the causal connection between the hyperkeratosis and the hyperidrosis is not yet satisfactorily explained. The skin of the palms of the hands, under these circumstances, may become so hard and thickened that the movement of the fingers is rendered difficult and clumsy, and fine manual work is made impossible.

(*e*) *Localised Hyperkeratosis associated with the Elimination of Poisons by the Skin*.—Certain drugs which are eliminated

[1] *Histo-Pathology*, Walker's Trans., 1896, p. 287.

[2] *Monats. f. prakt. Derm.*, 1893, XVII., p. 417.

[3] By the funnel of the sweat-duct is meant the portion in the interpapillary process which is enclosed by the dipping down of the granular layer. In the stratum corneum the duct is represented simply by lacunae between the horn-cells.

[4] *Monats. f. prakt. Derm.*, 1894, XVIII., p. 70.

in the sweat, in their passage through the epidermis cause a hyperkeratosis. This is peculiarly the case with arsenic. The administration of a few grains of arsenious acid may be followed by a hyperkeratosis of the palms and soles. The skin assumes the typical pigmented appearance which is associated with the elimination of arsenic. It becomes mottled, assumes a brownish tint, and presents here and there dark brown punctiform spots; but in addition to this pigmentation, the skin becomes harsh and thickened from hyperkeratosis, and hard horny growths like corns may develop in it.

(*f*) *Precancerous Hyperkeratosis.*—Any persistent localised hyperkeratosis may in late adult life form the basis of a cancerous growth. Instances have been reported where the horny growths of arsenical hyperkeratosis have been followed by cancer. The hyperkeratoses also which result from the irritation of the skin caused by soot in chimney-sweeps, or by tar in tar-workers, or which appear on the lip from smoking a clay pipe, are frequently the precursors of a malignant proliferation of the prickle-cell layer.

Cutaneous Horns, in a considerable percentage of cases, also result in malignant growth. These horny protuberances are purely epidermal structures, which may develop from a wart, or may be connected with a hair-follicle or a sebaceous gland. At first, in the formation of the cutaneous horn the proliferation of the prickle-cell layer is commensurate with the hyperkeratosis; but, later, the cornification is greatly in excess. The irritation caused by the presence of these horny excrescences causes the prickle-cell layer to assume malignant characters.

II. **Parakeratosis, or Imperfect Cornification.**—In the hyperkeratoses we had a simple increase in the horny layer in which the individual cells were in a state of perfect cornification. We have now to consider another pathological group in which there is frequently, though not invariably, an excessive formation of horn-cells, but in which the cells are imperfectly cornified and form friable masses and scales. To this scaly condition of the skin, such as occurs in psoriasis, Auspitz[1] has applied the name *Parakeratosis*. This name has been retained by Unna and his school.

The essential features of parakeratosis are (1) persistence of the nuclei in the horn-cells; (2) incomplete formation

[1] Ziemssen's *Handbook of Skin Disease*, 1885, p. 103.

PLATE VII.

FIG. 1. LOCALISED TRAUMATIC HYPERKERATOSIS. CORN FROM THE FOOT. (× about 60.)

a. Thick blunt conical horny core.
b. Stratum corneum of the sole of the foot.
c. Granular layer.
d. Malpighian layer, not thickened.
e. Papillary body flattened out from pressure.

FIG. 2. PARAKERATOSIS VARIEGATA. (× about 1000.)

Central portion of a slightly raised papule.

a. Dilated blood-vessel.
b. Dilated lymph-space.
c. Connective tissue cell.
d. Leucocyte.
e. Dilated interepithelial lymph-channel.
f. Epithelial nucleus lying in nuclear space.
g. Leucocyte in nuclear space.
h. Œdematous prickle-cell.
i. Granular layer.
j. Œdematous cell of granular layer.
k. Persisting nuclei in horn-cell.
l. Desquamating horn-cell.

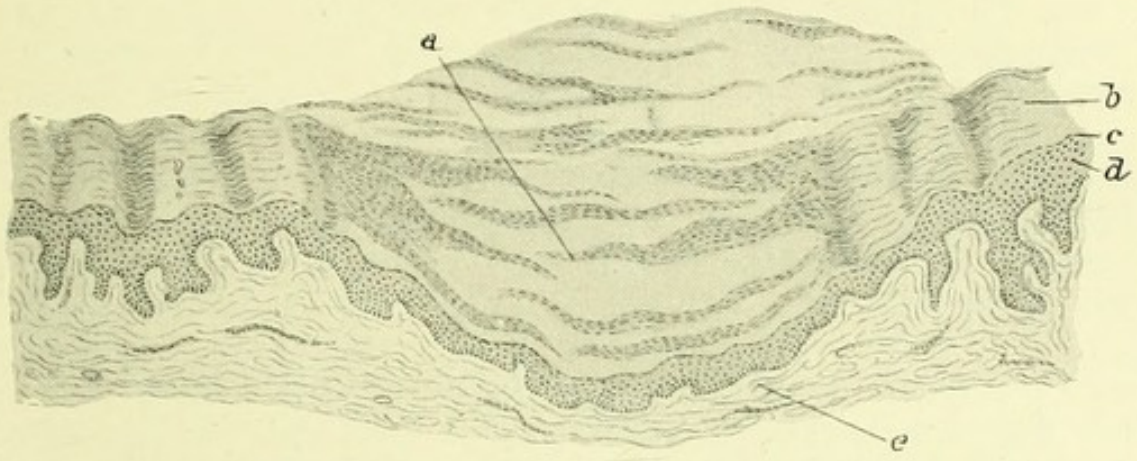

FIG. 1.

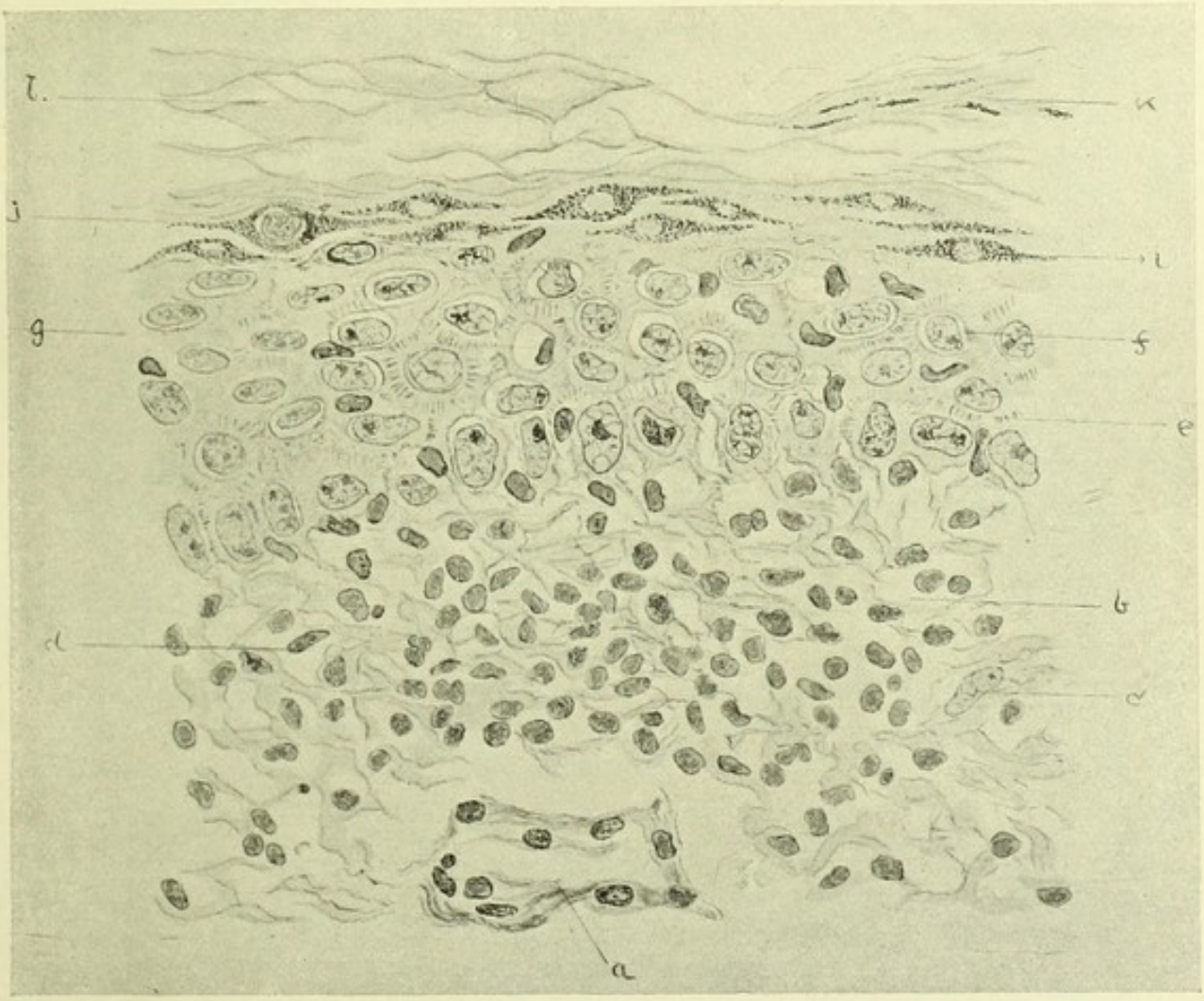

FIG. 2.

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of keratin so that the cells are loosely united and allow a certain amount of air, serum, and frequently leucocytes to collect between them; and (3) moistness of the horn-cells, which are in consequence swollen.

This change in the stratum corneum is invariably preceded by œdema of the prickle-cell layer, in which the cells are swollen and the interepithelial lymph-spaces are dilated and often packed with leucocytes. The transitional layers also participate in the œdematous change.

Keratohyalin granules are as a rule absent, nor can eleidin globules be detected. The œdema has interfered with the horny evolution of the prickle-cells. The condition has been not inaptly designated as a superficial cutaneous catarrh. We find it in psoriasis, eczema, pityriasis of the scalp, lichen planus, in the desquamations following the acute specific fevers, and in a large number of other skin-affections. The horn-cells in parakeratosis are more easily separated by maceration than those of the healthy skin. It is of interest to note the prevalence of collections of leucocytes between the horny scales in parakeratosis, since only recently these collections have been described as peculiar to psoriasis; but, as a matter of fact, they may be found throughout the whole group of the parakeratoses.

Besides these well-known pathological conditions of the skin, two more unusual affections have been described by Unna, to which he has applied the specific titles of *Parakeratosis scutularis* and *Parakeratosis variegata*. In the former condition the scalp is covered with thick crusts composed of imperfectly cornified scales mixed with sebaceous material; in the latter we have a dermatitis which has been recognised only recently in this country, but which forms a well-defined clinical entity.

The following *résumé* of the clinical and histological peculiarities of *Parakeratosis variegata* is taken from a case reported by Colcott Fox and myself[1]:

1. Parakeratosis variegata is a clinical entity.

2. We know little of its etiology, though from its general configuration and histology it suggests a vaso-motor disturbance associated with œdema, infiltration of cells in the corium, and secondary changes in the epidermis.

3. The initial lesion is a macule, or maculo-papule, of small size, flat on the surface, and covered with a fine adherent scale, which may be scratched off without bleeding being caused.

[1] *Brit. Journ. of Derm.*, 1901, XIII., p. 319.

4. By the coalescence of the lesions a peculiar retiform arrangement results, in which areas of normal skin are enclosed in a reddish scaly network, and which, combined with differences in the colour of the lesions in the more dependent parts of the body, produces the marbled or variegated appearance which is one of the most pronounced characteristics of the dermatitis.

5. It affects the skin almost universally, except as a rule that of the face, scalp, palms, and soles.

6. It consists histologically of a superficial inflammation affecting the sub-epidermal layer, with dilatation of the vessels, œdema, and an infiltration of cells ; and an œdematous condition of the epidermis with more or less interference with the process of cornification (Pl. VII., Fig. 2).

III. **Dyskeratoses or Anomalies of Cornification.**—Occasionally partially cornified cells may undergo degenerative changes, with the result that peculiar roundish bodies about the size of prickle-cells are formed, which have a granular protoplasm frequently enclosed in a double-contoured membrane. These structures were at one time regarded as vegetable organisms of the nature of psorosperms. Darier described them in association with a remarkable affection of the pilo-sebaceous apparatus, in which this anomalous type of cornification occurred, and which he named *Psorospermosis follicularis vegetans.*[1] The clinical picture of this disease is as striking as the histological. The skin of the trunk, especially in the axillary and inguinal regions and about the neck, is covered with small pin-head-sized papules with dirty brownish crusts. These are here and there aggregated into larger, dirty, dry, or greasy crusts, and actual " papillomatous tumours " may form. These frequently ulcerate, and a muco-purulent secretion oozes from them. The essential pathological lesion is a hyperkeratosis of the follicle, the common exit of the follicle and sebaceous gland being dilated and filled with horny material. Between the prickle-cells of the stratum Malpighii the above-mentioned round bodies occur. The view that they are psorosperms is, however, no longer admitted, and they are generally believed to be partially cornified cells in a state of hyalin degeneration (*see* p. 172).

In the peculiar small dimpled tumours of *Molluscum contagiosum* we have another anomaly of cornification of

[1] *Inter. Atlas of Rare Skin Diseases*, No. 8, XXIII., XXIV.

much the same type, but it is one which has given rise to considerably more controversy.

In their histology the tumours of molluscum contagiosum (Pl. XI.) are small benign growths of the epidermis which develop from the prickle-cell layer. They grow down into the corium in the form of blunt, lobulated projections, which cause a condensation of the underlying fibrous bundles to form a capsule to the tumour. The main mass of the projection consists of prickle-cells enveloped in an intact basal layer. Passing down from the dimple on the surface, and extending in finger-like projections into the lobules, there is a cavity lined with a horny layer which may almost completely block the cavity. In the deeper parts of this there are numerous oval-shaped glistening bodies, which can be extruded on squeezing one of these small tumours between the thumb-nails. It is these bodies, known as *molluscum bodies*, which have been the cause of dispute. They are usually oval in shape, but frequently have a facetted appearance from pressure. They consist of a capsule within which there is a more or less oval homogeneous mass, and squeezed between it and the periphery there is a flattened nucleus or a mass of granular *débris*, the remains of the nucleus (Pl. IV., Figs. 7, 8, 9). It is almost universally admitted that these tumours are contagious, and Retzius,[1] Pick,[2] and Vidal[3] claim to have succeeded in inoculating them from man to man. From the fact that these oval bodies had a superficial resemblance to the *Coccidium oviforme*, several observers regarded them as parasites, and believed them to be the contagious element. The majority of writers now consider them to be horn-cells, which are peculiar, in that they contain a homogeneous mass of colloid or hyalin (a degenerative product of the protoplasm of the cell) instead of the usual waxy contents. This substance stains readily with acid fuchsin and the other dyes in use for hyalin (*see* p. 172). The researches of Török and Tommasoli[4] definitely proved that these molluscum bodies were not ordinary coccidia. They found that chemically they had the same power of resistance as ordinary horn-cells—namely, that they resisted strong acids, were indigestible in pepsin-hydrochloric acid, and swelled up under the influence of liquor potassae—in other words, that their capsule consisted

[1] *Deutsch. Klinik*, 1872, p. 39.
[2] *Brit. Journ. of Derm.*, 1892, IV., p. 233.
[3] *Le Progrès Méd.*, 1878, p. 478.
[4] *Monats. f. prakt. Derm.*, 1890, X., p. 149.

of keratin. These bodies differ from ordinary horn-cells in their shape, for they are oval or globular, instead of being flat; in not adhering so closely together, but lying like so many plastic keratin-coated capsules at the bottom of a tapering sack; and in containing a homogeneous hyalin mass and a broken-down nucleus. They are the result of an anomalous process of cornification.

Between them and the prickle-cells a thickened granular layer is present, the cells of which contain an abundance of keratohyalin in the form of coarse granules. A layer of cells containing eleidin may also be detected, so that the intermediate stages in the evolution of a horn-cell can all be demonstrated. The hyalin degeneration does not begin in the horn-cells, but may be demonstrated by suitable staining in the prickle-cells and in the cells of the transitional layers. In the prickle-cells, when the globules of hyalin are large, the nucleus of the cell may be pushed aside. Small hyalin droplets may also be found between the granules of keratohyalin and between the "lakes" and drops of eleidin.

The Staining of Molluscum Bodies.—The molluscum bodies are easily stained with any of the stains for keratin, such as hæmatoxylin, safranin, methylene blue, and picro-carmine. By these stains the homogeneous hyalin mass is not sufficiently clearly demonstrated, and special stains for hyalin, such as acid fuchsin, must be resorted to.

Method adapted from Unna (*Histo-Pathology*, Walker's Trans., 1896, p. 793).—

(*a*) Harden in alcohol and cut in celloidin.

(*b*) Stain the sections for ten minutes in polychrome methylene blue.

(*c*) Wash and differentiate in glycerin-ether mixture (Grübler).

(*d*) Counter-stain for ten minutes in 1 per cent. acid fuchsin.

(*e*) Wash.

(*f*) Dehydrate in alcohol.

(*g*) Clear in bergamot oil and mount in Canada balsam.

The capsule of the cell is stained blue, and the central homogeneous mass, red.

Or—

(*a*) Stain from ten to fifteen minutes in a 1 per cent. solution of acid fuchsin.

(*b*) Wash.

(*c*) Counter-stain in alum-hæmatoxylin or Delafield's hæmatoxylin for five minutes.

(*d*) Wash.

(*e*) Dehydrate in alcohol, clear, and mount.

NOTE.—This method is useful for the prickle-cells, and shows the commencing hyalin degeneration in these cells and the unaffected prickles. The hyalin masses are stained red, the remainder of the cells violet.

After Beck (*Archiv f. Derm. u. Syph.*, 1896, XXXVII., p. 167).—

(*a*) Fix in picric acid (concentrated aqueous solution) for twenty-four hours; wash, harden in alcohol, and cut in paraffin.

(*b*) Stain from ten to fifteen minutes in Löffler's methylene blue.

(*c*) Wash in water.

(*d*) Dehydrate in absolute alcohol coloured yellow by picric acid.

(*e*) Rinse in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The hyalin substance is stained reddish violet, the nuclei green, and the unaffected protoplasm yellow.

The molluscum bodies expressed from a tumour on to a slide may be fixed by the flame and stained by the methods described, and by the various other methods mentioned for the staining of macerated horn-cells (*see* p. 77).

IV. **Atrophy and Diminished Cornification.**—In all atrophic conditions of the skin the horny layer participates. In association with various general illnesses the process of cornification may be temporarily arrested or rendered defective, with the result that the power of resistance of the stratum corneum is impaired, and micro-organisms are enabled to penetrate more easily.

In certain nervous diseases, such as tabes dorsalis, atrophy of the stratum corneum is very liable to occur, and slight pressure on the skin is apt to cause bedsores. After prolonged illnesses the œdema which may result from the stagnant circulation is associated with defective cornification (parakeratosis) and desquamation.

CHAPTER XII.

PATHOLOGICAL CHANGES INVOLVING THE EPIDERMIS—Continued.

ACQUIRED CONDITIONS AFFECTING THE PRICKLE-CELL LAYER, HYPERTROPHIES AND ATROPHIES.

CHANGES in the prickle-cell layer occur in association with almost every form of dermatitis. Many of the new growths of the skin, both benign and malignant, have their origin in this stratum; and in a large number of the "infectious inflammations" of the skin it is this layer of the epidermis which is chiefly involved. Even when the pathological process is located in the deeper layers of the skin, the epidermis is secondarily affected to a greater or less degree. The researches of Virchow, Auspitz, Unna, and others have enabled us to classify the majority of the affections which primarily involve the prickle-cell layer. These may be divided into (1) *hypertrophies*, (2) *atrophies*, (3) *dystrophies*, and (4) *pseudo-hypertrophies*. Under "dystrophies" of the epidermis are included the various "infectious inflammations," such as eczema and psoriasis, where such pathological changes as proliferation, with intercellular œdema and vesiculation, occur.

This classification does not profess to be in any way complete: in the present state of our knowledge it is impossible that any classification could be so; but it may be of some service in emphasising the pathological conditions in which the epidermis is markedly affected, and in helping the student to grasp the leading principles in the pathological anatomy of this layer of the skin.

I. **Hypertrophy of the Prickle-Cell Layer.**—A primary hypertrophy of the prickle-cell layer occurs as the result of an irritation, which is not sufficient to cause either a degeneration or a malignant proliferation. In such instances the newly formed cells which constitute the hypertrophy are perfect prickle-cells, and retain their intercellular protoplasmic fibrils.

The basal layer of the epidermis remains intact, and forms a limiting layer to the proliferating epidermis. The cells immediately above the basal layer—the so-called daughter-cells—no longer become differentiated, but assume the function of the cells of the basal layer, and proliferate; and where the growth is rapid, mitotic figures may be detected in the nuclei several rows above the basal layer. The proliferative activity takes place in a downward direction, and the interpapillary processes become elongated, thickened, and spread out irregularly into the corium. The suprapapillary epidermis also proliferates until the prickle-cell layer is several times its original thickness. True hypertrophies of this layer are generally circumscribed, and result in the formation of benign new growths, such as *condylomata* and *warts*. Formerly it was customary to include such affections under the heading of "papillomata," but there is a tendency now to abandon the term "papilloma," as it is somewhat of a misnomer. A "papilloma" in the sense of a tumour, produced exclusively by the proliferation of the papillae, does not exist. There is always, *pari passu* with the increase of the papillae, a corresponding increase of the interpapillary epidermis, and as a rule the epidermal proliferation is the initial change. As Unna has pointed out, even in the most exaggerated papillary growths there is an early stage in which a button-shaped down-growth of the epidermis is present, and at first there is frequently an actual flattening of the underlying papillary body. The adjective "papillated," as applied to many of these growths, is free from this objection, as it simply refers to a clinical appearance, and does not imply that the neoplasm originated in the papillary layer. It has been suggested that the term "Epithelioma" should be employed to designate all the epidermal neoplasms, but the confusion which would arise by applying this term so universally is obvious, since it has come to be restricted in this country to the malignant growths of the epidermis.

One of the most important characteristics of the malignant epithelial cells, such as are met with in the carcinomata, is the absence of the fibrillated structure of the prickle-cells, and this characteristic serves to distinguish them from those of the benign neoplasms in which the protoplasmic fibrils are retained. On account of this distinctive feature Auspitz has applied to the true hypertrophies of the prickle-cell layer the name *hyperacanthomata* (*ἄκανθα*—a prickle). Unna has followed Auspitz's example, and has employed the term *acanthomata* for the benign epidermal tumours, and *acanthosis*

for any proliferation of the prickle-cell layer in which the fibrillary structure of the cell is retained.

Hyperacanthomata (Benign Neoplasms).—

1. *Hypertrophy affecting the Prickle-Cell Layer alone (Primary). Example: Condyloma Acuminatum.*—Although very frequently a hypertrophy of the prickle-cell layer is associated with proliferation of the stratum corneum, it sometimes happens that acanthosis may occur without hyperkeratosis, proving that these two processes are independent of one another.

The *Condyloma acuminatum* (venereal wart) is an instance of primary acanthosis without hyperkeratosis. These condylomata are the familiar filiform or cauliflower-like benign growths, which are single or multiple, vary in size from a pin's head to a small egg, and are situated frequently on or in the neighbourhood of the genitalia in venereal diseases. They begin as small flat papules which on section show simply a circumscribed thickening of the prickle-cell layer and a flattening of the underlying papillae. Gradually the interpapillary processes grow down into the corium in the form of irregular projections, and an elongated appearance of the papillae is produced. As the growth progresses the tumour becomes raised up. Oblique sections of it give the appearance of cut-off islands of the corium enclosed in a coarse epidermal network. The prickle-cells are enlarged to several times their ordinary size, they retain their fibrillary structure, and mitotic figures may be detected in them almost as far up as the granular layer. The basal layer of the epidermis is intact, and is continued round the neoplasm. There is no hyperkeratosis, but the surface of the lesion is broken up by deep fissures, which extend down into the interepithelial processes.

The blood-vessels of the papillary layer are dilated and surrounded by leucocytes, and there is a certain amount of dilatation of the interepithelial lymphatics, so that leucocytes and Herxheimer's spirals may be detected between the prickle-cells. These vascular changes are secondary to the epidermal proliferation, and the latter is the result of the irritation of the skin by the venereal discharges.

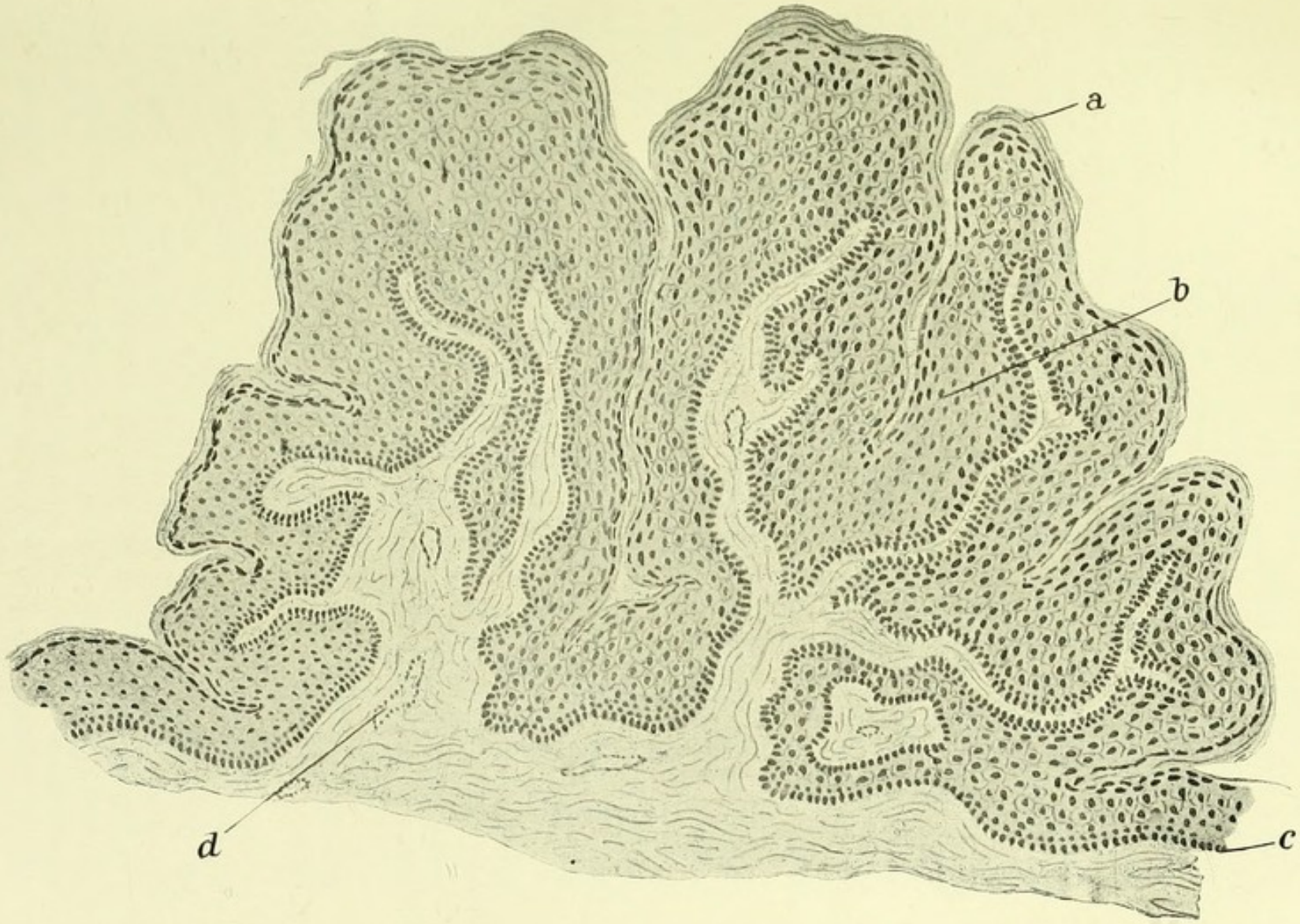
Lichenification is the name applied by the French school of dermatologists to a condition of the skin in which patches of various sizes occur, which are made up of flat, shiny papules, densely packed together and resembling those of lichen planus. It is the result of scratching or rubbing. In it there is a diffuse acanthosis of the prickle-cell layer.

PLATE VIII.

HYPERTROPHY OF THE PRICKLE-CELL LAYER (ACANTHOSIS). CONDYLOMA ACUMINATUM. (× about 250.)

a. Stratum corneum not thickened.
b. Prickle-cells actively proliferating and unusually large.
c. Basal layer intact.
d. Dilated blood-vessel.

PLATE VIII.



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2. *Hypertrophy of the Prickle-Cell Layer, with Hyperkeratosis. Example: Verruca vulgaris.*—As in condyloma so in *verruca*, there is an initial stage in which there is simply a circumscribed thickening of the prickle-cell layer and a flattening of the papillary body; but in verruca there is, in addition, an increase in the stratum corneum. Although the horny layer is thickened, the process of cornification is a somewhat imperfect one—a fact which is made evident by the presence of nuclei in the horn-cells above the papillae. Gradually a down-growth of the prickle-cell layer occurs, and the papillae appear to be elongated; mitotic figures are observed high up in the Malpighian layer, and the inter-epithelial lymphatics are dilated. The stratum corneum dips down in fissures in the interpapillary processes, especially at the sweat-orifices. In verruca also secondary changes occur in the vessels of the papillary body; but they are less marked than in the condylomata. In young people warts frequently persist in the early, small, flat stage, when they are known as *Verruca plana seu juvenilis.*

Another instance of acanthosis with hyperkeratosis occurs in the warty form of lichen planus, the so-called *Lichen verrucosus*; but this condition is associated with an infiltration of cells in the corium, which are more than simply leucocytes, and are possibly derived either from the fixed cells of the fibrous bundles or from the vessel-walls. It is doubtful if the epidermal changes in this disease are primary.

There is a rare disease known as *Acanthosis nigricans* which also belongs to this group. For a description of the clinical appearances of it, reference may be made to the cases described by Pollitzer and Janowsky[1] in the *International Atlas of Rare Skin Diseases.*

In this disease the acanthosis and hyperkeratosis are associated with a deep pigmentation of the cells of the basal layer and those immediately above it.

3. *Hypertrophy of the Prickle-Cell Layer Secondary to Changes in the Corium.*—The *Infective granulomata* of Virchow—for example, syphilis, tuberculosis, yaws—are all associated with acanthosis of the epidermis, and sometimes with hyperkeratosis also. Acanthosis and hyperkeratosis invariably accompany the lesions of yaws. Acanthosis is common in connection with syphilis, especially in the large papular syphilides; but hyperkeratosis is unusual. In tuberculosis cutis, especially when it occurs about the

[1] *Inter. Atlas of Rare Skin Diseases*, No. 4, X., XI.

extremities, acanthosis, with or without marked hyperkeratosis, is a constant accompaniment of the granuloma, as such names as *Lupus papillomatosus* and *L. verrucosus* imply. In mycosis fungoides—another of the infective granulomata—acanthosis is generally present, and is greatest when the skin of the extremities is affected. In this disease the granuloma tends to approach the surface and encroach upon the proliferated epithelium, so that the basal layer becomes broken and blurred, and the acanthosis becomes gradually replaced by ulceration. In the sarcomata of the skin the epidermis immediately above the neoplasm is thinned; but at the sides of it an acanthosis is usually present.

In the infectious inflammations, such as psoriasis, eczema, and herpes zoster, before the characteristic changes of the nature of dystrophies occur in the epidermis, there is an initial acanthosis.

II. **Atrophy of the Prickle-Cell Layer.**—Atrophy of the prickle-cell layer of the epidermis is accompanied by a flattening of the papillary body and a corresponding diminution of the interpapillary processes. The layer becomes greatly diminished in thickness, and in sections the imaginary line between the epidermis and the corium becomes less wavy, and may even become straight. The atrophy may be due to a number of causes, the more common of which may be thus classified :

1. *Atrophy from External Pressure.*—Continuous external pressure on the epidermis causes it to atrophy; for example, the continuous pressure of a bandage or a plaster-of-Paris dressing is followed by a gradual atrophy of the prickle-cell layer. When the stratum corneum becomes thickened in small areas, as in flat corns, atrophy of the underlying epidermis commonly results.

2. *Atrophy from Internal Pressure.*—When there is pressure on the epidermis exerted by any underlying new growth, such as a sarcoma or a fibroma, atrophy of the prickle-cell layer usually occurs. In sclerodermia, from the pressure exerted by the scleromatous corium, the prickle-cell layer is as a rule markedly thinned.

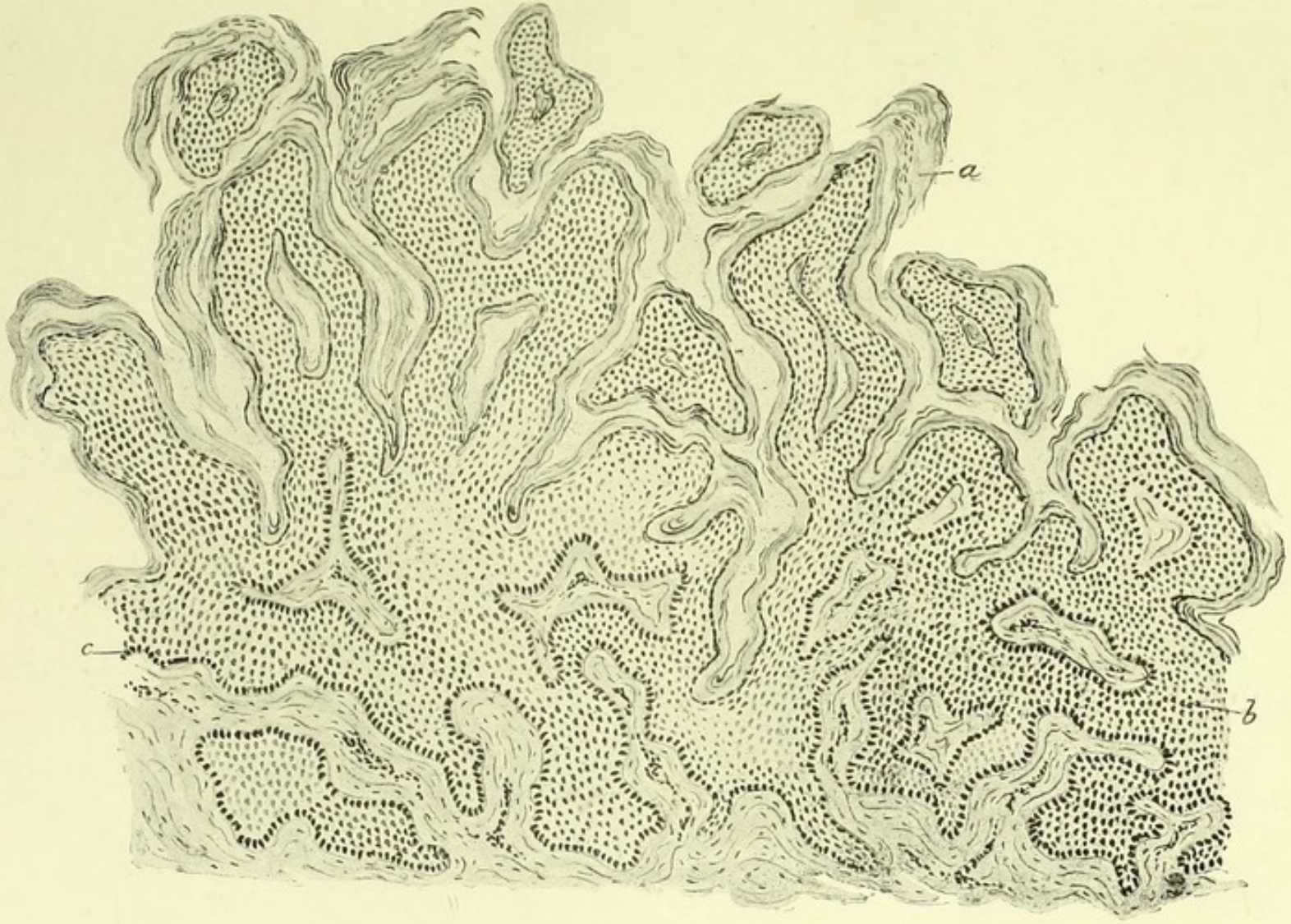
3. *Atrophy from Traction.*—The striae atrophicae of pregnancy are instances of this type of atrophy. A similar atrophy of the skin results from the stretching caused by ascitic fluid.

PLATE IX.

HYPERTROPHY OF THE PRICKLE-CELL LAYER, WITH HYPERKERATOSIS. ACANTHOSIS NIGRICANS. (× about 100.)

a. Thickened stratum corneum.
b. Proliferating prickle-cell layer (Acanthosis).
c. Intact and pigmented basal layer.

PLATE IX.



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4. *Idiopathic Atrophy.*—A diseased condition of the skin has lately been recognised in which the most marked feature is an atrophy affecting both the epidermis and the corium. The pathology of the affection is not yet fully explained, and in consequence the name *Diffuse idiopathic atrophy of the skin* has been applied to it. A congenital atrophy of the skin of the same nature has been described by Charcot as *Géromorphism cutanée.*

5. *Senile Atrophy.*—In the thin shiny atrophic skin which so generally accompanies old age—the so-called "senile skin"—one of the most marked features in its histology is a drying up and wasting of the prickle-cells. Associated with the atrophy there is usually an accumulation of pigment in the cells of the basal layer. It would seem that either these cells are capable of elaborating pigment even when they have lost much of their vitality, or that the pigment is a product of degeneration of the cell-protoplasm.

CHAPTER XIII.

PATHOLOGICAL CHANGES INVOLVING THE PRICKLE-CELL LAYER OF THE EPIDERMIS—Continued.

DYSTROPHIES.

UNDER the provisional heading of *Dystrophies of the Epidermis* a series of pathological processes will be described in which the epidermis is markedly involved, owing to the presence of more or less œdema within and between the prickle-cells. The name has been adopted because when the œdema becomes excessive the vitality of the prickle-cells is impaired, and they are no longer capable of evolving into perfect horn-cells. This name is open to several objections, from which the heading "Œdemas of the Epidermis" is free; but as I wish to include here a short description of the formation of pustules in the epidermis, I have employed it in preference to the latter more definite title.

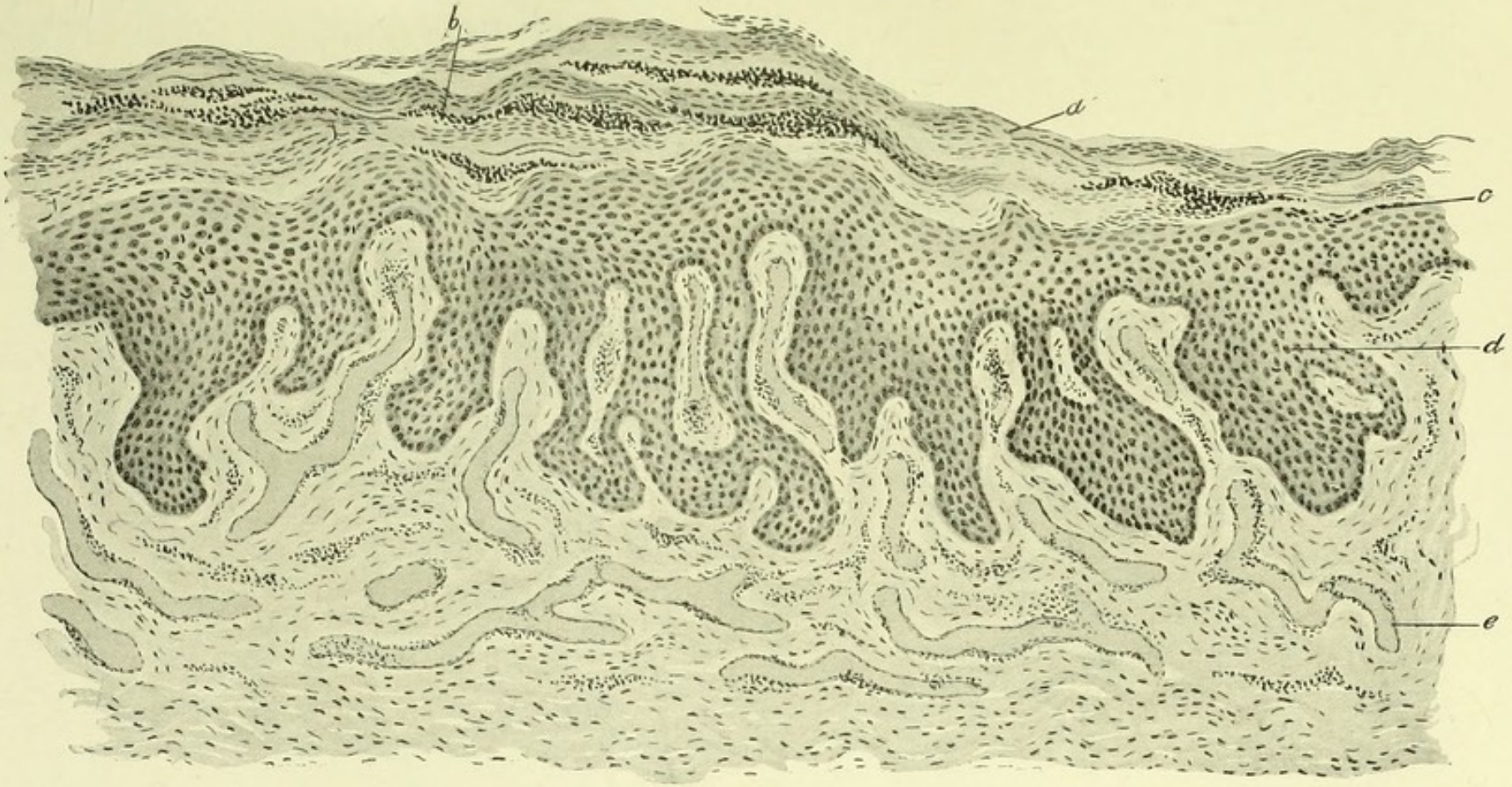
NOTE.—The same plan will be adhered to in describing the dystrophies of the epidermis as in the hypertrophies, and only those diseases will be referred to which serve to illustrate a type of pathological change. While in this way the pathology of a considerable number of skin-diseases will be briefly described, still I must again observe that this section of the book does not profess to be a complete text-book on the subject, but rather an introduction to the general pathological changes which underlie diseases of the skin, the appreciation of which it is hoped will simplify the understanding of the larger text-books on dermatology.

I. **Œdema.**—Œdema affecting the epidermis occurs in a large number of skin-affections. It is associated with a dilatation of the blood-vessels and a widening of the lymphatic spaces of the papillary body. It may occur suddenly from a rapid dilatation of the vessels and extravasation of serum, as

PLATE X.

DYSTROPHY OF THE EPIDERMIS. ŒDEMA AND PARAKERATOSIS. PSORIASIS. (SEMI-DIAGRAMMATIC.) (× about 200.)

a. Imperfectly cornified scale in which the nuclei persist in the horn-cells.
b. Collections of broken-down leucocytes between the horny lamellae.
c. Portion of the stratum granulosum; most of this layer has disappeared.
d. Proliferating epidermis; prickle-cells œdematous; interepithelial lymphatics dilated, and leucocytes present in them.
e. Dilated papillary and sub-papillary blood-vessels (injected).



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in lesions of the urticarial type. The latter, and all the other forms of the so-called "angioneurotic œdema," will be described in the chapter dealing with the blood-vessels of the skin and their pathological relations.

Here I will describe in the first place the type of œdema which affects the epidermis gradually, which may or may not go on to vesiculation, but which is invariably accompanied by impaired cornification.

(*a*) *Slight Œdema, with Imperfect Cornification. Example: Psoriasis.*—Psoriasis is the classical example of slight œdema of the epidermis, with "parakeratosis." The cardinal features in the histology of a recent papule of psoriasis may be thus briefly tabulated (Pl. X.):

1. Dilatation of the blood-vessels chiefly affecting the veins of the papillary and sub-papillary layers of the corium.
2. Elongation of the papillae.
3. Cellular infiltration and œdema of the superficial layers of the corium.
4. Proliferation of the prickle-cell layer, with downgrowth of the interpapillary processes (acanthosis).
5. Dilatation of the interepithelial lymphatic spaces.
6. Deficiency in the transitional layers and imperfect cornification.

The epithelial proliferation is confined to the interpapillary processes, while the portions of the epidermis immediately above the swollen œdematous papillae are little, if at all, thickened. This fact, combined with the dilatation of the papillary vessels, explains the great liability of the papule of psoriasis to bleed when the scale is scratched off. The basal layer of the epidermis in the lesions of psoriasis is everywhere perfect.

The œdematous dilatation of the interepithelial lymphatics, though present, is slight; between the cells only a few leucocytes can be detected, and there is little or no evidence of actual œdema of the prickle-cells ("parenchymatous œdema"). The transitional layers are absent, neither keratohyalin granules nor eleidin droplets being visible. The presence of keratohyalin granules gives to the skin its whitish opacity, and the absence of these granules in psoriasis accounts to some extent for the vivid redness of the papule after the scab has been removed. The horn-cells are moist, they retain their nuclei, and are deficient in keratin. The persistence of the horn-cells in this soft pliable condition causes them to adhere together in lamellae or squames, and prevents their

being rubbed off singly, like the dry horn-cells in perfect cornification. When the cells and lamellae become partially dried, air makes its way between them and gives to the scales the silvery appearance so characteristic of psoriasis. Between the lamellae, rows and clusters of leucocytes usually collect, and these form a striking feature in the histological picture.

In the corium, superficial vascular dilatation, œdema separating the fibrous bundles, and a cellular infiltration are invariably present. The cellular infiltration is chiefly focussed around the dilated vessels. It consists of polynuclear leucocytes and clusters of mononuclear cells about the same size. The nature and origin of the latter cells are doubtful, as it is uncertain whether they are small mononuclear leucocytes (lymphocytes) or young connective-tissue cells derived from the vessel-walls or from the connective-tissue bundles. A definite proliferation of the endothelial cells, and also of the connective-tissue cells, may here and there be detected. The problem whether the epidermal or the vascular changes are primary in psoriasis is still the subject of controversy.

Hebra regarded psoriasis as essentially an inflammation of the corium associated with secondary changes in the epidermis; Unna believes that the epidermis is primarily affected by a parasite (morococcus), and that this induces a chemotactic action, which causes the blood-vessels to dilate, and attracts the leucocytes to the stratum corneum; and Brooke[1] suggests that "one cause is producing changes in the vessels and in the epidermis at the same time, and that the changes in either region are a by-product of the other."

(*b*) *Pronounced Œdema, with Imperfect Cornification. Example: Seborrhoic Dermatitis (Eczema Seborrhoicum of Unna, Flannel Rash, Lichen Circinatus, etc.).*—Clinically this affection may closely resemble psoriasis, but usually the lesions are easily distinguished from the latter disease. The scales are less silvery, and are yellowish and greasy; the colour of the lesions has a yellowish tinge, and is not so vivid as in psoriasis, and their distribution is different. The histological picture may also closely resemble that of psoriasis; but as a rule the œdema of the prickle-cell layer is far more pronounced than in the latter disease.

The following characteristics in the histology of seborrhoic dermatitis may be tabulated:

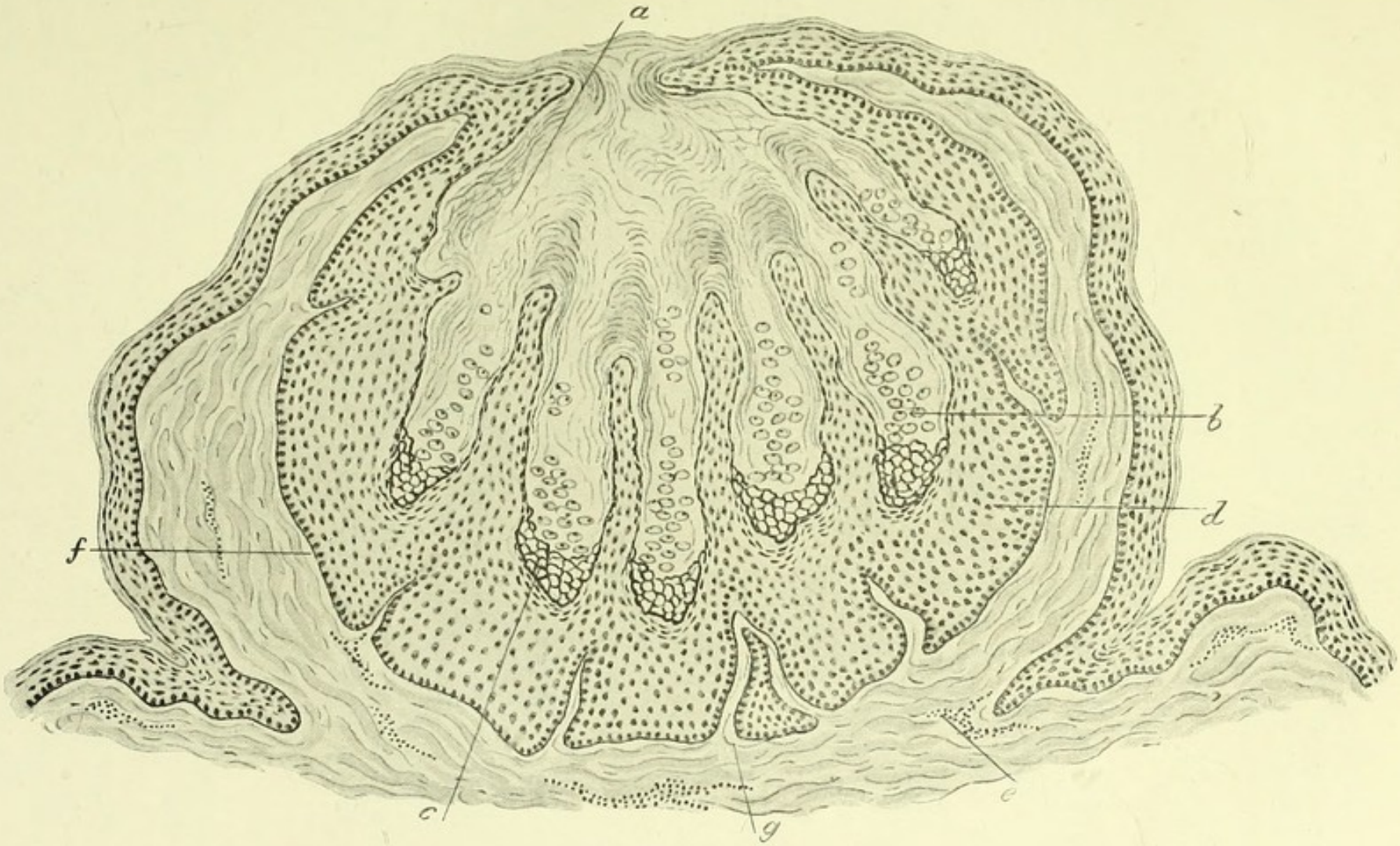
1. Dilatation of the vessels of the corium to a greater or less degree, but not generally so marked as in psoriasis.

[1] *Allbutt's System of Medicine*, 1899, VIII., p. 560.

PLATE XI.

ANOMALY OF CORNIFICATION. SECTION OF A SMALL DIMPLED TUMOUR OF MOLLUSCUM CONTAGIOSUM. (× about 120.)

a. Dimple and cavity lined and almost completely filled with horn-cells.
b. "Molluscum bodies."
c. Transitional layers.
d. Proliferated Malpighian layer.
e. Dilated blood-vessel.
f. Condensed fibrous capsule.
g. Papillae flattened or persisting as a cleft, giving to the tumour a lobulated appearance.



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2. Elongation and frequently narrowing of the papillae.

3. Œdema of the corium and infiltration of leucocytes, and possibly small connective-tissue cells around the dilated vessels and in the neighbourhood of the hair-follicles and glands.

4. Proliferation of the prickle-cell layer.

5. Œdema of the prickle-cells and dilatation of the inter-epithelial lymphatics.

6. Where the œdema is most pronounced the transitional layers are absent, the cornification is deficient, and fatty *débris* is frequently present between the horny lamellae.

The basal layer of the epidermis is intact, as it is in psoriasis. The interpapillary processes are not only lengthened, but broadened, and the presence of the excessive œdema causes them to have a swollen appearance. The prickle-cells are swollen, and stain more faintly than usual on account of the parenchymatous œdema of the cells. Here and there cells may be detected in which the fluid has collected around the nucleus and caused a nuclear space to form, in which the nucleus is lying. But notwithstanding the œdema, the nuclei seem to be unaffected, and their chromatin stains as vividly as in healthy cells. The inter-epithelial spaces are greatly dilated and the prickles are stretched to the utmost. Here and there polynuclear leucocytes and lymphocytes are compressed between the prickle-cells.

As in psoriasis, so in this form of dermatitis, the etiology is still one of the unsolved problems of dermatology.

When the œdema in and between the cells reaches a certain stage the cells are no longer able to resist the pressure of the œdematous fluid, and they separate; fluid collects between them, and vesiculation results.

The Formation of Vesicles.

The physiology of the formation of vesicles is a complex and difficult problem. Vesicles result from the co-operation of a number of factors. Recently Weidenfeld[1] performed a series of interesting experiments on the subject, from which he concluded that the most important factor in the production of vesicles was increased pressure in the lymphatic spaces of the skin. His experiments were carried out as follows: To the lower end of a glass cylinder, 8 in. long by 1 in. in diameter, a piece of skin excised from a cadaver

[1] *Archiv f. Derm. u. Syph.*, 1900, LIII., p. 3.

was bound with the corium towards the lumen of the cylinder. The cylinder was half filled with water, and the other end was closed by an indiarubber cork with two holes bored in it. Two small glass tubes were fitted into the holes in the cork. One of these glass tubes was connected by a piece of indiarubber tubing with an apparatus by which sudden shocks could be transmitted to the skin through the water in the cylinder; and the other tube was connected with a simple apparatus by which the pressure of the atmosphere could be varied, so that the water in the tube could be gradually forced into the spaces in the corium and thence into the interepithelial spaces, and in this way the pressure in the vessels and lymphatic spaces in the skin could be imitated to some extent. When the pressure of the fluid on the corium reached a certain degree, vesiculation took place. Increased pressure in the lymphatic spaces of the skin did not explain the formation of every sort of vesicle, however, and Weidenfeld qualified his assertion by recognising that a flaccid type of blister may form in the epidermis by a disintegration of the prickle-cells, caused by poisonous substances circulating in the epithelial lymph-stream, without any increase in the pressure in the lymphatics.

Weidenfeld's conclusions were somewhat similar to those which Auspitz[1] had previously put forward. Auspitz considered that vesicles were produced in two ways:

1. They were the result of, or secondary to, an inflammation of the corium, accompanied by a dilatation of the blood-vessels and lymphatic spaces and a serous exudation.

2. They were sometimes independent of changes in the corium, and were the result of a want of resistance of the prickle-cells in a circumscribed area, by which the cells readily separated and allowed fluid to collect between them. If congestive phenomena were present in the corium, they were not primary, but accidental accompaniments.

To this second type of vesicular formation Auspitz gave the name of *Acantholysis*.

Four factors may be said to play a more or less important *rôle* in the formation of vesicles. These are:

1. Increased pressure of lymph in the interepithelial lymphatic spaces of the epidermis.

2. Actual œdema of the epithelial cells.

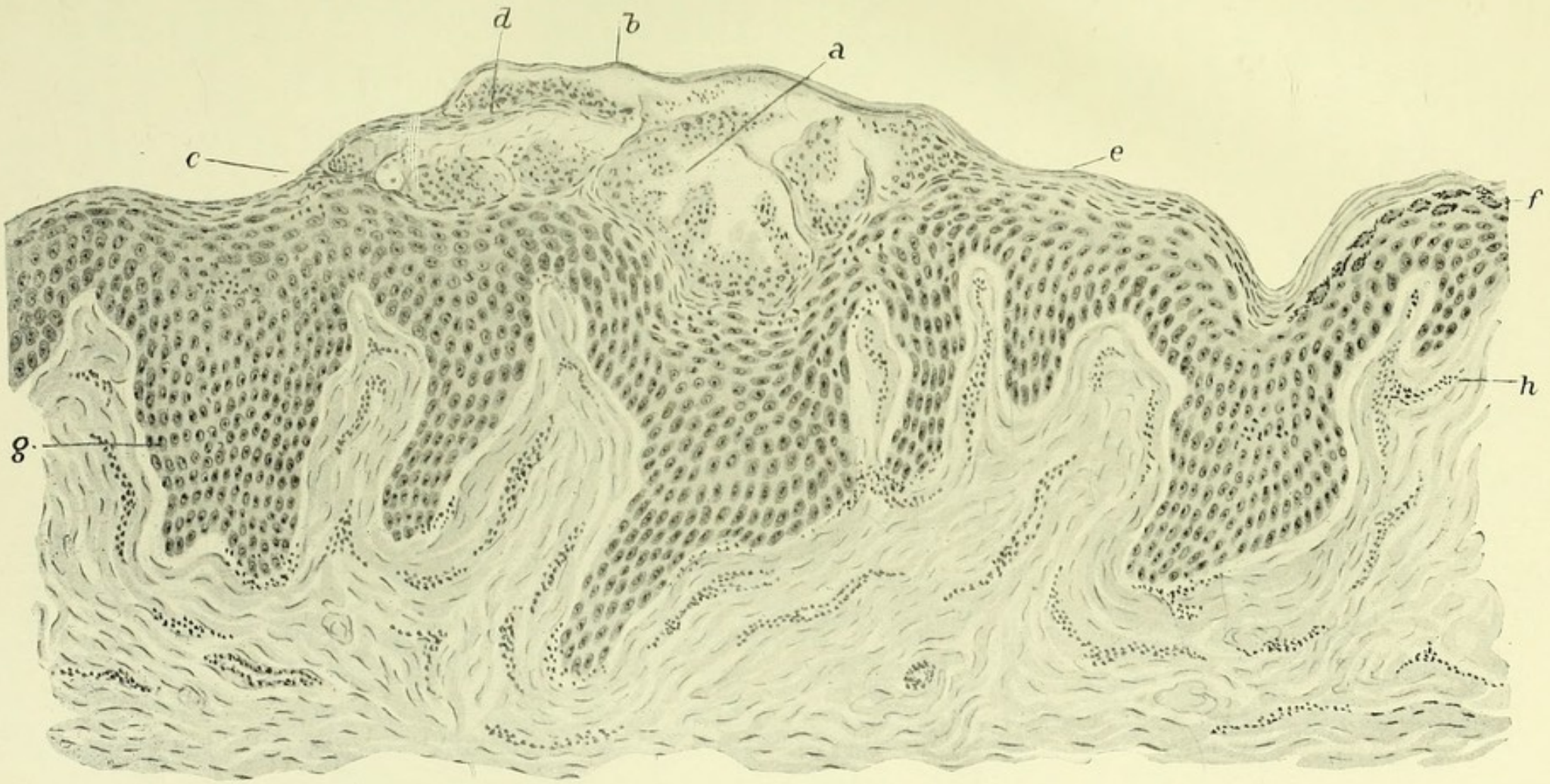
3. Poisonous substances circulating in the lymph-stream causing a destruction or necrosis of the epithelial cells.

[1] Ziemssen's *Handbook of Skin Disease*, 1885, p. 117.

PLATE XII.

Interepithelial Vesicular Formation.
Superficial Vesicle of Eczema. (× about 400.)

a. Vesicle broken up into imperfect loculi by septa composed of flattened epithelial cells.
b. Roof of the vesicle formed by a thin layer of the stratum corneum.
c. Floor formed by flattened epithelial cells, some of which are partially cornified.
d. Contents of the vesicle; leucocytes and epithelial *débris*.
e. Imperfectly cornified layer.
f. Stratum granulosum.
g. Proliferated and œdematous Malpighian layer.
h. Dilated blood-vessel surrounded by an inflammatory cellular infiltration.



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4. Initial want of vitality of the epithelial cells by which they are less able to withstand the interepithelial œdema and the poisonous substances circulating in the lymph.

These four factors are not invariably present together; but the first two of them are essential.

According as the œdema of the interepithelial spaces or actual œdema of the prickle-cells is in excess in the early stage of the vesicles, Darier[1] has divided them into two classes—namely, "interstitial" and "parenchymatous" vesicles; and this division, though arbitrary, is of service in simplifying the description of the formation of vesicles, and may with advantage be adopted.

I. **Intercellular or Interstitial Vesicular Formation.** *Example: The Vesicles of Eczema, Herpes Zoster, etc.*—The vesicle of *eczema* is situated in the epidermis (Pls. XII., XIII.), and its formation appears to be the result of profound interepithelial œdema. As the œdema advances a time comes when the intercellular protoplasmic bridges are no longer able to hold the prickle-cells together and to resist the constantly increasing lymph-stream; the cells become separated, the space so formed becomes rapidly distended with fluid, and a small unilocular vesicle is produced. When the interepithelial œdema has reached a certain degree, the cells all become separated from one another, and a spongy condition of the epidermis is produced which Unna calls "*spongy metamorphosis.*" These vesicles appear first above the papillae in which the vascular dilatation is greatest. As the fluid in the vesicle increases, the prickle-cells around it become compressed and assume a spindle shape. Neighbouring vesicles gradually coalesce to form large irregular vesicles, which may be unilocular, but are more often broken up by persisting bands of prickle-cells into a number of variously sized loculi. The cells surrounding the vesicle become œdematous and distended with fluid, which collects within the meshes of the intracellular spongioplasm, and distends the nuclear space. The nuclei of the prickle-cells are much more resistant than the rest of the cell, and may frequently be detected intact in the vesicles after the remainder of the cell has broken down into a mass of *débris*.

Not only may the vesicles of eczema present an endless variety in shape and size, but their situation in the epidermis may also vary indefinitely. They may be situated superficially

[1] *La Pratique Dermatologique*, 1901, I., p. 90.

and may be covered only by a thin layer of imperfectly cornified cells; on the other hand, they may be found in the Malpighian layer, with the basal layer as a floor. The situation of the vesicles is not, however, accidental, but is determined by several considerations:

(*a*) The vesicle occurs naturally in the region of least resistance, which is generally, in eczema, the superficial portion of the prickle-cell layer—the site where the granular layer begins to form in the healthy epidermis, this layer being usually defective when marked œdema occurs.

(*b*) The rapidity of the œdematous process also determines the situation of the vesicle. If the œdema occur rapidly, the greatest strain will be put on the papillary body and the prickle-cells nearest the basal layer, and in acute cases the vesicles are frequently found in this situation. If the œdema be more gradual in its progress, it picks out the situations of least resistance—namely, the superficial part of the prickle-cell layer.

(*c*) Occasionally if the œdema diminish slightly, the prickle-cells which form the floor of the vesicle may become cornified, and a granular layer be detected; in such cases the vesicles may come to be situated entirely within the stratum corneum.

Contents of the Vesicles.—The vesicles contain a spontaneously coagulable fluid of the type of blood-plasma, a varying number of leucocytes, a few œdematous prickle-cells which have as a rule lost their prickles, and occasional epithelial nuclei. When the fluid oozes out, it coagulates, to form, with leucocytes, epithelial *débris*, horny squames and fat, the familiar crusts of eczema.

Much discussion has arisen around the subject of the presence of *micro-organisms* in the vesicles of eczema. Unna[1] maintained that his morococci and various other cocci were present. Galloway and Eyre[2] have found cocci which gave white cultures; while Sabouraud[3] declares that the vesicle in the early stages is sterile.

On the assumption of the presence of micro-organisms, Unna regards the epidermal changes as primary, and believes them to be due to the irritation caused by the presence of the micro-organisms, which he considers to be capable of causing (1) the epithelial proliferation, and (2) by the process

[1] *Monats. f. prakt. Derm.*, 1899, XXIX., p. 106; *Ibid.*, 1900, XXXI., pp. 1, 65, 213.

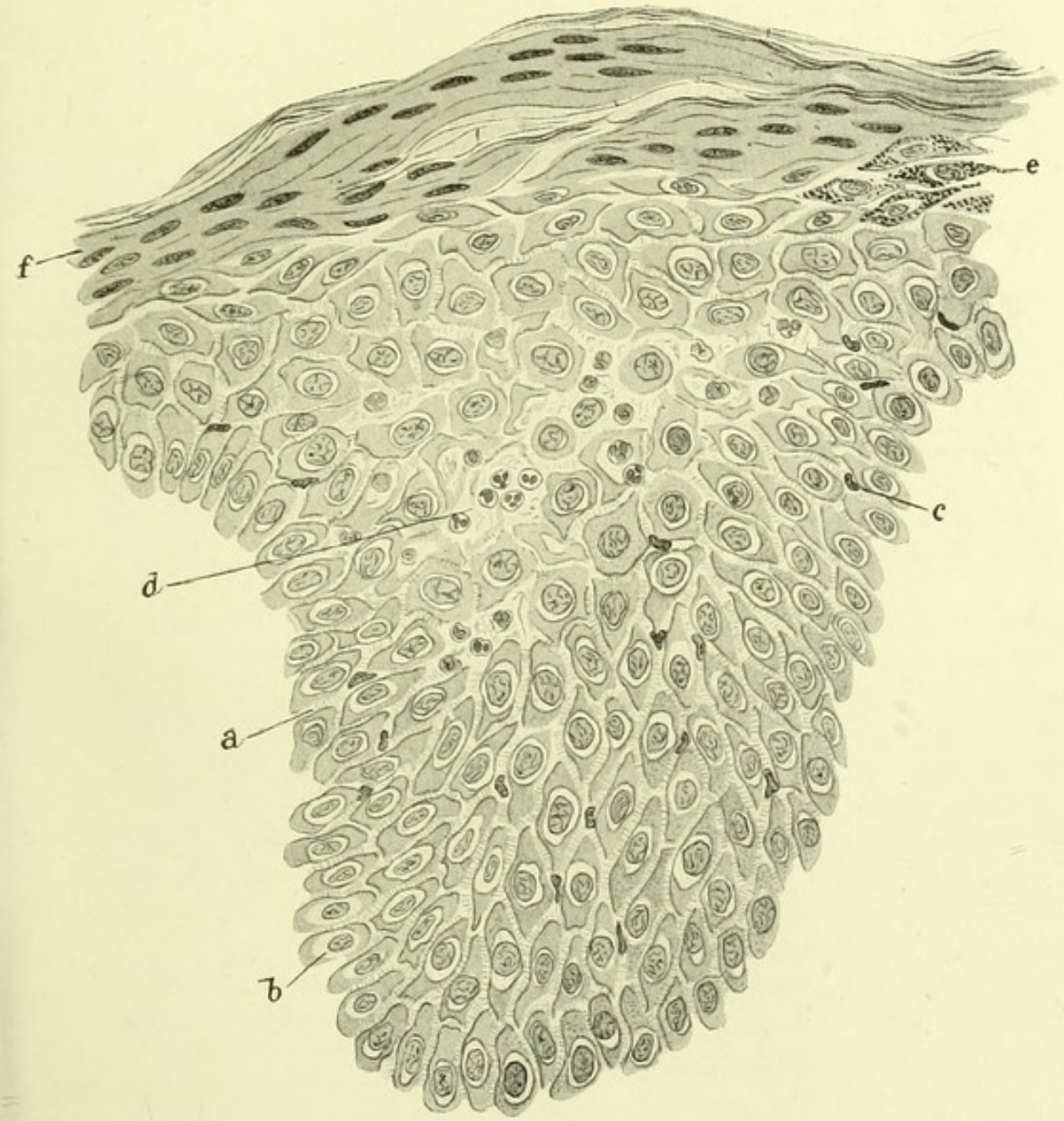
[2] *Brit. Journ. of Derm.*, 1900, XII., p. 307.

[3] *Ann. de Derm. et de Syph.*, 1899, p. 305.

PLATE XIII.

INTEREPITHELIAL VESICULAR FORMATION.
COMMENCING VESICLE OF ECZEMA. SLIGHTLY MORE DEEP-SEATED THAN USUAL. (× about 800.)

a. Marked interepithelial œdema.
b. Dilated nuclear spaces.
c. Leucocytes between the prickle-cells.
d. Commencing vesicle containing leucocytes, breaking-down prickle-cells, epithelial nuclei, prickle-cells which have lost their prickles and become globular, and fibrinous *débris*.
e. Stratum granulosum.
f. Imperfect horn-cells with nuclei.



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of "serotaxis," the vascular dilatation, œdema, and vesiculation. Any irritant, chemical or thermal, acting externally on the skin is capable of stimulating the epithelium and causing proliferation, and at the same time of inducing the epithelial cells to secrete a poisonous ferment-substance which will produce a secondary reaction in the vessels of the papillary body and an exudation to counteract the poison. Consequently Unna's theory has much to recommend it. On the other hand, there are a number of competent workers who regard the changes in the corium as primary; the latter draw special attention to the important bearing of the state of the general health on the efflorescence of eczema.

A few other examples of interepithelial vesicular formation may also be mentioned.

Dysidrosis.—The vesicle in dysidrosis is similar in formation and general structure to that in eczema. It is no longer generally believed that the vesicles in dysidrosis are retention-cysts of the sweat-ducts, but they are now regarded as the result of an inflammatory process. Unna has described a specific bacillus of dysidrosis (*see* Chap. XXXVII.). The vesicles are superficial in situation, and occur immediately below the stratum corneun. The vesicles of *miliaria* have a similar situation to those of dysidrosis.

In *Dermatitis herpetiformis* (Duhring [1]) the vesicle may form in precisely the same manner as in eczema; but it is not infrequently present beneath the epidermis, between the basal layer and the papillary body. Its presence in the latter situation is due to the fact that in this disease there is an acute inflammatory process in the papillary layer, accompanied by exudation of serum and an intense diapedesis of leucocytes, among which eosinophiles may be detected.

Scabies forms an interesting instance of an external irritant causing vesiculation by a process of chemotaxis. The products of the acari act on the vessels, causing an inflammatory exudation and the formation of a vesicle. The latter is generally situated superficially in the epidermis immediately beneath the stratum corneum.

Herpes Zoster.—The formation of the vesicles in herpes zoster merits a more careful study, since associated with these vesicles peculiar degenerated roundish cells occur, which have been named *balloon-cells*, and whose nature has been much disputed. This type of epithelial degeneration, "ballooning,"

[1] *Monats. f. prakt. Derm.*, 1888, VII., p. 158; and *Cutaneous Medicine*, 1898, II., p. 447.

will be best understood by a short description of the formation of a vesicle in herpes zoster (Pl. XIV., Fig. 1).

In the situations where vesicles are about to form there is a rapid intercellular œdema, followed by an actual œdema and a dilatation of the nuclear spaces of the prickle-cells; but there is no marked epithelial proliferation such as occurs in eczema. When the protoplasmic bridges give way, a vesicle is formed. Associated with these epidermal changes there is an acute superficial inflammation in the corium which really precedes the epithelial œdema. This consists of a dilatation of the papillary and sub-papillary blood-vessels, an œdema affecting these regions, so that the fibrous elements are separated, swollen, and do not stain well, and an infiltration of cells such as is generally met with in inflammatory conditions (*see* p. 154).

The vesicles may form anywhere in the prickle-cell layer; but, as in eczema, they are usually found in the region of the transitional layers. Occasionally the vesicle is deep-seated and situated between the epidermis and the papillae. This is the usual situation of the vesicle in supra-orbital herpes zoster, and explains the reason why scarring occurs there when the healing is complete. The vesicles are at first, if not in their whole course, unilocular. By the coalescence of several vesicles, large multilocular vesicles may be produced; but the septa between the loculi generally give way and a single vesicle is formed, in which partial septa, composed of contorted and breaking-down prickle-cells, may persist. At the base or sides of the vesicles, either lying free within them or in the œdematous neighbourhood of them, peculiar swollen round cells may be observed. In appearance these cells slightly suggest sporozoa, and have several times been described as such and put forward as the cause of the disease. To Unna is due the credit of recognising the origin and defining the character of these bodies. He called them *balloon-cells* (Pl. XIV., Fig. 3), and believed them to be the result of a colliquative degeneration of the prickle-cells. They are cells which have lost their prickles, and have become roundish in shape, and whose protoplasm has lost its differentiation into spongioplasm and hyaloplasm, and has become transformed into a cloudy homogeneous mass which attracts acid dyes eagerly, and stains by Weigert's method for staining fibrin (*vide* p. 74). The nuclei of these cells retain their vitality, stain like the nuclei in healthy epidermal cells, and are capable of dividing; they consequently may present a number of nuclei, and may so form epithelial multinuclear or giant-cells. Because these cells

PLATE XIV.

FIG. 1. VESICLE OF HERPES ZOSTER. (× about 150.)

Stained with polychrome methylene blue and orange-tannin.

a. Dilated vessel; infiltration of leucocytes and small connective tissue cells; œdema affecting the collagen and elastin, which stain faintly.
b. Œdematous interpapillary process.
c. Monolocular vesicle.
d. "Balloon-cells."
e. Stratum corneum.
f. Fibrin.

FIG. 2. RETICULAR DEGENERATION OF THE EPITHELIUM IN HERPES ZOSTER.

Stained with polychrome methylene blue and orange-tannin.

a. Reticular degeneration of prickle-cell.
b. Leucocyte.
c. "Balloon-cell."
d. Balloon-cell with divided nucleus.

FIG. 3. BALLOON DEGENERATION IN HERPES ZOSTER.

Stained with polychrome methylene blue and orange-tannin.

a. Balloon-cell.
b. Balloon-cell with divided nucleus.
c. Balloon-cell with the remains of chromatin.
d. Polynuclear leucocyte.
e. Lymphocyte.

FIG. 4. COIL-GLAND. (× about 500.)

Stained with polychrome methylene blue and neutral orcein.

a. Part of the coil nearest the duct, probably beginning of duct showing a cubical epithelium in two layers. The cells have a slightly striated appearance.
b. Distal part of coil consisting of cylindrical epithelium in a single layer.
c. Nuclei of muscle-cells cut across. This muscular layer is only found towards the blind end of the coil, being absent near and in the duct.
d. Transverse section of coil similar to *a*. Shows a connective tissue corpuscle between two cells.
e. *Débris* inside the lumen.
f. Capillary.
g. Elastic fibres.
h. Collagen bundles.
i. Nucleus of collagen bundle.
k. Fat-cell.

FIG. 5. FAT-CELLS. (× about 800.)

Stained with polychrome methylene blue and glycerin-ether. The green colour is intentionally made more vivid in the drawing to bring out the outlines of the cells.

a. Fat-cell showing a "mantle" composed of the protoplasm of the cell, which has been pushed to the periphery by the fat, and a flattened nucleus.
b. The envelope formed by the protoplasm.
c. The fat-globule.
d. Connective tissue corpuscle.
e. Connective tissue corpuscle.
f. Capillary running between the fat-cells, with leucocytes.

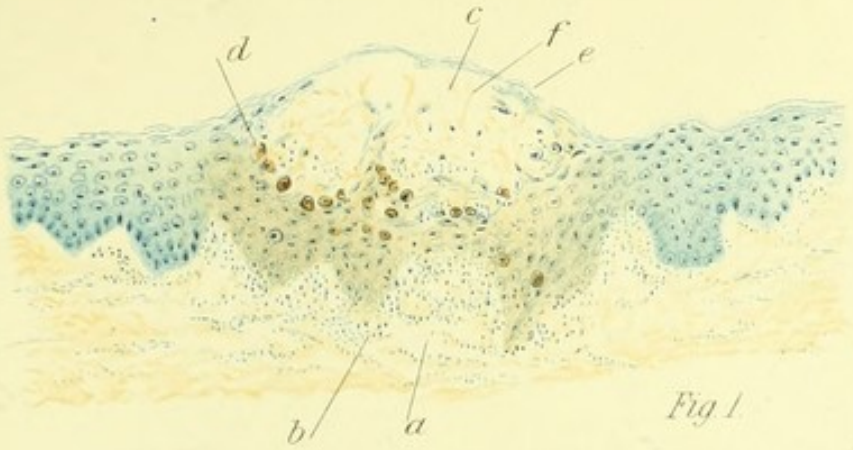
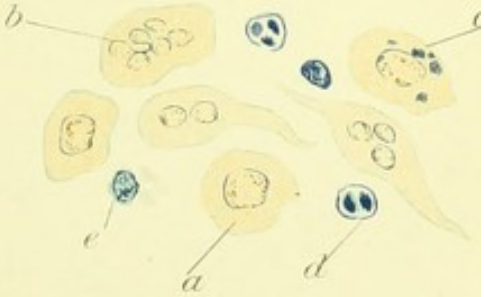


Fig 1.

Fig 2.

Fig 3.



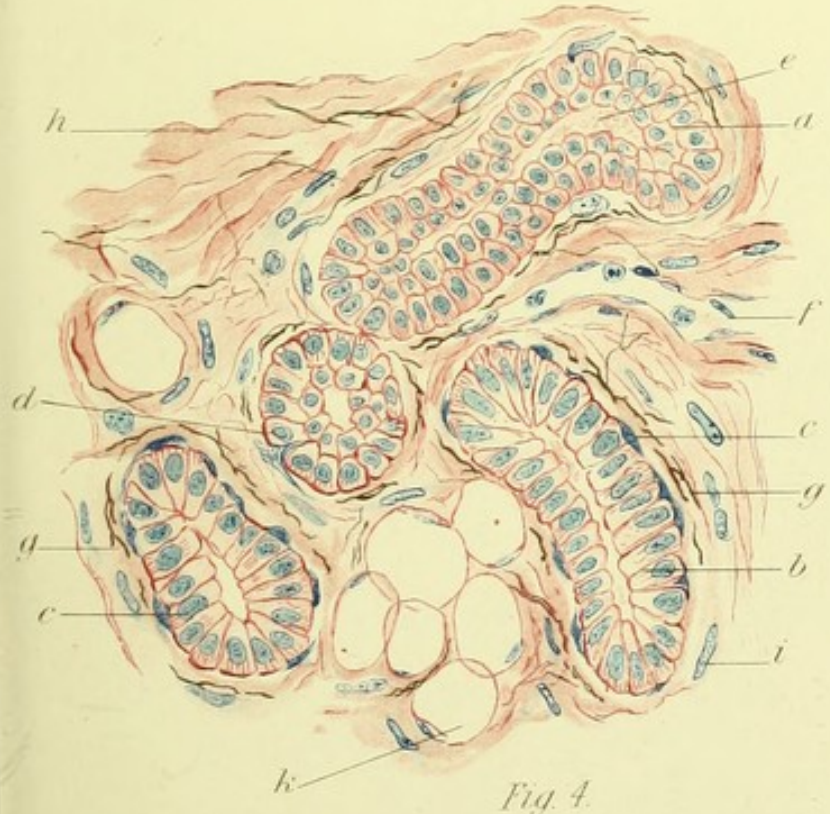


Fig 4.

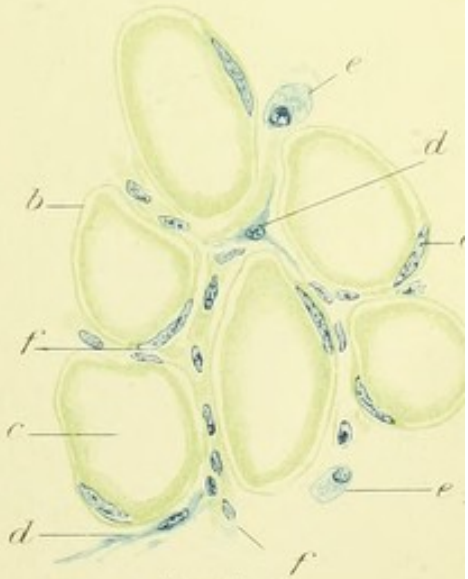


Fig 5.

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have lost their fibrillary skeleton, they are unusually plastic, and they may assume from pressure all manner of shapes. When they are not subjected to pressure they are more or less globular in form ; they gradually become more and more swollen and homogeneous, till they finally break up.

It has been asserted by Kopytowski [1] that this process of "ballooning" is not a new form of degeneration, but simply a "coagulation necrosis" such as Weigert described. This view is based on the fact that fibrin is deposited in the degenerating cells, but is opposed by the fact that the presence of excessive intracellular œdema is not met with in Weigert's coagulation necrosis.

Unna employed the name "ballooning" in opposition to another type of degeneration, in which a spongy vacuolation occurs through the persistence of the intracellular spongioplasm. The latter variety, which he names "reticulation" (Pl. XIV., Fig. 2), will be described in connection with the intracellular or parenchymatous formation of vesicles. Other writers regard reticulation and ballooning not as two distinct types, but as stages in a common process of dissolution. This view was suggested by the occasional presence of the two varieties together, and the detection of transitional forms.

The vesicles of *Erythema multiforme* are also a common situation in which ballooning occurs.

II. **Intracellular or Parenchymatous Vesicular Formation.**—This form of vesicular formation occurs so constantly in association with that which has just been described, that it is only for the sake of simplifying the description that it is placed under a separate heading. Here the actual cell becomes œdematous, and the vesicle is formed by the coalescence of a number of these œdematous cells. The interepithelial œdema is not in such excess as in the former type, so that the protoplasmic fibrils do not give way, and the œdematous cells remain in contact with each other. In this way a multilocular vesicle is formed in the first instance ; but as the œdema increases the walls between contiguous cells give way and the vesicle tends to become unilocular.

In 1880 Leloir [2] designated this process of colliquation of the cell as the *Altération cavitaire.* He noted that in the prickle-cells so affected the endoplasm surrounding the nucleus became clearer and less dense than the exoplasm, and that

[1] *Archiv f. Derm. u. Syph.*, 1900, LIV., p. 17.
[2] *Archiv de Physiol.*, 1880, p. 228.

liquefaction took place at first in the endoplasm, so that a large central cavity or nuclear space was produced. This cavity eventually became limited by a fine fibrillated membrane, which was all that was left of the exoplasm of the cell. Frequently the dilatation of the cells became so great that the intercellular spaces were obliterated, and an appearance was produced which Leloir likened to a vegetable tissue. The nuclei became difficult to stain, and finally broke up, and the limiting barriers between the cells gave way and a vesicle resulted. The "reticulation" of Unna differs from the "altération cavitaire" in being caused by an œdematous vacuolation in the meshes of the spongioplasm, so that the cell is transformed into an open-meshed reticulum, instead of having a distended central space. Both types occur together, and the reticulation is the more common of the two (Pl. XIV., Fig. 2).

These types of vesicular formation occur generally when the prickle-cells are resistant and the prickles old and tough, while the interstitial variety is more likely to be present when the prickle-cells are newly formed and weak.

The parenchymatous formation of vesicles may be easily studied in *varicella* and *variola*. Unna believes that reticulation occurring chiefly at the periphery of the vesicle, and causing bulging there, is the cause of the umbilication of the vesicle in small-pox, and that the umbilication is rarely due to a hair passing through the vesicle, as was formerly taught.

Bullae.

Bullae differ from vesicles principally in size. The distinction between the two is arbitrary, and the exact size at which the vesicle becomes a bulla cannot be stated definitely. For the sake of convenience, blebs, which are smaller, or about the size of a hemp-seed, may be named vesicles, while larger blisters may be called bullae. Bullae are always due to the dilatation of an already existing space. When they occur in the epidermis they result from the excessive dilatation of the interepithelial spaces, and when they form in the papillary body they take their origin in a dilated interfibrillary lymphatic space.

The situation of the bullae in the skin is, to a great extent, determined by the region of the body which is affected. For example, when bullae form in the skin of the palms or the soles, the fluid generally collects beneath the epidermis, and the latter is raised up *in toto*, to form the roof of the bulla.

This fact is dependent on the power of resistance of the prickle-cells, which are particularly tough in these regions. About the face, flexor aspects of the extremities, and abdomen, on the other hand, the prickle-cells are weaker and their intercellular bridges more readily give way; consequently the bullae are commonly found within the epidermis.

The factors at work in the production of bullae are the same as those which cause vesiculation—namely, œdema and the circulation of poisonous substances in the œdematous fluid. Like vesicles, they occur in association with a large number of skin-diseases, but they may be purely local lesions resulting from the action of thermal or chemical irritants.

Examples of Bullous Forms of Dermatitis.—In *Dermatitis herpetiformis*, *Erythema multiforme* (*bullosum*), and *Urticaria bullosa*, the interepithelial and papillary lymphatic spaces may become so dilated with serous fluid that bullae are produced. The contents of these bullae are at first serous, but when pus-cocci gain entrance a positive chemotaxis is set up, leucocytes are attracted, and the contents of the bulla become purulent.

The *pemphigus group* of diseases are essentially bullous. In the various forms of pemphigus the bullae are the result of an acute œdema, plus a diminished resistance of the prickle-cells. In spite of the enormous literature which has collected around the subject of *Pemphigus vulgaris*,[1] there is still much diversity of opinion regarding the formation of the bullae in this disease. It has been customary, especially in this country, to define pemphigus as a bullous eruption arising on apparently healthy skin, in which the lesions occur in crops, and which is associated with various general symptoms. The presence of a previous erythema in the site of the bulla, or of a hyperæmic inflammatory halo around it, has been

[1] Several other conditions are described as pemphigus which have no just claim to be placed under that heading, and it is better to reserve the name for the usual types, *P. vulgaris*, and *P. foliaceus*, which may be regarded provisionally as an advanced stage of *P. vulgaris*, in which there is a marked tendency to exfoliation. The other diseases sometimes classed with pemphigus are *P. vegetans* (Neumann), which Unna regards as a vegetating erythema bullosum; *congenital pemphigus*, or *epidermolysis bullosa*, which has already been referred to; *acute pemphigus*; *syphilitic pemphigus*, which is simply a bullous syphilide; *P. neonatorum*, which may be a congenital syphilide, or is more often of the nature of an acute pemphigus in infants due to infection, and may occur as an epidemic in the practice of some midwife; *P. contagiosus*, which is a variety of impetigo contagiosa, occurring in hot climates (Manson); and *P. circinatus*, which is a form of erythema multiforme.

regarded as precluding the diagnosis of pemphigus and as suggestive of an inflammatory bullous eruption such as occurs in the other diseases mentioned above.

Auspitz asserted that the bullae of pemphigus were due to a diminished resistance of the prickle-cell layer in circumscribed areas, so that the cells were easily separated to form a bulla by the sudden escape of fluid from the vessels of the papillary layer; but that inflammatory phenomena, if they did occur, were purely secondary or accidental. He also assumed that a pre-existing cachectic condition of the epithelium was essential for the formation of the bullae.

In a recent paper on the subject, Kreibich[1] maintains the opposite view—namely, that the bullae do not develop on perfectly healthy-looking skin, but that there is always a pre-existent erythematous inflammation, in which the vessels and lymphatics of the superficial layers of the corium are not only dilated, but with the dilatation there is an inflammatory serous transudation and an infiltration of small cells.

Kromayer,[2] Jarisch,[3] and Gilchrist[4] also describe an œdema between the fibrous bundles of the papillary body and sub-papillary layer.

Another subject in connection with pemphigus on which there are several distinct opinions is that of the *situation of the bullae* in the skin. Certain writers declare that they are as a rule situated in the epidermis. Kaposi stated that they were very superficial, and were entirely within the stratum corneum. Jarisch[5] and several other observers have described cases in which the bullae formed in the region of the transitional layers, the roof of the bullae being constituted by the stratum corneum, and the floor by the prickle-cell layer, the cells of which had become spindle-shaped. Gilchrist,[6] on the other hand, has reported a case in which the bullae occurred immediately beneath the epidermis, with the flattened papillae as their floor.

Such a diversity of opinion, which locates the bullae in every possible situation in the epidermis, points to the conclusion that their situation is not constant, but it is regulated most probably by the considerations already referred to, which determine the location of the vesicles in the skin.

[1] *Archiv f. Derm. u. Syph.*, 1899, L., p. 209.
[2] *Dermat. Zeitschr.*, 1897, IV., p. 457.
[3] *Archiv f. Derm. u. Syph.*, 1898, XLIII., p. 341.
[4] *Cutaneous Medicine* (Duhring), 1898, II., p. 460.
[5] *Archiv f. Derm. u. Syph.*, 1898, XLIII., p. 341.
[6] *Cutaneous Medicine* (Duhring), 1898, II., p. 463.

It has been claimed for the serous exudate which dilates the lymphatics in pemphigus that it possesses peculiar macerating properties, in virtue of which a dissolution of the prickle-cells is caused.

The disease known as *acute pemphigus* differs from that which has just been referred to, in that it seems to be a specific infective disease, due to a specific organism or organisms, following a septic wound.

The Contents of the Bullae of Pemphigus.—The contents of the bullae consist of an albuminous fluid, faintly alkaline in reaction, with the characters of blood-serum, in which fibrin-forming bands, polynuclear leucocytes in all stages of disintegration, epithelial nuclei, and the *débris* of epithelial cells may be detected.

Cultivations from it may be sterile (Gilchrist),[1] may show ordinary skin-cocci, streptococci (Luithlen),[2] or, in the case of "acute pemphigus," diplococci (Demme,[3] Bulloch[4]).

Bullae resulting from Thermal Irritation.—The production of a bulla from a burn may be thus shortly described. According to Unna the contact of a red-hot cautery with the skin causes first of all a softening of the horny layer, and then a charring and destruction of the cells. Steam is rapidly evolved from the moisture contained in the cells, and this forcing its way between the prickle-cells, causes the latter to separate, and so prepares the way for the passage of the serous fluid which subsequently exudes from the underlying vessels. The heat does not only cause a dilatation of the blood-vessels, but also an exudation of serum and an extravasation of leucocytes. The serous fluid passes now into the spaces in the epidermis already weakened and dilated by the action of the steam, and, collecting there, distends them till a bulla is formed. The action of the serous fluid is aided by the presence in it of toxic products from the charred epithelial cells, which have a necrosing action on the cells with which the fluid is in contact, and also cause a positive chemotaxis, attracting more serum and further distending the bulla. The scarring which results when a burn heals is dependent on the depth at which the bulla forms. If the papillae be laid bare, a scar is certain to result; but if a flooring of epidermis be present, no scar will be occasioned.

[1] *Trans. American Derm. Assoc.*, 1899, p. 96.
[2] *Dermat. Zeitschr.*, 1899, VI., p. 487.
[3] *Verhand. d. Congress. f. inn. Med.*, Wiesbad., 1886, p. 336.
[4] *Brit. Journ. of Derm.*, 1896, VIII., p. 210.

Bullae resulting from Chemical Irritants.—Cantharides is a type of chemical irritant the local action of which is quickly followed by the formation of bullae. Chemical irritants act by causing a spasm, followed by an excessive dilatation of the underlying vessels and a profuse exudation of a fluid like blood-plasma. This fluid dilates the interepithelial lymphatics, probably has a necrosing action on the prickle-cells, and causes a superficial vesicle, followed by a bulla, to form in the epidermis. By the breaking down of the cells a ferment is produced, which causes fibrin to be deposited from the fluid in the same way as the fibrin-ferment derived from the white blood-corpuscles causes fibrin to be deposited in the process of coagulation of the blood. This fibrin is usually present in considerable quantity in bullae which result from chemical irritation or from burns.

PUSTULES.

Pustules, if not invariably, at least in the large majority of instances, develop from vesicles. They have an initial vesicular stage, and the purulent element is added subsequently.

The peculiar evidence that the vesicle has become a pustule is the presence in it of pus-cells, which are simply leucocytes which have undergone a fatty degeneration. In a newly formed vesicle leucocytes are absent from the contents, but they soon begin to collect. To constitute a pustule, it is necessary that they should be present in considerable numbers, as in all vesicles a certain number of leucocytes gradually make their appearance. The French school of dermatologists claim that there is a type of impetigo which affects the follicles (Impetigo of Bockhart),[1] in which the lesions are pustular from the first and have no vesicular stage. The existence of this condition of *pustule d'emblée* is now generally admitted. The leucocytes are attracted to the vesicles through the positive chemotaxis, exerted by the products of micro-organisms, or by the toxins which result from the breaking down of the epithelial cells. Several varieties or degrees of chemotaxis have been described which are dependent on different degrees of virulence of the poison which occasions it. For example, a chemotaxis in which serous fluid alone is attracted has been described ; a second in which serofibrinous fluid is attracted ; and a third in which serum and leucocytes are attracted. It is on this account that vesicles in some instances persist as such, while in others they almost immediately

[1] *Monats f. prakt. Derm.*, 1887, VI., p. 450.

become pustules. The presence of virulent staphylococci in the stratum corneum about the mouth of the follicles is said to cause, by the toxins so produced, a sudden reaction in the blood-vessels, followed by an attraction of serum, then of leucocytes and serum, into the epidermis. The external application of several chemical irritants, such as croton oil, is followed by much the same chain of events. It will be unnecessary to describe specially the pustular diseases, as pustules may occur in association with all the vesicular and bullous forms of dermatitis.

Ulceration.

When the destruction of the epidermis is complete, an ulcer results. The floor of the ulcer is formed by the exposed papillary layer of the corium; but even the papillary body and the rest of the corium may be affected in the destructive process, and the ulcer may reach as far down as the subcutaneous fasciae. The edge of the ulcer is as a rule raised and infiltrated from a proliferation of the epidermis, and an actual infiltration of inflammatory cells and occasionally of plasma-cells. The blood-vessels of the floor and edges are dilated, and more or less œdema is present. Ulceration is always preceded by a condition of diminished resistance of the affected region. The indolent leg-ulcer which occurs in association with varicose veins is the result of the breaking down of an epithelium, which is weakened and more or less sodden by œdema. The ulcers which occur in connection with tuberculosis and syphilis develop in skin weakened by the virus of these diseases.

Ulceration is, in many instances, simply a further stage of pustulation. Pustulation occurs in the first instance, but the irritant is so powerful that necrosis follows, and the epidermis and superficial parts of the corium are involved in the necrotic process. In this way vesiculation, pustulation, and ulceration may be regarded as stages in a single process. An excellent instance of this chain of events may be found in the ulcers produced by an over-exposure to the Röntgen rays, the exposure to a "wrong" tube, or an exposure in individuals who have a type of skin which has a weak power of resistance to them. In such cases the exposure is followed by an inflammatory reaction which is associated with vesiculation, the vesicles become more or less purulent, and after the lapse of a week or longer they are replaced by an ulcer which is singularly difficult to heal.

On the other hand, ulceration may occur with little or no preceding suppuration, as the result of a nerve-lesion interfering with the trophic influences which determine the nutrition of the area supplied. The familiar "perforating ulcer" of the soles of the feet which occurs in association with peripheral neuritis, locomotor ataxia, and other spinal and cerebral neuroses is an example of this. The ulcer is the result of a simple process of necrosis. The cells in the area supplied by the nerve die from inanition and gradually disintegrate.

CHAPTER XIV.

PATHOLOGICAL CHANGES INVOLVING THE EPIDERMIS—Continued.

PSEUDO-HYPERTROPHIES.

Pseudo-Hypertrophy.—By a *pseudo-hypertrophy* of the epidermis is meant an increase in its bulk, not, as in hypertrophy, by an addition to the number or an increase in the size of its normal elements, but by the addition of elements which have reverted to a simpler type. Under this heading may be included the carcinomata of the skin, rodent ulcer, and Paget's disease. In this reverted condition the prickle-cells cease to differentiate into horn-cells, but adopt the simpler function of the mother-cells of the basal layer, and are only capable of proliferating. The cellular proliferation is unlimited, and all the examples of this provisional group are more or less malignant.

A short description of the histological pictures in these examples of this pathological process will serve better to illustrate it than a discussion of the subject in the abstract.

Carcinoma of the Skin.—In this country it is customary to describe the malignant proliferations of the epidermis as "epitheliomata." On the Continent this term is employed in a less restricted sense, and includes also the benign epithelial proliferations, such as condyloma acuminatum and molluscum contagiosum.

A carcinoma of the skin is a neoplasm formed of actively proliferating epithelial cells, which are not fully differentiated, and which rapidly multiply and invade the lymphatic spaces between the fibrous bundles of the corium.

Carcinomata in the skin are generally secondary, and result either from a previous benign growth, such as a wart or a pigmented nævus, or from an extension on to the skin of a carcinoma affecting the mucous membranes.

It will be advisable here to make a slight digression in order to discuss the questions *of what constitutes a malignant epithelial proliferation and the characteristics or criteria of*

malignancy. According to Adami's definition, malignancy in a tissue is "the property of local invasion of surrounding tissues with that of the formation of new growths in distant organs." This definition, amplified with regard to the epidermis, might be put as follows: A malignant proliferation of the epidermis is one which is capable of unlimited growth, has the power of invading the surrounding tissues, cannot be checked except by complete extirpation, unless in exceptional cases, and is capable of forming growths of a similar nature in organs at a distance (metastasis).

The cells composing the proliferation belong to a simpler type than the prickle-cells; so simple or undifferentiated do they become that it is, as a rule, impossible to tell whether they are developed from the epidermis (epiblastic) or from the cellular elements of the corium (mesoblastic), unless a definite connection can be traced between the outlying cellular foci and the epidermis. The fibrillated structure of the prickle-cells is to a great extent, or completely, lost, and the cells become gradually round or oval in shape and unconnected with each other. In the more malignant forms the basal layer becomes broken up or blurred by the proliferation and down-growth of the cells above it, and ceases to form a regular limiting layer, as it does in the simple hypertrophies, such as condyloma acuminatum. The capacity of the cells to proliferate rapidly is made evident by the large numbers of mitotic figures which may be detected in their nuclei.

The degree of malignancy varies greatly in the different types of carcinomata of the skin. As a general rule, it may be stated that the greater the number of mitotic figures the smaller and rounder the cells, and the more the basal layer has disappeared the greater is the malignancy.

It is practically impossible to draw a hard and fast distinction between malignant and benign epithelial growths. Up to a certain stage they are all benign, and neoplasms which are usually benign in their whole course may assume malignant characters. For example, warts and pigmented nævi, which are benign growths, may, under the influence of irritation, become malignant.

Classification of the Carcinomata of the Skin.—Both the clinical and histological features vary so greatly in different cases of carcinoma of the skin that it is almost necessary to classify them in some form or other.

The general arrangement of the cells of the carcinoma

forms a practical basis on which to classify them. This arrangement is determined to a great extent by the character of the skin in the region affected and the type of epithelium from which it originated.

On this basis the carcinomata of the skin may be divided into three classes—namely, (1) tubular, cylindrical, or alveolar carcinomata; (2) pavement carcinomata or epitheliomata; (3) vegetating or fungating epitheliomata. It must not be forgotten, however, that this classification is an arbitrary one, and only useful for purposes of description.

1. *Tubular Carcinomata.*—The tubular or cylindrical carcinomata are the most common type met with in the skin. In them the malignant epidermis grows down in cylindrical processes, which, as they increase in size, coalesce to form a diffuse infiltration of cells, or pass along the lymphatic spaces of the corium to form a network. Occasionally the processes are clubbed at the ends, and at other times they form acini. The cylinders and acini are generally limited at first by a regular layer of cells like those of the basal layer of the epidermis; but, later, this limiting layer becomes broken down. The cells have lost their prickles, and are oval or roundish in shape; and as they have no tendency to become cornified, they are peculiarly pliable and apt to assume distorted shapes. They are not rich in protoplasm, their nuclei are small and stain deeply, and numerous mitotic figures may be detected.

Owing to the presence of a more or less complete limiting layer of cells, this type of carcinoma is not markedly malignant.

2. *Pavement Epitheliomata.*—Pavement epitheliomata are superficially spreading carcinomata of a much more malignant type than the cylindrical variety. They rarely possess a limiting layer of regular cells, and mitotic figures are present in large numbers in their nuclei. The cells have a considerable body of protoplasm, and present vesicular nuclei which stain faintly. Here and there the cells are capable of evolving into horn-cells, and it is in this type of carcinoma that the so-called "horny pearl" or "cell-nest" is found. *Cell-nests* are simply concentric rings of cornified cells surrounding a core consisting of a single horn-cell, a deposit of *débris*, or one or more cells in a state of hyalin degeneration, and enclosed by layers of uncornified cells, beyond which there is occasionally a regular limiting basal layer like that of the epidermis. The pavement epitheliomata appear

to develop from the more differentiated upper cells of the Malpighian layer, and consequently they have a greater tendency to cornify than the cylindrical variety, in which the seat of origin seems to be the basal layer (Pl. XV.).

3. *Vegetating or Fungating Carcinomata.*—In these the epithelial proliferation is so rapid that the surface becomes papillated, and broken up, and may form irregular cauliflower-like growths. These cancers occur at the junction of the skin and mucous membranes.

In association with the epithelial proliferation in all these cancers, changes due to irritation occur in the corium, such as dilatation of the blood-vessels, extravasation of leucocytes, proliferation of the connective-tissue cells, and an infiltration of plasma-cells. Occasionally organisation occurs, and the so-called "scirrhous" element is added.

Darier, in *La Pratique Dermatologique*, Vol. II., etc., employs the following classification, with an anatomo-pathological basis:

1. *Épithéliome papillaire, végétant superficiel ou verruqueux.*—The papillary or verrucose epitheliomata. They are not common.

2. *Cancroïde vulgaire, Épithéliome pavimenteux lobulé corné.*—The most common and malignant type of epithelioma. It frequently begins in the mucous membranes, as in the lips, but it may originate in cicatrices or be engrafted on lupus.

3. *Épithéliome plan cicatriciel.*—This forms a variety of the pavement epitheliomata, and corresponds to Besnier's *épithéliome perlé.* It is frequently mistaken for rodent ulcer.

4. *Ulcus rodens.*

5. *Épithéliome adénoïde.*—These cancers are encapsuled and lobulated like a gland, and are generally very benign.

6. *Carcinomes de la Peau.*—They are malignant epithelial tumours of the alveolar type. There are two forms of them: (*a*) Carcinomata, which develop from an epithelioma—the cells of which break through the limiting barrier and disseminate into the lymphatics; (*b*) Carcinomata secondary to deep-seated tumours.

7. *Épithéliomatose multiple sénile.*—This condition is sometimes known as *acné sébacée concrète*, or again as *kératomes séniles.* It has no connection, however, either with the sebaceous glands or with acne. It usually begins in multiple senile warts. These ulcerate, and the surface becomes covered with a yellow crust.

PLATE XV.

Pseudo-Hypertrophy of the Epidermis. Pavement Epithelioma. (× about 100.)

a. Basal layer has disappeared, and the cancerous cells are invading the lymphatic spaces of the corium.
b. Cell-rests; concentric layers of horn-cells surrounding a central core.
c. Disappearing sebaceous gland.
d. Cellular infiltration in the corium.

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The Epidermal Structures from which Carcinomata may Develop.—A malignant proliferation of the epidermis may take its origin not only from the cells of the basal and Malpighian layers of the epidermis, but also from the cells of the outer root-sheath of the hair-follicle and the cells of the sweat-glands. This fact does not form a suitable basis for the classification of the carcinomata, since from the appearance of the diseased cells it is practically impossible to tell from which part of the epidermis the cancer has developed. The sebaceous glands generally disappear in the malignant focus, and it is difficult to be certain that the cells of these glands have contributed to the formation of the neoplasms. It is unlikely that the fully formed sebaceous cells should do so, as they are in a state of degeneration ; but there is no reason why the mother-cells of the gland should not proliferate.

The Degenerations which occur in the Carcinomata of the Skin.—

1. *Horny Pearls*, such as have already been described, may be placed under the heading of a degeneration, but it is more correct to regard them as a process of repair.

2. *Giant-Cell Degeneration.*—Occasionally the nuclei divide without the protoplasm of the cell dividing at the same rate, and so epithelial giant-cells form, which may be regarded as degenerate cells.

3. *Calcification.*—A calcification of the cells has in rare instances been noted in carcinoma in association with the formation of sebaceous cysts.

4. *Hyalin Degeneration.*—A hyalin degeneration of the epithelial cells frequently occurs in carcinomata of the skin. "Colloid degeneration" is another name for this type of degeneration (*see* p. 172).

5. *Mucoid Degeneration.*—A mucoid degeneration also occurs in many carcinomata. In it the protoplasm of the cancer-cells becomes clear and more liquid. The nuclei become pale, disappear, and the whole cell liquefies. In this way cavities form, in which lie unaffected cells or cells undergoing hyalin degeneration. Curious appearances are thus occasioned. Darier considers this to be the cause of the formation of the peculiar structures which are present in Paget's disease.

The Diseased States of the Skin which are apt to develop into Carcinomata.—

1. *Warts, Corns, and Cutaneous Horns* in elderly people must always be regarded as possible sources of carcinoma,

since, if they be irritated, they readily assume a tendency to malignant proliferation.

2. *Lupus Vulgaris* is not infrequently associated with malignant epithelial growths. Several cases have also been reported in which carcinomata have developed in connection with lupus erythematosus.

3. *Nævi*, using the term in the sense of circumscribed congenital anomalies of the epidermis (*see* p. 125), are a very frequent starting-point for carcinomata. The unpigmented nævi rarely, but the pigmented more frequently, become malignant, and the so-called nævo-carcinoma is one of the most rapidly malignant types of cancer. The deeper the pigmentation of the mole, the greater is the likelihood of such an occurrence.

4. *Paget's Disease.*—This disease, first described by Sir James Paget in 1874, is a peculiar type of persistent dermatitis which clinically in its early stages somewhat resembles chronic eczema, and in which the affected skin forms a raised indurated patch with a definite margin and a raw, vivid red, oozing, or crusted surface. In the later stages of the disease its malignant character becomes evident, and a carcinoma develops. It usually attacks the breast in middle-aged women; but it may develop on the male breast and in other situations, such as the scrotum, vulva, and umbilicus. Histologically, though Paget's disease is a somewhat rare affection, it is the subject of no inconsiderable literature; but in spite of this there are several points in its pathology which still require elucidation. Special interest has recently been aroused in its pathology from the fact that peculiar structures resembling coccidia or sporozoa have been described in the diseased epidermis. Several observers have asserted that these structures are parasites, and that they are the cause of this form of carcinoma. This view has met with strong opposition, and it is now almost universally admitted that, instead of being organisms, they are the result of peculiar epithelial changes of a degenerative nature.

Sections of an early stage of this disease show a proliferation and down-growth of the epithelium, associated with a marked œdema of the prickle-cells, by which they tend to become swollen and their nuclear spaces to become greatly distended Many of these cells break down. The proliferation and œdema attack also the cells of the milk-glands and ducts about the nipple. Within the œdematous cells there are occasionally peculiar, darkly stained, somewhat

granular structures with a double-contoured limiting membrane. These are the bodies which were believed to be psorosperms. They vary greatly in appearance; some of them are round and closely simulate psorosperms, while others are irregular or broken up. They stain readily with safranin and hæmatoxylin, and Unna believes them to be the result of a partial cornification of œdematous cells. They have also been described as the result of hyalin and mucoid degenerations. The vessels in the papillary and sub-papillary layers are here and there dilated, and in these situations there is a dense cellular infiltration consisting partly of leucocytes, but, to a greater extent, of small connective-tissue cells and plasma-cells, showing that the infiltration is more than one of simple inflammation, and is really in the nature of a granulomatous change. As the disease advances the epidermis gradually breaks down, and ulceration of the surface takes place. Organisation occurs in the granulomatous cells surrounding the lactiferous ducts, causing a retraction of the nipple; a malignant proliferation of the gland-cells, and occasionally of those of the Malpighian layer of the epidermis, supervenes, and an alveolar cancer results.

5. *Xeroderma Pigmentosum.*—Under this title Kaposi first described a peculiar pigmented and warty precancerous condition of the skin which eventually gave rise to a tubular carcinoma. In this disease it is the exposed regions, such as the face, ears, and neck, which are affected. It is characterised by the appearance of freckles, punctiform telangiectases, and whitish depressed atrophic scars or pits. According to Kaposi, the freckle-like lesions appear first. These are surmounted in about a year by telangiectases, which are again replaced by pitting and atrophy. It begins in early life, and occurs in families, generally affecting the female sex. When the patient reaches adult life warty growths appear, and these take on a malignant character. The pathological changes are first seen in the corium, and are of the nature of proliferation of the vessels and increased pigmentation. The epithelium becomes involved late in the disease, and finally becomes carcinomatous. The type of cancer which results is the tubular variety. The cells are spindle-shaped, and the limiting basal layer is preserved for a long time, hence there is no very marked malignant tendency (Kreibich).

Unna has described a somewhat allied condition in sailors and those exposed to severe weathers, to which he has given the name of "*sailor's skin*," and in which a diffuse persistent

redness appears about the ears and spreads over the neighbouring skin. Gradually the skin becomes pigmented in a mottled manner, and its surface becomes verrucose. Finally a tubular carcinoma supervenes.

Rodent Ulcer (*Jacob.*) — The familiar malignant ulcer which occurs so frequently about the junction of the nose and cheek is a special type of carcinoma of the skin. Before the ulcer forms, a nodule appears, and in this condition the histological peculiarities of the disease can be more easily studied than when the lesion has broken down in the centre. The nodule is the result of a malignant proliferation of the epidermis of the cylindrical type, which spreads down irregularly into the corium, and may even penetrate as far as the hypoderm. At one time the proliferating epithelium may take the form of acini, at another it may form alveoli, and not infrequently a network arrangement occurs. The processes and acini are limited by a regular basal layer of cubical or cylindrical cells. Horny pearls are rarely present. Cystic degeneration is commonly found, with the production of cysts in the tumour-mass containing broken-down cellular *débris* and nuclei. Rodent ulcer has its origin generally in the surface epithelium (Pl. XVI.), but it may arise from the prickle-cell layer of a hair-follicle. Mitotic figures are not very numerous in the nuclei of the cells, and the growth is comparatively slow. In the nodular stage the underlying fibrous tissue is condensed, and may become scirrhous ; and it forms a barrier to the spread of the disease, which accounts for the nodule being superficial and peculiarly hard. As the growth increases, the irritation produced by it causes a reaction in the corium of an inflammatory nature, which results in the desquamation of much of the epithelium on the surface, and eventually in ulceration. A cellular infiltration occurs in the corium, consisting of leucocytes, plasma-cells, and a few mast-cells in the neighbourhood of the dilated blood-vessels. At the edges of the ulcer the fibrous thickening persists, and the epithelium commences to proliferate irregularly, and so the rolled nodular "cartilaginous" border, which is one of the most important clinical features of the disease, is produced.

The Causation of Carcinoma Cutis or Malignant Proliferation of the Epidermis.—At the present time there are several rival hypotheses regarding the etiology of carcinomata, but none of them has as yet been definitely proved. Of these hypotheses the following may be mentioned :

PLATE XVI.

Pseudo-Hypertrophy of the Epidermis. Rodent Ulcer. (× about 100.)

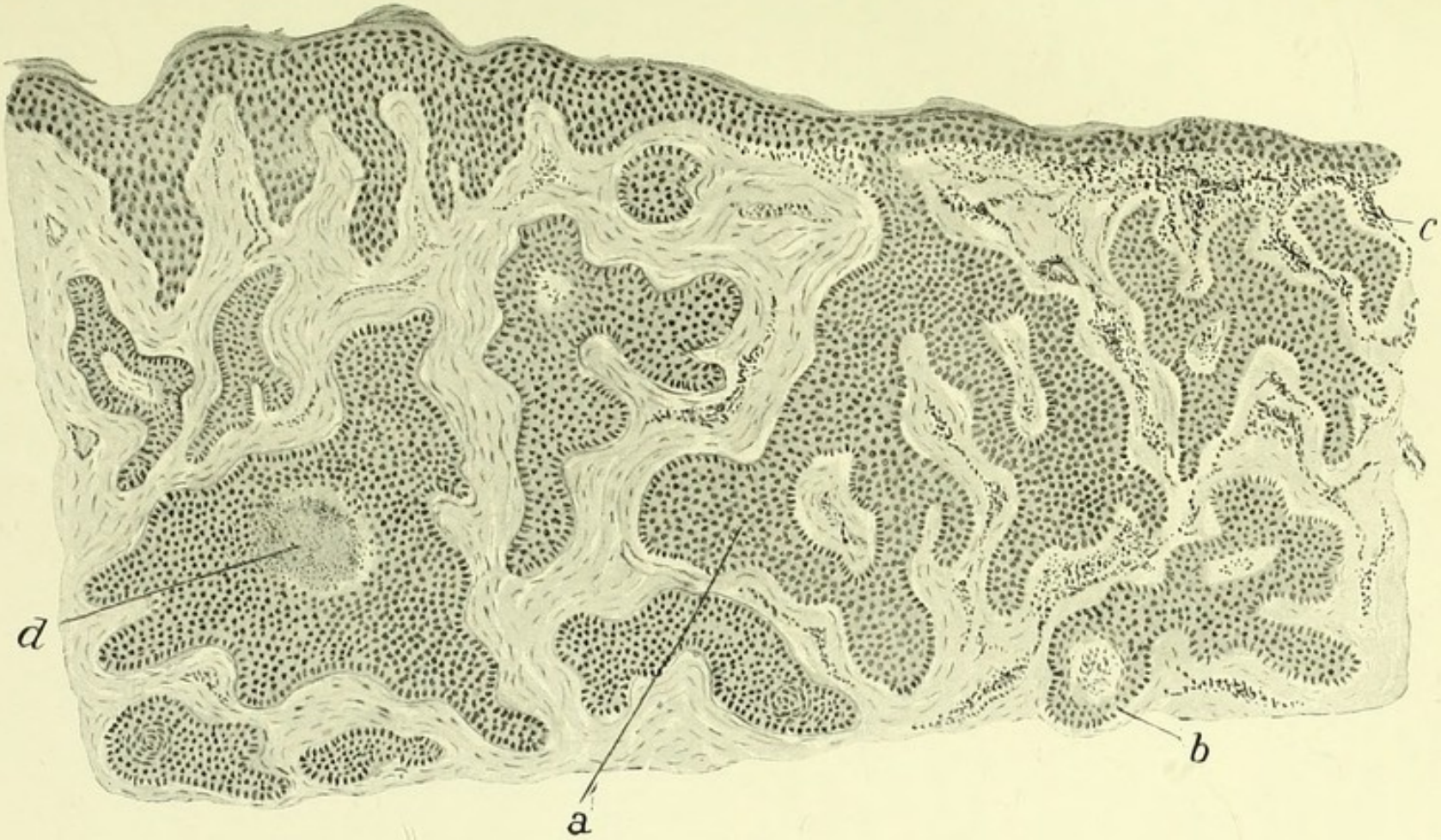
Section of a rodent ulcer in the nodular stage before the centre has broken down completely to form an ulcer. The left side shows a section of the raised "cartilaginous" border, while the right side is part of a depressed central portion which is beginning to break down.

a. Malignant proliferation of the epidermis of the tubular type; cylindrical processes and acini present.

b. Basal limiting layer persisting almost universally.

c. Cyst containing broken-down cellular *débris*.

d. Cellular infiltration in the corium, consisting of leucocytes, plasma-cells, and mast-cells; the infiltration is specially abundant towards the right side.



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1. Malignant proliferation of the epidermis takes place from embryonic inclusions or "cell-rests." These are pieces of the germinal layer of the epidermis which are supposed to have become cut off in the embryo and included in the tissue, and are believed to be capable of active proliferation and the formation of new growths (Durante,[1] Cohnheim,[2] and others).

2. It is due to a loss of the proper relation between the epithelium and the corium, with a proliferation of the former in excess of the latter (Thiersch).

3. It is the result of a congenital tendency of the cells.

4. It is due to a disturbance of the proper relation of growth and functional activity.

5. It is due to a parasite, either a protozoön (Ruffer,[3] Soudakewitch,[4] Plimmer[5]) or a fungus (Russell,[6] Sanfelice[7]). (*See* description of the "Cancer-parasite" on page 356.

The chief problem under discussion, on which much research-work is at present being carried out, is whether carcinoma is parasitic in origin or not. A number of observers have described, in and between the epithelial cells in carcinoma, peculiar structures which they have regarded as parasites, which in one or two instances they have cultivated outside the body, and by inoculating them in lower animals have succeeded in producing tumours. Other workers as strongly assert that these "bodies" are degenerative products of the cancer-cells, of the type of mucoid or hyalin degeneration. I have frequently found structures in the cells of epitheliomatous growths which seemed to resemble the cancer-bodies which have been described, but they invariably stained with the reactions for hyalin degeneration. Only in one instance did I find a definite yeast-fungus, and that was in a case of doubtful multiple carcinoma,[8] from a piece of tissue given to me to examine microscopically by Mr. George Pernet. In this tissue there were several broken-down cavities in which a budding fungus was present. The tissue was preserved in spirit, which was very muddy when I received it. I regarded the yeast as a secondary

[1] *Archiv. di Palasciano*, 1871.
[2] *Vorlesungen über allg. Path.*, Berlin, 1877, I., p. 634.
[3] *Journ. of Path. and Bact.*, 1893, p. 198.
[4] *Ann. de l'Instit. Pasteur*, 1892, VI., p. 145.
[5] *The Practitioner*, 1899, LXII., p. 453.
[6] *Brit. Med. Journ.*, December, 1890, II., p. 1360.
[7] *Zeitschr. f. Hygiene*, 1898, XXIX., p. 463.
[8] *Brit. Journ. of Derm.*, 1900, XII., p. 350, and 1901, XIII., p. 302.

contamination, but it strongly suggested that the fungus had been growing in the tissue during life (Pl. XL., Fig. 1).

There are several considerations which should not be lost sight of in connection with this vexed problem:

1. Granted that cancer is due to a parasite, and that the latter is either a protozoön of the nature of a coccidium, or a blastomyces, the organism must be an extraordinarily virulent one, considering the small number of them found and the difficulty experienced in finding them.

2. There is a stage in the development of most carcinomata, before the signs of malignancy become very marked, when, histologically, the basal layer still remains intact, and when the new growth resembles more a wart or condyloma than a cancer. Are the "parasites" the cause of the early benign stage as well as the later more malignant development? If so, we must also seek for a parasitic origin for condylomata.

3. Certain benign tumours may take on malignant characteristics—for example, warts and nævi. It is difficult to explain the reversion of the cells to the rapidly proliferating undifferentiated type which occurs in malignant epithelial growths by the action of a yeast or a coccidium. Such a reversion is more easily explained by injury or irritation; and carcinomata have been known for years to occur locally from irritation—*e.g.*, the lip-epithelioma from smoking a clay pipe, and "chimney-sweep's cancer." But in a large number of cases an unknown predisposing factor must be conceded.

CHAPTER XV.

CONGENITAL ANOMALIES OF THE EPIDERMIS.

A. Chiefly involving the Stratum Corneum.

I. Diffuse Hyperkeratosis.—The most pronounced example of a diffuse congenital hyperkeratosis is the condition which is popularly known as "*harlequin fœtus.*" Unna makes a definite distinction between this disease and ichthyosis, but many other observers regard it as being only a severe type of the latter affection. In it there is a universal thickening of the stratum corneum, which gives the child the appearance of being encased in an armour made up, in severe cases, of horny plates about a third of a centimetre in thickness, and separated by furrows into variously shaped plaques. At first the horny armour is unbroken, but shortly before birth the growth and movement of the body cause the casing to crack and the furrows to form—the cracks in the limbs being chiefly arranged transversely, as the growth is greatest in the long axis. Sections of this rare affection show that the pilo-sebaceous follicles are poorly developed, that the granular layer is not increased, and that there is a great thickening of the stratum corneum.

In the ordinary types of *ichthyosis* the surface of the skin presents a wrinkled appearance resembling crushed tissue-paper, as if the stratum corneum were growing in excess of the deeper layers and were too large for the rest of the skin. This wrinkling ends in the formation of scales of various sizes: these in mild cases resemble fish-scales; but where the hyperkeratosis is more pronounced they may simulate crocodiles' scales, or take the form of rough spiny protuberances. Wherever hyperkeratosis is present, the horny tissue tends to assume a dark colour, and it is on this account that the scales in ichthyosis have a dirty greyish appearance.

Sections of ichthyosis show that the hyperkeratosis extends

for some distance into the hair-follicles, but not sufficiently deeply to cause the formation of follicular papules. When the sections are digested, it is found that there is only slight, if any, thickening of the horny network, and little difficulty is experienced in macerating the cells (*see* p. 76).

Ichthyosis, though generally considered to be a congenital affection, is not so in the true sense of the word, as it does not appear at birth, and sometimes not till between the first and second years, while "harlequin foetus" is invariably detected at birth.

II. Congenital Regional Hyperkeratosis.—A congenital thickening of the stratum corneum of the palms of the hands and soles of the feet has frequently been described. A case of this nature was investigated by Thost,[1] who noted in association with proliferative changes in the epidermis a decided hypertrophy of the sweat-coils. He named the affection "Ichthyosis congenitalis palmaris et plantaris." Unna[2] has applied the name "Keratoma palmare et plantare hereditarium" to the same affection. Ichthyosis hystrix also belongs to this category; to an advanced instance of this affection Tommasoli[3] has given the graphic title of "Akrokeratoma hystriciforme hereditarium." These titles are as unnecessary as they are confusing. In them all we have simply a verrucose nævus in which the interpapillary processes are greatly elongated, the blood-vessels more or less dilated, and the stratum corneum transformed into conical or irregular masses overlying the elongated papillae.

B. Congenital Affections chiefly involving the Prickle-Cell Layer.

There is no universal congenital anomaly of the prickle-cell layer of the epidermis comparable to the universal hyperkeratosis of harlequin fœtus.

There are, however, a number of regional and circumscribed congenital anomalies of this layer which merit a special reference. The majority of these come under the heading of nævi.

Regional and Circumscribed Congenital Anomalies.—In this country we are in the habit of reserving the name "nævus" for those congenital growths in the skin which consist of

[1] *Diss. Heidelberg*, 1880.
[2] *Vierteljahrschr. f. Derm. u. Syph.*, 1883, p. 289.
[3] *Inter. Atlas of Rare Skin Diseases*, No. 9, XXVIII.

dilated, freely communicating blood-vessels, held together by connective tissue. By nævi we generally mean vascular nævi, such as the venous nævi, capillary nævi, and lymphatic nævi. But, except in this country, this restriction of the term nævus has been abandoned, and the name is generally employed in a much wider sense, in which it practically includes all the congenital circumscribed cutaneous anomalies. As this wider meaning of the term is becoming more and more universal, it is advisable for the student to become familiar with it.

For practical purposes nævi may be divided into :

1. Vascular nævi (cavernous angiomata, etc.): *see* page 262.
2. Soft nævi (moles).
3. Hard or mixed nævi.
4. Linear nævi.
5. Giant nævi.
6. Dermoid cysts.

The first and last of these do not require a description here, but the remaining four are of such importance to the dermatologist that it will be necessary to refer to them in some detail.

1. *Soft Nævi.*—Clinically they take the form of soft flat warts or of brownish yellow pigmented moles, and are sometimes covered with hairs. A large number of the so-called soft flat warts are nævi. They may be only slightly raised (*nævus spilus*), or they may become button-shaped, and may even present an irregular surface like a raspberry (*nævus molluscifórmis*). Such nævi possess a singularly constant and characteristic histology. The main mass of the growth consists of a limited cell-infiltration in the corium, composed of almost parallel rows of roundish or cubical cells, which pass downwards in an oblique direction from the neighbourhood of the basal layer of the epidermis. Between the rows of cells the fibrous elements of the corium, and chiefly the elastic fibres, are attenuated. The cellular mass acts only as an inert body, and the movements of the skin and the contractions of the healthy connective tissue around and beneath it tend gradually to make the nævus project. This process is what Unna graphically describes as the "birth of a nævus." The cells are oval or cubical in shape, and have large oval vesicular nuclei. From their appearance alone it would be impossible to decide their origin. v. Recklinghausen

considered them to be derived from the endothelium of the lymphatics. Unna argued that they originated in the epithelium, since he was able to demonstrate an actual connection of these columns with the epidermis in the pigmented nævi of children. He pointed out, in opposition to v. Recklinghausen's view, that they were arranged vertically instead of horizontally like the lymphatics, and that no actual lumen could be detected between the rows of cells. He believed that groups of cells became cut off from the epidermis in embryonic life, and formed "cell-rests" in the Cohnheim sense. These cells lost their epidermal characteristics, became simpler in type, and proliferated to form the rows or columns. This theory, if it be correct, is of great importance, as it explains the connection of nævi with carcinomata, and the reason why nævi so readily assume malignant characters (Pl. XVII.).

The so-called "*Fibroma molluscum*" is sometimes considered to be a pedunculated wrinkled form of this soft nævus, and in three out of thirteen cases of it Unna was able to detect the peculiar columns of cells. According to this view, it may be regarded as a soft nævus which has become œdematous, and in which the epithelial cell-rows gradually liquefy and disappear, leaving a rarefied œdematous stroma.

2. *Hard and Mixed Nævi.*—These nævi are sometimes known as *nævi verrucosi*—a name which explains their character. They have usually the structure of ordinary warts, but are congenital, and frequently appear on the hands.

3. *Linear Nævi.*—These form a varied and complex group of curious congenital anomalies whose real nature is far from being understood. As a rule they take the form of lines or bands which frequently occur on the lower extremities (*nævus unius lateris*). They may resemble patches of psoriasis or lichen planus, or may present horny spines, projections, and excrescences (*ichthyosis hystrix*); they may be partially or wholly pigmented.

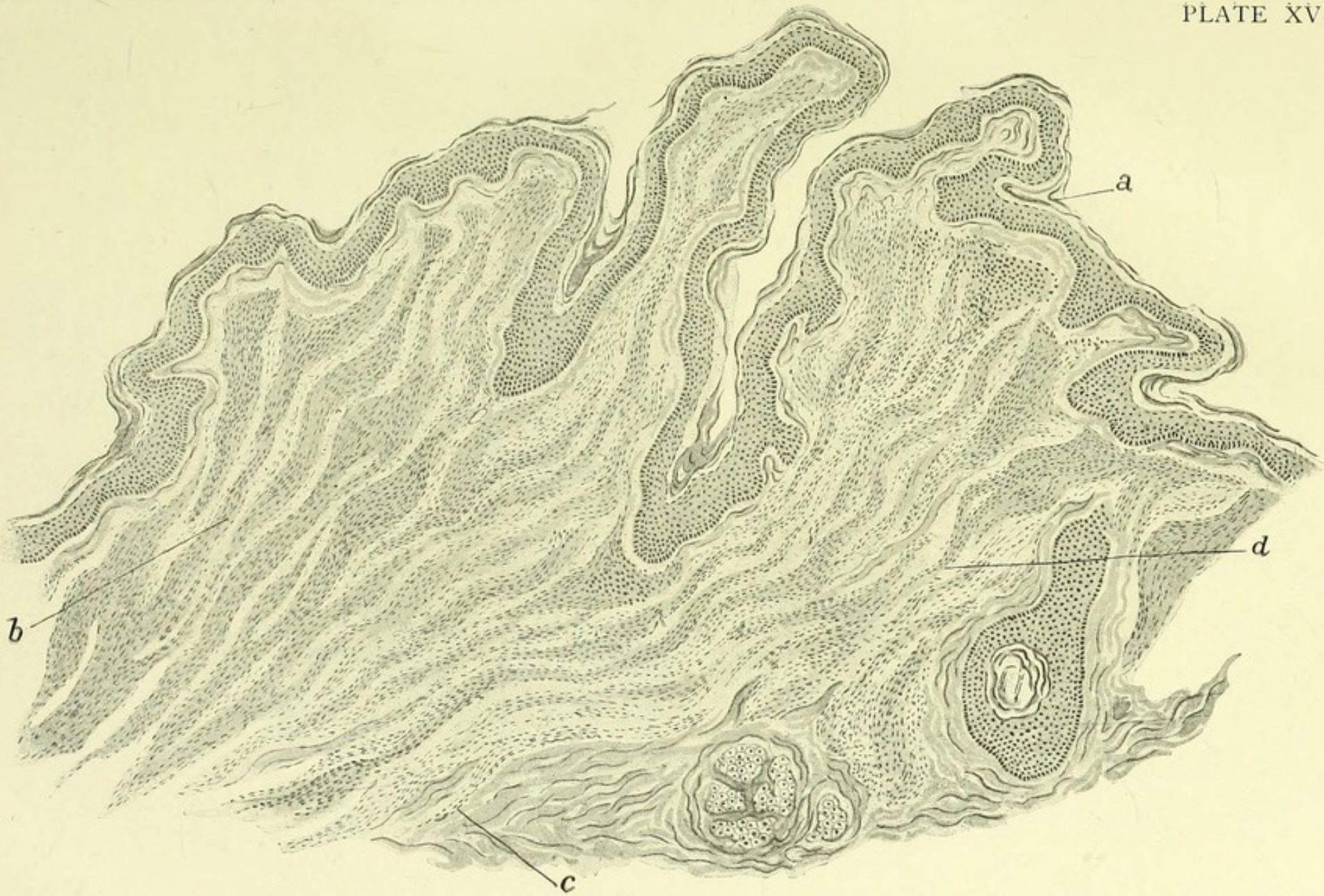
4. *Giant Nævi* are pigmented, frequently hairy patches occupying large areas of the skin—for example, the whole of a limb. Their clinical appearances are multiform, but their histology is that of the soft nævi, with, as a rule, verrucose changes in the epidermis.

Histologically, as well as clinically, these nævi vary not only in different cases, but not infrequently in different positions in the same case, and the characteristic structure of

PLATE XVII.

Congenital Anomaly of the Epidermis.
Slightly Verrucose Nævus (× about 80.)

a. Stratum corneum slightly thickened, Malpighian layer showing slight tendency to proliferate.
b. Rows of cells spreading down obliquely into the corium.
c. Well-defined lower limit of the nævus.
d. Fibrous elements attenuated between the cell-columns.



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the soft nævus occurs in comparatively few of the lesions. The fact of the occasional distribution of nævi in lines has given rise to much discussion. A number of explanations of this peculiarity have been put forward, but none of them has as yet been generally accepted. A few of them may be mentioned:

(*a*) The linear arrangement has been said to be due to the nævus following the distribution of a cutaneous nerve, and to be the result of an "intra-uterine tropho-neurotic disturbance," such as might be caused by an intra-uterine affection of the spinal ganglia (v. Bärensprung). The majority of cases do not, however, conform sufficiently closely to the area of distribution of a nerve to make this explanation generally acceptable.

(*b*) Philippson suggested that they corresponded to Voigt's lines (imaginary lines separating the cutaneous areas supplied by the different cutaneous nerves), an explanation which is rarely satisfactory.

(*c*) They have been said to follow the "lines of cleavage" of the skin (*see* p. 131). Since most of these lines are curved and the nævi may form almost straight lines, this explanation is also inadequate.

(*d*) It has also been suggested that they may correspond with the "metameric segments" or "protovertebrae."

(*e*) Lastly, it has been urged that their distribution corresponds with that of the underlying superficial blood-vessels.

At present these explanations are simply in the nature of hypotheses, each of which is capable of explaining a certain number of the facts observed, but none of them is wholly satisfactory.

TABLE OF PATHOLOGICAL CHANGES INVOLVING THE EPIDERMIS, WITH EXAMPLES.

CONGENITAL: INVOLVING CHIEFLY THE STRATUM CORNEUM.

Hyperkeratoses.—

I. *Diffuse* . . . Harlequin fœtus or Hyperkeratosis universalis congenita, etc.

II. *Regional* . . Keratoma palmare et plantare hereditarium, Ichthyosis hystrix, etc.

INVOLVING CHIEFLY THE STRATUM MALPIGHII.

Hypertrophy.—

Regional . . . Nævi (excluding vascular nævi)—*e.g.*, Soft, pigmented, and hairy nævi, hard nævi, linear nævi, and giant nævi.

ACQUIRED: INVOLVING CHIEFLY THE STRATUM CORNEUM.

Hyperkeratoses.—

I. *Diffuse* . . . Pityriasis rubra pilaris, Ichthyosis (?), etc.
II. *Circumscribed* . . .
1. Simple, traumatic . . . Corns, Callosities.
2. Associated with vascular changes . . . Angiokeratoma, Erythema keratodes (Brooke), etc.
3. Chiefly affecting the orifices of the pilo-sebaceous follicles . . . Pityriasis rubra pilaris, Comedo and Acne, Keratosis follicularis (Unna), or Lichen pilaris (Bazin), Keratosis follicularis contagiosa (Brooke), etc.
4. Associated with hyperidrosis.
5. Associated with the elimination of poisons—*e.g.*, Arsenical keratosis.
6. Of undetermined origin . . . Porokeratosis (Mibelli) or Hyperkeratosis eccentrica (Respighi).

Parakeratoses.—Psoriasis, Eczema, Seborrhoic dermatitis, Pityriasis alba, Pityriasis rubra (Hebra).
Pityriasis rosea (Gibert).
Parakeratosis variegata (Unna), or Lichen variegatus (Crocker).
Erythrodermie pityriasique en plaques disseminées (Brocq).
Desquamative stages of the acute exanthemata.

Dyskeratoses.—Psorospermosis follicularis vegetans (Darier).
Molluscum contagiosum.
May occur in carcinomata.

Atrophies.—From general illnesses, nervous disturbances, pressure, etc.

INVOLVING CHIEFLY THE STRATUM MALPHIGHII.

Hypertrophies or Acanthomata.—

I. Simple . . . Condyloma acuminatum, Lichenification.
II. With hyperkeratosis . . . Verruca vulgaris.
Acanthosis nigricans (pigmented).
III. With dyskeratosis . . . Molluscum contagiosum.
IV. Secondary to changes in the corium . . . Infective granulomata (Syphilis, Yaws, Tuberculosis verrucosa cutis, etc.).

Atrophies due to—

I. External pressure . . . Bandages, etc.
II. Internal pressure . . . Sclerodermia, etc.
III. Traction . . . Striae atrophicae of pregnancy, etc.
IV. "Idiopathic" (of unknown origin).
V. Senile.

Dystrophies.—

1. Slight œdema and parakeratosis . . . Psoriasis, Pityriasis.
2. Pronounced œdema and parakeratosis . . . Seborrhoic dermatitis. Eczema.
3. Vesiculation—
(*a*) Interepithelial or interstitial . . . Herpes zoster, Eczema, Dysidrosis, Dermatitis herpetiformis, Scabies, etc.
(*b*) Intra-epithelial or parenchymatous . . . Varicella, Variola, etc.

4. Bullous formation—
   - Dermatitis herpetiformis.
   - Erythema multiforme.
   - Urticaria bullosa.
   - Pemphigus—
     - Pemphigus vulgaris, Pemphigus foliaceus, Pemphigus vegetans, Pemphigus acutus.
     - Pemphigus congenitalis (Epidermolysis bullosa).
     - Pemphigus syphiliticus (Bullous syphilide).
     - Pemphigus neonatorum (Congenital bullous syphilide, acute pemphigus, Urticaria bullosa or bullous erythema).
     - Pemphigus contagiosus (Impetigo contagiosa of the Tropics).
     - Pemphigus circinatus (Erythema multiforme).
   - Chemical irritation . . . Cantharides.
   - Thermal . . . Burns.
   - Light (actinic rays).
5. Pustulation—
   - Primary . . . Impetigo of Bockhart.
   - Secondary to vesiculation . . . Impetigo contagiosa (Tilbury Fox), Scabies, etc.
6. Ulceration—
   - Further stage of pustulation in weakly resistant tissues or due to increased virulence of the pyogenic organisms.
   - Necrotic process associated with nerve-disturbances or with the breaking down of the infective granulomata . . . Syphilis, Tuberculosis, Leprosy, etc., or of the epidermis in Carcinomata and Rodent ulcer.

PSEUDO-HYPERTROPHIES OR MALIGNANT PROLIFERATIONS.

I. **Carcinomata of the Skin.**—
   1. Tubular or cylindrical.
   2. Pavement epithelioma.
   3. Fungating or vegetating.
   4. Rodent ulcer.

II. **Precancerous States of the Skin.**—
   1. Paget's disease.
   2. Sailor's skin (Unna).
   3. Xeroderma pigmentosum (Kaposi).
   4. Pigmented nævi.
   5. Warts, cutaneous horns (?)
   6. Lupus vulgaris, Lupus erythematosus, and tertiary syphilides (?)

CHAPTER XVI.

THE MINUTE STRUCTURE OF THE CORIUM.

The Histological Architecture of the Corium.—The corium is the dense fibrous layer of the skin which is situated beneath the epidermis. It supports and protects the hair-follicles, glands, nerves, nerve-terminations, blood-vessels, lymphatics, and fat-cells, and it is to this layer that the skin owes its strength and elasticity.

Structurally it is built up chiefly of white fibrous tissue and a variable amount of yellow elastic tissue ; and connected with or independent of these fibres there are certain well-recognised cellular elements.

For descriptive purposes the corium is divided into a superficial and a deep layer, which are known respectively as the *papillary layer* or *papillary body* and the *reticular layer* or *pars reticularis*. A sub-papillary layer is referred to by a number of writers as separating the two. This division is purely arbitrary, as no definite lines of demarcation exist between the layers. Beneath the reticular layer is the subcutaneous tissue, which many observers now look upon not as an independent structure, but as the deepest layer of the corium, in which the cells have become differentiated to contain fat. This latter view has much to commend it, since the subcutaneous tissue is derived from the same embryonic layer as the corium, and pathological processes affecting the corium rapidly involve the hypoderm.

In the papillary layer the *white fibrous bundles* are thin, loosely packed together, and tend to have a vertical direction. In the reticular layer these bundles are more numerous than in the papillary layer ; they are also thicker, and they split and cross each other in various directions and form a complicated network, the meshes of which are small and diamond-shaped, and generally have their long axes arranged horizontally. The direction of the long axes of the meshes depends on the direction of the greatest tension of the skin. It is

a familiar fact that when a puncture-wound is made by an awl this wound is not circular in shape, but ragged and in the form of a slit, this effect being caused by the tension of the fibrous bundles. Dupuytren[1] studied this problem in connection with puncture-wounds received during warfare, and more recently Langer and Heitzmann[2] have elaborated his observations. By making a series of punctures with an awl they were able to map out the direction of the long axes of these meshes over the whole skin, in a series of constant lines, which are known as the *lines of cleavage.*

In the subcutaneous tissue the bundles unite to form the large trabeculae and septa which separate and support the fat-lobules.

The *papillary layer* is the site of origin of so large a number of the pathological processes which affect the skin that it merits a detailed description. It is the layer on which the epidermis lies, and on which the epidermis is dependent for its nutrition—a fact which explains the constant implication of the epidermis when the papillary layer is diseased. There is no separation of the two layers by a "homogeneous basement membrane" such as used to be described, but the cells of the basal layer of the epidermis are bathed by the same lymph which circulates in the lymphatic spaces between the fibrous bundles of the papillary body.

The actual *papillae* are the conical projections of the corium, in which are found the terminal capillary loops and certain nerve-terminations. According as they support the former or the latter they are known as *vascular papillae* or *sensory papillae.* They are situated on ridges of varying heights, which are arranged more or less parallel to each other; frequently there are two rows of papillae on each ridge. In certain situations, such as the finger-tips, where these ridges are well developed, they give rise to markings which are so constant during life and differ so much in different individuals that they are often relied upon for the identification of criminals. The papillae may be single, or more rarely there may be two or more of them situated on a common base, forming a *compound papilla* (Pl. V., Fig. 1).

By macerating a piece of skin, such as that of the palm of the hand, in a weak alkaline solution (10 per cent.

[1] *Ueber die Verletzungen durch Kriegswaffen. Aus der Franz.*, 1836, p. 27.

[2] *Archiv f. Derm. u. Syph.*, 1890, XXII., p. 3

solution of potash) for a few days, the epidermis may be peeled off and the naked papillae studied.

It is advisable to have some knowledge of the relative length and number of the papillae in different parts of the skin, otherwise it is extremely difficult to detect pathological alterations in size. The papillae are largest in the palm of the hand and sole of the foot, especially on the flexor aspects of the finger-tips and toes. They are small and sparse where the skin is thin, as on the flexor aspects of the arms and the inside of the thighs, and they may even be absent in these situations. They are most numerous about the clitoris, penis, and the areolae of the nipples. As a rule they are about twice as long as they are broad.

As the papillae are less dense than the epidermis the down-growing interpapillary epithelial processes exert an important function in altering the shape of the papillae, and any proliferative activity on the part of the epidermis causes corresponding alterations in the papillae. The papillary layer is in consequence of this a singularly inconstant structure. On the other hand, no increase takes place in the papillae without corresponding changes occurring in the epidermis, so that a "papilloma" in the sense of a new growth of papillae, without a down-growth and proliferation of the interpapillary epithelium, does not exist.

Sappey[1] calculates that there are on the whole surface of the body about a hundred and fifty million papillae, but in so variable a structure as the papillary body an estimate of the number of the papillae is of no practical value.

A Short Note on the Development of the Corium.—It will greatly facilitate the understanding of the pathological changes which occur in the corium if we consider briefly a few of the outstanding facts in its development.

In the first place, it differs essentially from the epidermis and the epidermal appendages in being developed from a totally different layer of cells of the blastoderm, so that neoplasms due to a proliferation of the elements of this layer belong to an entirely different category from those which may arise from epidermal structures. It is well to remember, however, that the actual cells composing the new growth in the corium may have lost their specific characters to such an extent that it is impossible to be certain whether they have reverted from epidermal or from connective-tissue cells, unless

[1] *Traité d'Anatomie Descriptive*, Paris, 1877, III., p. 535.

a definite connection can be traced between them and the fully differentiated cells of either layer.

In the blastodermic vesicle two layers are early separable—namely, the *primitive ectoderm*, from which the epidermis and its appendages develop, and the *primitive entoderm*, from which the epithelial lining of the alimentary tract evolves. A third layer, however, soon forms between them ; this appears on either side of the linear thickening on the surface of the blastoderm named the *primitive streak*. This new layer of cells is derived from one or both of the above primary layers, and is known as the *mesoderm* or *mesoblast*, and from it the corium and the blood-vessels are developed. This close developmental connection between the corium and the blood-vessels is another important fact which it is well to emphasise, since in proliferations of the endothelial lining of the vessels a type of reverted cell is presented which is quite indistinguishable from other reverted connective-tissue cells.

At the end of the second month of fœtal life the layer of cells known as *Remak's skin-plate*, from which the corium develops, consists of round or spindle-shaped cells. These are not arranged in rows like the embryonic epidermal cells, but are irregularly distributed. In early fœtal life the long axes of the spindle-cells tend to be arranged at right angles to the axis of the body, since the tension to which these cells are subjected in the process of growth appears to be greater in the horizontal than in the vertical direction. At birth the limbs are stretched and the joints used and the tension of the skin occurs in new directions, so that the cells and the fibrous bundles become arranged irregularly, and frequently have a spiral tendency.

The evolution of the embryonic connective-tissue cells and their relation to the formation of white fibrous tissue are problems the definite solution of which would be of the greatest importance in explaining the cellular pathology of the corium ; but, unfortunately, they are still subjects for controversy.

According to certain observers the mode of evolution of the fibrous tissue is as follows: At first the cells are roundish in shape, with actively dividing nuclei, and are said to be amœboid. They gradually become spindle-shaped, branching occurs at their tapering extremities, and the branches unite with those of neighbouring cells to form an irregular network of embryonic connective tissue, in the meshes of which there is a muco-albuminous semi-fluid substance or matrix.

The tapering branches of the cells lengthen and soon become split up, near the extremity, into a brush of fibres; this gives the first indication of the formation of the white fibrous bundle. The remainder of the branch becomes gradually split up, and so the greater portion, if not the whole, of the protoplasm of the cell becomes differentiated into fibres, while the nucleus remains in the centre, and may be surrounded by a halo of undifferentiated or disappearing protoplasm. All the original round cells do not undergo this process of evolution, but a few of them persist in their original roundish form, and instead of differentiating retain the function of reproduction. This explanation of the evolution of the white fibrous bundles, known as the "direct method," is not universally admitted. Certain authorities maintain in opposition to it that the cells secrete an intercellular homogeneous substance, which becomes fibrillated; the latter process has been named the "indirect method." Whichever theory is the correct one—and there are strong arguments in favour of each—it is certain that many of the roundish cells, which were possibly amœboid, have been replaced by white fibrous bundles, and that the nuclei of these cells have remained, while the protoplasm of the cell has become transformed into fibres; and also that between these bundles a certain number of the roundish cells have not become differentiated, and probably retain a purely reproductive function. There are thus two elementary types of cells in the corium: the differentiated cell, in which the nucleus persists as an oval or fusiform structure, while the protoplasm has been replaced by a fibrous bundle; and the roundish cell which has not differentiated into fibres.

By the third month the fibrous bundles are arranged densely near the surface, while deeper down they have formed a large-meshed network, in which fat-globules have begun to appear.

The line of contact of the corium and epidermis remains an even line till nearly the end of fœtal life; but at that time the papillae begin to form and the epidermis to grow down between them, and so the line of demarcation assumes its wavy character.

The Histological Elements of the Corium.

The elements of the corium in health may be divided into the *cellular* and the *fibrous elements.*

The Cellular Elements of the Corium.

I. *Fixed Cells.*—
   1. *Connective-Tissue Cells proper.*
   2. *Vacuolated Cells.*
   3. *Mast-Cells.*

II. *Migratory Cells.*—
   Various Blood-Cells.

The Fibrous Elements of the Corium.

1. *White Fibres composed of Collagen.*
2. *Yellow Elastic Fibres composed of Elastin.*

The Cellular Elements.

It is only by becoming thoroughly conversant with the cells of the corium in the healthy skin that it is possible to appreciate abnormal types of cells and pathological changes in them.

The cellular elements of the healthy corium may be divided roughly into *fixed cells* and *migratory cells.*

The *migratory cells* are the various forms of leucocytes which are present in the corium. They are in largest number near the blood-vessels and lymphatics of the papillary layer, but are never very numerous in health. The polynuclear leucocytes are easily distinguished, but the small mononuclear leucocytes (lymphocytes) may at times be practically indistinguishable from young connective-tissue cells.

The *fixed cells* of the corium, as their name implies, are incapable of active amœboid movement. The majority of them are absolutely fixed to fibrous structures; a few of them are unattached and may be carried about in the lymph-stream, but their movement is passive (Pl. XVIII., Fig. 1).

The Fixed Cells of the Corium.

1. **Connective-Tissue Cells proper and Nuclei of Cells.**—These cells vary to a great extent both in shape and in size. The most common type is a large cell with a spindle-shaped body; but instead of being spindle-shaped, they may be triangular or even polygonal. As a rule they have long processes, which may branch and taper to fine threads, and in young connective tissue, such as "granulation tissue," these threads frequently unite with those of other cells to form a meshwork (Pl. XVIII., Fig. 2).

In the body of the cell the spongioplasm forms an irregular network, which is more irregular near the nucleus than at the periphery of the cell. In the latter situation the spongioplasm is generally arranged in long meshes, and passes out of the cell in the form of fine branching processes, surrounded near the cell by a certain amount of the hyaloplasm. Where the fibrils of the network of spongioplasm cross each other, small nodes may be detected with high powers of the microscope which give to the cell-protoplasm a granular appearance.

The *nucleus* of the cell varies in shape with that of the cell, being oval when the cell is spindle-shaped, and roundish when the cell is polygonal. It has a distinct nuclear membrane, an intranuclear network, and one or more nucleoli.

The meshes of the intranuclear network are open, and in consequence the nucleus has been frequently described as a "vesicular nucleus," in contradistinction to the type of nucleus met with in the mononuclear leucocytes, where the meshes of the network are small, and close, and the nucleus stains more deeply.

It is unusual to find round connective-tissue cells, except in an early stage in the development of the cell or in pathological conditions. It is common, however, to find cells which appear to be round and which are most probably spindle-cells in cross section.

These cells are smallest in the papillary layer and largest in the subcutaneous, and they vary indefinitely in the reticular layer. As a rule they appear to be flattened and squeezed between the fibrous bundles. Sometimes they surround a bundle, and by the union of their processes form a network covering the bundle and the walls of the lymphatic spaces between the bundles like an endothelium. These latter cells are sometimes described as *endothelioid cells*, in the same way as cells resembling epithelial cells are frequently referred to as "epithelioid cells"; but these terms are confusing and should be avoided.

Frequently only the nucleus of the connective-tissue cell can be detected, and even by the most careful protoplasmic staining not a trace of protoplasm can be recognised around it. These nuclei may be attached to fibrous bundles, or may appear to lie free between them. Under certain conditions the nuclei can evolve again into fully formed connective-tissue cells. In young connective tissue, nuclei of the above type may be detected, which are surrounded by a thin halo of protoplasm. These young cells are usually known as

PLATE XVIII.

FIG. 1. CONNECTIVE TISSUE CELLS OF THE HEALTHY CORIUM (SEMI-DIAGRAMMATIC.)

a. Ordinary connective tissue cells.
b. Vacuolated cells.
c. Connective tissue nuclei.
d. Polynuclear leucocyte.
e. Lymphocyte.

FIG. 2. CONNECTIVE TISSUE CELLS OF GRANULATION TISSUE. (× about 1000.)

a. Spindle-shaped connective tissue cell with well-marked nucleus, having an intranuclear network and nucleolus. The spongioplasm of the cell has a longitudinal arrangement.
b. Longer spindle-cell showing the spongioplasm becoming fibrous at the extremities.
c. Branching and early fibrous formation.
d. Large connective tissue cells with several nuclei (Unna s plate-cells).
e. Fine fibrils between the cells, probably belonging to cells not shown in the section.
f. Connective tissue cell in which the spongioplasm is arranged in large regular meshes, giving the cell a vacuolated appearance.
g. Spindle-cell in transverse section.

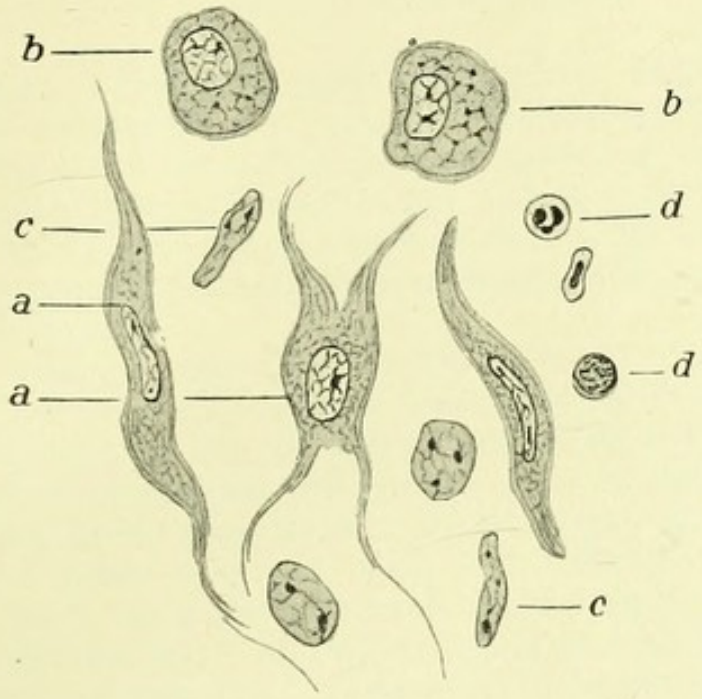

FIG. 1.

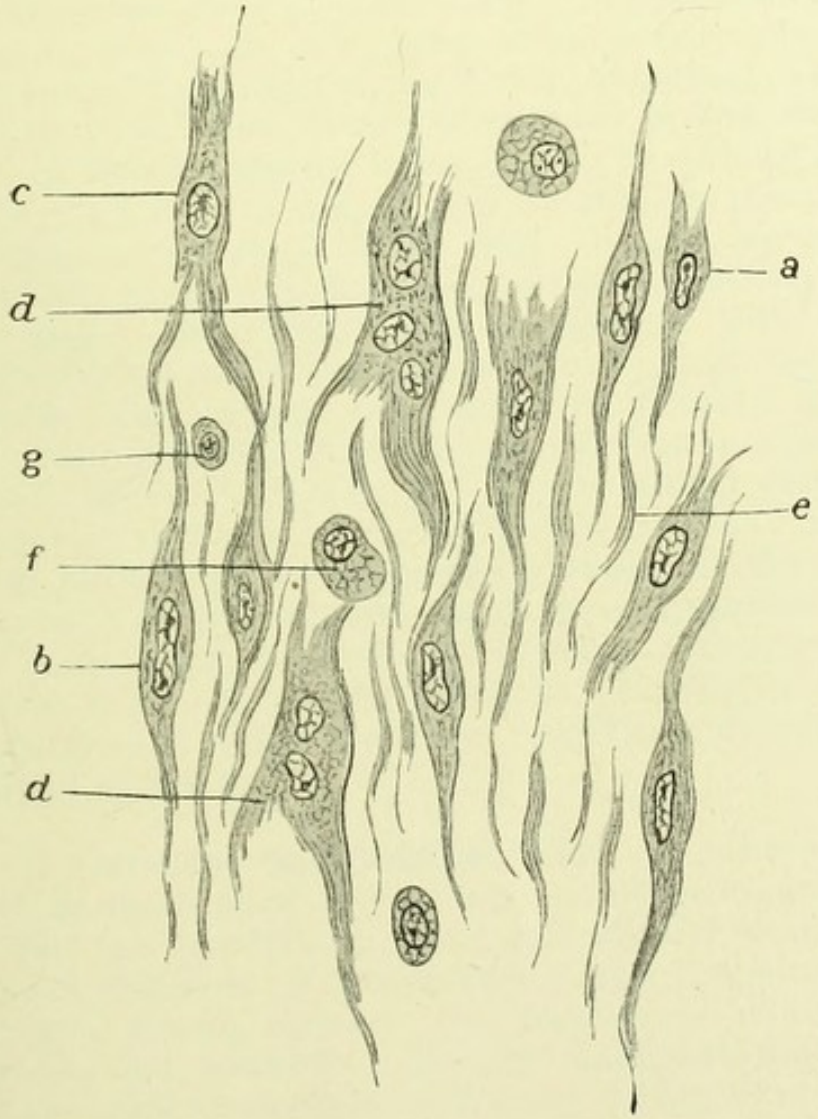

FIG. 2.

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fibroblasts. They are generally slightly larger than mononuclear leucocytes, and are oval or oat-seed shaped. The difficulty which may exist in distinguishing these fibroblasts from mononuclear leucocytes has led to great confusion with regard to the cells of the corium and to the improbable view that unstable structures, such as leucocytes, may develop into fibrous tissue.

In young connective tissue, such as the "granulation tissue" of a wound, there is a peculiar variety of connective-tissue cell whose significance is not wholly understood. It is a large wedge-shaped cell, forked at both ends by processes which are better developed at the base than at the apex. The sides of these cells are even and unbroken by processes. They have, as a rule, several nuclei, which are the result of a proliferation of an original nucleus without a division of the body of the cell. These have been named by Unna "plate-cells," and seem to occur only in organising tissue.

From the study of these fully developed connective-tissue cells it does not at present seem possible to decide the problem of the origin of the fibrous bundles. The fact that wherever the white fibrous bundles are present cells or nuclei may be found, while the latter may occur without the presence of bundles, is extremely suggestive that the connective-tissue fibres have their origin in the cells. In granulation tissue the long spindle-cells at their fibrous extremities begin to attract the stains for collagen (the component substance of the white fibres), while ordinary cell-protoplasm does not. The presence also of such large numbers of nuclei in the corium which are independent of cells would seem to suggest that the protoplasm of the cells had either wholly disappeared or become transformed into the fibrous bundles. Such facts as these all strongly corroborate the theory of the direct transformation of the cell-protoplasm into collagenous fibres. On the other hand, however, the occasional presence of lymph-spaces around the cells, which can be readily detected by staining with nitrate of silver, is difficult to explain on the above hypothesis.

2. **Vacuolated Cells (Schäfer).**—The second type of cell met with in the healthy corium has no processes, and is peculiar in that the protoplasm of the cell appears to be vacuolated. This appearance is produced by the spongioplasm, which forms a coarse network, the meshes of which are large, regular, and roundish. Schäfer maintains that these cells possess distinct cavities containing a fluid like lymph. The

cells are roundish and occasionally spindle-shaped, and their nuclei are similar to the ordinary connective-tissue cell nuclei.

They were described by Waldeyer[1] under the heading of "Plasma-Cells," in which group he also included the coarsely granular cells or mast-cells, which form the third type of cell in the corium. The name plasma-cell (Unna[2]) is now generally reserved for a characteristic type of cell which occurs in a number of pathological conditions of the skin, but chiefly in the infective granulomata.

Occasionally mitotic figures have been detected in the vacuolated cells. These cells appear to correspond to the roundish cells which have been referred to in the preceding note on the development of the white fibrous tissue as cells which did not evolve, but retained the simpler function of reproduction. It is just possible that they bear the same relation to the connective-tissue cells of the corium as the cells of the basal layer of the epidermis bear to the prickle-cells; in other words, that they are the mother-cells of the fibrous corium, the function of which is that of reproduction and not of differentiation.

3. **Mast-Cells.**—The third variety of connective-tissue cells are those known as mast-cells (Pl. XXII.), and they differ from the already mentioned types in that their hyaloplasm contains numerous coarse granules which have a marked affinity for basic anilin dyes. In France these cells are sometimes known as "cellules isoplastiques" (Audry).[3] They vary greatly in shape and size, and correspond to the foregoing forms of connective-tissue cells. Some are round or oval, while others are spindle-shaped or polygonal and occasionally branched. The granules of the mast-cells are deeply stained by basic anilin dyes, and in consequence the mast-cells are singularly noticeable objects in the microscopic field. The granules more or less obscure the nucleus, are irregular in shape, some being round while others are angular; and though they vary slightly in size, they may be described in general as coarse granules. The nuclei of the cells are peculiar in possessing as a rule no well-stained intranuclear network nor nucleoli, though occasionally both may be detected. Mitotic figures have not been observed in the nuclei as far as I am aware; but I have frequently observed mast-cells which were hour-glass shaped, with two nuclei, and

[1] *Schultze's Archiv*, 1875, XI., p. 176.
[2] *Monats. f. prakt. Derm.*, 1895, XX., p. 477.
[3] *Ann. de Derm. et de Syph.*, 1896, VII., p. 9.

which appeared as if they were dividing by amitosis. These cells are sometimes surrounded by a halo of protoplasm which stains like the granules, and occasionally granules may be detected around the cells, as if the hyaloplasm had broken up and the granules had been discharged. Mast-cells are invariably present in the healthy corium and subcutaneous tissue, though not as a rule in large numbers. They are specially numerous in the neighbourhood of the blood-vessels, hair-follicles, and sebaceous glands. They are found in quantities in the skin of pigmented regions, such as the dartos of the scrotum and the areolae of the nipple, and on this account it has been suggested that they have a certain relation to the pigmentation of the skin. Mast-cells are present not only in the healthy skin, but in most pathological conditions, and occasionally in such increased numbers as to be of diagnostic value—for example, in urticaria pigmentosa. In the healthy corium it is unusual to find more than one mast-cell in the field of a microscope with medium powers (III. × 7), and in many fields no mast-cells may be detected. When several appear in a microscopical field it indicates a pathological condition.

The Nature and Origin of the Mast-Cells.—Much discussion and difference of opinion have arisen with regard to the nature and origin of these granular cells. This is partly due to their having been confused with other types of granular cells in the corium. Schäfer, for example, has described a form of coarsely granular cell in the corium near the blood-vessels and in the subcutaneous tissue, which from his description closely corresponds in shape and size to a mast-cell, but which is not a mast-cell, since its granules have a different chemical reaction, and instead of attracting basic anilin dyes have a strong affinity for eosin, which is acid. These cells described by Schäfer correspond in their staining affinities to Ehrlich's coarsely granular eosinophiles of the blood. In the connective tissue Klein has described granular cells in which the granules are deeply stained by hæmatoxylin,—essentially a basic dye; these are most probably mast-cells. Another cause of confusion with respect to the mast-cells of the corium is the fact that Ehrlich has described as mast-cells certain cells in the blood, and these correspond in their staining reactions to the mast-cells of the connective tissue.

Two chief opposing views regarding the origin of the mast-cells have in this way arisen—namely, (1) that they are derived from the blood, and are leucocytes with basic

granules; and (2) that they are a form of connective-tissue cell. It would be futile to attempt to discuss the numerous arguments in favour of either view, since I believe both to be correct, in so far that cells with basophilic granules occur in the blood as well as in the connective tissue, but are not necessarily derived the one from the other. I hold that the mast-cells of Ehrlich are a form of leucocyte, while the mast-cells which are present in the corium are not leucocytes, but are peculiar connective-tissue cells, since they correspond in size and shape with the latter, and only differ in their staining reactions and in the presence of the basophilic granules. I have noted also that mast-cells may so closely resemble "plasma-cells," which I believe to be pathological connective-tissue cells, that it is strongly suggested that mast-cells may also be derived from plasma-cells.

The most likely explanation of the nature of the mast-cells is that they are connective-tissue cells, or, in the case of the blood, leucocytes, the protoplasm of which has undergone a chemical change, possibly degenerative, whereby basophilic granules have been eliminated (Audry).[1] The facts that the granules are occasionally present around the cells and may actually lie free in the lymphatic channels, and that in their staining reactions they have a close similarity to mucin (Unna) —one of the products of degeneration of collagen—strongly testify to Audry's hypothesis. The close analogy in the formation of the mast-cell granules to that of keratohyalin seems to me to be a peculiarly suggestive fact, and one which goes far to support the view that the granules are a separation-product of the protoplasm of the cells.

A third possibility has been suggested—namely, that mast-cells are migratory cells which have incorporated chromatin particles; but there is no definite proof that the cells are migratory. Their occasional presence between the epithelial cells is not a proof of this, since they may have been carried there passively. I have certainly detected them in this situation, but only in conditions where a certain degree of inter-epithelial œdema was present, and in which it was easy for them to be carried there passively by the lymph-stream.

The Staining of the Connective-Tissue Cells of the Healthy Corium and Subcutaneous Tissue.—The only group of the connective-tissue cells which requires a special technique in staining is that of the mast-cells; the methods for staining the nuclei—hyaloplasm and spongioplasm—described for the

[1] *Monats. f. prakt. Derm.*, 1896, XXII., p. 393

epithelial cells, are equally applicable to the other cells of the corium.

The Staining Methods for the Mast-Cells.—The granules can be stained to a certain extent by any basic anilin dye, but they are particularly well defined by those dyes which possess metachromatic properties; for example, toluidin blue, polychrome methylene blue, borax methylene blue, safranin, and thionin. They can also be well stained by dahlia and methyl green and by Gram's method.

I. *After Ehrlich* (*Archiv f. mikr. Anat.*, 1876, XII., p. 263).—Harden in alcohol.

(*a*) Stain for twelve hours in a saturated solution of dahlia in absolute alcohol:

Dahlia, alcoholic solution	50 c.cm.
Glacial acetic acid	12·5 „
Liq. destillat	100 „

(*b*) Wash in water.

(*c*) Differentiate and dehydrate in alcohol.

(*d*) Clear in bergamot oil and mount in Canada balsam.

The mast-cell granules are stained blue.

NOTE.—By the above method the nuclei of the cells are not clearly brought out, so Westphal has modified it by the addition of alum-carmine to the dahlia solution.

Concentrated alcoholic solution of dahlia .	100 parts.
Alum-carmine	100 „
Glycerin	100 „
Acetic acid	20 „

By this means the nuclei are stained red and the granules blue. Both the above method and the modification are more applicable to blood-films than to sections.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 370).—Harden in alcohol.

(*a*) Stain the sections from a quarter of an hour to twelve hours in polychrome methylene blue.

(*b*) Wash in water.

(*c*) Differentiate for a few minutes in glycerin-ether mixture (a few drops of the mixture to a watch-glass of water).

(*d*) Wash thoroughly in water.

(*e*) Dehydrate in alcohol and decolorise till most of the colour has gone.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The protoplasm of the mast-cells is stained a bluish violet tint, the nuclei blue, and the granules red.

NOTE.—The decoloration should be almost complete. Instead of the glycerin-ether mixture, glacial acetic acid may be employed. Tissues hardened in sublimate can also be stained by the above method. In those hardened in Müller's fluid the colour of the granules will be less red and more bluish.

III. *After Unna* (*Ibid.*).—

(*a*) Stain the sections from three hours to a night in polychrome methylene blue, to which has been added a pinch of alum in a watch-glass of the stain.

(*b*) Wash in water.

(*c*) Absolute alcohol, bergamot oil, Canada balsam.

This stains the mast-cells, leaving the surrounding tissue only faintly stained. (The addition of the alum weakens the polychrome methylene blue solution.)

THE FIBROUS ELEMENTS OF THE CORIUM.

White Fibrous Bundles (Collagen).—

Terminology.—Within recent years, especially on the Continent, it has become customary to substitute the more definite term collagen, or collagenous fibres and bundles, for white fibres and white fibrous bundles. *Collagen* is the name given to the albuminoid substance of which the white fibres are composed. Since the term is constantly employed in the modern literature on the histo-pathology of the skin, it will help to accustom the student to its use if I adopt it here.

Morphology—The collagenous bundles (Pl. XIX., Fig. 1) are composed of fine fibres united together by a small amount of a semi-fluid, interfibrillary substance which is closely allied to mucin. This semi-fluid substance is stained brown with nitrate of silver and precipitated by acetic acid. The fibres are about the breadth of the diameter of a red blood-corpuscle ($\frac{1}{3200}$th of an inch). These fibres in turn are found to be composed of fibrils which have been estimated at from $\frac{1}{50000}$th to $\frac{1}{20000}$th of an inch in thickness (Clarkson). The bundles vary in thickness, according as they are made up of a greater or smaller number of these fibres.

Seen longitudinally, the bundles present a wavy appearance which entirely disappears when the skin is stretched.

PLATE XIX.

FIG. 1. COLLAGENOUS BUNDLES IN LONGITUDINAL AND TRANSVERSE SECTION (SEMI-DIAGRAMMATIC).

a. Collagenous bundle in longitudinal section.
b. Connective tissue nuclei.
c. Lymphatic space between the bundles.
d. Collagenous bundle in transverse section.
e. Splitting off of component fibres.

FIG. 2. ELASTIC FIBRES FROM THE PARS RETICULARIS (SEMI-DIAGRAMMATIC).

Shows coarse fibres, branching, and united by fine fibrils; also the tendency of the fibres to curl up at the ends when broken.

a. Coarse fibre.
b. Fine branching fibre curling up.
c. Coarse fibre curling up.
d. Fine uniting fibrils.

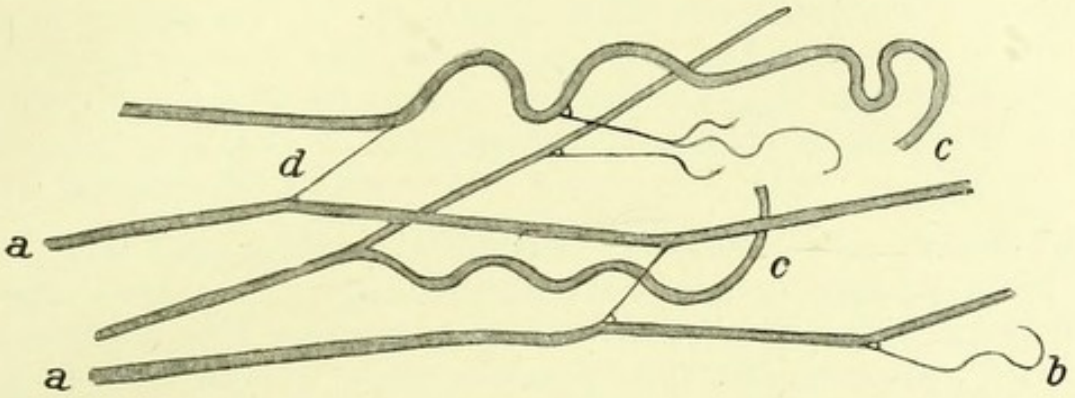

FIG. 2.

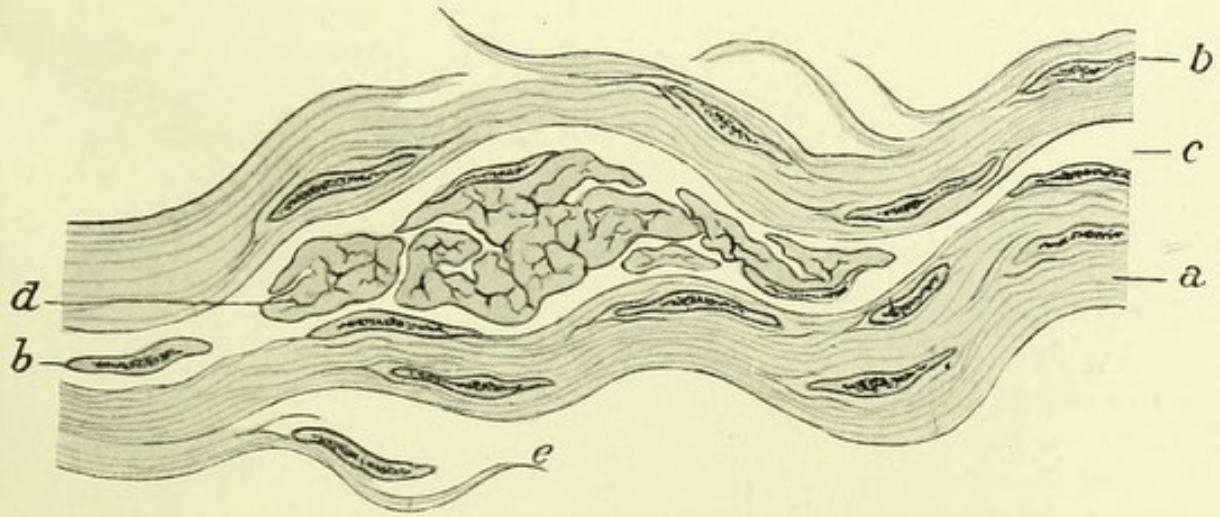

FIG. 1.

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They are flexible and slightly extensible ; their margins are faintly outlined, and they do not refract light so strongly as the elastic fibres. In transverse sections the bundles form irregular figures, and the sections of the individual fibres vary in shape from round to oval or angular. These fibres are incapable of branching and uniting again to form a true network, as the elastic fibres do ; but as the bundles frequently split and join again, the appearance of a coarse network may be produced. Spindle-shaped connective-tissue nuclei, in greater or less number, are situated on the bundles or between the fibres.

The Composition of Collagen.—Collagen is an albuminoid substance, and is probably the anhydrid of gelatin, since by boiling it with water it is converted into the latter substance. It is insoluble in water, alcohol, and salt solutions; it swells up with dilute acids, alkalies, and digestive ferments, and is readily destroyed by strong acids and alkalies.

The Staining Properties of Collagen or White Fibrous Tissue.—The white fibrous tissue or collagenous bundles, like the elastic fibres, attracts acid dyes, but not with the same avidity as the latter. For example, collagen may be readily stained by eosin, acid fuchsin, and water-blue. It is of the greatest importance to have a serviceable stain for the collagen, and a good counter-stain for the protoplasm and nuclei of the cells. One of the simplest, and at the same time one of the most effective, stains for collagen is orcein (Unna), and by counter-staining with polychrome methylene blue excellent results may be obtained.

I. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XVIII., p. 511).—Harden in alcohol, imbed, and cut in celloidin.

(*a*) Stain the sections for five minutes in polychrome methylene blue.

(*b*) Wash in water, and dry off water with filter-paper.

(*c*) Put for fifteen minutes in neutral orcein solution :

Orcein (Grübler)	1 part
Alcohol, absolute	100 parts

(*d*) Differentiate in alcohol.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The nuclei are stained dark blue ; the protoplasm of the cells, both of the connective tissue and the epithelium, light blue ; the collagen, deep red ; the elastin, brownish red ; the skin-muscles, bluish red ; the mast-cell granules, carmine red.

Unna claims the following advantages for this method of staining, which I can heartily endorse, having employed it constantly for several years:

(*a*) It is simple and rapid.

(*b*) It stains the collagen excellently, and gives a good counter-stain for the nuclei and cell-protoplasm.

(*c*) It differentiates the mast-cells, and is a good method for plasma-cells.

(*d*) It brings out the smooth muscles of the skin.

(*e*) It demonstrates pathological changes in the collagen through changes in the staining capacity.

(*f*) It stains many of the micro-organisms in the stratum corneum.

II. *After Beneke* (*v. Kahlden, Tech. d. histol. Untersuch.*, 1898, p. 105).—Harden in alcohol.

(*a*) Stain the sections from five to fifteen minutes in concentrated anilin-gentian violet solution.

(*b*) Wash in a 6 per cent. salt solution.

(*c*) Dry with a piece of filter-paper.

(*d*) Transfer from two to three minutes to iodine solution.

(K=1, KI=2, H_2O=100.)

(*e*) Dry with filter-paper.

(*f*) Decolorise in anilin oil, two parts, and xylol, three parts.

(*g*) Clear in bergamot oil and mount in Canada balsam.

This method is practical and useful. By it the collagen is stained violet and the elastin reddish.

The Elastic Fibres of the Corium.—

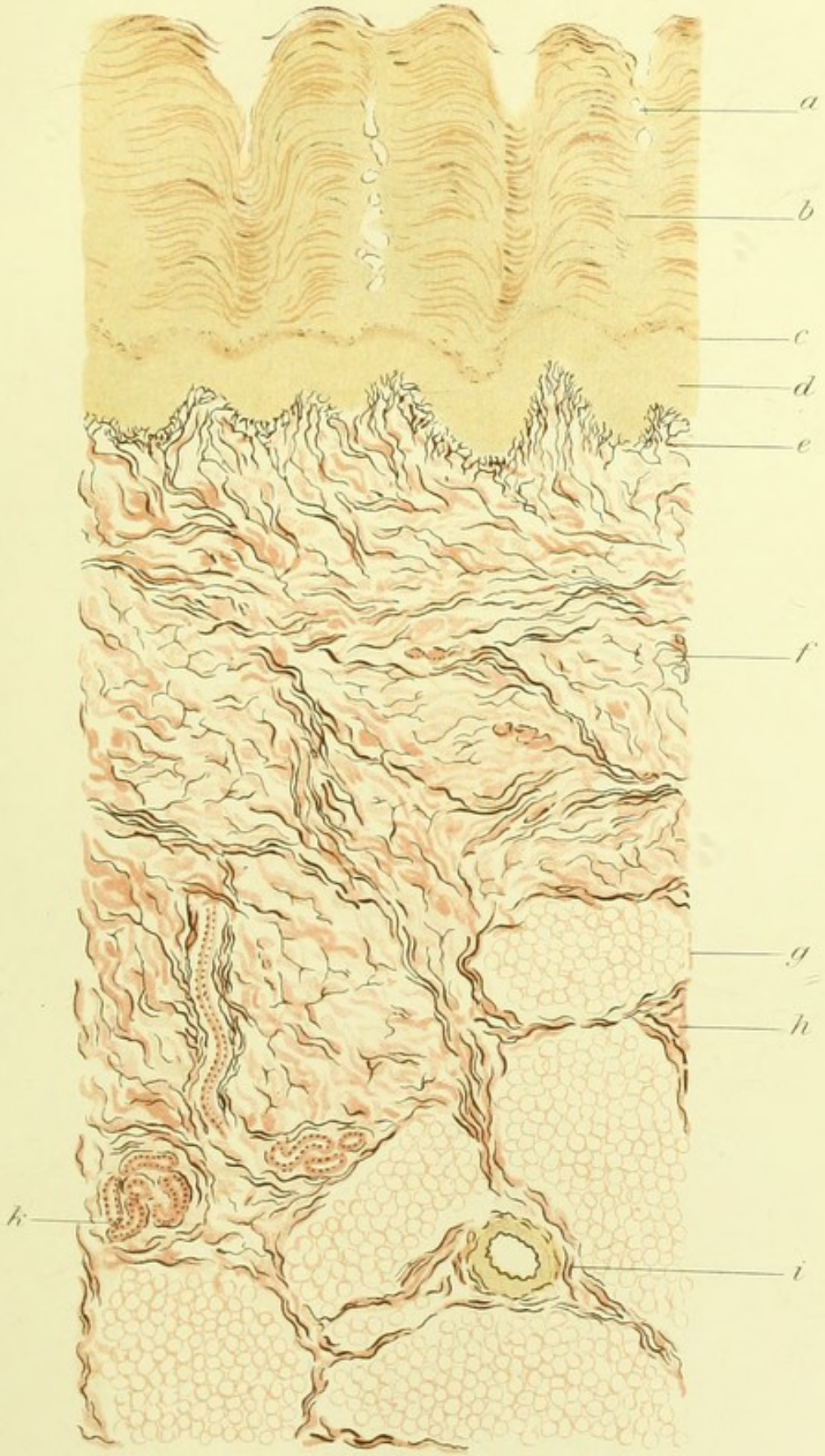
Morphology.—The elastic fibres appear as homogeneous, strongly light-refracting threads (Pl. XIX., Fig. 2), which are widely distributed throughout the corium and subcutaneous tissue. They are straight or slightly wavy, and are capable of branching at varying angles and anastomosing again so as to form a more or less continuous network. They vary greatly in breadth, the broadest fibres, such as those which occur in the sole of the foot, being five or six times thicker than the thin fibres which are present in the skin of the trunk. According to Stöhr they vary from immeasurably fine fibrils to fibres 11 μ in breadth. The coarse fibres are connected together by finer fibrils. In section the fibres are angular in outline. Transverse lines crossing them have frequently been noted. When these fibres are overstretched they break across without splitting, and tend to curl up.

PLATE XX.

Section of the Sole of the Foot of an Adult, showing the Distribution of the Elastic Fibres. (× about 60.)

Stained with acid orcein.

a. Sweat-pore.
b. Stratum corneum.
c. Stratum lucidum and stratum granulosum.
d. Stratum Malpighii.
e. Papillary layer, showing fine elastic fibrils passing up between the cells of the basal layer of the epidermis.
f. Distribution of the elastic fibres in the pars reticularis.
g. Fat-lobule.
h. Septum between fat-lobules, composed of collagenous and elastic fibres.
i. Transverse section of a small artery, showing the wavy elastic lamina, and the elastic fibrils in the tunica extima.
k. Coil-gland and duct, with elastic fibres between and around the alveoli.



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The Distribution of the Elastic Fibres.—The elastic fibres (Pl. XX.) are arranged parallel or obliquely to the collagen bundles of the corium and subcutaneous tissue, and by anastomosis form a network enclosing the bundles. They are frequently so close to each other that in sections where the collagenous bundles are cut transversely the elastic fibres appear to form a membrane rather than a network around the collagen. The fibres are most dense in the pars reticularis of the corium, where they form a network the meshes of which tend to be elongated horizontally. From this meshwork finer fibres pass up in a more vertical direction into the papillae, and split into fibrils, which pass between the cells of the basal layer of the epidermis, and from it fibres also pass down in the trabeculae of the subcutaneous tissue. Elastic fibres envelop the sweat-coils and pass up in a wavy manner along the sweat-ducts. They are present also around the sebaceous glands, and nerve-terminations, and in the hair-follicles. They pass between and surround the muscular fibres of the arrectores pilorum, and by means of them the muscles are attached to the collagenous bundles of the papillary layer of the corium. They form the elastic laminae of the subcutaneous blood-vessels, and their presence between the collagenous bundles brings them into close relation with the lymphatic spaces of the corium.

The distribution of the elastic fibres is so universal and regular that they form a scaffolding or skeleton supporting and holding together the various elements of the corium and subcutaneous tissue, and from their intimate connection with the muscles, vessels, and glands of the cutis they are of the greatest importance in regulating the functions of these structures.

The Elasticity of the Elastic Fibres.—From their name it would naturally be supposed that these fibres possessed to a marked degree the powers of extension and retraction, but recent observations have shown that their elasticity is not nearly so great as was formerly supposed, and that when they are even moderately stretched they rupture. Their elasticity is considerably less than that of the collagenous fibres—a fact which is borne out in the striae of pregnancy, where the elastic fibres have ruptured, but the collagenous fibres are in many cases, though stretched and attenuated, still unbroken. The elastic fibres play only a slight *rôle* in giving to the skin its elasticity (Tomsa), and the power of extension of the skin is due to a far greater extent to the

involuntary skin-muscles (Unna) than to the elastic tissue. The chief function of the elastic tissue in the skin seems to be that of supporting the various structures in the corium, instead of giving it elasticity. If the elastic fibres were as retractile as the name implies, it would not be necessary for them to form the wavy line which the elastic lamina of an artery presents on transverse section.

Composition and Chemical Reactions of the Elastic Fibres.—The fibres are composed of an albuminoid substance named *elastin*. It resists weak acids, weak alkalies, and digestive ferments more strongly than collagen does; but after their prolonged action, or the action of strong acids or alkalies, it swells up and disintegrates.

The resisting power of the elastic fibres is said by Schwalbe[1] to be due to the presence of a resistant membrane enclosing the fibre. In unstained sections the elastic fibres may easily be rendered visible by treating the section for three or four hours with acetic acid, which causes the collagen to swell up and become cloudy, while the elastic fibres, being unaffected, stand out in bold contrast.

The following is given as the percentage composition of elastin by Müller[2]: C—55·09, H—7·11, N—15·71, O—20·7.

The Origin of the Elastic Fibres and their Capacity of Regenerating.—There is not a unanimous opinion regarding the origin of the elastic fibres. It has frequently been asserted that they do not appear in the skin till after birth, but Passarge and Krösing[3] have detected them between the seventh and eighth months of fœtal life. It has been variously suggested (1) that the fibres are produced by an activity of certain embryonic cells; (2) that they are simply elongated and modified cell-processes; (3) that they result from a modification of the protoplasm of the cell; and (4) that they are the result of a growth of the nuclei. On the other hand, several observers are convinced that the origin of these fibres is independent of cells or their nuclei, and that they originate in the intercellular ground-substance, either by a simple differentiation of the latter into peculiar fibres, or by a deposition in it of rows of granules, which, uniting together, build up the fibres. Perhaps the most popular theory is the last, but the subject still forms a suitable field for the labours of the histologist.

[1] *Zeitschr. f. Anat. u Entwickelungsgesch.*, 1877, II., p. 236.
[2] *Zeitschr. f. rat. Med.*, Leipzig, X., Pt. 2.
[3] *Monats. f. prakt. Derm., Ergänzungsheft*, I., 1894.

It is extremely doubtful whether new elastic fibres can form in the skin after the tissue has been destroyed by rupture, inflammation, or necrosis. When the fibres have ruptured they do not seem to possess the power of growing together again, as do the ends of a ruptured nerve. In scars and in the slowly developing granulomatous infiltrations of the corium, fine elastic fibrils have been noted, which have been regarded as newly formed fibrils (Kromayer),[1] but this opinion is still *sub judice.*

The Staining of Elastic Fibres.—

Elastin has a peculiar affinity for acid anilin dyes. It attracts orcein and fuchsin in acid solutions with a far greater avidity than collagen does. It is the most strongly acidophilic element in the healthy skin. Stained with picro-carmine, the elastin attracts the picric acid and is stained yellow, while the collagen is stained red by the carmine.

The Staining Methods for Elastin.—

I. *After Unna* (*Monats. f. prakt. Derm.*, XIX., 1894, p. 397).—Harden in alcohol and imbed in celloidin.

(*a*) Stain sections from twenty to thirty minutes in an acid solution of orcein :

Grübler's orcein	1 part
Hydrochloric acid	1 „
Absolute alcohol	100 parts

(*b*) Decolorise in absolute alcohol till the colour has almost disappeared from the sections.

(*c*) Clear in bergamot oil and mount in Canada balsam.

The elastin is stained dark brown ; the collagen is either unstained or assumes a faint reddish brown colour, depending on the extent of the decoloration.

NOTE.—Better preparations are obtained if the celloidin be previously removed from the section by alcohol-ether. If the section be thick the addition of a trace of hydrochloric acid to the alcohol will greatly facilitate the decoloration.

It is difficult to obtain a suitable *counter-stain* for the acid orcein method by which the tint of the elastic fibres is not blurred. I have found hæmatoxylin to be most serviceable in this connection, and the method I employ is the following :

II. *Orcein-Hæmatoxylin Method.*—Harden in alcohol and cut in paraffin.

[1] *Monats. f. prakt Derm.*, 1894, XIX., p. 117.

(*a*) Stain from three to five minutes in Delafield's hæmatoxylin solution.

(*b*) Rinse in water, then dry with filter-paper.

(*c*) Transfer to Unna's acid orcein solution, and heat over the flame or in an incubator for thirty minutes, in the case of paraffin sections, using a vessel sufficiently large to hold the slide.

(*d*) Differentiate in alcohol.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The elastin is stained dark brown; the collagen, a light brick red; and the nuclei, purplish brown.

III. *After Weigert* (*Centralbl. f. allg. Pathologie u. path. Anat.*, 1898, p. 289).—Harden in alcohol, formalin, sublimate, or Müller's fluid; imbed and cut in paraffin or celloidin.

(*a*) Stain the sections for twenty minutes or longer in Weigert's fuchsin solution:

Basic fuchsin	1 part
Resorcin	2 parts
Water	100 „

Heat 200 c.c. of the above to the boiling-point, and add 25 c.c. of liq. ferri perchlor.; continue boiling for a few minutes longer; cool and filter. Boil the precipitate with 200 c.c. of 94 per cent. alcohol, cool, filter, add alcohol to the filtrate till it reaches 200 c.c., and add 4 c.c. of hydrochloric acid (Lee).

(*b*) Differentiate in alcohol.

(*c*) Clear in xylol and mount in Canada balsam.

The elastic fibres are stained a dark bluish purple, and the remainder of the section is only faintly stained. A good counter-stain may be obtained by previously staining the section for ten minutes in Löffler's methylene blue, when the elastin is stained blackish and the nuclei purple. The sections may also be subsequently counter-stained with carmine.

NOTE.—Weigert's method has a certain advantage over the acid orcein method in paraffin sections, as it is more rapid in its action, but the results obtained with orcein are more defined.

IV. *After Schütz* (*Archiv f. Derm. u. Syph.*, 1892, Bd. XXIV., p. 739).—Harden in alcohol.

(*a*) Stain sections for five minutes in carbol-fuchsin.

(*b*) Wash in water.

(*c*) Stain from two to three seconds in an acid solution of methylene blue:

Methylene blue	1 part
Sulphuric acid (25 per cent.)	50 parts

(*d*) Put the sections for a few seconds in 25 per cent. sulphuric acid.

(*e*) Wash in water.

(*f*) Differentiate and dehydrate in absolute alcohol.

(*g*) Clear in bergamot oil and mount in Canada balsam.

The elastin is stained red, the remaining tissues blue.

NOTE.—By this method it is difficult without considerable practice to obtain good preparations, as the acid decolorises the sections rapidly, and only experience can guide one as to the exact time the section may be permitted to remain in it.

V. *After Unna* (*v. Kahlden, Fletcher's Trans.*, 1894, p. 126).—

(*a*) Stain for twenty-four hours in the following mixture:

Fuchsin	0·5 grms.
Nitric acid (25 per cent.)	10 c.cm.
Alcohol	25 „
Distilled water	25 „

(*b*) Two to three seconds in 25 per cent. nitric acid.

(*c*) Decolorise in dilute acetic acid.

(*d*) Dehydrate rapidly in alcohol.

(*e*) Clear in cedar-wood oil and mount in Canada balsam.

The elastic fibres are stained red.

VI. *After Manchot* (*Virchow's Archiv*, 1890, CXXI., p. 104).—Harden in alcohol or Müller's fluid, imbed in celloidin, and remove the celloidin before staining.

(*a*) Stain sections for half a minute in a concentrated aqueous solution of fuchsin.

(*b*) Wash in water.

(*c*) Decolorise in a syrup-thick solution of sugar with the addition of a few drops of sulphuric acid (3 ♏ to the 10 c.c.).

(*d*) Put the section on a slide and mount in non-acidulated sugar-syrup.

The elastin is stained a reddish violet.

This is a rapid, very delicate method, and the mounting in syrup gives a better definition to the fibres than balsam does, but it requires great skill to obtain satisfactory results with it, and it is not so permanent as the acid orcein or the Weigert method.

VII. *After Röthig* (*Archiv f. mikros. Anat.*, 1900, LVI., p. 354).—Harden in alcohol and imbed and cut in celloidin or paraffin.

(*a*) Stain the sections from two to twenty-four hours in the following solution of "kresofuchsin":

Kresofuchsin.	0·5 parts
Alcohol (95 per cent.)	100 „
Hydrochloric acid	3 „

Take 40 c.c. of the above mixture, add to it 24 c.c. of 95 per cent. alcohol, a few drops of picric acid, and 32 drops of water.

(*b*) Transfer to 95 per cent. alcohol.

(*c*) Completely dehydrate in absolute alcohol.

(*d*) Clear in xylol and mount in Canada balsam.

By this method the elastin is stained a deep blue.

If a counter-stain be desired, orange G may be employed, and in this case the nuclei are stained brown, the elastin blue, and the collagen yellow.

CHAPTER XVII.

THE PATHOLOGY OF THE CORIUM.

INFLAMMATION OF THE SKIN OR DERMATITIS IN GENERAL.

A **dermatitis** signifies simply an inflammation of the skin, and under this heading the majority of skin-diseases may be classed. The skin is *par excellence* the organ in which the changes which occur in inflammation can be most easily studied, and consequently it will not be amiss here to discuss briefly the salient features of inflammation of the skin in the light of the more recent researches on the subject.

Burdon Sanderson has defined *inflammation* as the "succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality." Adami[1] goes further than this, for he considers that inflammation is more than a series of changes constituting a reaction to injury; it is also a "local attempt at repair of actual or referred injury."

The injurious agent may affect the epidermis primarily, as in the case of a trauma, or the exposure of the skin to thermal or chemical irritants, or to the action of pyogenic organisms; on the other hand, the irritant may be situated in the corium, as when micro-organisms or their toxins are circulating in the cutaneous blood-vessels or have collected in the lymphatics. According to the intensity of the irritant, apart from its situation in the skin, a series of changes occur in the blood-vessels and fixed tissues of the corium, which constitute what is known as the "inflammatory reaction." The earliest evidences of this reaction of the skin to irritation occur in the blood-vessels nearest the site of the irritation. In the case of the irritant acting on the epidermis it is the underlying vessels of the papillary and sub-papillary layers

[1] *Allbutt's System of Med.*, 1896, I., p. 54.

which are primarily involved; but where the irritant is located in the corium it is the blood-vessels in its immediate neighbourhood which react first. These blood-vessels become dilated, leucocytes and plasma exude from them, and the blood-current is slowed. The initial stimulation of the skin causes a constriction of the vessels, but this is soon replaced by an inhibition of the vaso-constrictor nerves, which keep up the tone in the vessels, and a dilatation occurs. The leucocytes which extravasate from the blood-vessels infiltrate the lymphatic spaces around them and quickly make their way to the site of the irritation. They pass out of the vessels and spread through the tissue in virtue of their power of amœboid movement, being attracted to the irritant by the influence known as "positive chemotaxis"—a power which is also responsible for the increased exudation of plasma. Different irritants or different states of virulence of the same irritant are capable of causing different degrees of chemotactic action; so that while one irritant may produce only an exudation of plasma with a slight extravasation of leucocytes, another may cause a profuse leucocytic infiltration. In the case of virulent micro-organisms it is the toxins produced by them which constitute the chemotactic agent, and the polynuclear leucocytes so attracted are capable of destroying the irritating organisms by incorporating them. They possess what is known as the power of *phagocytosis*, and in consequence of this power these leucocytes (small granular oxyphiles) were named *microphages* by Metchnikoff. The eosinophiles (coarse granular oxyphiles) also have the power of destroying irritating organisms, not by phagocytosis, but by their power of discharging certain secretory products in the form of granules, which cause the destruction of micro-organisms (Kanthack and Hardy [1]).

When the irritant is chemical or thermal, the chemotactic agent is either the irritant itself or poisonous products eliminated by the epidermal cells owing to the action of the irritant.

When the leucocytes break up, a ferment is produced which causes a deposition of fibrin from the plasma, and the formation of a serous exudate. The amount of exudation varies greatly according to the intensity of the irritant. The exudation, like the leucocytes, plays an important part in the repair of the inflammatory process. It dilutes and sometimes destroys the irritant, and by the deposition of fibrin it limits the diseased area. But the vascular changes do not

[1] *Journ. of Physiol.*, 1894, XVII., p. 81.

constitute the whole of the phenomena of the inflammatory reaction; changes also occur in the fixed cells of the corium. These are usually of the nature of a hyperplasia; but if the irritation be very intense, they may be destructive in character and may result in various forms of degeneration of the cellular and fibrous elements of the corium. The fixed-cell hyperplasia will be referred to in connection with the "cellular infiltration of inflammation."

In the process of repair the young connective-tissue cells (fibroblasts) perform an important *rôle*; they evolve into new fibrous tissue. The extravasated leucocytes now gradually break up, and their *débris* is eventually absorbed. It has been stated, but not definitely proved, that leucocytes may develop into fibroblasts, and so participate in the process of organisation and reconstruction.

When the irritant is of sufficient virulence to destroy the vitality of the leucocytes which incorporate it, the leucocytes undergo a fatty degeneration and become pus-cells, and the inflammatory reaction has reached the stage of suppuration.

Types of Cells which form the Various Pathological Cellular Infiltrations of the Corium.

The infiltration of the corium by cells derived from the epidermis (epiblastic cells) has already been referred to in connection with carcinoma and nævi. We have now to consider the mesoblastic cellular infiltrations which are derived from the connective-tissue cells of the fibrous corium or from the walls of the blood-vessels,[1] and with which are associated a more or less profuse deposition of blood-cells.

Under the heading of mesoblastic cellular infiltrations of the corium three important types may be described—namely:

1. **The Cellular Infiltration of Simple Inflammatory Conditions.**
2. **That of the So-called "Granulomata."**
3. **The Malignant Cellular Infiltration of the Sarcomata.**

An arrangement such as this is far from being adequate, but it may be of some service in directing attention to the essential character of the cells which occur in the various

[1] Since the walls of the vessels are mesoblastic, like the fibrous corium in which they lie, it is impossible to dissociate the cellular hyperplasias of them from those of the other connective-tissue cells. But for purposes of convenience the description of special cell-proliferations of the vessels, such as endotheliomata and angio-sarcomata, will be deferred to the chapter dealing with the subject of the blood-vessels and lymphatics.

pathological conditions of the corium, and may thus be an assistance in diagnosis. This attempt to classify the cellular infiltrations of the corium is made with the object of discouraging the employment of loose expressions, such as an infiltration of lymphoid cells, a cellular exudation, a small-celled infiltration, an infiltration of embryonal cells, and the like. These expressions are too vague to be of diagnostic value, and can convey little information to those who have not seen the specimen which they are meant to describe. An infiltration of embryonal cells is a phrase which is frequently employed; but only in the sense of the "cell-rests"[1] of Cohnheim is such an expression intelligible, and an infiltration of cells, caused by the reversion and proliferation of cells of a fully formed tissue, though the cells may have become so simple in their structure as to resemble closely the undifferentiated cells of embryonic life, should not be designated an "embryonal cell-infiltration."

I. The Cellular Infiltration of the Corium which occurs in Simple Inflammatory Conditions.

When the skin is injured and an inflammatory reaction occurs, the lymphatic spaces of the corium are found to be more or less densely infiltrated with leucocytes. These are, as a rule, collected in foci around the vessels, pilo-sebaceous follicles, and the sweat-apparatus, and only rarely form a diffuse infiltration in the corium. The leucocytes are chiefly finely-granular oxyphiles, and are easily recognised by their multipartite nuclei and by the irregular shapes which they assume in consequence of their power of amœboid movement. Mononuclear leucocytes are also present among them, and occasionally eosinophiles (coarsely-granular oxyphiles).

But the irritation, if it be prolonged or severe, does more than cause a simple extravasation of leucocytes; it causes at the same time a proliferation of the fixed cells of the corium, both of the connective-tissue cells proper and the cells of the vessel-walls. These daughter connective-tissue cells are small and round, and have a deeply stained nucleus, surrounded by a slight halo of faintly stained protoplasm. They have reverted to a simple type in which they so closely resemble small mononuclear leucocytes (lymphocytes) that it is practically impossible to distinguish between them;

[1] Groups of cells which have persisted from embryonal life without having become differentiated, and which have retained their embryonic potentiality for rapid proliferation.

PLATE XXI.

FIG. 1. CELLULAR INFILTRATION IN SIMPLE INFLAMMATORY CONDITIONS. ECZEMA. (× about 1000.)

a. Shows a longitudinal section of a capillary, with a few polynuclear leucocytes.
b. Small round cells with a faintly stained halo of protoplasm around the nucleus. The origin of these cells is undecided.
c. Connective tissue nucleus.

FIG. 2. A FEW OF THE SMALL ROUNDISH CELLS, ENLARGED.

The nuclei show a wide-meshed intranuclear network, and a few chromatin bodies.

FIG. 3. PLASMA-CELLS. (× about 1000.)

a. Showing several chromatin bodies around the nuclear membrane.
b. Plasma-cell with two nuclei.
c. Polynuclear leucocyte.
d. Lymphocyte.
e. Connective tissue nucleus.
f. Capillary in longitudinal section.

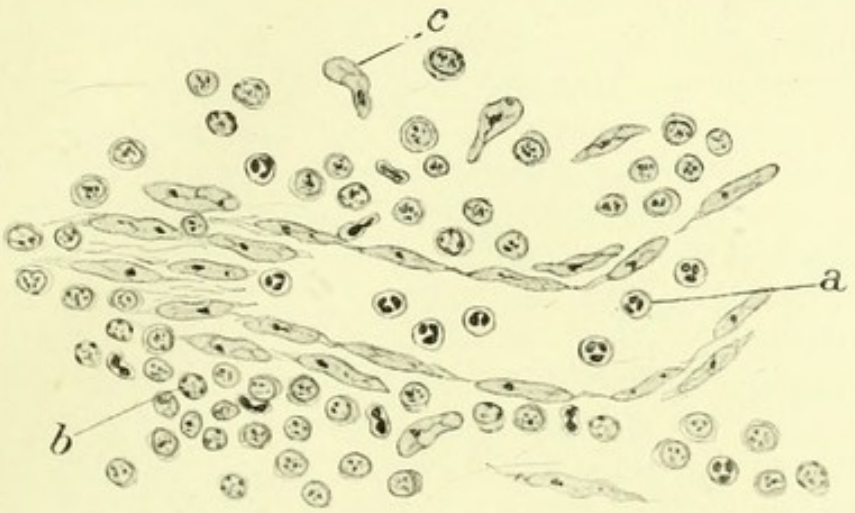

FIG. 1.

FIG. 2.

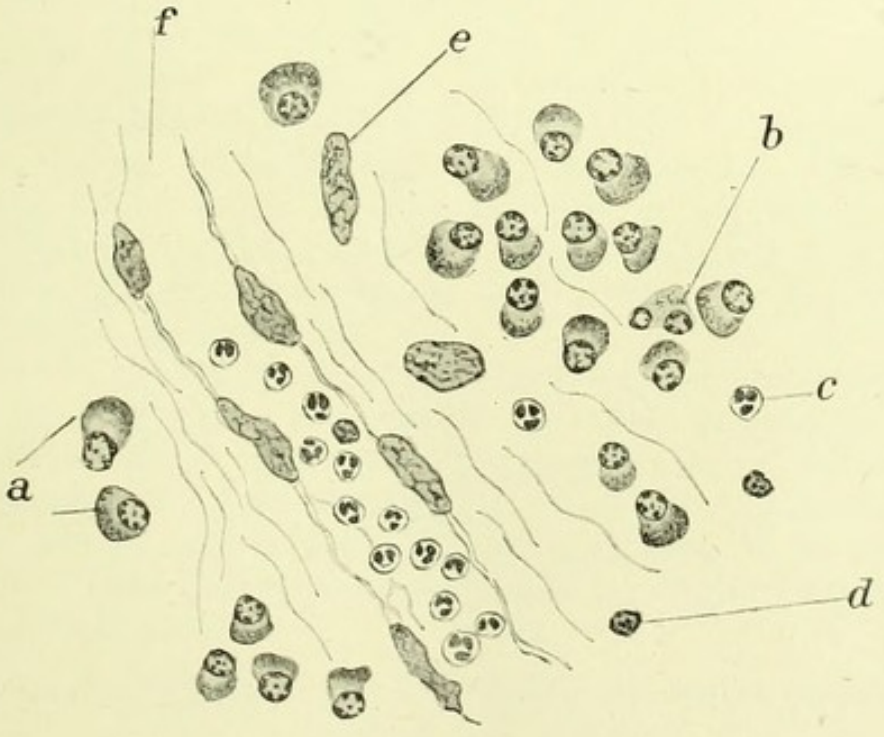

FIG. 3.

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consequently there is a great difference of opinion regarding the nature of the small mononuclear cells which infiltrate the corium in inflammatory conditions of the skin (Pl. XXI., Fig. 1), such as psoriasis and eczema. Certain observers declare that they are young connective-tissue cells, and cite as corroborative evidence the facts that they occur in clusters around vessels, and that the walls of the latter show distinct signs of a cellular proliferation; others maintain that they are chiefly lymphocytes. From their morphology and staining reactions by the present methods it seems scarcely possible definitely to decide their nature.

The fixed-cell proliferation takes place rapidly, and, combined with the leucocytes, is the cause to some extent of the swelling which is one of the cardinal signs of inflammation. Owing to the rapidity of the hyperplasia of fixed cells, it has been thought that they divided by the direct method, as it has been stated that the complicated process of mitosis is a somewhat slow one, as Darier expresses it, "la karyokinèse n'y apparait que très tardivement, à partir du quatrième jour seulement." (This assumption, however, has not been definitely proved.) Where the inflammation is more chronic, mitotic figures can generally be detected.

Another element may be added to the cellular infiltration in simple inflammatory conditions, if the action of the irritant has been prolonged—namely, the "plasma-cell" of Unna (*see* p. 157). When these cells occur, a much more persistent type of cellular infiltration is produced, which forms a connecting link between the simple inflammations and the granulomata. Plasma-cells may be found in the indolent nodules which occur in acne vulgaris, in the lumpy lesions produced by the large-spored fungus of ringworm (ectothrix) affecting the beard-region, as well as in a large number of other forms of dermatitis.

The irritant may cause a swelling of the connective-tissue cells so that their protoplasm becomes unusually distinct, and stains well. The irritation may, however, be so severe that instead of a cellular hyperplasia resulting from the action of the poison, the nutrition of the cells may be so interfered with that their vitality is destroyed and cellular degenerations occur (*see* p. 171).

Résume of the Types of Cells which occur in Simple Inflammatory Conditions of the Skin.

Any of the cells which are present in the corium in health may be found in inflammatory conditions—namely, ordinary

connective-tissue cells, vacuolated cells, and mast-cells. Besides these, there are:

Fixed Cells.—

1. Daughter-cells derived from the fixed cells of the fibrous corium and the vessel-walls. These are small roundish cells, with round, darkly stained nuclei, and a slight halo of faintly stained protoplasm.
2. Swollen connective-tissue cells.
3. Degenerated connective-tissue cells.
4. Plasma-cells.
5. Endothelial cells.

Migratory Cells.—

1. Polynuclear leucocytes, which are present in largest numbers where the irritant is a pyogenic microbe.
2. Small mononuclear leucocytes or lymphocytes.
3. Eosinophiles—occasionally, as in dermatitis herpetiformis, pemphigus, etc.

II. Types of Cells which occur in the Cellular Infiltrations of the So-called "Infective Granulomata" (Tuberculosis, Syphilis, etc.).

In the *infective granulomata*, in addition to the various types of cells which occur in simple inflammatory conditions of the skin, large numbers of *plasma-cells*, *multinucleated cells*, and sometimes *giant-cells* occur. Since plasma-cells and giant-cells are of almost pathognomonic importance for this group of diseases, it will be necessary to describe them somewhat carefully, and to consider their significance.

Plasma-Cells.

Name.—Waldeyer,[1] as has already been stated, was the first to introduce this confusing name. He used it in a totally different sense from that in which it is now employed. He meant by plasma-cells the vacuolated cells and the mast-cells of healthy connective tissue.

Unna[2] applied the name to cells (peculiarly rich in protoplasm) which occurred pathologically in the corium. He thought at first that these cells were identical with the cells described by Waldeyer, but afterwards found reason to change his opinion.

[1] *Max Schultze's Archiv*, 1875, XI., p. 176.

[2] *Monats. f. prakt. Derm.*, 1895, XX., p. 477, and 1891, XIII., p. 364.

Waldeyer then advised the restriction of the name to the type of cell described by Unna, and by a general consensus of opinion this view has been adhered to, so that by plasma-cells are now generally meant those cells, rich in protoplasm, which occur in the corium pathologically, and which were first carefully described by Unna. The name is unfortunate and confusing, since it suggests a connection with blood-cells, and this connection Unna did not admit.

The Morphology of Plasma-Cells.—The cells are oval, roundish, or rhomboidal in shape, and vary in size from that of a leucocyte to twice its diameter. Their *nuclei* are large, corresponding in shape to that of the cell, are generally placed eccentrically, and vary considerably in appearance according to the method and the depth of the staining. Sometimes they resemble the nuclei of connective-tissue cells, being of the type known as vesicular nuclei, with an open intranuclear network and a few darkly stained chromatin bodies; at other times the intranuclear network is not noticeable, and the nucleus appears as a clear space with an occasional chromatin body, or six to eight coarse chromatin bodies arranged around the periphery. Two nuclei may sometimes be present in one cell. By the method of staining employed by Unna (*see* p. 160) the protoplasm of the body of the cell is more darkly stained than the nucleus, being especially dark towards the periphery of the cell, and around the nucleus a faintly stained zone may generally be detected. Unna maintains that the hyaloplasm of these cells is distinctly granular, and in consequence he names it the "*granuloplasm*." These cells divide usually without the production of mitotic figures, but occasionally mitoses have been observed. Beside this ordinary type of plasma-cells, small round cells whose nuclei are similar to those of the plasma-cells, but in which little or no granuloplasm can be detected around the nucleus, have been described by the same observer as "daughter plasma-cells," since he believed them to result from the division of the larger variety. These small cells occur in enormous numbers in the infiltration of tuberculosis cutis. Several observers, however, regard these small cells as small mononuclear leucocytes or lymphocytes.

The Conditions in which Plasma-Cells occur.—Plasma-cells occur in a large number of pathological conditions of the skin of a chronic inflammatory nature. In the infective granulomata (tuberculosis, syphilis, mycosis fungoides, etc.), for example, they occur so constantly and in such numbers as to be almost pathognomonic, and in consequence Unna

has suggested the term "plasmoma" for the type of cellular infiltration which occurs in these affections. They are present also in the corium in association with malignant proliferation of the epidermis, being found in the fibrous stroma of carcinoma, Paget's disease, and rodent ulcer. They occur in the neighbourhood of a sarcomatous infiltration, but seem to belong to a different category from the actual sarcoma-cells. They occur profusely in the indolent inflammatory nodules associated with acne vulgaris and sycosis of the beard-region. In acute inflammatory or suppurative processes they are generally absent.

Recently cells have been described in the lymph-nodes, lymphoid tissue of the spleen, and in the bone-marrow in health, which have been regarded as identical with plasma-cells. Hodara,[1] whose observations were corroborated by Darier, made a series of preparations with the view of deciding this point, and came to the conclusion that the cells which had been described as plasma-cells in the healthy blood-forming organs were not the plasma-cells of Unna, but were variously shaped mononuclear leucocytes (the "polyeidocytes" of Darier).

Nature and Origin of Plasma-Cells.—Ever since Unna's masterly description in 1891, the subject of the nature of the plasma-cells has been associated with continuous controversy. Unna at that time maintained that plasma-cells were pathologically altered connective-tissue cells, which had originated either in the fixed cells of the corium or in the adventitia of the blood-vessels, and he has seen no reason up to the present time to retire from this position, though it has been assailed on all sides.

The alternative view is that they are mononuclear leucocytes or lymphocytes—a view which has been strongly advocated by v. Marschalkó,[2] Jadassohn,[3] Justi,[4] and several other eminent histologists.

The following reasons may be formulated for the belief that plasma-cells are of connective-tissue origin:

1. It is possible to trace stages in the reversion of connective-tissue cells to plasma-cells, and in the evolution of a plasma-cell into a connective-tissue cell. In other words, plasma-cells are capable of organising.

[1] *Ann. de Derm. et de Syph.*, 1895, VI., p. 586.

[2] *Archiv f. Derm. u. Syph.*, 1895, XXX., p. 241, *and Centralbl. f. allg. Path.*, 1899, X., p. 851.

[3] *Berlin. klin. Wochenschr.*, 1893, XXX., p. 222.

[4] *Virchow's Archiv*, 1898, CL., p. 197.

2. The nuclei of plasma-cells as a rule show a closer similarity to connective-tissue nuclei than to those of mononuclear leucocytes, the nuclei of the former being generally "vesicular" and faintly stained, while in the leucocytes the nuclear network is denser, and the nuclei more darkly stained.

3. The size and shape of the plasma-cells differ greatly from those of the ordinary small mononuclear leucocytes, which form about 25 per cent. of the total number of leucocytes in the healthy blood.

4. Plasma-cells, though frequently collected in foci around the vessels, are not necessarily so, and may be found more or less diffusely distributed in the corium, independent of vessels. Leucocytes, on the other hand, are more definitely grouped around the vessels from which they have escaped.

The following reasons may be cited in support of the leucocytic origin of plasma-cells :

1. It is possible to trace transitional stages between lymphocytes and plasma-cells.

2. In the blood-forming organs large mononuclear leucocytes occur which are similar in shape and size to plasma-cells, while the small plasma-cells are identical with ordinary lymphocytes.

v. Marschalkó believes that though the great majority of the plasma-cells in the corium degenerate, a few of them are capable of developing into connective-tissue cells. It follows from the above assertion that the latter plasma-cells are, as it were, connecting links between leucocytes and fixed cells, and suggests that leucocytes are sometimes capable of organising.

Pappenheim,[1] who has recently introduced a new method of staining for plasma-cells (*see* p. 162), finds that morphologically and in their staining-capacity plasma-cells are indistinguishable from lymphocytes ; yet he states as a fact, without further proof, that lymphocytes and plasma-cells are two distinct types, the former belonging to normal reticular tissue, the latter being pathological.

A third view, which is in the nature of a compromise, has recently been suggested by Almkvist[2]—namely, that there are two varieties of plasma-cells : (1) those of Unna, which are of connective-tissue origin, and (2) those of v. Marschalkó, which are lymphocytes. This view makes the issue more confused

[1] *Monats. f. prakt. Derm.*, 1901, XXXIII., p. 340.
[2] *Archiv f. Derm. u. Syph.*, 1901, LVIII., p. 91.

than ever ; but as it is based chiefly on slight differences in staining reactions, and as the two types never exist together, it cannot be regarded as absolutely convincing.

The *origin of plasma-cells* is one of the most important subjects in the histo-pathology of skin-disease, but it is still an undecided problem. Those who believe in their leucocytic origin, and at the same time grant that they may organise, adopt a view which, if it were true, would greatly upset the existing ideas in pathology. This fact is, however, no argument against the hypothesis which they advocate. Still, it will require much more evidence than has up to the present been forthcoming in this polemic to convince one that an unstable structure like a leucocyte may evolve into a connective-tissue cell or even develop into the variety of cell which forms the most prevalent type in the granulomata of syphilis, tuberculosis and rhinoscleroma.

The Staining of Plasma-Cells.—Unna claims for his polychrome methylene blue solution a specific action in staining the protoplasm of plasma-cells. As in the staining of mast-cells with this dye, so in the case of plasma-cells, a certain degree of metachromism is evidenced by which the nuclei of the cells are stained blue, while the protoplasm assumes a violet tinge. The fact that the protoplasm attracts the violet constituent of the dye shows that it is basophilic in reaction, as the methylene red is the basic element in the stain : when the protoplasm of a cell becomes basophilic it indicates a degenerative change.

v. Marschalkó[1] does not admit that this stain is specific, or that it brings out certain specific characters, and recommends pure methylene blue. Pappenheim has recently introduced a compound stain, pyronin-methyl-green, by which he claims to be able to differentiate the nucleus and the protoplasm of the plasma-cell more definitely than by the method of Unna.

I. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 236).—Harden in alcohol.

(*a*) Stain from fifteen minutes to twelve hours in polychrome methylene blue (Unna).

Methylene blue	1 part.
Caustic potash or potassium carbonate .	·05 or 1 „
Aq. destil.	100 parts.

Allow this stain to stand for several weeks before use.

[1] *Centralbl. f. allg. Path. u. path. Anat.*, 1899, X., p. 851.
[2] *Monats. f. prakt. Derm.*, 1901, XXXIII., p. 79.

PLATE XXII.

FIG. 1. SECTION OF PAPILLA FROM THE SOLE OF THE FOOT. (× about 200.)

Stained with acid orcein to show elastin.

a. Stratum corneum.
b. Stratum lucidum.
c. Stratum granulosum.
d. Stratum mucosum.
e. Compound papilla, with elastic fibres which have a vertical direction and become fine fibrils.
f. Fine fibrils of elastic tissue passing in between the cells of the basal layer of the stratum Malpighii.
g. Large horizontal elastic fibres between the collagen bundles.
h. Collagen bundles in longitudinal section.
i. Collagen bundles in transverse section.

FIG. 2. SECTION OF SENILE SKIN STAINED TO DEMONSTRATE ELACIN. (× about 600.)

Stained with acid orcein, polychrome methylene blue and orange-tannin. Elastin, brown; elacin, blue; collagen, orange.

FIG. 3. MAST-CELLS. (× about 1000.)

The drawing was made from a section of Lupus vulgaris stained with polychrome methylene blue and glycerin-ether. The mast-cells were in different fields of the microscope.

a. Spindle-shaped mast-cell showing blue nucleus; no intranuclear network or nucleoli; large basophilic granules.
b. Mast-cell dividing without mitosis.
c. Irregularly branching mast-cells.
d. Mast-cell shaped like a plasma-cell.
e. Mast-cell with nucleus like that of a plasma-cell.

FIG. 4. PLASMA-CELLS. (× about 1000.)

Stained with polychrome methylene blue after Unna's Method I.

a. Plasma-cells with darkly stained periphery and lighter halo around the nucleus; faintly stained nucleus.
b. Transitional stage between connective tissue nucleus and a plasma-cell.
c. Connective tissue nucleus.
d. Mast-cell.

FIG. 5. PLASMA-CELLS. (× about 1000.)

Stained by Pappenheim's method.

a. Plasma-cells, granuloplasm reddish, nuclei bluish violet.
b. Connective tissue nucleus, red nucleoli.
c. Lymphocyte.
d. Mast-cell, with orange-coloured granules.

FIG. 6. LEPRA BACILLI IN MASSES AND IN CELLS. (× about 1000.)

Stained with carbol-fuchsin and methylene blue.

a. Clump of bacilli in glœa.
b. Bacilli in protoplasm of a cell.
c. Large clump of bacilli made up of two small clumps in glœas and several scattered bacilli.
d. Spindle-cell with a few bacilli.
e. Isolated bacilli.
f. Swollen cell with bacilli; nucleus pushed to the periphery of the cell.

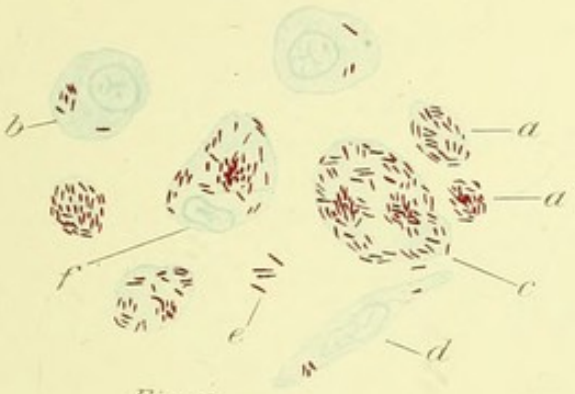

Fig 6.

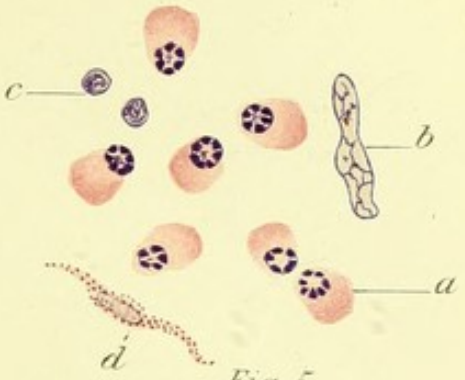

Fig 5.

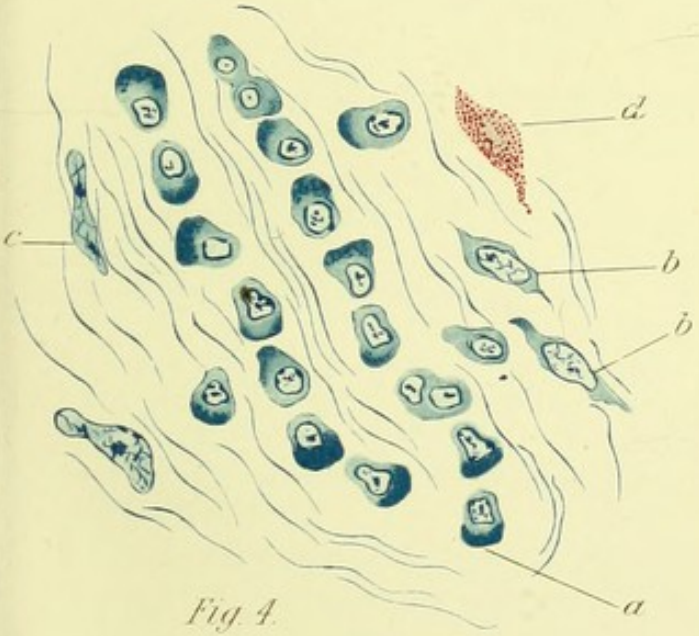

Fig 4.

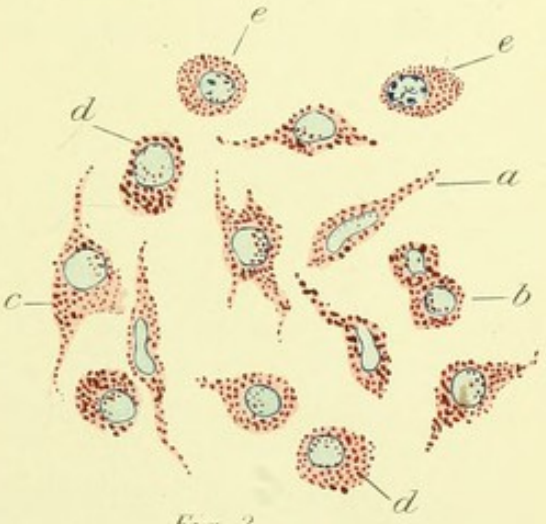

Fig 3.

Fig 1

Fig 2.

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(*b*) Wash in water.

(*c*) Decolorise and differentiate in glycerin-ether mixture (Grübler) (three to four drops of the stain to a watch-glass of water, or stronger if necessary).

(*d*) Wash thoroughly in water.

(*e*) Dry carefully on a spatula with a piece of filter-paper.

(*f*) Decolorise in absolute alcohol till the structure of the section is clearly defined.

(*g*) Clear in bergamot oil and mount in Canada balsam.

The plasma-cells are stained a bluish violet, the nuclei blue, and the mast-cell granules a cherry red.

II.—

(*a*) Stain for fifteen minutes in polychrome methylene blue.

(*b*) Wash in water.

(*c*) Dry thoroughly on a spatula.

(*d*) Decolorise and differentiate from three to five minutes in the following mixture :

Alcohol	10 parts
Anilin oil	25 „
Xylol	15 „

(*e*) Clear in xylol for a few minutes and mount in Canada balsam.

The colour of the cells is a more intense blue than when the glycerin-ether mixture is employed.

NOTE.—Instead of using the mixture at stage (*d*) in the above method, if there be much difficulty in decolorising, put the section after drying it, in equal parts of absolute alcohol and xylol for one minute, in pure xylol for one minute, and finally from five to ten minutes in a watch-glass containing anilin oil to which a few grains of alum have been added ; by this means over-stained sections can generally be decolorised.

III.—

(*a*) Stain from five to fifteen minutes in polychrome methylene blue.

(*b*) Wash in water and dry thoroughly.

(*c*) Differentiate and dehydrate from five to fifteen minutes in absolute alcohol, to which has been added $\frac{1}{4}$ per cent. of orcein.

(*d*) Transfer to absolute alcohol for a few minutes to remove the excess of the stain.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The plasma-cells are stained blue, the mast-cells red, and the collagen reddish brown.

IV. *After Bergonzini* (*Anat. Anzeiger*, 1891, VI., p. 595).—Harden in alcohol.

(*a*) Stain from three to four minutes in the following composite anilin stain :

Acid fuchsin	·5 part
Methyl green	1 „
Gold orange	1 „
Aq. destil.	100 parts

(*b*) Wash in water.

(*c*) Differentiate and dehydrate in absolute alcohol.

(*d*) Clear in bergamot oil and mount in Canada balsam.

NOTE.—I have not found this stain to be very satisfactory.

V. *After Pappenheim* (*Monats. f. prakt. Derm.*, XXXIII., 1901, p. 80).—Harden in alcohol and cut in celloidin.

(*a*) Stain the sections for five minutes in the following solution :

Pyronin	0·2 grms.
Methyl green	0·4 „
Distilled water	15 c.c.

(*b*) Wash in water till the fluorescent pyronin begins to come off.

(*c*) Differentiate in an alcoholic solution of resorcin :

Resorcin	1 grm.
Absolute alcohol	10 c.c.

(*d*) Dehydrate in absolute alcohol.

(*e*) Clear in bergamot oil and mount in Canada balsam.

The chromatin network and granules are stained bluish green, the nucleolus red, and the protoplasm of the cell bright purplish red, the granular nature of the hyaloplasm being evident ; the mast-cell granules are stained orange.

NOTE.—The amount of the constituents is not given definitely by Pappenheim in the above paper, and the figures given above are those which I have found to be most satisfactory.

GIANT-CELLS.

In the histological architecture of the lesions of tuberculosis the large multinucleated cells known as giant-cells usually form a striking feature. It is a common error to regard these giant-cells as structures which are peculiar to tuberculosis and of pathognomonic value, for they may

occur in syphilis ; and smaller multinucleated cells may also be present in a large number of chronic inflammatory affections of the skin.

The Morphology of Giant-Cells.—Various types of giant-cells have been recognised, such as the giant-cells of bone (myeloplaxes or osteoclasts) ; giant-cells which appear when a foreign body, such as a section of a sponge, is grafted on the skin ; and the giant-cells which occur in the infective granulomata. The last variety is the one with which we are chiefly concerned in tuberculosis of the skin ; it has a more degenerate structure than the other types, differs from them in its morphology, and appears to belong to a different category.

The Giant-Cell of Tuberculosis Cutis.—When fully developed the giant-cells in tuberculosis of the skin present a homogeneous or very finely granular central portion, which is surrounded by a more or less complete ring of nuclei. In size they vary from twice to many times the breadth of a leucocyte. They may be round or oval in shape ; but as a rule their outline is broken and irregular, on account of a number of small processes which stretch out from the central mass into the surrounding tissues. It is generally believed that the shape of the cell is in a great measure determined by the extent to which the fibrous elements, and chiefly the elastin, persist in the region where the cell has formed. In the neighbourhood of the giant-cells the collagen fibres have generally disappeared ; but the elastin, which is more resistant to the tuberculous poison, may frequently be detected with careful staining, in the form of broken-up fragments in the centre of the giant-cells, passing out at the periphery, and thus causing the irregularity in the outline of the cells.

The nuclei of the giant-cells are similar to those of plasma-cells. They stain vividly in contrast to the central mass, which has a weak affinity for basic or nuclear dyes ; they vary in numbers from eight to ten up to a hundred or more ; and, occasionally, instead of being arranged in a ring, they may be grouped at the poles of the cell.

Sometimes tubercle bacilli may be detected in the central mass of the giant-cell, but, like the degenerate protoplasm in which they lie, they are difficult to stain (Pl. XXVI., Fig. 1).

It has from time to time been asserted that these giant-cells possess the power of amœboid movement, and are

phagocytic, like the myeloplaxes of bone; but this is not generally admitted.

The Significance of Giant-Cells.—The giant-cells in tuberculosis signify an attempt on the part of the cellular elements of the corium to resist the toxins eliminated by the tubercle bacilli. They have been defined as "cell monstrosities produced by the altered condition of growth imposed upon them by the presence in them, or in their neighbourhood, of some irritating body, more especially a living parasite" (Boyce). They are anomalous structures, in which the central portion is a product of degeneration, while the peripheral part exhibits an increased vitality in which a nuclear proliferation occurs in response to the irritant. The central mass has degenerated from the action of the irritant, and the peripheral portion has proliferated in order to limit its influence.

The Origin of Giant-Cells.—The mode in which these giant-cells originate is still disputed. The chief point at issue in the dispute is whether they develop from a single cell by a rapid proliferation of the nucleus without a corresponding division of the cell-protoplasm, or are formed by the coalescence of a number of cells. We may broadly regard the former view as that which pertains in the German school, while, as a rule, though there are of course individual exceptions, the latter view is chiefly adhered to by the French histologists.

Development from a Single Cell.—According to this theory, the nucleus of a large connective-tissue cell assumes a capacity for rapid reproduction, at first by mitosis, but later without the formation of karyokinetic figures. The protoplasm of the cell does not correspondingly divide, and so a cell with a number of nuclei is produced. The fact that the nuclei divide amitotically has been explained as being the result of the poisonous action of the toxin on them, which, though incapable of causing their disintegration, so far impairs their vitality that division occurs in this simple manner.

Development from a Number of Cells.—The alternative theory that a giant-cell is formed from a group of cells which arrange themselves around a few tubercle bacilli has also many supporters.

Since the nuclei in these cells may frequently be detected in the process of division, the balance of opinion favours the theory of their development from a single cell.

An intermediate view is taken up by Unna to explain the giant-cell formation in the skin. According to him, the giant-cell is derived from "homogenised plasma-cells." By *homogenisation* he means that the protoplasm of the plasma-cell becomes swollen and more homogeneous by losing its granular appearance. It also undergoes a chemical change, in which it ceases to attract basic dyes with the same avidity as ordinary plasma-cells do. He believes that giant-cells are generally the product of the coalescence of a group of such homogenised plasma-cells, but admits that sometimes a homogenised plasma-cell may show a nuclear proliferation with the division of the protoplasm, and in this way a multinuclear cell may develop from a single cell.

The Type of Cell from which Giant-Cells are Developed.—The French school hold that giant-cells originate from large mononuclear leucocytes, while a number of observers consider them to be of connective-tissue cell origin. The problem really resolves itself into that of, what are "plasma-cells"? since it seems generally admitted that they develop from cells pertaining to the latter type. The fact that giant-cells develop from plasma-cells seems a strong argument that plasma-cells are derived from the fixed cells of the corium. A giant-cell is a resistant structure, while a leucocyte, especially when it leaves the vessels, readily breaks up, and seems far too fragile to give rise to it.

Multinucleated Cells or Chorioplaques.—In addition to true giant-cells, such as occur in tuberculosis, cells with two to ten or more nuclei, arranged in a cluster in the centre or at the poles of the cell, may also be found. These multinucleated cells, or *chorioplaques*, as these are called to distinguish them from true giant-cells, differ from the latter in that their nuclei are not arranged in a ring or crescent, and from the fact that the protoplasm of the cell does not degenerate into a finely-granular mass. They are derived from a single cell of the plasma-cell type.

The Conditions in which True Giant-Cells and Chorioplaques occur in the Skin.—True *giant-cells*, though they occur very constantly in tuberculosis of the skin, are by no means confined to that type of granuloma, and giant-cells indistinguishable from those of the latter disease may be found in papular syphilides and in a gummatous syphilide of the skin.

Chorioplaques occur much more frequently than true giant-cells. They are present in association with the latter in

tuberculosis and in syphilis, but may also be detected in the granulomata of yaws, rhinoscleroma, mycosis fungoides, and leprosy. They also appear in the granulomatous masses, which are present in acne vulgaris, in trichophytosis of the skin, and, in fact, in any chronic indurated affection of the skin where there is a definite attempt at resistance on the part of some of the cells against some active virus. They make their appearance also in sarcomata, and form the type of giant-cell which is met with in the giant-celled sarcomata.

Pathological Increase of Mast-Cells in the Corium.

A slight and sometimes considerable increase in the number of mast-cells in the corium is a common occurrence in many of the inflammatory conditions of the skin ; but its significance is not yet understood, and its inconstancy renders it, as a rule, of little value for purposes of diagnosis. In tuberculosis cutis an increase of mast-cells, generally most marked in the neighbourhood of the blood-vessels, is frequently present. In erythema multiforme there is often a marked increase in the number of these cells.

In urticaria pigmentosa the inordinate increase in the number of mast-cells is so striking as to be of pathognomonic value. In 1887 Unna drew attention to this fact, and his observations have been since corroborated by a number of observers, among others Bäumer,[1] Gilchrist,[2] and Brongersma.[3] In this disease rows and columns of mast-cells may be found grouped around the blood-vessels, hair-follicles, and sweat-glands, and granules from these cells may occasionally be detected lying free in the lymphatic spaces of the corium and subcutaneous tissue. Gilchrist's experiments proved that the mast-cells appeared suddenly, and that their appearance was synchronous with the formation of the wheal; for in the case of a child suffering from urticaria pigmentosa he was unable to find an increase of mast-cells in the apparently healthy skin—but if the skin were irritated and a wheal formed, and this were excised, fixed, and suitably stained, large numbers of these granular cells were noted.

As has already been pointed out (*see* p. 138), the prevalent view regarding the origin of the mast-cells of the corium is

[1] *Archiv f. Derm. u. Syph.*, 1896, XXXIV., p. 323.
[2] *Johns Hopkins Bull.*, 1896, VII., p. 140.
[3] *Brit. Jour. of Derm.*, 1899, XI., p. 179.

that they are degenerated connective-tissue cells, and are not identical with the mast-cells of the blood (Ehrlich). If they were simply blood-cells, it is natural to suppose that at one time or another in the course of this disease a marked increase of them would have been noted in the blood or in the walls of the blood-vessels; but as far as I am aware neither has been recorded. This disease is not a true urticaria, but a condition in which there is a cellular infiltration of mast-cells in the papillary body with which urticarial lesions are associated; and it has been suggested that the mast-cell granules act as a toxin, and produce the urticarial wheals.

The Types of Cells which infiltrate the Corium in the Sarcomata.

The types of cells which occur in the different forms of sarcoma cutis vary greatly in their shape, structure, and size. They may take the form of small roundish cells closely resembling mononuclear leucocytes; they may be several times larger, and be oval or cubical in shape; or they may form spindles, oat-shaped bodies, and not infrequently multinucleated structures ("giant-cells"). The sarcomatous cells are often pigmented. It is customary to classify the sarcomata, according to the type of cell which predominates, into: (1) small round-celled sarcomata; (2) large round-celled sarcomata; (3) spindle-celled sarcomata; and (4) giant-celled sarcomata.

The Small Round-Celled Sarcomata are rare in the skin, being found more generally affecting internal organs such as the liver; but a few small round cells may generally be found in association with the large round-celled and spindle-celled varieties of sarcoma cutis.

The cells resemble most closely the type of cell which is found in the cellular infiltration in simple inflammatory conditions, such as eczema (Pl. XXI., Fig. 1). They are not much larger than mononuclear leucocytes, but they differ from them in presenting, when stained by polychrome methylene blue, a more definite halo of protoplasm, and nuclei with a number of darkly stained chromatin bodies.

The Large Round-Celled Sarcomata form a considerable proportion of the skin-sarcomata. In them the cells are usually roundish, but through pressure may become cubical or polyhedral (Pl. XXIII., Fig. 1). They have a large round nucleus situated either in the centre of the cell or more or less

eccentrically, like the nucleus of a plasma-cell. The nucleus is difficult to stain deeply, and has comparatively little chromatin. The protoplasm of the cell is granular and easily stained. A few of these cells have two or three nuclei, and numerous mitotic figures may be detected by suitably fixing and staining them.

The Spindle-Celled Sarcomata.—The spindle-cells in sarcoma are identical with those found in embryonic connective tissue (Pl. III., Fig. 1). Some of them are small, with fine tapering poles; others are oat-shaped; while some are large and fusiform. Not infrequently they branch at the extremities to form branching cells like those found in granulation tissue (Pl. XVIII., Fig. 2). The nucleus is oval or spindle-shaped, and in the larger spindle-cells is vesicular in character. It is richer in chromatin than those of the round cells, and stains more vividly. The protoplasm of the cell is similar to that of healthy connective-tissue cells, and has a spongioplastic network and a homogeneous or finely-granular hyaloplasm (Pl. XXIII., Fig. 2).

Giant-Celled Sarcomata.—When giant-cells occur in large numbers in a sarcoma of the skin it generally signifies that the sarcoma is secondary to one affecting underlying bone: for example, they may be found in a sarcoma about the chin, when the jaw is affected (malignant epulis). They are not true "giant-cells," but belong to the variety of multinucleated cell known as a chorioplast or chorioplaque (*see* p. 165). The number of nuclei which they contain may vary from several up to fifty or more. Multinucleated cells seldom occur in association with skin-sarcomata other than those secondary to osteo-sarcomata. The cells are the result of a rapid amitotic proliferation of the nucleus without a corresponding division of the cell-protoplasm.

Pigment-Celled Sarcomata.—Any of the varieties of sarcoma-cells may occasionally be pigmented. In the very vascular sarcomata, such as the "angio-sarcomata," the sarcomatous cells in the neighbourhood of the vessels may have within and between them deposits of a brownish yellow pigment, giving the characteristic reactions of blood-pigment (Perls' test, *vide* Chap. XXXII.). On the other hand, true pigment-granules of melanin occur in many of the spindle-celled sarcomata; these have been named nævo-sarcomata, since they are believed to have originated in a pigmented mole. Recent research tends to prove that the pigmented cells of moles

PLATE XXIII.

FIG. 1. LARGE ROUND-CELLED SARCOMA. (× about 1000.)

a. Large round cell, with coarsely granular protoplasm.
b. Polygonal cell.
c. Chorioplaque.
d. Attenuated fibrous stroma.

FIG. 2. SMALL SPINDLE-CELLED SARCOMA.

a. Spindle-cell.
b. Leucocyte.
c. Polygonal cell.

FIG. 3. LARGE SPINDLE-CELLED SARCOMA.

Protoplasm of cells coarsely granular.

FIG. 4. NEUROFIBROMA CELLS. (× about 1000.)

a. Spindle-shaped connective tissue cell.
b. Round and polygonal cells.
c. Mass of spindle-cells.

FIG. 5. MYCOSIS FUNGOIDES. CRENATION AND FRAGMENTATION OF THE CELLS. (× about 1000.)

a. Connective tissue nuclei.
b. Crenated cells.
c. Chorioplaque.
d. Remains of collagen and cellular *débris*.
e. Nucleus surrounded by a mass of protoplasmic *débris*.

PLATE XXIII.

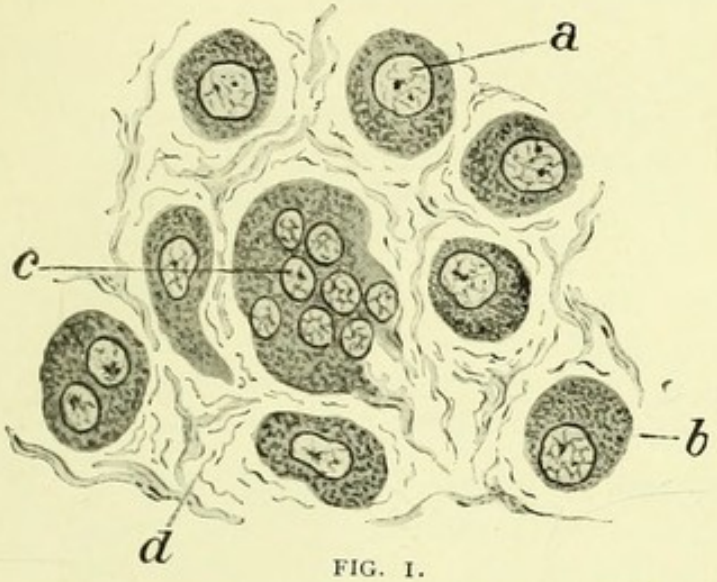

FIG. 1.

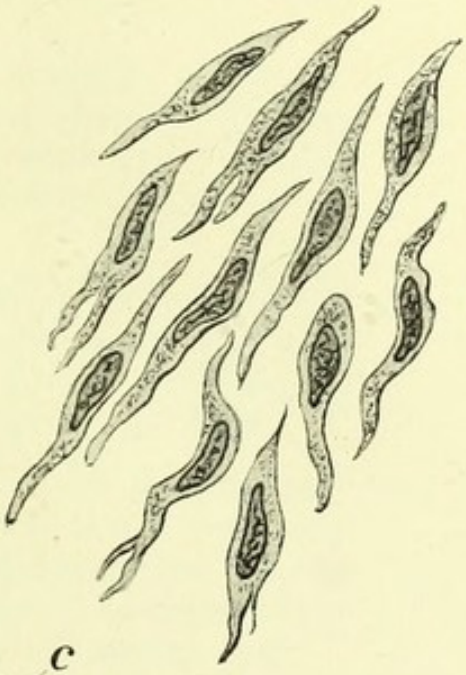

FIG. 3.

FIG. 5.

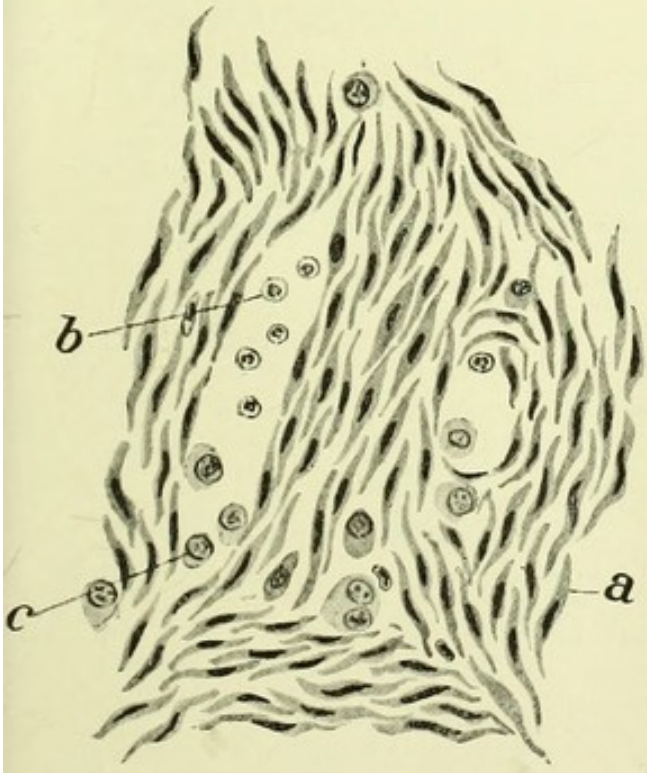

FIG. 2.

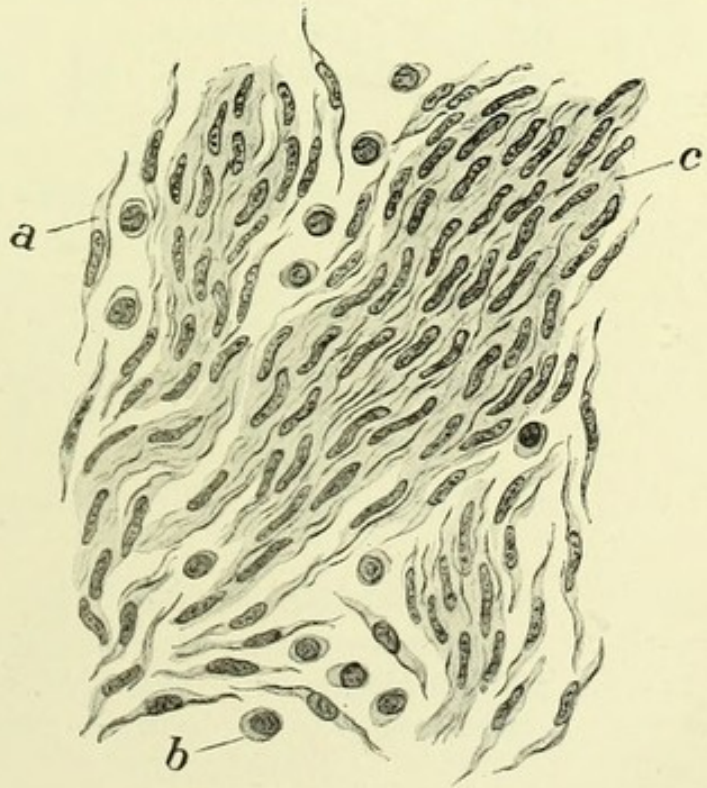

FIG. 4.

J. M. H. M., del.

are epithelial in origin, and that the rapidly malignant growths which were once believed to be nævo-sarcomata are in reality nævo-carcinomata. A few spindle-celled sarcomata which have developed in pigmented regions have melanin granules in the cells.

Besides these malignantly proliferating cells, towards the margin of the cellular mass, plasma-cells, mast-cells and ordinary connective-tissue cells may be found, and around the vessels, leucocytes are present in varying numbers.

The Nature and Origin of Sarcoma-Cells.—It is generally admitted that a sarcoma-cell of whatever type is a mesoblastic cell, derived in the skin from the connective tissue of the corium and the walls of the blood-vessels. The connective-tissue cell or fibroblast has "reverted to a simpler type"; it has ceased to fulfil its ordinary function of producing fibrous elements, and has assumed instead the more primitive function of reproduction. The first stage in the retorgression would be the spindle-cell, and the last the round or polygonal cell, the "giant-cell" being simply a monstrosity caused by an imperfect power of reproduction.

The cellular infiltration in the large round-celled variety is strikingly similar to that which occurs in the infective granulomata, and the large polygonal cells have so close a resemblance to plasma-cells that it has been several times asserted that they belong to the same category. Unna believes that the plasma-cell is an intermediate stage between the connective tissue cell and the large sarcoma-cell, in which the basophilic protoplasm of the plasma-cell is being converted into the coarsely granular protoplasm of the sarcoma-cell, and he has found numbers of unaltered plasma-cells at the margins of the sarcomatous mass.

Unna formulates the following differences between the plasma-cell and the large round sarcoma-cell:

1. The protoplasm of the sarcoma-cell is more coarsely granular, but is not so intensely and universally stained as that of the plasma-cell.
2. The chromatin has disappeared to some extent, and the nucleus stains more feebly.

To the other school represented by Neisser, Jadassohn, and v. Marschalkó, who believe in the leucocytic origin of plasma-cells, Unna's theory is untenable, and the existence of plasma-cells as a connecting link between connective-tissue cells and round sarcomatous cells is out of court.

The similarity of the polyhedral or round cells of sarcomata to Unna's plasma-cells is most striking, and their association in sarcomata is undeniable. The natural theory of a causal connection between the two seems more than probable, as cells may be met with where the greatest difficulty is experienced in deciding to which category they belong.

The whole question of cellular pathology is so beset with difficulties that much patient work is still required before these problems are settled.

CHAPTER XVIII

DEGENERATIONS OF THE CELLS AND FIBRES OF THE CORIUM.

The Degenerations of the Cells.

The great variety of the degenerations which may affect the cells of the corium, and the present limited knowledge regarding them, render it inadvisable to refer here to more than a few of the leading types. Any irritant, whether physical or chemical, which is capable of causing a cellular infiltration of the corium may, if its action be sufficiently prolonged or its virulence increased, be responsible for a degeneration of the cells.

Fatty Degeneration.—In necrotic processes affecting the corium, before the infiltrating cells break up, they not infrequently undergo a fatty degeneration. At first the affected cell becomes swollen, owing to the presence of an albuminous precipitate; but this is soon replaced by fat-globules. These globules run together and eventually break through the cell, and the latter disintegrates. In generalised xanthoma of the skin a fatty degeneration occurs in the connective-tissue cells; these become swollen, from being filled with fat-globules which push the nucleus to one side, and they gradually break down, and allow the fat to infiltrate the lymphatic spaces of the corium. In later stages a connective-tissue hyperplasia may replace the broken-down degenerated cells.

The Giant-Cell Degeneration.—The true giant-cells which occur in tuberculosis, and occasionally in old-standing syphilides, may be regarded as examples of a degenerative process affecting the protoplasm of a cell. This degeneration is peculiar, in that there is an increased vitality of the nuclei of the cells. It is a transformation of the cell-protoplasm in which the spongioplasm and the more or less granular hyaloplasm become converted by the influence of the infective virus into a homogeneous or finely-granular mass, which

stains faintly and no longer attracts basic dyes; but this is not a true caseation in Virchow's meaning of the term, which signified a dry fatty degeneration.

Hyalin Degeneration is a homogeneous degeneration of the cellular protoplasm which may affect not only the cells of the corium, but also those of the epidermis. In discussing the degenerations of the collagenous bundles I shall have to refer to "colloid degeneration" and to the fact that many observers regard colloid and hyalin as identical substances, and use the terms synonymously. It is very doubtful, however, if the degenerative substance which occurs in "colloid milium" is identical with that which is present in the cells of rhinoscleroma, where hyalin is found in quantity; and until this point is definitely settled, it seems to me to be advisable to restrict the use of the term "hyalin degeneration" to that type of degeneration which is intracellular, and which gives different staining reactions to amyloid, glycogen, and colloid, and to employ the term "colloid degeneration" for that in which the fibrous bundles are primarily implicated. This latter view, as it is supported by differences in staining reactions, as well as in the physical conditions of the two substances, strongly recommends itself, and if it were generally adopted would save much of the confusion which at present harasses the subject.

Hyalin is a semi-fluid substance which is strongly light-refractive and has a marked affinity for acid anilin dyes. It appears in the cell in the form of small, round granules about the size of mast-cell granules. These run together to form globules or clumps of various sizes, the cell swells and breaks up, and only then do the globules of hyalin lie free in the tissues.

The Hyalin Degeneration of the cells of the granuloma in rhinoscleroma has recently been carefully described by v. Marschalkó,[1] who tabulated the following stages in the degenerative process:

1. The protoplasm of the plasma-cell in which hyalin degeneration is commencing stains badly with such basic dyes as hæmatein or methylene blue, and this defective staining is most marked near the nucleus.

2. The cell becomes swollen; its margin loses its definition and may become toothed. The nucleus at this time seems healthy and stains normally.

[1] *Archiv f. Derm. u. Syph.*, 1900, LIII., p. 163.

3. The protoplasm of the cell becomes filled with granules, which are acidophilic in reaction, and attract strongly picrate of ammonia. The nucleus is unaffected. The granules consist of hyalin, and they are supported by the persisting spongioplasm. They are derived from the granuloplasm of the cell.

4. The granules coalesce to form globules, which give the cell an appearance resembling a mulberry. The nucleus, which either remains in the centre of the cell or becomes pressed against the side, gradually breaks up, and the chromatin alone persists as fine clumps lying between the hyalin globules of the swollen cell.

5. The cell now breaks up and the globules are discharged into the surrounding stroma.

The Conditions in which Hyalin Degeneration occurs.—Hyalin degeneration occurs not only in the infiltrating cells of rhinoscleroma, but also in syphilis, sarcoma and various suppurative conditions. It occurs also in epithelial cells in carcinomata. It is a degeneration of no great pathognomonic significance.

The Staining Reactions of Hyalin.—The substance *hyalin* is acidophilic in reaction, and is stained bright red by eosin and orange red by the van Gieson method (picrin and acid fuchsin).

I. *After Apáthy* (*Die Mikrotechnik der Thierschen Morphologie, I., Braunschweig*, 1896).—

(*a*) Harden in alcohol, after fixing for twenty-four hours in sublimate. It is advisable to remove the sublimate crystals before imbedding by putting the fixed tissue for twenty-four hours in 90 per cent. alcohol, to which 1 per cent. iodine has been added. Cut in celloidin.

(*b*) Stain from ten minutes to several hours in Apáthy's hæmatein mixture (Lee's *Vade-Mecum*, 5th edition, p. 186).

(*a*) Alum, 9 per cent., in water; glacial acetic acid, 3 per cent., in water; salicylic acid, 0·1 per cent., in water.

(*b*) Hæmatoxylin, 1 per cent. in 70 per cent. alcohol, preserved for six weeks in a bottle not quite full.

Mix one part of (*a*), one of (*b*), and one of glycerin.

(*c*) Wash in water, then put for a few seconds in alkaline water to fix the hæmatoxylin.

(*d*) Transfer for two to ten minutes to picro-rubin solution.

Picrate of ammonium	·8 grm.
Acid fuchsin	·2 grm.
Alcohol, 10 per cent.	100 c.cm.

(*e*) Wash in water.
(*f*) Alcohol, bergamot oil, Canada balsam.

Hyalin stains an intense yellow, with a tinge of orange, and the normal protoplasm has a violet tinge.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX p. 613).—Harden in alcohol and cut in celloidin.

(*a*) Stain for five minutes in a 2 per cent. aqueous solution of acid fuchsin.
(*b*) Wash in water.
(*c*) Transfer to a saturated aqueous solution of picric acid for two minutes, and to a
(*d*) Saturated alcoholic solution of picric acid, two minutes.
(*e*) Differentiate and dehydrate in alcohol.
(*f*) Clear in bergamot oil and mount in Canada balsam.

The hyalin is stained red, and the healthy protoplasm yellow.

III. *Ibid.*—

(*a*) Stain from twenty to thirty seconds in a 1 per cent. solution of water-blue.
(*b*) Wash in water.
(*c*) Stain for one or two minutes in a solution of carbol-fuchsin.
(*d*) Wash in water.
(*e*) Differentiate in alcohol, to which has been added a crystal of iodine to the watch-glass of alcohol.
(*f*) Absolute alcohol, bergamot oil, Canada balsam.

The nuclei and large hyalin clumps are stained cherry red, the protoplasm and small hyalin granules blue.

This indicates that in the clumps—*i.e.* the older hyalin—the attraction for acid dyes is less marked, since the acid element in this stain is the water-blue ; and it only stains the small granules, which are the first indication of hyalin degeneration.

IV. *After Noyes* (*Monats. f. prakt. Derm.*, 1890, X., p. 344).—

(*a*) Stain sections from two to three hours in weak hæmatoxylin solution.
(*b*) Wash in water.
(*c*) Stain for twenty-four hours in eosin.
(*d*) Dehydrate and differentiate in alcohol.
(*e*) Clear in bergamot oil and mount in Canada balsam.

The hyalin is stained a deep red, and the nuclei violet.

(Noyes uses the terms hyalin and colloid synonymously.)

V. *After Pelagatti* (*Virchow's Archiv*, CL., p. 247).—

(*a*) Stain sections for five minutes in a 2 per cent. aqueous solution of magenta.

(*b*) Wash in water.

(*c*) Stain for five minutes in a concentrated solution of water-blue and tannin (Grübler).

(*d*) Wash in water.

(*e*) Absolute alcohol, xylol, Canada balsam.

The hyalin is stained red and the surrounding tissue light blue.

Mucoid Degeneration.—In rhinoscleroma and leprosy another type of cellular degeneration occurs, to which Darier has given the name of "dégénérescence muqueuse." This type of degeneration is the cause of the formation of the "Mikulicz cells" in the former, and the "lepra-cells" in the latter disease (*see* p. 197). In this degeneration the cell becomes swollen up from the presence of specific bacilli in its protoplasm; reticulation occurs and the protoplasm stains more and more faintly. The nucleus frequently gets pushed to one side by the clusters of bacilli, and it shrinks and degenerates. The cell becomes converted finally into a homogeneous-looking mass densely packed with bacilli.

Œdematous Degeneration of connective-tissue cells occasionally takes place where marked œdema affects the corium. In lupus erythematosus, for example, œdematous connective-tissue cells may be found, and they may also occur as the result of the action of the actinic rays of the spectrum on the skin (Pl. II., Fig. 2). These cells are swollen, stain badly, and in the meshes of their stretched spongioplastic network œdematous fluid is present.

Crenation.—Crenation of the cells is a peculiar degenerative process in which the cells become irregular, toothed and crenated before they disintegrate. The nucleus breaks up last, and intact nuclei may be noted amidst the cellular *débris*. This type of degeneration occurs in the granuloma of mycosis fungoides (Pl. XXIII., Fig. 5).

The Degenerations of the Fibrous Elements of the Corium.

The Degenerations of Collagen.

The subject of the degenerations of the fibrous elements of the corium is, at the present time, in a state of almost

hopeless confusion. It is a peculiarly complex one, and has been rendered so partly by the promiscuous use by various writers of imperfectly defined terms, such as mucoid, colloid, hyalin, and the like, and partly by the recent addition of a series of new terms, such as collacin, collastin and basophilic collagen (Unna [1]), which indicate various degenerative products of collagen chiefly distinguished by their staining reactions. It will thus be necessary to append here a brief *résumé* of Unna's results and his methods of demonstrating these degenerative products.

(*a*) *Basophilic Collagen.*—In the process of degeneration of collagen it undergoes at first a change in reaction in which it ceases to attract acid dyes, such as water-blue and acid orcein, as it does in health, but assumes a marked affinity for basic dyes, such as carbol-fuchsin and safranin. Basophilic collagen retains the same structure as normal collagen, and can only be distinguished from it by its staining peculiarities. It is found that the degeneration begins in the centre of the bundle, and in many of the bundles the centre alone is affected. This degeneration may be found in myxœdema, mycosis fungoides, and various other conditions.

(*b*) *Collastin.*—This is a degenerative product of collagen which stains with the acid dyes which stain elastin. In this the original structure of the collagen may remain unaltered, or it may break up into coarse irregular masses or blocks, which eventually crumble into small fragments. Unna regards it as a combination of elastin with collagen. In myxœdema he remarks : " It is certain that some of the basophilic collagenous fibres are impregnated or covered externally with elastin, and that we are dealing with fibres of collastin " (Unna).

(*c*) *Collacin* is a degenerative combination-product of collagen and elacin (degenerated elastin). The structure of the collagenous bundle is retained, but the staining reaction is that of elacin or basophilic elastin. It gives a more intense basophilic reaction than basophilic collagen.

Collastin and collacin occur in colloid milium, senile degeneration of the skin, and myxœdema.

The Methods of Staining the Degenerations of Collagen.

After Unna (*Monats. f. prakt. Derm.*, 1894, Bd. XIX., p. 474).—The tissue to be hardened in alcohol.

1. *For Basophilic Collagen.*—

(*a*) Stain the sections for five minutes in carbol-fuchsin.

[1] *Monats. f. prakt. Derm.*, 1894, XIX., p. 465.

(*b*) Wash in water.

(*c*) Fix the stain in a 33 per cent. aqueous solution of tannin, and wash in a 1 per cent. solution of water-blue for half a minute.

(*d*) Differentiate in 1 per cent. acid alcohol for a few seconds.

(*e*) Dehydrate in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

The basophilic collagen is stained red, the normal collagen blue.

2. *For Collastin.*—

(*a*) Stain the sections for ten minutes in warm acid orcein.

(*b*) Partially decolorise in spirit.

(*c*) Stain them for a few minutes in a 2 per cent. aqueous solution of acid fuchsin.

(*d*) Wash in water.

(*e*) Put the section for one minute in a saturated aqueous solution of picric acid.

(*f*) Then for one minute in a saturated alcoholic solution of picric acid.

(*g*) Differentiate and dehydrate in absolute alcohol.

(*h*) Clear in bergamot oil and mount in Canada balsam.

The collastin and elastin are stained brown, the collagen and nuclei red, the protoplasm yellow.

3. *For Collacin.*—

(*a*) Stain the sections for ten minutes in acid orcein.

(*b*) Partially decolorise them in spirit.

(*c*) Stain them for five minutes in carbol-fuchsin.

(*d*) Wash in water.

(*e*) Fix them for half a minute in a 33 per cent. aqueous solution of tannin.

(*f*) Wash in water.

(*g*) Counter-stain for one minute in a 1 per cent. solution of water-blue.

(*h*) Differentiate for a few seconds in acid alcohol (1 per cent. hydrochloric acid).

(*i*) Differentiate and dehydrate in absolute alcohol.

(*j*) Clear in bergamot oil and mount in Canada balsam.

The collacin, elacin and nuclei are stained red, the collastin and elastin brown, and the collagen blue.

It is comparatively simple to demonstrate the basophilic reaction in degenerating collagen; but the proof of the presence of collacin or collastin, based on slight differences of staining-

reaction, requires considerable skill and experience in technique. Several observers have corroborated Unna's results. Personally, I must frankly confess that although I have made a number of attempts to demonstrate collacin or collastin in tissues where they have been described, I have not as yet succeeded in doing so, though I had no difficulty in demonstrating basophilic collagen.

Colloid Degeneration.—The term "colloid" has been employed so loosely and with so many different meanings that it is difficult at present to find any agreement among authors as to what is meant by it.

It was a name originally applied to the peculiar transparent jelly-like substance of the thyroid gland. Klebs[1] regarded "colloid degeneration" as a degeneration in which homogeneous masses were deposited which were similar to thyroid colloid, and he included under the heading of albuminous degenerations colloid, amyloid, hyalin and mucoid degenerations. v. Recklinghausen,[2] on the other hand, believed colloid to be a collective term, which included amyloid, hyalin, and mucoid degenerations. Ernst[3] showed that the colloid which resulted from a connective-tissue degeneration differed in its staining reactions from thyroid colloid, since by v. Gieson's method (acid fuchsin and picric acid) the degenerative product stained red, while thyroid colloid stained yellow.

In the present state of our knowledge colloid degeneration may be regarded as a homogeneous, structureless substance, occurring in refractile masses or blocks, which results from the degeneration of the fibrous elements of the corium, and which is neither amyloid nor glycogen, but whose chemical nature is still uncertain. It seems to be a complex albuminous substance.

Unna considers[4] that collastin may become swollen and transformed into colloid, but that collacin and elacin are not capable of doing so, merely breaking up into fragments.

Colloid degeneration has been specially described in association with the disease known as "colloid milium of Wagner." The small transparent nodular lesions of this disease contain gelatinous masses of colloid.

The Staining of Colloid.—Colloid stains badly; it attracts

[1] *Allg. Path.*, 1889, II., p. 103.
[2] *Handb. der allg. Path.*, 1883, p. 397.
[3] *Virchow's Archiv*, 1892, CXXX., p. 377.
[4] *Histo-Pathology* (Walker's Trans.), 1896, p. 988.

acid dyes more strongly than basic ones. The following method after v. Gieson may be employed :

After v. Gieson (*v. Kahlden*, 1898, p. 45).—

(*a*) Harden in alcohol or Müller's fluid.

(*b*) Stain for half an hour in Delafield's hæmatoxylin solution.

(*c*) Wash thoroughly in water.

(*d*) Stain from three to five minutes in the following mixture :

Saturated aqueous solution of acid fuchsin.
„ „ „ „ picric acid

(*e*) Wash in water.

(*f*) Alcohol, xylol, Canada balsam.

By this method the colloid is stained a yellowish red, and the hyalin the same tint.

Myxomatous Degeneration.—Collagen may degenerate into a jelly-like substance containing mucin, similar to the Whartonian jelly of the umbilical cord. This is known as myxomatous or mucoid degeneration. It affects only the fibrous elements, for the cells may be detected lying apparently healthy in the midst of the gelatinous mass. In fact, in myxo-sarcoma the cells seem to be actively sending out branches and forming a network in which the jelly lies.

Myxomatous degeneration is most commonly found in the sarcomata, but is present also in other conditions, such as lipomata, fibromata and myxœdema. It is the mucin contained in this transparent jelly-like substance which gives it its peculiar chemical characters and staining properties.

Mucin.—Mucin is precipitated by and is insoluble in alcohol and water. It differs from colloid in being precipitated by acetic acid. It stains reddish by v. Gieson's method instead of yellow, like colloid. It is basophilic in reaction, and has the power of breaking up certain dyes into their metachromatic colours : for instance, polychrome methylene blue, toluidin blue, and thionin. By these dyes the mucin is stained reddish, and the healthy tissue blue. In its staining properties it thus closely resembles the mast-cell granules, and it has been suggested that the latter are possibly mucin or contain mucin. It stains also with hæmatoxylin and safranin.

Special Methods for Staining Mucin.—

I. *After Hoyer* (*Archiv f. mikr. Anat.*, XXXVI., 1890, p. 310).—

(*a*) Fix the tissue from two to eight hours in a 5 per cent.

sublimate solution. Harden in alcohol, imbed and cut in paraffin.

(*b*) Stain the sections from five to fifteen minutes in thionin solution (two drops of saturated solution of thionin in 5 c.c. of water).

(*c*) Wash in water.

(*d*) Alcohol, bergamot oil, Canada balsam.

II. *After Mayer* (*Lee's Vade-Mecum*, 1900, p. 454).—Stain the sections in his "mucicarmine." "One gramme of carmine is rubbed up in a capsule with 0·5 grammes of aluminium chloride (must be dry, not damp and yellow) and 2 c.c. of distilled water. The capsule is heated over a small flame for two minutes, until the originally light red mixture has become quite dark. Stir thoroughly. The liquid having become thick, add a little 50 per cent. alcohol, in which the warm mass ought to dissolve easily, and rinse the whole with more alcohol into a bottle. Make up to 100 c.c. with 50 per cent. alcohol; let it stand for at least twenty-four hours, and filter. This gives a stock-solution which is, as a rule, to be diluted for use ten times with distilled water."

Mucicarmine stains only the mucus in the sections. The section may be counter-stained with hæmatoxylin.

III. *After Unna* (*Monats. f. prakt. Derm.*, 1895, XX., p. 371).—Fix in 10 per cent. pot. bichromate. Harden in alcohol, imbed and cut in celloidin.

(*a*) Stain the sections for a few minutes in polychrome methylene blue.

(*b*) Wash in water.

(*c*) Fix for several minutes in 1 per cent. potassium ferricyanide.

(*d*) Wash.

(*e*) Alcohol, bergamot oil, Canada balsam.

Mucin and mast-cell granules stain red, the tissues blue.

NOTE.—This peculiar basophilic reaction of mucin is another evidence that collagen in degenerating becomes more acid.

Œdema of the Collagen.—In œdematous conditions of the corium the fibrous bundles may be dissociated into their component fibres by œdema. But as a rule the fibres recover when the fluid becomes absorbed and no destruction takes place.

Rarefaction of the Collagen usually occurs in association with the granulomata. It is often referred to as a "reticular metamorphosis," but it is in reality a destructive process, in which the collagen and elastin fibres become attenuated and finally break down.

The Degenerations of Elastin.

Elastin.—When elastin degenerates there is at first a diminution in its staining avidity for acid dyes. This was noted by Schmidt,[1] Reizenstein,[2] and other observers. As the degeneration proceeds, a basophilic substance is produced which no longer attracts acid dyes, but stains with basic solutions such as safranin and methyl blue. This substance was named by Unna *elacin*, and he defines it as "the substance of such fibres which, although presenting the outward appearance of elastic fibres, yet are clearly of a different chemical nature, since they cease to attract acid dyes, but take up basic dyes, in alkaline solution, with great avidity." It develops first in the upper part of the corium, and later in the deeper portions of the pars reticularis (Pl. XXII., Fig. 2).

Elacin occurs in senile skin, in myxœdema, and in a number of other degenerated states of the corium.

The Methods of Staining Elacin.—

I. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 402).—Harden in alcohol and cut in celloidin; remove the celloidin by alcohol-ether before staining.

(*a*) Stain in acid orcein for twenty minutes.

(*b*) Decolorise in alcohol, leaving the elastin alone stained.

(*c*) Wash in water.

(*d*) Stain for a quarter of an hour in polychrome methylene blue.

(*e*) Wash in water.

(*f*) Differentiate for ten minutes in a 33 per cent. aqueous solution of tannic acid.

(*g*) Wash in water.

(*h*) Dehydrate in absolute alcohol.

(*i*) Clear in bergamot oil and mount in Canada balsam.

Elastin is stained brown, elacin dark blue.

NOTE.—By omitting the acid orcein the elacin alone is stained. By adding 10 per cent. of orange to the tannin

[1] *Virchow's Archiv*, 1891, CXXV., p. 239.
[2] *Monats. f. prakt. Derm.*, 1894, XVIII., p. 1.

solution the collagen is stained yellow, and acid fuchsin may be substituted for acid orcein to stain the elastin.

II. *After the same Author.*—

(*a*) Stain from two to five minutes in a 1 per cent. water-blue solution.

(*b*) Wash in water.

(*c*) Stain in a 0·1 per cent. solution of safranin in anilin water for three minutes.

(*d*) Differentiate for a few seconds in faintly acidulated alcohol (1 per cent. hydrochloric acid).

(*e*) Dehydrate in absolute alcohol.

(*f*) Clear in bergamot oil and mount in Canada balsam.

Elacin is stained red, collagen blue.

NOTE.—The elastin may be previously stained by acid orcein or acid fuchsin.

Colloid Degeneration of Elastin.—Schmidt and Reizenstein have described minutely a still further degeneration of elastin in senile skin, in which the elastic fibres become swollen and homogeneous, and break up into various-sized masses, clumps or granules. This degeneration is of the same type as the colloid degeneration of collagen.

CHAPTER XIX.

PATHOLOGICAL CONDITIONS CHIEFLY INVOLVING THE CORIUM.

CHANGES IN THE FIBROUS ELEMENTS.

Hypertrophy of the White Fibrous Tissue or Collagen.

An increase in the white fibrous stroma of the corium may take place either by a thickening and lengthening of the pre-existing bundles of collagen, or by a growth of new ones. It is difficult to draw a hard and fast line between these two processes, and any attempt to do so will be more or less unsuccessful, as they generally occur together. Till it is definitely proved how the collagen fibres develop—whether they are simply the result of the differentiation of the intercellular ground-substance, or are produced by a transformation of the processes of the connective-tissue cells—it is advisable to refrain from being dogmatic with regard to their pathology. This subject of the origin of these fibres is, however, of the first importance to the histologist; and though it is not definitely settled, the former is the more probable and certainly the more workable hypothesis.

The hypertrophies of the collagen may be divided into: (1) **Diffuse Hypertrophies** and (2) **Circumscribed Hypertrophies.**

1. **Diffuse Hypertrophy.**—Under this heading may be considered the formation of scar tissue in general. *Scar tissue* or *granulation tissue* (Pl. XVIII., Fig. 2) is a valuable material for the study of the formation of new fibrous tissue or *fibromatosis*, as it is sometimes designated. It was on account of certain close resemblances in the histological architecture of tuberculosis and syphilis to that which occurs in a granulating wound that Virchow named this group of diseases the *infective granulomata*. A brief

reference to the changes which occur in the transformation of the flabby, moist granulations of a wound healing by second intention into firm, permanent scar tissue, will be helpful in explaining the structure of the infective granulomata.

A section of a moist superficial granulation of a granulating wound has in its centre a wide, vertical capillary loop. This is surrounded and supported by a fine fibrillary network, which is distended with serous fluid, and in the meshes of which lie a few leucocytes, numerous oval or polygonal cells several times larger than leucocytes (fibroblasts), and a number of connective-tissue spindle-cells. This fine fibrillary network is connected with branching cells, from which it possibly originated.

The endothelial cells of the capillaries are large, and may here and there be seen to be proliferating; and new capillaries may develop. As the healing process advances the œdema diminishes and the number of polygonal cells becomes less; but the spindle-cells increase in number, and new collagen fibres form which press upon and gradually tend to obliterate the capillary loop. There is considerable diversity of opinion with regard to these oval or polygonal cells and their relation to the connective-tissue spindle-cells. The majority of writers, however, regard them as the precursors of the spindle-cells, and name them fibroblasts. Unna maintains, on the other hand, that certain of them are plasma-cells which have originated from the spindle-cells.

The spindles and branching cells are much larger than the ordinary connective-tissue spindles, and their spongioplasm forms a network the fibres of which pass out into long, tapering processes. *Chorioplaques* and curious large flat cells with two or more nuclei may frequently be detected in granulation tissue; the latter are in the form of blunt wedges, with large processes stretching out from the blunt end, and have been named by Unna "*plate-cells*." Between the branching spindles, and without any apparent connection with them, fine collagen fibrils may be observed. These are probably connected with cells which do not appear in the section, but are in a different plane, since one of the most striking peculiarities of the cells is the great length of their tapering branches. The process by which the polygonal cell becomes a spindle-cell, the spindle-cell a branched cell, and the branches of the cell become converted into collagen, is generally described as the process of *organising*; but whether an actual transformation of the intercellular semi-

solid substance into fibrils of collagen also takes place has yet to be proved.

This organisation, fibromatosis or new formation of collagen fibres not only occurs in association with granulating wounds, but also in a large number of affections of the corium. After recurrent attacks of erysipelas and lymphangitis, where a persistent œdema has occurred, the œdema causes a rarefaction of the fibrous stroma which is followed by a fibromatous process. These stagnating conditions were for a long time considered to be due to a blocking of the lymph-vessels ; but they are now generally believed to be the result of a blocking of the superficial veins from an endophlebitis and thrombosis. Elephantiasis and the so-called lymphodermic swellings may be relegated to this class, and they illustrate a fibromatosis which has supervened on a destruction caused by œdema.

In the diffuse variety of the peculiar, hard and shiny condition of the skin known as *sclerodermia*, the hardness is due to a hypertrophy of the white fibrous tissue. In the whole of the affected area the collagen of the pars reticularis is thickened, and new fibres have developed and formed a dense compact mass, from which the lymph-spaces have to a great extent, if not entirely, disappeared. The blood-vessels, hair-follicles, and coil-glands are also diminished or obliterated by the growth and pressure of the fibrous mass. This condition is more the result of a hypertrophy of pre-existing collagen bundles than of the formation of new ones.

In syphilis, tuberculosis, and several of the other infective granulomata a new formation of the fibrous elements results in the production of scar tissue and occasionally in considerable hypertrophy.

2. **Circumscribed Hypertrophy.**—A circumscribed hypertrophy of the collagen is comparatively rare, but it does occur in the benign neoplasms of the skin known as *fibromata* (Pl. XXIII., Fig. 4). These usually develop from the perineurium and the fibrous tissue in the interior of the peripheral nerves ; but they may arise also from the other white fibrous elements of the corium. The fibrous nodule is made up of thickened collagen bundles, which interlace with each other irregularly, and, as a rule, it is only moderately cellular. The vessels and follicles are pushed aside by the growth, and become atrophic. In the more diffuse and softer forms of fibromata new collagen fibres occur in large numbers,

and the tumour is more cellular, owing to the presence of young connective tissue cells, spindles, and plate-cells between the fibres.

Keloids form another instance of a circumscribed hypertrophy of the collagenous tissue. In them there is an increase in the length and breadth of the existing collagenous bundles; and these lie in compact masses parallel to the surface. The formation of keloids denotes an idiosincrasy of the corium by which hypertrophy of the collagen readily occurs on the slightest injury, and it is more than probable that the so-called spontaneous keloids are the result of a slight, perhaps unheeded, injury in a susceptible skin, or inflammatory changes due to the presence of some micro-organism.

Atrophy Affecting the White Fibrous Bundles.

The pathological conditions in which an atrophy and destruction of the collagen occur are very numerous. In the infective granulomata, such as syphilis, tuberculosis and leprosy, the collagen bundles are atrophied, shrivelled and eventually disintegrate, as if the cell-infiltration had developed at their expense. In scar-leaving diseases, such as lupus erythematosus, rarefaction and degeneration of the collagen occur. The collagen and elastin also disappear where the cellular infiltration is densest in sarcoma and carcinoma. In the various œdematous conditions of the corium—for example, in the œdematous papillary layer in eczema—the collagen becomes attenuated, and in all the necrotic processes it rapidly breaks down.

Hypertrophy and Atrophy of the Elastic Tissue.

There is no circumscribed **hypertrophy** of the elastic tissue. Occasionally its fibres are increased in thickness, but never independently of similar changes in the collagen. I have noted a decided thickening of the elastic fibres in diffuse sclerodermia.

Destructive changes in the elastin are far more commonly met with. An **atrophy** of the elastin may occur in association with a hypertrophy of the collagen, and it is a constant accompaniment of a rarefaction of the latter fibrous element. Elastin seems to be more resistant to the toxins of the infective granulomata, and consequently persists longer than the collagen. If the elastic fibres be destroyed, an atrophic scar results. The elastic tissue forms an exo-skeleton

supporting the collagenous bundles, and when it is ruptured the unsupported collagen is allowed to expand, the superficial furrows of the skin disappear, and a smooth scar is produced. In this way the white striae of pregnancy and the radiating lines at the corners of the mouth in congenital syphilis are caused.

In operation wounds where healing takes place by "first intention," a regeneration of the elastic tissue may possibly take place, and little or no scarring result; but this observation has not been definitely proved.

Erythematous and œdematous affections of the skin leave the elastic fibres intact; they are stretched as long as the œdema is present, but usually recover when the œdema goes. The peculiar tissue-paper-like scars of tertiary syphilis and the atrophic scars which occur in lupus, leprosy, and in a number of other affections, are in great measure the result of a failure to regenerate on the part of the destroyed elastic tissue.

CHAPTER XX.

PATHOLOGICAL CONDITIONS OF THE CORIUM (*Continued*).

THE INFECTIVE GRANULOMATA.

UNDER the heading of "infective granulomata" it is now customary to place a number of inflammatory conditions chiefly affecting the corium, which form the connecting link between the simple inflammations such as eczema, and the neoplasms such as fibroma and sarcoma.

The following diseases fall into this class:

1. Tuberculosis cutis.
2. Syphilis cutis.
3. Leprosy.
4. Mycosis fungoides.
5. Yaws.
6. Actinomycosis.
7. Rhinoscleroma.
8. "Blastomycetic dermatitis" (Gilchrist and Stokes).

The basis of the histological structure in each of these granulomata may be said to be the plasma-cell, and for this reason Unna has suggested the name "plasmomata" for them. Multinucleated and true giant-cells may also be present, and there is a greater or less abundance of leucocytes. The presence of the peculiar cellular infiltration of the granuloma is always associated with a rarefaction and often a disintegration of the fibrous elements of the corium. Though there is a general similarity in the histological picture in all these granulomata, there are specific differences in detail which generally enable them to be differentiated by the microscope; but in preparations where the characteristic peculiarities are not very marked a diagnosis by the microscope may be extremely difficult or even impossible. The term "infective granulomata" is an appropriate one, in spite of the fact that in several of them the infective virus has not up to the

PLATE XXIV.

FIG. 1. NODULE OF LUPUS VULGARIS. (× about 1000.)

Stained with polychrome methylene blue.

a. Connective tissue nucleus.
b. Giant-cell.
c. Plasma-cell.
d. Small round plasma-cell or daughter plasma-cell (Unna).
e. Mast-cell.
f. Collagen.

FIG. 2. CELLULAR FOCUS OF SYPHILIS. (× about 800.)

Section of a papular syphilide, showing a vessel near the subcutaneous tissue surrounded by an infiltration of plasma-cells. Stained with polychrome methylene blue.

a. Lumen of a vessel in which three polynuclear leucocytes are present.
b. Proliferating endothelium of the vessel.
c. Plasma-cells.
d. Plasma-cell, with two nuclei.
e. Multinuclear cell.
f. Mast-cell.
g Collagen still persisting.

Fig. 2.

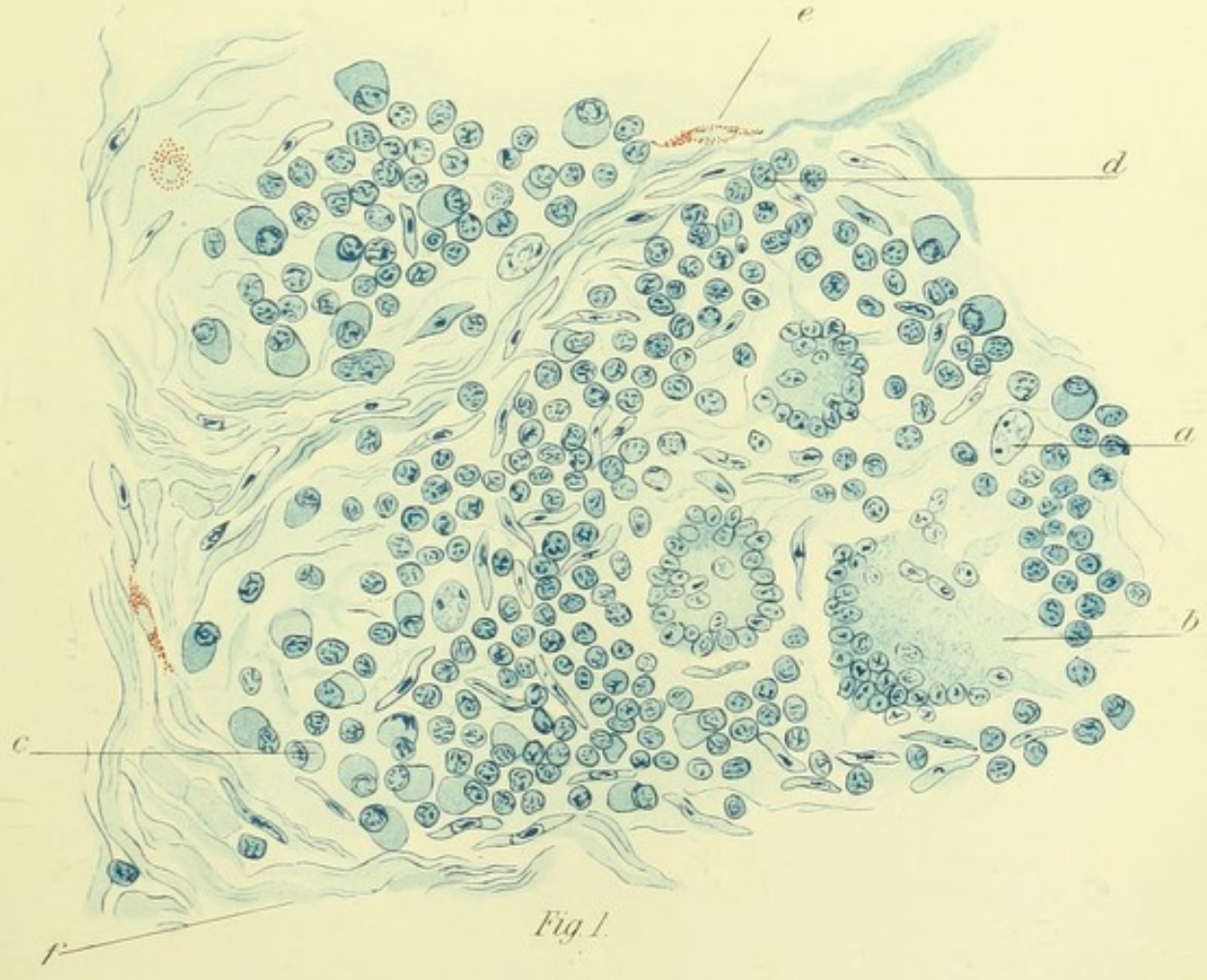

Fig. 1.

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present been found or its infectivity proved. A few of them are clearly the result of the reaction of the skin to a known virus, such as the tubercle bacillus or the leprosy bacillus, while the others present such a distinct general resemblance to them in their histology as to warrant the assumption that a specific virus exists in them also, and will in all probability be isolated in the future.

I will now describe briefly the main peculiarities in the histology of the members of this most important group.

I. Tuberculosis Cutis.

Every year our knowledge of the cutaneous manifestations of tuberculosis is becoming more complete, and we are gradually recognising the fact that in association with tuberculosis of the skin we may have almost as multiform an array of lesions as occurs in syphilis. The various lesions in the skin are the direct result of the presence and action of the tubercle bacillus and its toxin, and before a lesion can be definitely labelled as tubercular the tubercle bacillus must be demonstrated in it.

But besides this essential criterion much assistance can be obtained in the diagnosis from the peculiar histological picture which is generally associated with tuberculosis of the skin. The skin-manifestations of tuberculosis are *lupus vulgaris*, *scrofulodermia* and *miliary tuberculosis*; but besides these definitely tubercular lesions of the skin there are several others such as *lichen scrofulosorum*, *erythema induratum* and the so-called *tuberculides*, which, from their occurrence in association with generalised tuberculosis, have been included under this heading, although as yet the presence of the tubercle bacillus and the histological architecture of tuberculosis cutis have not been conclusively demonstrated.

Lupus Vulgaris.—In the lesions of lupus vulgaris, both in the nodular and the diffuse type of the disease, tubercle bacilli have been frequently detected. In twenty-four out of twenty-five cases Doutrelepont [1] was able to demonstrate the bacilli. This is, however, an exceptionally high average, and in the experience of most observers the search for tubercle bacilli in cases of lupus is not generally so successful. It is tedious and requires unlimited patience. The nodule of lupus with the peculiar granuloma which

[1] *Die Ætiologie des Lupus Vulgaris*, Bonn, 1884, and *Monats. f. prakt. Derm.*, 1883, II., p. 161.

makes it up is the result of the reaction of the skin to the local action of the tubercle bacillus (Pl. XXV.).

The architecture of the lupus nodule (Pl. XXIV., Fig. 1) is similar in most respects to that of tubercular nodules met with in other organs, and must be already familiar to the student. In the centre of the nodule there are one or more true giant-cells and perhaps several smaller multinucleated cells. Between and surrounding these are numbers of small round cells with round vesicular nuclei, which Unna regards as "daughter plasma-cells" and several other observers believe to be small mononuclear leucocytes. Outside these there is a zone of larger cells, composed of plasma-cells and ordinary connective tissue cells, a few of which may resemble endothelial cells. The tubercle bacilli are found in and between the central giant-cells. The fibrous elements become attenuated and disappear in the nodule, the elastin persisting longer than the collagen. Blood-vessels do not penetrate the nodule, nor do they show marked proliferative changes around it. The nodule is encapsuled by the surrounding unaffected collagen and elastin. Where the skin is moist and the lymphatic spaces large, the plasma-cell infiltration spreads along in the spaces, and a diffuse type of lupus results in which giant-cells are not so prevalent. Plasma-cells may here and there be detected which are evolving again into spindle-cells, and this explains the tendency to organise and form scars which occasionally occurs in the benign variety known as *sclerotic lupus.*

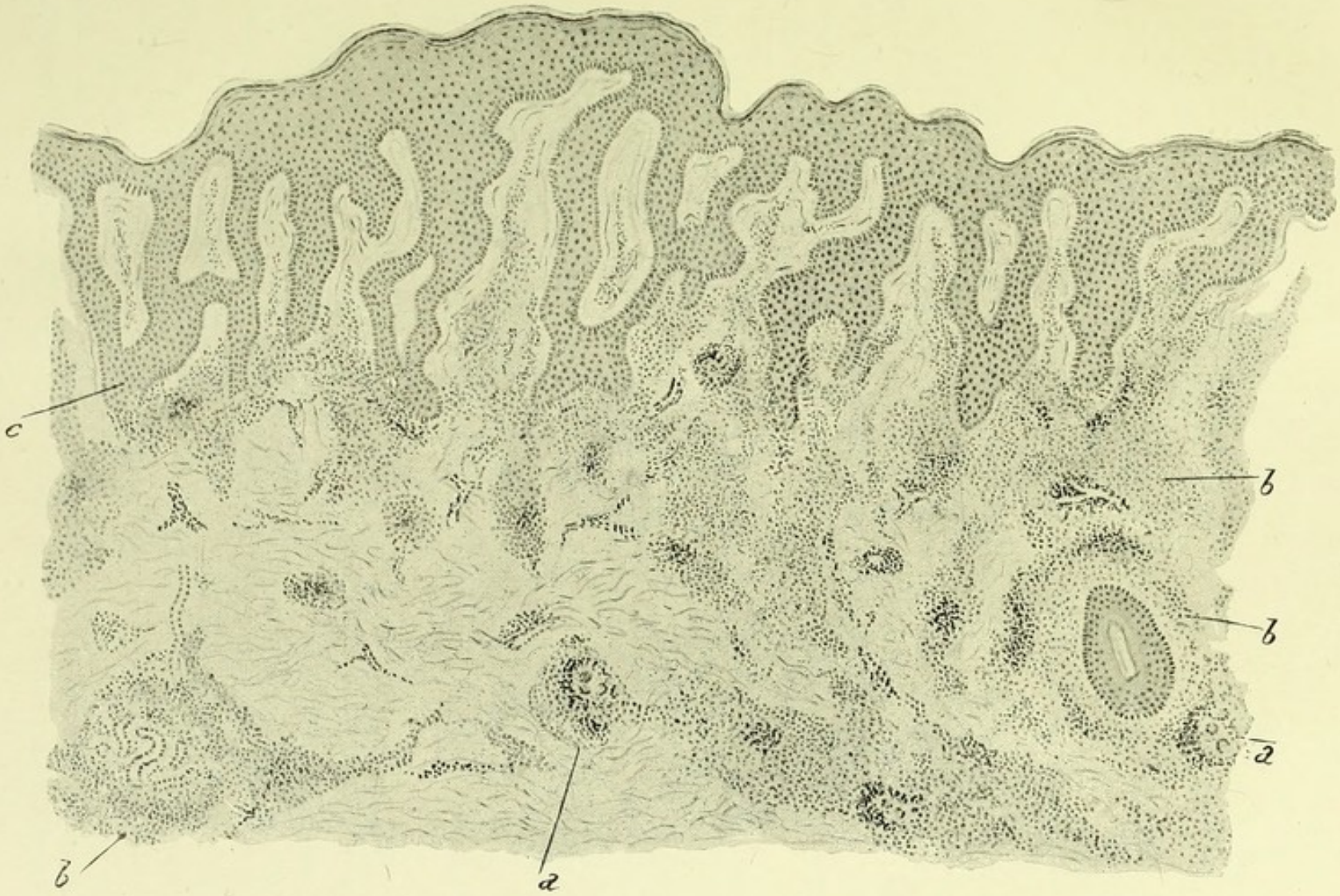
Associated with these changes in the corium, secondary phenomena may occur in the epidermis, such as epithelial proliferation and increased cornification, and so the various types of lupus which have been named *Lupus papillomatosus*, *Lupus verrucosus*, and *Tuberculosis verrucosa cutis* (post-mortem wart) are produced. Occasionally in weak subjects secondary inoculation with pyogenic cocci takes place, and this results in suppuration and sometimes in ulceration.

Scrofulodermia.—Another variety of tuberculous affection of the skin in which tubercle bacilli have been demonstrated is that known as *scrofulodermia.* It is a secondary implication of the skin from some deep-seated focus of tuberculosis such as a tubercular gland or tubercular disease of bone. In it a plasma-cell infiltration of the diffuse type occurs in the subcutaneous tissue and the corium. Where the subcutaneous lymphatic glands are much involved they gradually suppurate, and a flabby ulcer is the almost invariable result.

PLATE XXV.

LUPUS VULGARIS. (× about 100.)

a. Tubercular foci, with giant-cells in centre.
b. Plasma-cell infiltration collected in foci around the blood-vessels, hair-follicles, and sweat-glands.
c. Acanthosis of the epidermis.



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Miliary Tuberculosis of the skin is an acute type of tuberculosis cutis which appears as punched-out painful ulcers situated at the edge of the skin and mucous membranes. The architecture is tubercular, and masses of bacilli have been found in the necrotic centre. It may be the result of a direct inoculation or be secondary to persistent visceral tuberculosis.

Lichen Scrofulosorum is probably another manifestation of tuberculosis in the skin. It is characterised by groups of small papules, the result of a peculiarly indolent type of folliculitis, and occurs usually in tubercular patients. Though the histological architecture of the lesions does not do more than suggest a form of tuberculosis, tubercle bacilli have been demonstrated and successful inoculations performed by a few observers, such as Jacobi[1] and Pellizari; others maintain that it does not result from the actual presence of tubercle bacilli in the skin, but is due to the action of the tubercular toxin.

Erythème Induré des Scrofuleux (Bazin).—Many of the cases of erythema induratum of Bazin have a similar histological architecture to that of the above cases, and successful inoculations have been carried out, showing that they are definitely tubercular. Galloway,[2] in 1899, and in a more recent paper, has drawn attention to the fact that several cases which have been included under this heading are not tubercular, but are the result of a necrotic process dependent on a disorder of the circulation. This opinion has been corroborated by Whitfield.[3]

Tuberculides.—The term "*tuberculides*" has been applied to a class of skin-eruptions which have been observed in association with tuberculosis in other parts of the body. In these lesions neither have tubercle bacilli been found nor successful inoculations performed, nor has a histological architecture resembling that of tuberculosis cutis been detected. As the lesions were believed to be due not to the local action of tubercle bacilli, but to tubercular toxins circulating in the skin produced by bacilli situated at a distance, they have been designated as *toxi-tuberculides* by several French dermatologists. A very confusing nomenclature has grown

[1] *Archiv f. Dermat. u. Syph., Ergänzungsheft*, I., 1892.
[2] *Brit. Journ. of Derm.*, 1899, XI., p. 206, and 1902, XIV., p. 199.
[3] *Ibid.*, 1901, XIII., p. 386.

up around the subject of the so-called tuberculides, and such names as folliclis, acne scrofulosorum, and necrotising chilblains have all been employed to distinguish the same or at least closely allied conditions.

The term "tuberculide" is simply a provisional heading, and when any member of the group is definitely proved to be tuberculous, it can no longer be included under it. There are, indeed, several dermatologists who doubt the existence of lesions of the type known as tuberculides due to tuberculous toxins, independent of the presence of tubercle bacilli.

The essential lesion in the "tuberculides," according to the observations of Colcott Fox,[1] is a small, extremely indolent granuloma tending to undergo central softening and death, and thus leaving scars. These lesions are generally bilateral and symmetrical in their distribution. They appear as deep-seated nodules, commonly about the size of a split-pea, and situated deeply in the hypoderm or deeper layers of the cutis. At first they can be felt rather than seen. The nodule gradually assumes a peculiar purplish blue tint, the depth of the purple being determined by the position of the lesions, those being deepest in tint which are situated on the extremities. The central parts of this nodule necrose, with or without suppuration, and a pitted scar is left. These small nodular lesions Fox names *Tuberculides of intermediate size*, being intermediate between the small lesions of *Lichen scrofulosorum* and the large nodules of *Erythema induratum* of Bazin, which are not infrequently included in this group, though recent researches are tending to prove that both are tuberculous.

The histological architecture of the "tuberculides" has been variously described, but the subject is far from being completely worked out.

In a case of "tuberculides" exhibited by Dr. Colcott Fox at the Dermatological Society of London,[2] and in which a histological examination was made by Dr. Ormsby and myself,[3] we found that the histology was apparently identical with that of a small deep-seated nodule slightly larger than a split-pea, excised from the leg of a boy suffering from tuberculous dactylitis. In the latter case we found two tubercle bacilli in a giant-cell (Pl. XXVI., Fig. 1). In both cases the nodules examined had the closest similarity, clinically and histologically, and in our search for tubercle

[1] *Brit. Journ. of Derm.*, 1900, XII., p. 383.
[2] *Ibid.*, 1901, XIII., p. 15.
[3] *Ibid.*, 1901, XIII., p. 367.

PLATE XXVI.

FIG. 1. TUBERCLE BACILLI IN A GIANT-CELL. (× about 1000.)

From a case of deep-seated tuberculous lesions on the arm.

a. Giant-cell with two tubercle bacilli.
b. Plasma-cell.
c. Daughter plasma-cell.
d. Connective tissue cell.
e. Connective tissue cell.
f. Attenuated collagen fibres and œdema.

FIG. 2. TRANSVERSE SECTION OF A THICKENED SUBCUTANEOUS VEIN.

From a deep-seated tuberculous nodule.

It shows a proliferation of the endothelium, and a great thickening of the walls. Around the vein is a dense cellular infiltration; the supporting stroma is attenuated and œdematous. This is the condition of the veins in Bazin's disease (Erythema induratum).

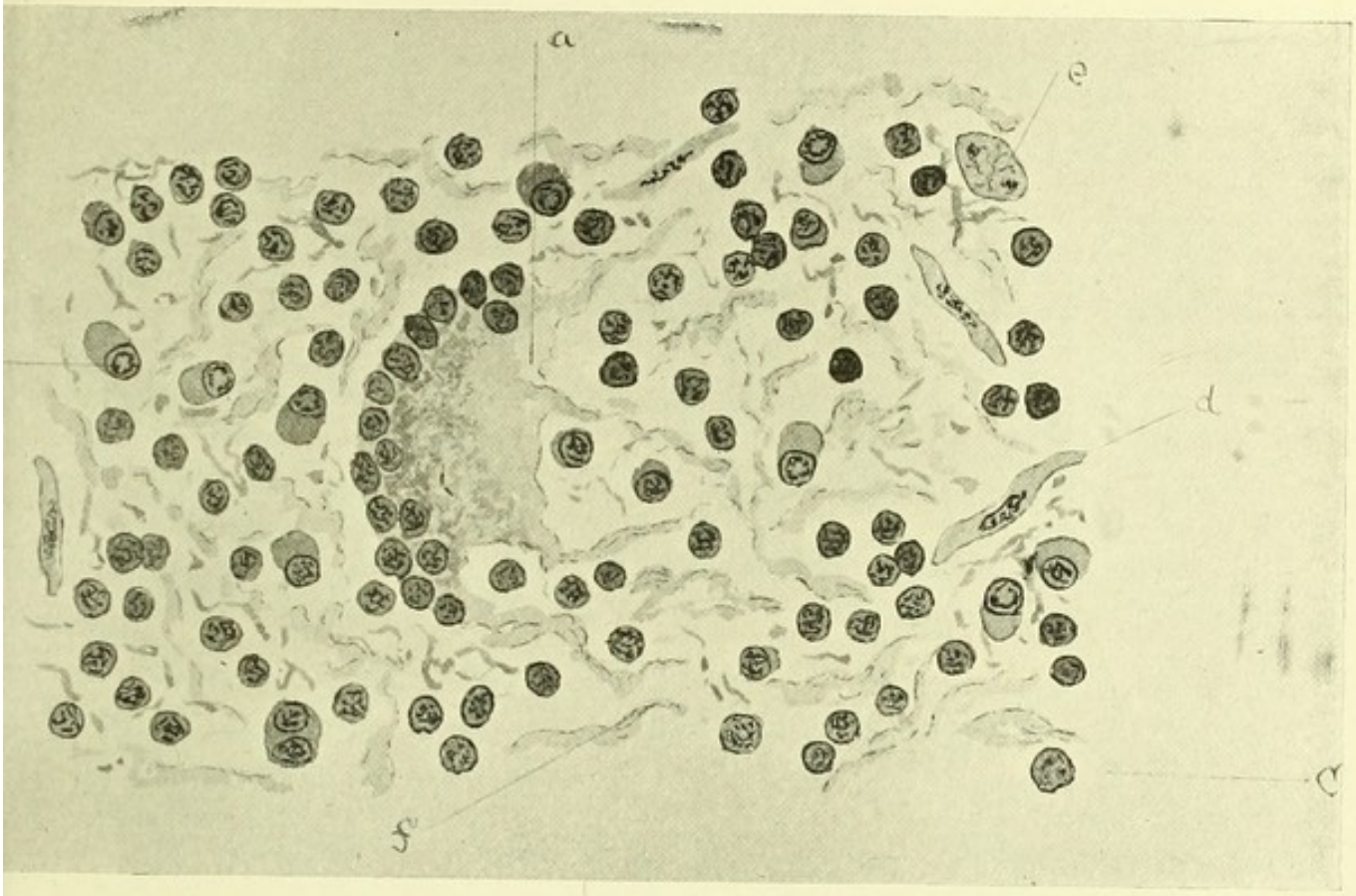


FIG. 1.

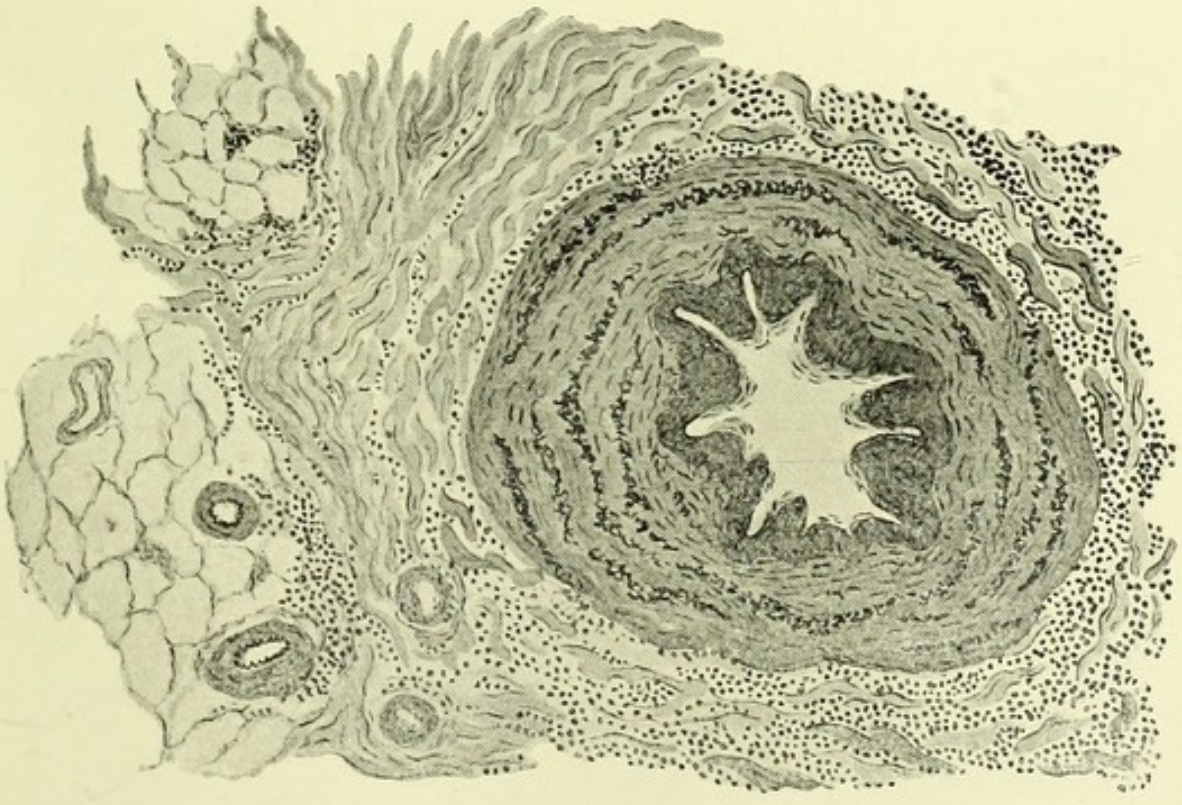


FIG. 2.

J. M. H. M., del.

bacilli we believed that we were as likely to find them in the one case as in the other.

The following is a brief *résumé* of the histological appearances in the two cases:

1. In both cases the initial lesion appeared to be in the hypoderm, and consisted of proliferative changes in, and cellular hyperplasia around, the veins in that region (Pl. XXVI., Fig. 2).

2. In both, the cellular infiltration rapidly encroached upon and replaced the fat-tissue, forming cellular areas more or less encapsuled by the remains of the interlobar septa. It is this early cellular infiltration, chiefly confined to the hypoderm, which gives rise to the deep-seated nodules, which are scarcely visible clinically, but are usually appreciable to the touch.

3. In both, the cellular infiltration extended upwards along the capillaries, forming foci in the neighbourhood of the sweat-coils, hair-follicles, and sebaceous glands, and finally reaching the papillary layer.

4. In both, the character of the cellular hyperplasia was similar. In the hypoderm it was more markedly tubercular in appearance in the second than in the first case, but in both, the foci in the corium presented equally the characteristic tubercular architecture. Tubercle bacilli were found in a giant-cell in the latter case.

5. A fibrous stroma supporting the cellular hyperplasia was either entirely absent or was represented by œdematous, degenerated collagen and elastin.

6. In both cases the cellular hyperplasia developed at the expense of the tissue in the neighbourhood, and finally became necrotic.

7. The papillary and sub-papillary vessels were congested as soon as the infiltration reached the corium, and this accounted for the congested appearance which the nodules presented clinically.

8. The epidermis was only secondarily affected.

NOTE.—The finding of tubercle bacilli in scrofulodermia, where fistulous openings occur, has been frequently successful, but as far as I am aware tubercle bacilli have not been demonstrated previously in a lesion of the type which occurred in our second case, a lesion which clinically and histologically appeared to be identical with that excised in Fox's case of tuberculides. This fact strongly suggests the probability that certain of the cases of the so-called

tuberculides will in the near future be definitely proved to be tubercular.

It will be noted that *Lupus erythematosus* is omitted from this list. This omission is made purposely, as, though it is frequently asserted that the disease is a tubercular manifestation, the evidence for regarding it as such is insufficient. It conforms to none of the necessary criteria of tuberculosis, its histological architecture does not even suggest tuberculosis cutis, and only in the few cases where it happens to occur in tubercular patients does the injection of tuberculin produce a general or local reaction.

II. Syphilis.

The primary lesion and the later skin-manifestations of syphilis strongly suggest that they are also evidences of a local reaction of the skin to a specific virus. The generalised roseolar eruptions, on the other hand, suggest the action of a toxin circulating in the blood. The nature of the specific virus of syphilis is still unknown. Lustgarten,[1] Doutrelepont[2] and others have described specific bacilli, but none of these has as yet been established.

In spite of the polymorphism which characterises the skin-lesions of syphilis, certain peculiarities occur in their minute anatomy which are sufficiently constant to be of some diagnostic value. All the lesions, with the exception of those of the roseolae, are more or less indurated, owing to the formation of a granuloma in the corium. The granuloma is, as a rule, much more fibrous than that of tuberculosis, owing to the persistence and actual new formation of collagen; and this fact accounts for the singular hardness of many of the syphilides. The granuloma in syphilis is a vascular structure, and is rich in capillaries, and, as Unna has pointed out, it is the presence of these, combined with the brown colour of the plasmoma, which gives the reddish brown or "raw ham" tint to the lesions.

The multiformity of the skin-lesions in syphilis is due to a number of factors, such as the situation of the lesions, the secondary inoculation of them by pyogenic organisms, and the secondary changes, such as proliferation, œdema, and imperfect cornification in the epidermis.

It will be useful to describe shortly the salient histological

[1] *Wien. med. Wochenschr.*, 1885, XXXV., p. 517.
[2] *Vierteljahrschr. f. Derm. u. Syph.*, 1887, XIX., p. 101.

features of a few types of syphilides, and then to tabulate the more important peculiarities which are generally present.

The Chancre or Initial Sclerosis.—Sections of a chancre show that the epithelium has proliferated. This is not so marked in the centre as at the margins of the lesion, because in the centre there is considerable upward pressure exerted by the underlying granuloma, which tends to cause a flattening of the epidermis. Between the epithelial cells leucocytes are here and there present, and the interepithelial spaces are dilated. The cornification in the centre is imperfect and the granular layer is frequently absent; there is more or less desquamation present, and an excoriated surface is apt to result. But the chief feature in the histology of the chancre is not the state of the epidermis, which is only secondarily involved, but that of the underlying corium. Here we find, occupying the whole of the indurated region, a dense infiltration of perfect plasma-cells, frequently packed in rows between collagenous bundles. Some of these plasma-cells show signs of becoming spindle-shaped, and these spindles of becoming fibrous, indicating that they are evolving into new collagen bundles. Within this dense mass of collagenous bundles and plasma-cells dilated capillaries are present, and towards the subcutaneous tissue the small arteries show a proliferative change, in which not only the endothelium, but also the adventitial coat, is increased. In the neighbourhood of the blood-vessels mast-cells are scattered about. The elastin has to a great extent, if not entirely, disappeared.

The Papular Syphilides. — The papular syphilide may fairly be regarded as the type of lesion which occurs in the so-called secondary period of the disease, for many of the variations in it are dependent, not on differences in the underlying granuloma, but simply on a greater or less secondary implication of the epidermis. In the corium the granuloma, consisting chiefly of plasma-cells, shows the same profusion of collagen as in the chancre. The nuclei of the plasma-cells may proliferate to form multinucleated cells, and sometimes true giant-cells. The latter are not generally so complete in their peripheral ring of nuclei as the corresponding cells of tuberculosis. Sometimes these multinucleated cells are surrounded by a mass of plasma-cells, and an appearance very similar to a lupus nodule may be produced. Capillaries are present in the granulomatous mass, and a proliferation of the endothelium may be detected. The epithelium proliferates to a greater or less extent, and at the mucous orifices it

becomes sodden and œdematous, and the papule becomes transformed into the so-called "mucous patch or condyloma."

The Late or Gummatous Syphilides.—These have been explained by Neumann as recrudescences due to the persistence of the virus, for some time in abeyance, about the blood-vessels. The renewed activity of this virus causes a cellular proliferation and deposition of plasma-cells in localised areas. Other observers do not admit this origin in the blood-vessels, and believe that the proliferation of the endothelium in the vessels occurs simultaneously, but not previously to the deposition of the dense foci of plasma-cells. These foci are encapsuled in an envelope of collagen, and this exerts a continuous pressure, which increases as the number of cells within it is augmented. The pressure results in time in the formation of the "gummatous mass," consisting of cellular *débris* and a gelatinous intercellular substance due partly to a colloid degeneration of the collagen. When this dries up the mass becomes caseous, the overlying epithelium breaks down, and the characteristic ulcers are eventually produced.

The Characteristics generally present in the Syphilides (Pl. XXIV., Fig. 2).—

1. There is an infiltration of plasma-cells, which, owing to the persistence and new formation of collagen bundles, spread through the corium between the bundles, and are not infrequently arranged in rows.
2. The plasma-cells may form multinucleated cells and incomplete giant-cells. An arrangement of cells similar to that in a lupus nodule may occasionally be found.
3. In the late stages foci of plasma-cells become encapsuled, the intercellular collagen undergoes colloid degeneration, the cells break up, and a gumma is produced.
4. Collagen is, as a rule, present in the midst of the infiltration, and evidences of organisation in the shape of spindle-cells may sometimes, though not invariably, be noted.
5. The granuloma is vascular, and the vessels show proliferative changes, which are specially marked in the gummatous lesions. It is the small arteries which are chiefly involved.
6. Secondary changes, such as proliferation and œdema, with imperfect cornification, occur in the epidermis.

The differentiation by the microscope between the granulomata of syphilis and tuberculosis is always difficult, and in some cases impossible—for example, in the syphilitic

gummata, where a histological architecture may be present, which resembles that of a lupus nodule in every detail, with the exception of the presence of tubercle bacilli.

III. Leprosy.

It is customary to divide the skin-lesions of leprosy into two distinct types—namely, those which occur in the so-called "tubercular leprosy," and those of "anæsthetic leprosy." Thus two forms of leprosy are distinguished, but this distinction is a purely arbitrary one. It is now generally believed that in individuals who are susceptible to leprosy the virus becoming deposited in the cutis sets up a reaction there, and granulomata form which give the nodular or tuberculated appearance to the skin, and that in less susceptible individuals the virus becoming deposited about the peripheral nerves, causes the formation of localised atrophic and pigmented patches. Sections of the nodular lesions of leprosy, or *lepromata*, show a typical granuloma consisting of a hyperplasia of connective-tissue cells most of which are of the plasma-cell type, and occasionally large multinucleated cells. These cells are situated chiefly around the blood-vessels. The fibrous elements to a great extent disappear, and the blood-vessels do not penetrate the granulomatous mass. By suitable staining, vast numbers of the bacilli which Hansen[1] described may be demonstrated in the granuloma without the slightest difficulty, and the leproma appears to be the result of the reaction of the skin to these micro-organisms (Pl. XXII., Fig. 6). They are found in enormous numbers in the lymphatic spaces of the corium, and they may be present in the endothelial cells of the blood-vessels, and also in the plasma-cells and multinucleated cells. They do not occur to any extent in the epidermis or its appendages. They may lie singly or in twos or threes, and are very frequently arranged in bundles like cigarettes. On staining the sections by Ziehl-Neelsen's stain and then counter-staining in methylene blue, the bacilli are found to lie in homogeneous masses which look like cells and which have been described as "*lepra-cells*." There are several divergent opinions regarding the nature of the so-called "lepra-cells." Certain writers hold that they are the remains of cellular protoplasm which has undergone a mucoid degeneration from the presence of the bacilli of leprosy; others, that they are cross sections of lymphatics; and others, that the apparent cell is only a mass of mucin secreted

[1] *Norsk Magazin for Laegevidenskab*, 1874, IX.

by the bacilli, and forming a glœa supporting them. This glœa is said to form a branching network which passes along the lymphatic spaces, and the apparent cells are regarded as thickenings of it where clusters of bacilli occur.

In several of the smaller "thickenings" a nucleus or the remains of one may be detected; this may be a coincidence, but it is certainly suggestive that some of these masses are the remains of cells which have broken down, from the presence in them of clumps of bacilli.

IV. Mycosis Fungoides.

This rare and fatal disease is associated with a peculiar type of granuloma in which, in the later or tumour stage of the disease, the component cells undergo disintegration. Before breaking up, the cells become crenated and irregular, and the fibrous elements undergo a basophilic degeneration.

Two stages in the evolution of this disease are distinguished: (1) the pre-mycotic stage, in which the lesions somewhat resemble those of dry scaly eczema, but in which more or less induration is present, indicating the existence of an underlying granuloma; and (2) the late mycotic stage, when the lesions develop into large raised ulcerated nodules. The following is a brief *résumé* of the histological appearances in the two stages, from a report of three cases by Galloway and myself[1]:

I. **Pre-Mycotic Stage.**—

1. Proliferation of connective-tissue cells around the blood-vessels, hair-follicles, and sebaceous glands, and in scattered foci through the corium. This infiltration consists of:

(*a*) Large fusiform or roundish connective-tissue cells.
(*b*) Small round cells of doubtful origin.
(*c*) Mast-cells.
(*d*) A few plasma-cells.
(*e*) A few multinuclear cells.

2. The fibrous elements (collagen and elastin) seem healthy.

3. Secondary changes occur in the epidermis (acanthosis, œdema, parakeratosis).

II. **Tumour in Mycotic Stage.**—

1. The cell-proliferation increases, but, *pari passu*, there is a disintegration of the cells. They become irregular and crenated, and break up into small irregular fragments (Pl XXIII., Fig. 5).

[1] *Brit. Jour. of Derm.*, 1900, XII., p. 153.

2. Collagen and elastin become basophilic in reaction, and break down.

3. The epidermis breaks down and ulceration occurs.

McVail, Murray, and Atkinson[1] have described a short bacillus in association with a case of this disease, which they thought might be specific, but this observation has not been corroborated.

V. Yaws or Framboesia.

In yaws the granuloma is chiefly composed of plasma-cells which neither tend to form multinuclear cells nor true giant-cells, nor do they undergo degenerations like the cells in mycosis fungoides (Pl. XXIII., Fig. 5). The clinical lesions —namely, squames, papules, and tubercles—are stages in the evolution of a common histological process.

The following is a short *résumé* of a histological examination which I made on a series of cases, a full account of which was published in the *British Medical Journal* of September 21st, 1901.

The material for this histological study was obtained from the Kurunegalle Hospital, Ceylon, through the kindness of Sir William Kynsey, late Inspector-General of Hospitals, Ceylon. Eight typical cases of yaws, in different stages of the disease, were selected, and characteristic lesions were excised. The tissues were preserved in spirit, and for ordinary histological purposes were in no way injured by their journey from Ceylon.

I. **Changes in the Corium.**—

1. Blood-vessels: dilatation and tortuosity of those in the papillary and sub-papillary layers; no thickening of the vessel-walls or endothelial proliferation; vessels persist in the granuloma.

2. Cellular infiltration consisting of:

(*a*) Plasma-cell infiltration at first most marked in the neighbourhood of the vessels, follicles and glands, rapidly becoming diffused; no definite arrangement in rows; no large multinuclear cells (chorioplaques), or true giant-cells.

(*b*) Mast-cells, connective-tissue cells and small mononuclear cells; no tendency to organisation detected.

(*c*) Marked extravasation of polynuclear leucocytes.

[1] *Glasgow Hosp. Rep.*, 1898, I., p. 53.

3. Fibrous stroma :

(*a*) Collagen attenuated where the granuloma is densest ; no definite degenerative changes.

(*b*) Elastin similarly affected.

4. Hair-follicles, sebaceous glands, and coil-glands seemed healthy.

II. **Changes in the Epidermis.**—

1. Marked proliferation and down-growth of the inter-papillary processes so great in the older lesions as to resemble condyloma acuminatum.

2. Basal layer uninterrupted.

3. Œdema affecting prickle-cells and interepithelial spaces.

4. Disappearance of pigment in the affected area.

5. Transitional layers imperfect.

6. Cornification : marked hyperkeratosis and parakeratosis, with deposition of leucocytes and *débris* between the horny lamellae.

Bacteriology.—No specific microbe was definitely detected, though cocci, microbacilli, and sarcinae were found in the horny crusts.

Differential Histological Diagnosis.—Yaws belongs to the group of the *Infective granulomata.* It is distinguished from :

1. Actinomycosis and rhinoscleroma by the absence of their specific micro-organisms.

2. From the lepromata by the absence of Hansen's bacillus.

3. From mycosis fungoides by the absence of " fragmentation " of the infiltrating cells, and of degenerative changes with the formation of products of degeneration in the collagen and elastin ; by the presence of the epidermal changes peculiar to yaws.

4. From tuberculosis, apart from the tubercle bacillus, by the absence of the characteristic architecture with its giant-cells, daughter plasma-cells, more marked disintegration of the fibrous stroma, and complete disappearance of the blood-vessels.

5. From syphilis, by the following details, which, considered collectively, strongly suggest that yaws and syphilis are different histological entities :

(*a*) Cellular infiltration : plasma-cells not so definitely arranged in rows or clustered round the blood-vessels as in syphilis ; no large multinuclear cells (chorioplaques), or true

giant-cells, or intracellular hyalin degeneration noted in yaws.

(*b*) Fibrous stroma: rarefaction of the collagen more marked than in syphilis, but no organisation or colloid degeneration found, such as occurs in syphilitic gummata.

(*c*) Blood-vessels: no distinct proliferative changes in the vessel-walls or endothelium, as frequently occurs in syphilis.

(*d*) Epidermis: marked proliferation and down-growth of the epithelium, with great thickening of the horny layer (due to hyperkeratosis or parakeratosis), are characteristic features of yaws, while they are unusual in syphilis.

VI. Actinomycosis.

When actinomycosis affects the skin it does so secondarily by an extension from diseased bone such as the jaw or the vertebrae. A fistulous opening occurs in the skin leading down to the softened subcutaneous tissue, from which oozes a purulent fluid, in which are small yellow granules of the "ray fungus." Sections of skin in the neighbourhood of the fistula show a focus of cells enclosing ray fungi. These cells are chiefly plasma-cells, and many of them show a tendency to undergo hyalin degeneration; but there are also a number of connective-tissue cells which are swollen and vacuolated prior to breaking up. The fibrous elements soften and disintegrate, and an abscess usually forms.

Mycetoma or Madura foot is a closely allied condition both in its histological architecture and bacteriology.

VII. Rhinoscleroma.

Rhinoscleroma, though fortunately an exceedingly rare form of "infective granuloma," is a peculiarly interesting one, owing to the presence in the granuloma of swollen œdematous cells (cells of Mikulicz [1]), in which the bacilli of v. Frisch and Paltauf [2] can be detected. The histology has many points of resemblance to that of leprosy. Plasma-cells are present in large numbers. In the centre of the granuloma the fibrous elements disappear, while at the margin there is an increase of collagen, which explains the hardness which clinically characterises the lesion. The large cells of Mikulicz are generally regarded as cells which have degenerated, owing to the presence of the bacilli in their protoplasm.

[1] *Langenbeck's Archiv f. Chir.*, 1876, XX.
[2] *Fortschr. der Med.*, 1886, IV., p. 617.

The bacilli form clumps lying in and supported by a glœa. A Mikulicz cell may contain five or six of these glœas of different sizes with numerous bacilli; a few bacilli are present in the lymph-spaces. Hyalin degeneration frequently attacks the cells of the granuloma.

VIII. "BLASTOMYCETIC DERMATITIS" (GILCHRIST AND STOKES).[1]

More than thirty cases of this form of dermatitis have been reported in America. Clinically the lesions of this disease consist as a rule of warty patches, which tend to break down and ulcerate. The surface is papillated and crusted over with irregular masses, consisting of fibrin and the *débris* of leucocytes and epithelial cells. The lesions frequently present a close resemblance to those of the papillomatous type of lupus vulgaris.

I have had the opportunity of examining the material from two cases of this rare affection, and the following are the leading characteristics in its histology[2]:

The epidermis is more or less thickened, sometimes to such an extent that it resembles an epithelioma. The basal layer of the epidermis is generally intact. Between the prickle-cells there is a varying number of polynuclear leucocytes, forming small miliary abscesses, which here and there break through to the surface. The corium shows the presence of a granulomatous infiltration arranged in foci like that of nodular lupus. The granuloma here and there breaks down like that of mycosis fungoides to form miliary abscesses in the corium.

The most noticeable feature in the sections is the presence of the blastomyces.[3] The cells of this fungus are larger than prickle-cells, can be detected by the low powers of the microscope, and their minute structure can be studied with a magnification of about 600. Large numbers of these unicellular fungi may be detected in a single section. They are situated in the miliary abscesses, between the prickle-cells, in the crust on the surface, and in the superficial layers of the corium. They may occur singly or in clusters in giant-cells. They are not definitely grouped around the blood-vessels. Budding

[1] *Journ. of Exper. Med.*, 1898, III., p. 53.

[2] For the blastomycetic tissue I am indebted to Dr. Galloway, who obtained it through the kindness of Drs. Nevins Hyde and Ricketts of Chicago, and to Dr. Howard Morrow of San Francisco.

[3] For a description of the fungus *see* p. 356.

may be detected in the fungus, and in one instance I noted a chain of several oval buds like those of a yeast.

The appearance of the corium strongly suggests a local reaction on the part of its cellular elements to the fungus or its toxins; for wherever the fungus is present there is a more or less dense infiltration of polynuclear leucocytes and plasma-cells, with here and there typical giant-cells, and the detection of budding of the fungus *in situ* proves conclusively that it is not a type of cellular degeneration. In several cases inoculations in animals have been successful, producing "a local abscess and inflammatory granulation tissue, from which the fungus could be recovered,"[1] so that the evidence is now sufficiently strong to render it almost certain that the fungus is the cause of the granuloma, and not simply a harmless accidental inoculation.[2]

[1] Hyde and Montgomery, *Diseases of the Skin*, 1901, p. 777.

[2] For the most complete contribution to this subject *see* the admirable work of Buschke (*Bibliot. Med. Abt. D*[II.] *Derm. u. Syph.*, Neisser, Ht. 10, 1902).

CHAPTER XXI.

PATHOLOGICAL CONDITIONS OF THE CORIUM (*Continued*).

MALIGNANT NEW GROWTHS OF THE CORIUM.

SARCOMA AND ENDOTHELIOMA.

IN sarcoma and endothelioma we have a malignant tumour-formation, the elements of which are connective-tissue cells, which have reverted, adopted a habit of unlimited growth, and ceased to differentiate. Primary sarcomata of the skin are comparatively rare, and the tumours are more often the result of metastases from internal foci. The types of cells which form the infiltration in sarcomata have already been described, and, according to the type which predominated, Virchow divided the sarcomata into four classes—namely:

1. Reticulo-cellular sarcomata.
2. Round-celled sarcomata.
3. Spindle-celled sarcomata.
4. Giant-celled sarcomata.

It is customary to omit Class 1, since every variety of sarcoma may be described as reticulo-cellular. These classes are again divided into several varieties, such as *pigmented sarcoma*; *angio-sarcoma*, where the tumour is more than usually vascular; *myxo-sarcoma*, in which a myxomatous degeneration occurs in the intercellular fibres and cells; *fibro-sarcoma*, in which the fibrous elements persist to a considerable extent; and *lympho-sarcoma*, in which the histological structure somewhat resembles that of a lymphatic gland and the cells are like leucocytes. Certain observers believe that the cells which compose the lympho-sarcomata are leucocytes. If this be the case the tumours should not be named sarcomata. Ranvier has shown, however, that the cells in this class of sarcoma are capable of organising and of producing a fibrous

reticulum; consequently it would seem much more likely that they are derived from connective-tissue cells and not from blood-cells. Giant-celled sarcoma is as a rule secondary to one which has developed from bone, although a few multinucleated cells may be found in any of the classes.

There are several interesting features in the histological architecture of the sarcomata. The first result of the cellular hyperplasia is to cause a disappearance of the fibrous elements, the collagen and the elastin, in the infiltrated areas. The collagen becomes attenuated, and persists as delicate broken fibrils between the cells, and only traces of elastin can be found. Besides these attenuated fibres a fine fibrous network, the product of the activity of the cells, has been described by White[1] and Johnston.[2] This "*sarcoma reticulum*" may be demonstrated by van Gieson's method of staining (*see* p. 63), by which it stains yellowish red—a reaction which is also given by mucin. The skin-glands and the follicles disappear in the affected areas. The sarcomatous infiltration does not as a rule extend up to the epidermis, but a layer of unaffected corium generally separates it from the basal layer. The tumour-mass is always more or less vascular, and, where the vessels are numerous, dilated and tortuous, the term angiosarcoma is suitably applied to it. It was at one time taught that sarcomata were developed from the cells of the outer coat of the blood-vessels. In the corium this is impossible, since the vessels are simply capillaries, and possess only a single lining coat of the nature of an endothelium, which does not, as a rule, show proliferative activity, and the only definite change which occurs in the vessels is dilatation. The seat of origin of the sarcoma in the corium is the fixed cells of the fibrous stroma.

The question of the pigmented sarcomata, the so-called "melanotic sarcomata," has already been referred to (*see* p. 168).

The degree of *malignancy* varies greatly in the different varieties of sarcomata. The more the cellular element is in excess of the fibrous, the greater the malignancy. The fibro-sarcomata are comparatively benign growths, and the spindle-celled sarcomata are less malignant than the round-celled type. The smaller the cell and the greater the proliferative activity, the greater is the malignancy.

The Cause of the Sarcomata.—The problem of the cause of sarcomata is in very much the same position as that of the

[1] *Johns Hopkins Hosp. Bull.*, XI., p. 209.
[2] *Brit. Journ. of Derm.*, 1901, XIII., p. 241.

carcinomata. Of the various theories only three need be mentioned:

1. Embryonic "cell-rests."
2. Reversion of the cell to a habit of reproduction.
3. Parasitic theory.

1. *Cell-Rests.*—The sarcoma is developed from cells which have been deposited in the tissue in embryonic life and have not completed their developmental intention. If sarcomata were formed by a proliferation of nævus-cells, such a view would be tenable; but as these are generally regarded as epithelial, the one group to which the explanation would apply is removed.

2. *Reversion of the Cell to a Habit of Reproduction.*—The mother-cells of the connective tissue retain, like the cells of the basal layer of the epidermis, the simple function of reproduction, while the daughter-cells evolve and produce fibrous bundles; in sarcomata, instead of differentiating, the daughter-cells revert and assume the habit of reproduction. But what causes this reversion? Is it a toxin circulating in the blood; a local irritation such as might have transformed a scar into a sarcoma; or is it the result of the presence of a parasite? These questions have still to be answered.

3. *Parasitic Theory.*—Since Cobbold[1] described in sarcomatous cells an "endocellular parasite," which he considered to be a psorosperm, a great deal of patient research has been carried out on this subject by Sanfelice,[2] Roncali,[3] and others. Structures which have been variously regarded as psorosperms, sporozoa, coccidia, and blastomycetes have been from time to time put forward as the possible cause of the malignant growth. Many observers regard these bodies as types of intracellular and extracellular degenerations—a view which can be made to explain the majority of them. Sufficient evidence in the form of cultivation and inoculation experiments has not yet been forthcoming to establish any of the above-mentioned organisms as the causal factor in sarcoma.

The Degenerations of the Cells in Sarcomata.—Hyalin degeneration, mucoid or myxomatous degeneration, ulceration and necrosis may occur: for a description of these, *see* Chapter XVIII.

[1] *Pini. Bibliot. Med. Abt. D[II]. Derm. u. Syph.*, 1901, IX., p. 62.
[2] *Centralbl. f. Bakt. u. Paras.*, 1895, XVII., p. 625.
[3] *Il Policlinico*, 1895.

Endotheliomata originate in the endothelium lining the lymphatics or the blood-vessels. The endothelium is a mesoblastic structure, and its cells are capable of reverting to a type of cell which is similar to that of the reverted connective tissue cells of the corium. The cells in the endotheliomata are generally large and polygonal in character, and are similar to those of the "large round-celled sarcomata." When they originate from the lymphatic vessels, a structure may be produced which resembles a secreting gland, and considerable difficulty may be experienced in distinguishing it from carcinoma. Wolters[1] has described a case in which the endothelial proliferation blocked the blood-vessels, and formed a dense infiltration in the corium, in which here and there were clumps of cells, like endothelial cells, which had undergone a hyalin degeneration in the centre, and so formed cyst-like structures. This condition he named "Hæmangio-endothelioma," and the analogous growth from the lymphatic endothelium, "lymphangio-endothelioma."

One important point of distinction serves to differentiate the sarcomata from the endotheliomata—namely, that the vessels from which the proliferation takes place in the endotheliomata gradually disappear, so that no vessels are seen between the cells of the tumour.

TABLE OF PATHOLOGICAL CHANGES INVOLVING THE ELEMENTS OF THE CORIUM, WITH EXAMPLES.

Cellular Elements.

Cellular Infiltrations.—

I. *Inflammatory infiltration*—
In all the infective inflammations, such as Eczema, Psoriasis, Erysipelas, etc.

II. *Purulent infiltration*, as in Furuncle, etc.

III. *Infiltration with necrosis* . . . Carbuncle, Malignant pustule, Vaccinia, etc.

IV. *Plasma-cell infiltration :*

1. Infective granulomata : (*a*) Tuberculosis cutis.
(*b*) Syphilis.
(*c*) Leprosy.
(*d*) Actinomycosis.
(*e*) Yaws.
(*f*) Rhinoscleroma.
(*g*) Mycosis fungoides.
(*h*) Blastomycetic dermatitis

[1] *Archiv f. Derm. u. Syph.*, 1900, LIII., p. 269.

2. Chronic inflammatory conditions, such as Acne vulgaris, Sycosis barbae, etc.
3. In association with malignant proliferation, as in Sarcomata, Carcinomata.

V. *Giant-cell infiltration :*

1. True giant-cells . . . Tuberculosis cutis, tertiary Syphilides.
2. Multinucleated cells or chorioplaques.
   Infective granulomata.
   Sarcomata.
   Chronic inflammatory conditions, such as Acne vulgaris, etc.

VI. *Mast-cell infiltration* . . . Urticaria pigmentosa, etc.

Cellular Degenerations.—

1. Fatty degeneration . . . Generalised xanthoma, necrotic processes, etc.
2. Giant-cell degeneration . . . Tuberculosis and Syphilis.
3. Hyalin degeneration . . . Rhinoscleroma, Sarcoma, etc.
4. Mucoid degeneration . . . "Lepra-cells," Mikulicz cells of Rhinoscleroma, etc.
5. Crenation . . . Mycosis fungoides, etc.

Fibrous Elements.

I. **White Fibrous Tissue or Collagen.**—

1. *Hypertrophy.*—(*a*) Diffuse . . . . (i) Diffuse sclerodermia.
   (ii) Fibromatosis.
   (*b*) Circumscribed (i) Fibroma and Neurofibroma.
   (ii) Morphœa.
   (iii) Keloid.
   (iv) Scar.
2. *Atrophy and Attenuation.*—
   Infective granulomata.
   Œdematous conditions of the corium, etc.
3. *Degenerations of Collagen.*—
   (*a*) Basophilic degeneration . . . Myxœdema, Mycosis fungoides, etc.
   (*b*) Collastin . . . Colloid milium, Myxœdema, Senile skin.
   (*c*) Collacin . . . Colloid milium, Myxœdema, Senile skin.
   (*d*) Colloid . . . Colloid milium.
   (*e*) Myxomatous . . . Sarcoma, Lipoma, etc.
   (*f*) Œdematous . . . Lupus erythematosus, etc.

II. **Elastin.**—

1. *Atrophy* . . . Infective granulomata, striae of pregnancy, etc.
2. *Degeneration of Elastin*—
   Elacin . . . Senile skin, myxœdema, etc.

Malignant Proliferations.

I. **Sarcoma.**—

1. Round-celled.
2. Spindle-celled.
3. Giant-celled.

II. **Endothelioma.**—

1. Hæmangio-endothelioma.
2. Lymphangio-endothelioma.

CHAPTER XXII.

HAIR.

MINUTE STRUCTURE AND HISTOLOGICAL TECHNIQUE.

The General Characteristics of the Hairs.

1. **Situation.**—Hairs are present on all parts of the human skin except that of the palms of the hands, soles of the feet, red parts of the lips, glans penis, inner surface of the prepuce, inner surface of the labia majora, and dorsal aspects of the ungual phalanges of the fingers and toes.

2. **Number.**—The number of hairs to a given area of skin has been variously estimated. In two individuals v. Brunn[1] found that the average number of hairs to the square centimetre was three hundred at the vertex of the scalp, forty-four in the beard of the chin, and eighteen on the back of the hand. Erasmus Wilson[2] estimated that there were about a hundred and twenty thousand hairs on the whole scalp. These figures are quoted merely to give an indication of the approximate numbers; but as the number varies so greatly in different individuals, such calculations can be only of limited practical value.

3. **Colour.**—The colour of the hair is dependent on three factors:

(1) Pigment-granules situated in or around the cells of the cortex of the hair.

(2) The diffuse colour of the protoplasm of the hair-cells.

(3) The presence of air between the hair-cells.

The diffuse colour is said to produce blonde and reddish shades of hair, while pigment-granules are believed to be responsible for black and brunette tints. In elderly people

[1] Bardeleben's *Handb. der Anat. des Mensch., Haut*, 1897.

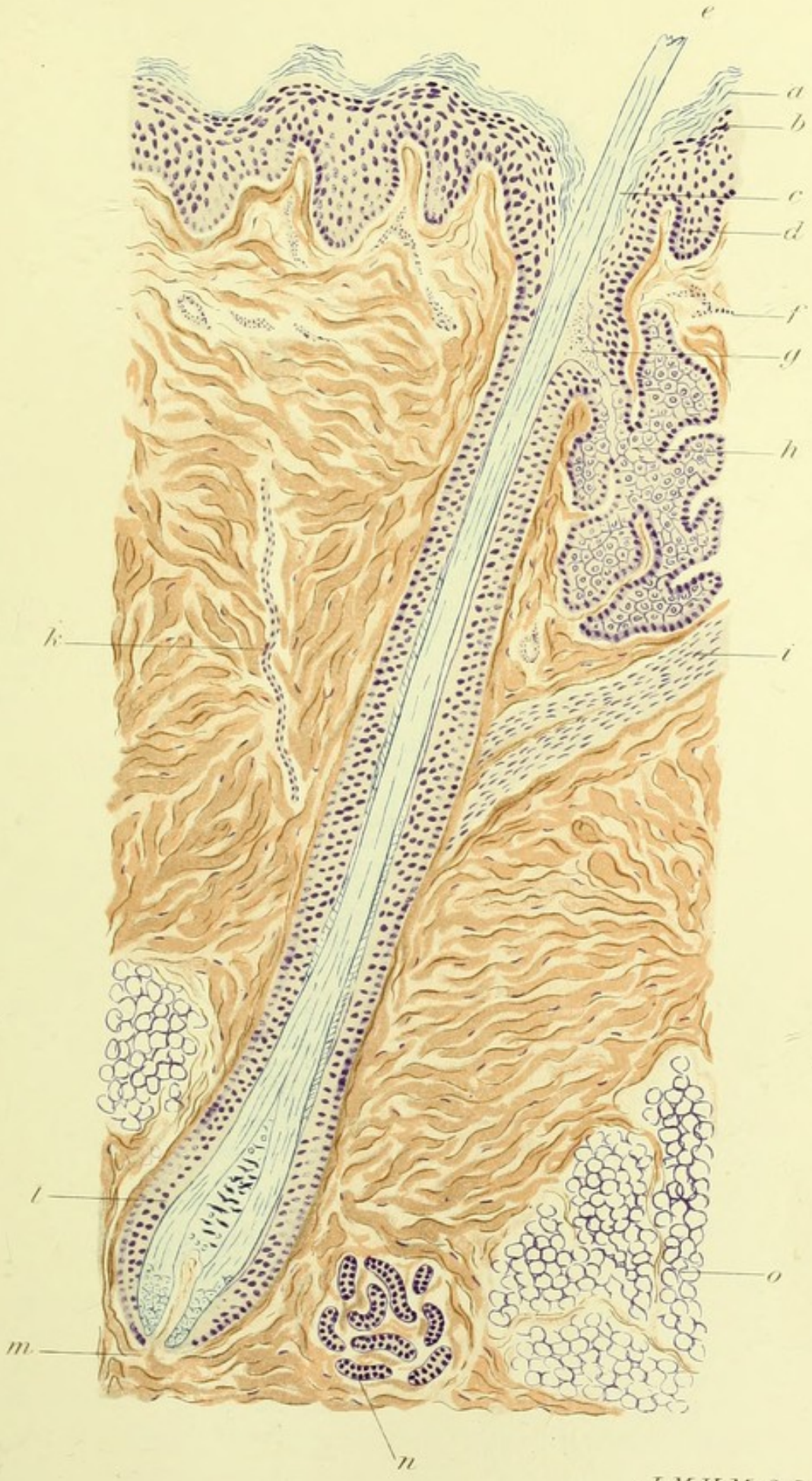
[2] *Lect. on Dermat.*, London, 1878, p. 99.

PLATE XXVII.

Longitudinal Section of a Pilo-Sebaceous Follicle (Semi-Diagrammatic).

Stained with polychrome methylene blue and neutral orcein.

a. Stratum corneum.
b. Stratum granulosum.
c. Funnel of the follicle.
d. Stratum Malpighii.
e. Hair.
f. Capillary.
g. Opening of the sebaceous duct.
h. Sebaceous gland.
i. Arrector pili.
k. Sweat-duct.
l. Hair-bulb.
m. Papilla.
n. Coil-gland.
o. Fat-cells.



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the pigment and diffuse colouring matter disappear, and the hair becomes grey. By the shrinkage and atrophy of the hair-cells and the presence of air between them the white hair of old age is produced.

4. **Shape.**—In health the hair tapers to a fine point. In section it may be circular, oval, or may form angular or irregular figures. Curly hairs are generally oval in section, while straight hairs are circular. The curl of the hair has been explained as the result of the follicles being curved. Curved follicles occur in the eyebrows, lips, and on the scalp of negroes, and in these situations the hair is curly.

5. **Size.**—Hairs vary greatly in length and thickness. They are thickest in the beard and about the genitalia, and thinnest on the trunk and limbs, where they form the lanugo.

6. **Types.**—Hairs may be divided into two types, according as they are implanted vertically or obliquely in the skin. The vertical hairs include the eyelashes (cilia), the hairs at the nasal orifices (vibrissae), and those at the orifice of the external auditory meatus (tragi). The hairs on the rest of the skin are more or less oblique in direction, and the longer the follicles are the greater is the obliquity, since the longer follicles are forced to take an oblique direction in the corium to get sufficient room.

Hairs are sometimes classified as follows:

(*a*) Long hairs, such as those of the scalp and beard.
(*b*) Stiff hairs or bristles—vibrissae, tragi.
(*c*) Lanugo hairs.

7. **Arrangement of the Hairs in the Skin.**—This subject is of importance, since in a large number of dermatoses the arrangement of the hairs to a great extent determines the grouping of the lesions. The hairs are implanted in invaginations of the skin known as hair-follicles. Usually there is only one hair in each follicle, though two or even more may be present. The hair-follicles are arranged in rows, which pass round the body and limbs, and which correspond to the "lines of cleavage," their direction and arrangement being due to the arrangement of the fibrous bundles of the corium. In several situations the rows are arranged in segments of circles radiating from a central point and forming whorls. The most familiar of these whorls is the one situated on the vertex of the scalp. Whorls[1] occur also about the inner

[1] For a detailed account of the arrangement of the hairs *see* v. Brunn, *Bardeleben's Sinnesorgane, Haut*, p. 32.

canthus of the eyes, on the auricles, in the axillae and groins, and on the sides of the chest. From the whorls the hairs radiate in a spiral direction, following the lines of cleavage.

Minute Structure of the Hair.

The hair consists of a *shaft* or *stem*, which widens out at the lower end of the hair-follicle into a bulbous extremity known as the *root* of the hair (Pl. XXIX.).

1. **Shaft or Stem of the Hair.**—The greater portion of the shaft is formed by the *cortex*, in the centre of which there is a more variable structure known as the *medulla*. The hair is protected externally by a sheath or *cuticle* formed of a single layer of cells (Pl. XXVIII., Fig. 1).

(1) *Cuticle.*—When an epilated hair is examined microscopically, a number of wavy transverse lines may be observed on its surface, which join each other irregularly, and on focussing the edge of the hair a toothed appearance is presented. These peculiarities are produced by the cells of the cuticle. These cells are quadrilateral and flat in shape, and are arranged in an imbricated manner, overlapping each other like slates, and have their long axes directed upwards and outwards at an acute angle to the axis of the shaft. By careful staining with hæmatoxylin the nuclei of these cells may be detected, and they appear to be situated, as a rule, near the base of the cell. These cells may be separated by macerating the hair in a weak solution of caustic potash.

(2) *Cortex.*—The cortex composes more than two-thirds of the shaft when a medulla is present, and the whole of it in the absence of a medulla. It consists of bundles of spindle-shaped cells, which give it a fibrillated appearance. The spindles have ridges on the surface, and lock into each other, so that a highly resistant structure is produced. The nuclei of the cells are fusiform in shape. The cells contain diffuse colouring matter of a yellowish or reddish tinge. Between them, and occasionally within them, pigment-granules may be found. Air-spaces may also be detected between the cells, and their presence renders the hair opaque and white in old age. By transmitted light the cortex appears dark; but if the hair be boiled in water or oil, it will appear light, from the fluid having soaked into the spaces. The cortex is quickly destroyed by treatment with alkalies, but the cells may be dissociated without being destroyed by means of

PLATE XXVIII.

FIG. 1. TRANSVERSE SECTION OF A HAIR ABOUT THE MIDDLE OF THE FOLLICLE (SEMI-DIAGRAMMATIC).

a. Medulla, showing a layer of polygonal cells with keratohyalin granules.
b. Cortex; fine pigment-granules in and between the cells.
c. Cuticles of hair and root-sheath.
d. Inner layer of the root-sheath, showing keratohyalin granules (internal root-sheath).
e. Outer layer of the root-sheath.
f. Prickle-cell layer of the follicle (external root-sheath).
g. Inner condensed layer of dermic coat of the follicle.
h. Dermic coat of the follicle, showing collagen bundles.

FIG. 2. SECTION OF AN ACINUS OF A SEBACEOUS GLAND (SEMI-DIAGRAMMATIC).

a. Connective tissue coating.
b. Layer of cubical cells with round nuclei.
c. Cells with a granular hyaloplasm and a few fat-droplets.
d. Polygonal central cells in which the spongioplasm remains and the hyaloplasm has been converted into a fatty substance.

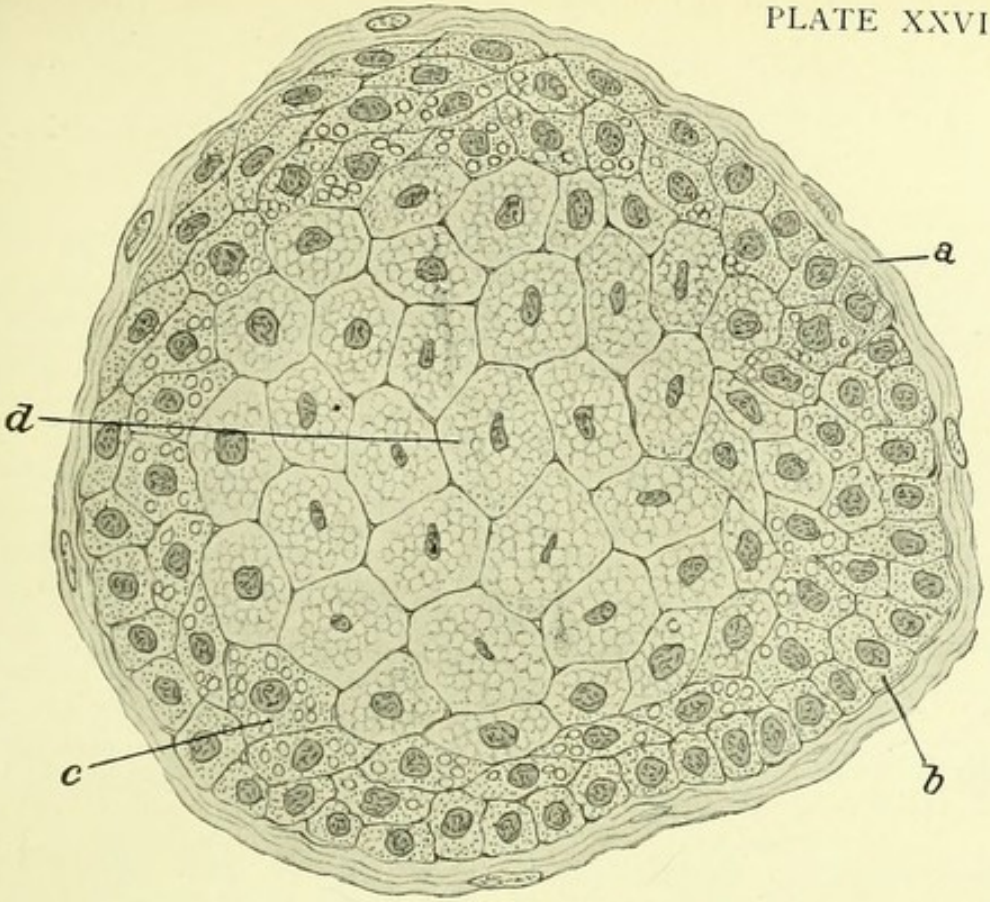

FIG. 2.

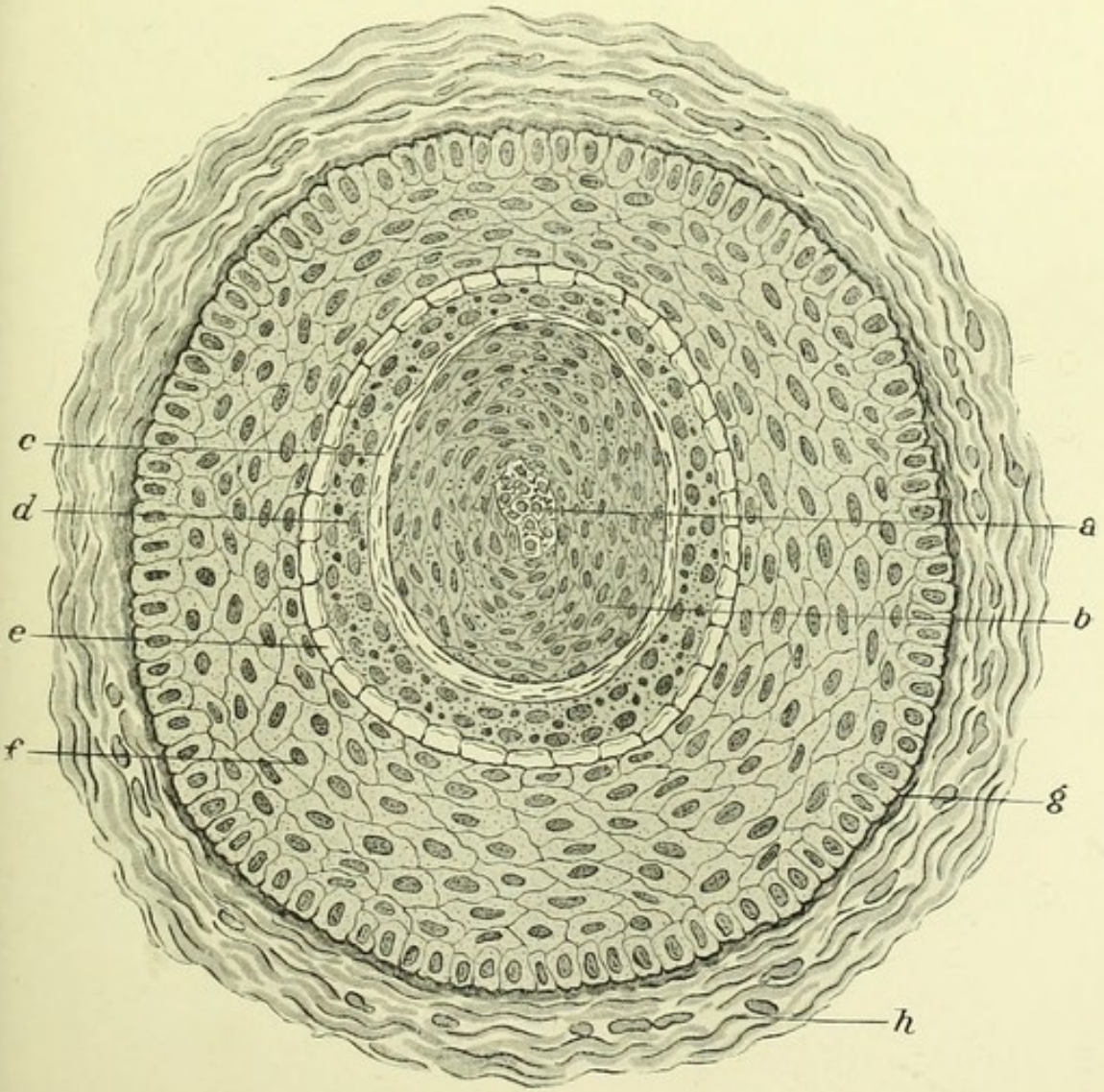

FIG. 1

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strong acids. For this purpose soak the hair for half an hour in sulphuric acid, then wash it thoroughly, mount in glycerin, and by pressing the cover-glass down firmly upon it the cells can be separated.

(3) *Medulla.*—The medulla forms the core of the hair and extends to near the tip. It is made up of *rouleaux* of plates composed of three or four flattened cells, which towards the bulb contain keratohyalin granules. Nearer the tip the granules disappear, and air-spaces may be detected between the cells. The cells are not pigmented. By transmitted light the medulla appears as a dark streak in the centre of the shaft, from the presence of air in and between the cells. Medullae only occur in the hairs of the scalp, beard, axillae, and pubes.

2. **The Root of the Hair.**—The hair-root is the bulbous lower extremity of the shaft. It is indented at its lower end by the up-growing conical, vascular process of connective tissue known as the papilla. The root is softer than the shaft and lighter in colour, and is made up of the same layers of cells. But the cells composing the root differ in appearance from those of the shaft, since they are far less differentiated; and near the papilla they present their original characters. When the hairs are long, the root and the lower part of the follicle are situated in the subcutaneous tissue; but when short, they are found in the pars reticularis of the corium.

The *cuticle of the root* consists of a single layer of cells, which, near the papilla, are cubical in shape, and have their axes directed downwards and outwards; but further up towards the shaft they become elongated, and their long axes become directed horizontally, and finally upwards and outwards. The nuclei of these cells are most distinct the nearer they are to the papilla.

The extension of the *cortex in the root* is composed of polygonal cells with well-marked nuclei, and it is only at the upper limit of the bulb that they assume their fusiform shape, and that the fibrous appearance of the cortex becomes evident. These cells contain diffuse colouring matter, and occasionally pigment-granules. Between the cells of the cortex of the bulb stellate pigment-cells have been described. Kölliker and Riehl regard them as connective-tissue cells which have originated in the papilla.

The *medulla of the root* is formed of cubical non-pigmented cells containing granules of keratohyalin.

Minute Structure of the Hair-Follicle.

The structure of the hair-follicle generally presents difficulties to the student, chiefly on account of its complicated terminology. When it is regarded, however, as a simple invagination of the skin enveloped by a condensed layer of connective tissue, its construction is readily understood. Considered from within outwards, the follicle in its upper third has epidermal layers, similar to and continuous with those of the epidermis—namely, a horny layer, transitional layers, a prickle-cell layer, and a basal layer. In the lower two-thirds the horny and transitional layers disappear, and only the prickle-cell and basal layers remain. The epidermic portion of the follicle is enveloped in a dense sheath of connective tissue derived from the corium. At the junction of the middle and upper thirds of the follicle the sebaceous glands open to lubricate the hair, and in this region, known as the *neck*, the follicle is most constricted. It widens towards the surface to form what is known as the *funnel.*

It will be necessary to describe the sheaths of the follicles in greater detail. (Pl. XXVIII., Fig. 1).

Epidermal Sheaths of the Follicle.—The continuation of the prickle-cell layer of the epidermis in the follicle is generally known as the *external root-sheath.* It consists of polygonal prickle-cells with round nuclei, which are arranged in several layers, but which form only a single layer of cubical cells near the papilla. This layer usually comes out when the hair is epilated, and the cells may be seen adhering to it.

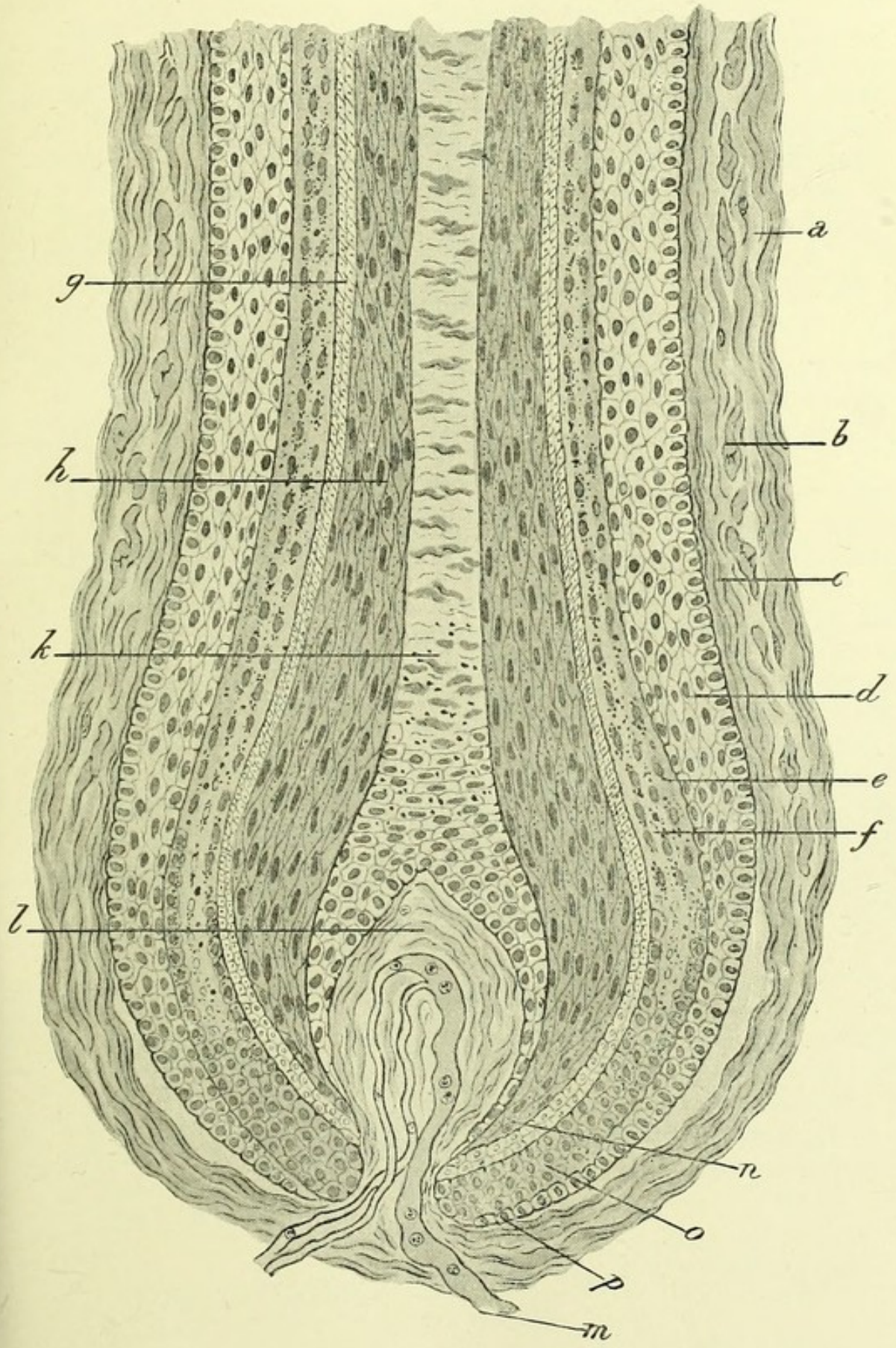
Between the prickle-cell layer and the hair there is a somewhat complicated structure, known as the *internal root-sheath.* It occupies the lower two-thirds of the follicle, extending from the neck to the papilla. It begins at the papilla as several layers of polygonal cells with round or oval nuclei, which contain granules of keratohyalin. As the cells ascend in the follicle, those next the prickle-cell layer become swollen and cornified and lose their nuclei, while the cells next the hair do not cornify so rapidly, and retain their nuclei and granules of keratohyalin. On this account the internal root-sheath splits up into two layers, the inner of which is usually known as the sheath of Huxley, and the outer as the sheath of Henle. The cells of the outer layer do not fit closely together, but spaces are here and there left between them, through which processes from the cells of the inner layer

PLATE XXIX.

LONGITUDINAL SECTION OF A HAIR-BULB AND FOLLICLE FROM A BEARD-HAIR (SEMI-DIAGRAMMATIC).

a. Outer coat of follicle, fibres longitudinally arranged.
b. Middle coat of follicle, fibres transversely arranged.
c. Inner coat of follicle, more condensed.
d. Prickle-cell layer of the follicle.
e. Outer layer of the root-sheath, showing keratohyalin granules.
f. Inner layer of root-sheath ; keratohyalin granules.
g. Cuticles of root-sheath and hair.
h. Cortex ; spindle-cells with pigment-granules.
k. Medulla ; keratohyalin granules below and eleidin "lakes" above.
l. Papilla.
m. Capillary loop.
n. Matrix of the cortex.
o. Matrix of the root-sheath.
p. Matrix of the prickle-cell layer of the follicle.

PLATE XXIX.



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extend, and for this reason the outer layer or sheath of Henle has been described as a fenestrated membrane. The distinction between the two layers of the internal root-sheath disappears in the upper part of the follicle as the inner layer also becomes cornified. On the inside of the internal root-sheath there is a *cuticle* formed of a single layer of elongated cells, with their long axes directed downwards and inwards. These cells fit into the cells of the cuticle of the hair, which have an opposite direction. Owing to the close union of the two cuticles, it is almost impossible to epilate a hair without pulling out part of the root-sheath.

Connective-Tissue Layer of the Follicle.—Outside the external root-sheath is the *connective-tissue layer of the hair-follicle.* This envelope is generally divided, for purposes of description, into three layers—an external, middle, and internal layer.

(*a*) The *external layer* is a thin, but dense, coat of connective-tissue cells and fibres, which have a tendency to be arranged longitudinally. Elastic fibres, blood-vessels, and nerves are also present, and towards the papilla, fat-cells.

(*b*) The *middle layer* is thicker than the external one, and consists of fibrous bundles arranged circularly.

(*c*) The *internal layer* has a more homogeneous appearance than the other two. It has often been described as a basement membrane, and has been said to be continuous with a similar structure beneath the epidermis. This layer has also been named the "hyalin layer" (Kölliker) or the "vitreous layer." It has been proved that it is not homogeneous, but made up of condensed collagen bundles. This layer is most noticeable in the lower third of the follicle, and fades away towards the neck.

The Papilla.

The papilla of the hair is a differentiated conical process of the corium, analogous to the papillae of the papillary layer. In shape it is conical or pedunculated. It consists of connective-tissue fibres and cells, supporting a vascular loop and medullated nerves. Numerous pigmented connective-tissue cells are present in it.

The Development of the Hair and the Hair-Change.

There are a few facts in connection with the development of the hair which are of such value in explaining several

of its pathological affections that it will not be out of place to refer to them briefly.[1]

Two problems have to be considered in connection with the development of the hair:

1. The mode of development of the lanugo or primary fœtal hairs.

2. The shedding of the lanugo towards the end of fœtal life, and the formation of secondary hairs in the old follicles.

In the fœtus all the hairs belong to the lanugo type of hair, but after birth they are replaced on the scalp, beard, pubes, and axillae by long or stiff hairs, while in the rest of the body new lanugo hairs take their place, forming the downy hairs of the glabrous skin.

1. **The Development of the Lanugo.**—In the rabbit, where the differentiation into the numerous layers which characterise the human hair is not so complete, the development is easily studied, and its main features are as follows: A solid process of epithelial cells grows down from the epidermis into the underlying connective tissue of the corium; a small vascular papilla of connective tissue forms below the down-growing process; the papilla increases in size, indents the fundus of the process, and from it a sheath of connective tissue spreads up to envelop the process and form a follicle; the axial cells of the process then become cornified, and a hair is formed; the hair grows and finally breaks through the overlying epidermis, and the development is complete. The growth of the human hair is an elaboration of this simple process. The first epidermal down-growths or hair-rudiments are found between the second or third months of fœtal life, situated about the forehead and eyebrows of the embryo, and they gradually spread over the rest of the skin. Between the fourth and fifth months the hair begins to form in the hair-rudiments of the face, and a month later the process of cornification has begun; this is indicated by the yellowish colour which the tip of the hair assumes when it is stained with borax-carmine. By the sixth month a lateral growth of the hair-rudiment has evolved into a sebaceous gland, and another lateral outgrowth has formed to give insertion to the fibres of the arrector pili muscle. When the hair has become sufficiently rigid, it is able to pierce the horny layer of the epidermis; but many of the hairs on reaching the stratum corneum are too soft,

[1] For a more detailed account *see* Author's paper in *Brit. Journ. of Derm.*, 1898, X., p. 233.

and, being diverted by the horny layer, grow along for some distance between it and the prickle-cell layer before breaking through. Others, again, such as the straight hairs about the face, push the horny layer out before them in a small projection before piercing it. In some cases the hairs become doubled back like the lash of a whip, and straighten out after breaking through the horny barrier. The fœtal hairs are generally colourless, except occasionally on the scalp.

It is very doubtful if new hair-follicles develop between the primary ones after the hairs have matured.

2. **The Hair-Change.**—The normal hair-change, or the shedding of the lanugo hairs *in utero*, begins in the face and head of the fœtus between the seventh and eighth months, and these hairs are replaced by new hairs which grow out of the old follicles. If this change has not taken place over the whole skin before birth, it is completed during the first few months of the child's life. During life the hairs have a limited existence; they are not shed periodically, however, like the hairs of animals which inhabit cold climates. In the scalp the hairs have been said to have an existence of from two to four years, when they are shed and new ones form (v. Brunn). It is not correct, therefore, to speak of permanent hairs as replacing the fœtal hairs. On the subject of the hair-change there is great diversity of opinion, and the chief point at issue is whether the hair-papilla persists or a new one forms. The theory that the new hair develops in the old papilla was supported by Langer, Biesiadecki,[1] Kölliker,[2] and Toldt,[3] etc., and the one that a new papilla forms by Steinlein, Klein,[4] and Stieda.[5] Ranvier[6] takes a middle position, and thinks that either may occur. Unna[7] describes the formation of "bed-hairs" as part of the developmental process. He considers that the lanugo hair is lifted off the old papilla, pushed up, and becomes fixed in the narrow regions of the follicle, and that it takes root in this position for some time, and so forms a "bed-hair." But whether it takes root is a doubtful point, and it is more than probable that the hair only becomes fixed there from the narrowness of the follicle in that position. Since the new papilla occupies

[1] *Stricker's Handb.*, Leipzig, 1871, p. 612.
[2] *Entwicklungs-Geschichte*, 1879, p. 786.
[3] *Lehrb. der Gewebelehre*, 1886, p. 565.
[4] *Elements of Histol.*, 1884, p. 285.
[5] *Biolog. Centralbl.*, VII., p. 353.
[6] *Traité Technique d'Histol.*, 1882, p. 895.
[7] *Ziemssen's Handbook*, 1885, p. 41.

exactly the same position as the old one, it is difficult to understand why so many writers regard the formation of a totally new structure as essential to the process, especially when the follicle, of which the papilla only forms a part, does duty for the new as well as for the old hair.

Besides the intermittent falling out of hairs, there occurs at certain periodic intervals changes in the amount of the hairy coating in man. At birth, or immediately after it, hairs actively grow on the scalp. At puberty hairs appear in certain regions, such as the beard, axilla, and about the genitalia. In middle life and later, hairs, or vibrissae, grow about the nostrils and ears. In females, after the menopause, there is an increase of hairs on the face, especially about the lips. These hairs, which may be called the periodic hairs, are usually pigmented and coarse, while those of the rest of the body retain their unpigmented condition.

Technique for the Study of the Structure of the Hair.

In epilating hairs, in order to prevent the hair from breaking, and so leaving the root in the follicle, it is necessary to epilate slowly and steadily and in the direction of the axis of the follicle. Hairs from different regions of the body should be studied, but for the demonstration of the various layers of cells the coarse beard-hairs are best, and they have the advantage of possessing a medulla.

The epilated hair may be examined in glycerin, xylol or Farrant's solution (equal parts of glycerin, mucilage of acacia, and saturated solution of arsenious acid). If a permanent specimen be desired, the cover-glasses should be ringed with cement after mounting. For the purpose of ringing specimens, a special turning table is made which greatly facilitates the operation. The slide is spun on this turning table and the cement applied to the edge of the cover-slip by a small brush. Hamilton's[1] cement gives excellent results, and forms on drying a permanent ring of hard enamel. It consists of:

Gum damar	2 oz.
Zinc oxide	2 drms.
Benzol	2 oz.

Dissolve the damar in the benzol, mix with the zinc oxide in a mortar, and filter through muslin.

[1] *Textbook of Path.*, 1889, I., p. 96.

Permanent preparations of hairs may also be obtained by mounting in Canada balsam; but this necessitates thorough dehydration in absolute alcohol, which causes a certain amount of shrinkage.

Depigmentation of the Hair.—The presence of much pigment in the cortex of the hair causes the minute structure to be blurred, and interferes with the staining for micro-organisms, since small pigment-granules sometimes closely resemble cocci. Hairs may be depigmented by one or other of the following methods:

1. *After Mayer* (*Lee's Vade-Mecum*, 5th edition, 1900, p. 327).—A few crystals of potassium chlorate are put in a tube, and to these two or three drops of hydrochloric acid are added, and, when the green colour of the chlorine begins to show itself, add several cubic centimetres of water. Immerse the hairs in this liquid for a night, when they will generally be completely depigmented.

2. *A solution of one part of peroxide of hydrogen and eight of glycerin* may also be used. The hairs are put in this from one or two days, when they are not only bleached, but slightly macerated.

Dissociation of the Elements of the Hair.—This is most easily done by immersing the hairs in a 40 per cent. solution of caustic potash. After half an hour the hair may be mounted in this fluid and examined, when it will be found that the cells of the cortex, cuticle, and even the medulla have swollen, and may be separated if the cover-glass be squeezed down on the hair. A similar result may be obtained by heating the hairs in sulphuric acid (25 per cent.), and, after washing, mounting them in glycerin.

The Staining of Hairs in Sections of the Skin.—Vertical and transverse sections of a piece of scalp imbedded in paraffin should be cut; celloidin is not so satisfactory.

To obtain good vertical sections of a hair is largely a matter of luck, and as a rule many sections will have to be cut before a perfect specimen is got. There is no difficulty, however, in getting transverse and oblique sections of hairs in their follicles. Hairs are readily stained by any of the stains for keratin and keratohyalin; for example, picro-carmine stains the keratin of the hair yellow and the nuclei bright red, and hæmatoxylin stains the

keratohyalin granules of the hair and the nuclei reddish violet.

The following method gives a good differential stain:

1. Stain the section for five minutes in a 1 per cent. solution of safranin in spirit.
2. Wash in water.
3. Counter-stain for ten minutes in water-blue tannin mixture (Grübler).
4. Wash in water.
5. Dehydrate in alcohol.
6. Clear in xylol and mount in Canada balsam.

The keratin and the nuclei of the hair are stained brilliant red, the uncornified protoplasm blue.

After Günther (*Dissertation*, Berlin, 1895, and *Dermato-histologische Technik*, Joseph and Loewenbach, 1900, p. 56).—

(*a*) Fix in Müller's fluid, harden in alcohol, imbed and cut in paraffin.

(*b*) Stain for twelve hours in Böhmer's hæmatoxylin.[1]

(*c*) Differentiate in acidulated alcohol. Wash thoroughly in ammoniacal water and then in pure water.

(*d*) Stain for six hours in a watch-glass of water, with the addition of three drops of a concentrated aqueous solution of picric acid and eight drops of eosin solution. Wash in 70 per cent. alcohol.

(*e*) Alcohol, xylol, Canada balsam.

Keratohyalin is stained red, keratin and the nuclei blue; the hair itself and the cuticle are stained yellow.

Staining of Hairs for Micro-Organisms.

To stain micro-organisms such as cocci and micro-bacilli in hairs, Gram's method gives the most satisfactory results, and the same procedure should be adopted which is described in Chap. XXXIX.[2] for the demonstration of the fungi of ringworm in and about the hair. Micro-organisms on the cuticle of the hair may be simply stained by carbol-fuchsin, Löffler's

[1] Böhmer's Hæmatoxylin.

(*a*) Make a solution of 1 part of hæmatoxylin in 12 of absolute alcohol.
(*b*) Also a solution of 1 part of alum in 240 of water.
Add two drops of (*a*) to a watch-glass of (*b*) (Lee).

[2] The description of the staining of hairs for the fungi of ringworm and favus will be deferred to the chapter on the Moulds which Affect the Skin (p. 370).

blue,[1] or carbol-methylene blue (Kühne [2]). The hair should be stained on a slide, a drop of the stain being allowed to remain on the hair from five to ten minutes. The hair is then washed and, if necessary, decolorised in alcohol. If a permanent preparation be desired, mount in Canada balsam; if not, examine in glycerin. The time required by alcohol to decolorise the hairs varies considerably. With carbol-fuchsin and carbol-methylene blue a longer time is required than in the case of Löffler's blue, since the addition of carbolic acid to the two former dyes greatly increases their power and penetration.

For the staining of micro-organisms in and about the hair in sections the methods described under the heading of the staining of micro-organisms in the stratum corneum are all serviceable, and the criticisms passed on these methods are equally applicable here (*see* Chap. XXXV.).

[1] LÖFFLER'S BLUE.

30 c.c. of a saturated alcoholic solution of methylene blue is added to 100 c.c. of 1 in 10,000 solution of potash.

[2] KÜHNE'S BLUE.

Methylene blue	1·5 grms.
Absolute alcohol	10 c.c.
5 per cent. solution of carbolic acid . .	100 ,,

CHAPTER XXIII.

PATHOLOGICAL AFFECTIONS OF THE HAIR AND THE HAIR-FOLLICLE.

I. Hypertrophies, Hypertrichosis, Hirsuties.

An increase in the number of the hairs (hypertrichosis) may be a congenital or an acquired condition.

(*a*) **Congenital Universal Hypertrichosis** has been observed in the so-called hairy men, and in some cases it has been definitely proved to be a family trait.

(*b*) **Congenital Local Hypertrichosis** is found in the various hairy nævi of the skin (*N. pilosus*). It occasionally occurs in the lumbar region in association with spina bifida.

(*c*) **Acquired Hypertrichosis** is a local or regional affection which frequently occurs in women about the face in association with uterine disturbances.

This excessive growth of hair rarely, if ever, affects the regions where no hair-follicles normally exist, such as the palms and soles. As a rule it is due to a change in the lanugo hairs, which become replaced by coarse pigmented long hairs.

II. Dystrophies of the Hair.

Dystrophy of the hair may be evident by defects in the colour or in the structure of the hair.

(*a*) **Defects in Colour: Whitening of the Hair (Leucotrichia).**—A patchy whitening of the hair has not infrequently been observed; this may sometimes occur in the form of white rings, which give to the hair an annular appearance. Its pathology is imperfectly understood, but it is probably analogous to the white dystrophic spots on the nails, and due to a temporary interference with the nutrition of the hair. The white patches or rings are the result of the

presence of air between the cells of the hair-shaft. Any interference with the circulation of the hair-papilla may be sufficient to cause a shrivelling of the soft cells of the bulb and the lower part of the shaft of the hair; this allows air to collect between the cells. Such an interference with the circulation and nutrition of the hair may occur in association with nervous worry, prolonged illnesses, chronic dyspepsia, and the like. With the restoration of the proper circulatory balance the new cells lose their shrivelled appearance and the white patches disappear.

The patches of white hair which may follow a severe attack of neuralgia, involving one or other of the cutaneous nerves of the scalp, and the sudden whitening of the hair after worry or severe illnesses, have the same pathology. A less probable explanation of the patchy whitening of hair is that it is due to a periodical interstitial development of gas between the cells of the shaft.

These forms of whitening of the hair are all temporary, and belong to a different category from that which occurs in old age; for in the latter condition, as well as in the disease known as *vitiligo*, where whitening occurs in patches, not only do the cortical cells of the hair shrink and air collect between them, but the pigment of the cells disappears, and recovery is thus impossible.

(*b*) **Defects in Structure.**—Hairs not infrequently assume a dry and brittle condition, with a tendency to split into two or more fibres; the splitting may be confined to the tips of the hair, or it may affect the hair in the whole of its extra-follicular portion.

The dystrophy is due to an interference with the nutrition of the hair at the papilla, resulting in imperfect hair-formation, and corresponds closely to the brittle condition of the nails, in which the free margin becomes irregular and the nail-plate tends to split. Such a dystrophy of the hair frequently follows prolonged fevers and wasting diseases, but it also occurs in association with pityriasis of the scalp, and is not infrequently the result of bad treatment, such as singeing and other allied malpractices.

A peculiar type of hair-dystrophy, occurring chiefly in Eastern countries, and affecting generally the hairs of the beard and moustache, has been described under the heading of *Trichorrhexis nodosa* (Pl. XXX., Fig. 3). In this disease the affected hairs present a number of greyish white nodules situated at the free end and at irregular intervals on the shaft

of the hair. On microscopical examination these nodes are found to be the result of a local splitting of the hair, which has been likened to the interlocking of the bristles of two brooms.

A number of causes have been suggested to explain this curious formation. It has been said to be due to the development of gas in the medulla of the hair, causing a fusiform swelling of the cortex, a separation of its fibre-like cells, and a rupture of the cuticle. It has also been explained as the result of a defective development of the hair, and more recently a micro-organism has been suggested as the probable cause. Any condition of the hair such as this is bound to harbour micro-organisms, since its brush-like swellings form a trap for them; and Hodara,[1] of Constantinople, has not only found a small bacillus constantly present in these hairs, but has succeeded in producing the condition by inoculating the bacillus on healthy hairs.

III. Atrophies of the Hair.

If the connection between the hair and the papilla be broken, or the papilla be destroyed, the hair becomes atrophic. A *partial atrophy* of the hair, in which only portions of it are affected, giving the hair a beaded appearance, occurs in a rare disease known as *Monilithrix* (Pl. XXX., Fig. 2). In this the affected hairs become short and like bristles; they readily fall out, showing that their connection with the papilla is to some extent lost. The lanugo hairs are never attacked in this disease. On microscopical examination of these beaded hairs the thickenings are found to be spindle-shaped, and retain their pigment and medulla. The intervening atrophic portions are thin, and have lost both their pigment and medulla. The intra-follicular part of the hair is similarly affected. The pathology of monilithrix is uncertain; in most cases it is congenital, and occasionally it runs in families. It is associated with more or less keratosis at the mouth of the follicle, and it is just possible that the constriction so caused has something to do with the intermittent type of atrophy which is present. This explanation, however, is insufficient, since when the hair is shed new hairs do not grow again in the same follicle, showing that an atrophy of the papilla is also present.

Atrophy of the Hair, Baldness, or Alopecia.—The pathology of the various forms of alopecia is still undecided. Baldness

[1] *Monats. f. prakt. Derm.*, 1894, XVIII., p. 573.

PLATE XXX.

FIG. 1. CLAVATE STUMP OR "POINT OF EXCLAMATION" HAIR OF ALOPECIA AREATA.

FIG. 2. MONILITHRIX.

Hair twisted and beaded.

FIG. 3. TRICHORRHEXIS NODOSA.

a. Node made up of two brushes.
b. Node with the upper brush split into three.

FIG. 4. INVOLUNTARY MUSCLE-CELLS FROM ARRECTOR PILI (SEMI-DIAGRAMMATIC).

a. Spindle-shaped involuntary muscle-cell.
b. Dividing nucleus.

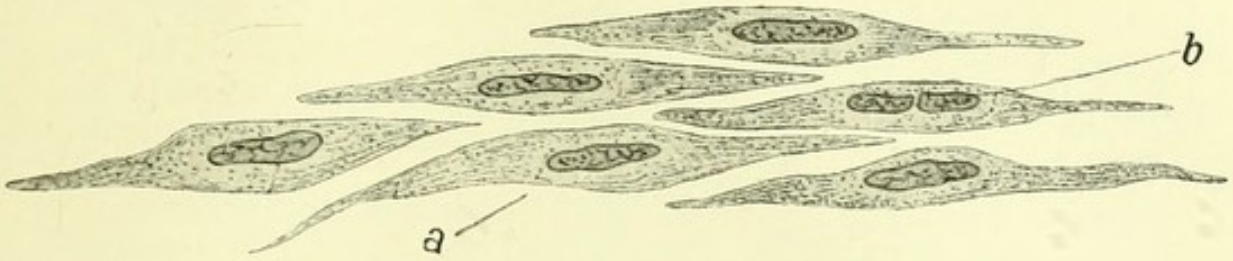


FIG. 4.

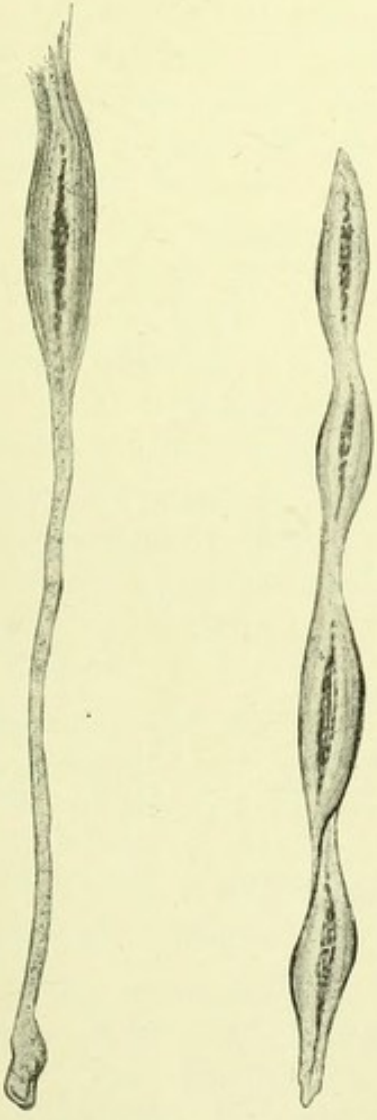


FIG. 1.

FIG. 2.

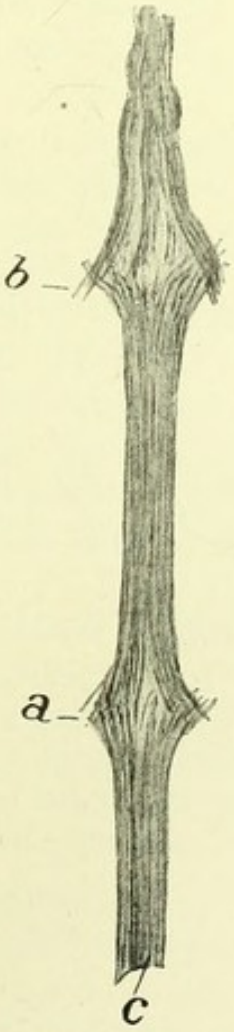


FIG. 3.

J. M. H. M., del.

may be a congenital or an acquired condition ; it may be a disease *per se* or only a symptom ; it may result from any cause which interferes with the growth of the hair, such as old age, prolonged and severe illnesses, poisons acting on the hair-papillae, injuries, scar-leaving diseases, or the presence of parasites in the hair-follicles.

1. **Congenital Alopecia.**—Both local and general congenital baldness have been described, but they are rare conditions ; and in the majority of cases where children are born bald the alopecia is due to an arrest in development, and hairs eventually appear, though it may be several years after birth.

2. **Acquired Alopecia.**—A classification of the acquired types of alopecia from the pathological standpoint is difficult, and in the present state of our knowledge it cannot but be incomplete. The following classification is based on Brocq's admirable description of baldness in *La Pratique Dermatologique*, Vol. I.

(*a*) *Traumatic Alopecia.*—Baldness may result from irretrievable injury to the hair-papillae, such as may be produced by epilation or by electrolysis or by a wound. Under this heading may also be included the baldness which occurs in association with sclerodermia and in connection with any scar-leaving dermatitis, such as small-pox.

(*b*) *Parasitic Alopecia.*—The action of the fungi of favus, and very occasionally those of ringworm, may result in baldness ; but this is usually temporary in character. The presence of pyogenic organisms in the hair-follicles may also result in a loss of the hair.

(*c*) *Alopecia dependent on General Morbid Conditions.*—A temporary baldness is a frequent consequence of acute fevers. It may also follow an attack of exfoliative dermatitis, and a patchy thinning of the hair is frequently associated with syphilis. Nervous disturbances such as worry, melancholia, and neuralgia may occasion a more or less complete baldness.

(*d*) *Alopecia dependent on Morbid States of the Scalp.*—Acute eczema, erysipelas, and even psoriasis have been known to result in the destruction of the hair-follicles, and in temporary baldness ; but by far the most common precursor of alopecia is some form of dandruff or scurfiness of the scalp. This type of baldness is peculiarly chronic, and, if untreated, is apt to become permanent. It has been variously termed *alopecia furfuracea, pityrodes, and seborrhœa sicca.* It is a

chronic inflammatory condition associated with vascular dilatation, epithelial œdema, and imperfect cornification, especially marked around the mouths of the follicles. In this condition the hairs, before falling out, have a peculiarly opaque appearance, lose their lustre, and may occasionally seem to be powdered over with dried sebaceous material. The part played by the sebaceous glands in the production of this affection is not yet definitely determined. It is evidently the result of a chronic inflammatory process affecting the follicle and its papilla, and strongly suggests a parasitic origin. Unna has found in association with this condition several micro-organisms, such as morococci, flask-shaped bacilli, and another small bacillus ; but a causal connection between these micro-organisms and this form of alopecia has still to be proved.

(*e*) *Alopecia Areata.*—Alopecia areata is a disease in which bald patches make their appearance on the scalp independent of age, general morbid conditions, or traumatism, and its pathology is at present a fruitful subject for controversy. The patches are sometimes circular in shape, spread eccentrically, and run together to form irregular areas ; at other times they take the form of irregular bands round the margin of the scalp. They may be pinkish in colour and dotted over with plugged hair-follicles, or they may be pale and atrophic, and shiny like the surface of a billiard-ball. The researches of Sabouraud[1] have led him to divide alopecia areata into two distinct types : (1) an *areate* variety, in which bald areas appear over the scalp and run together to form irregular patches ; and (2) a *band* type, in which the affected region forms a band round the margin of the scalp ; this enlarges towards the centre, but as a rule leaves some of the hair in the centre unaffected. The areate type he believes to be due to the action of a specific microbacillus, but the cause of the band variety, which is said to occur chiefly in childhood, has not yet been determined. This simple dogmatic distinction is not universally accepted, and in this country so many cases occur, in which transitional forms between the two varieties are present, that such a hard and fast distinction is untenable.

A case of recent alopecia areata frequently has the following characteristics. In distribution and shape the patches may closely resemble those produced by microsporon ringworm, and a mother-patch may be often detected

[1] *Maladies du Cuir Chevelu*, Paris, 1902.

surrounded by satellites. The borders of the patches are defined, and the affected skin is pinkish in colour, from a certain amount of inflammatory congestion. The surface of the patch is not at first smooth, but is stippled over with black specks, which are the plugged hair-follicles. At the margins of the patch various types of atrophic hairs may be detected ; some of these are split, while others are broken off a short distance above the follicle. The latter are atrophied and loose in the follicle, and on epilation exhibit an attenuated point or a small thickening at the bulb, which, compared with the thicker extra-follicular portion, gives them the appearance of a point of exclamation. These are the typical clavate stumps of alopecia areata (Pl. XXX., Fig. 1). If one of the plugs be squeezed out between the thumb-nails, it is found to consist of epithelial and cornified cells, sebaceous material, and occasionally small atrophic hairs coiled up in the mass. Numbers of small micro-organisms, both cocci and bacilli, are generally found on suitably staining the sebaceous plug. Sections of the affected regions show an inflammatory infiltration at the lower end of the hair-follicle and about the papilla. The funnel of the follicle is dilated, forming the "utricle peladique" of Sabouraud. The blood-vessels around the follicle are congested. Atrophy affects the papilla, and if this be severe, recovery is impossible ; and as organisation of the cells around the atrophic papilla occasionally takes place, scarring may result. When recovery does supervene, the first new hairs to form are slender, and unpigmented, and have no medulla. Gradually, however (it may be six months after the hairs have grown again), the new hairs become pigmented like those of the rest of the scalp.

There are certain characteristics in the patches of alopecia areata which strongly suggest that the condition has a *parasitic origin*. These are the following :

1. The pink inflammatory appearance of the lesions before they have been treated.

2. The distribution and method of spreading of the patches, which may closely resemble those of microsporon ringworm.

There is also the fact that an epidemic has been described.

Sabouraud believes that the parasite of the "areate" type of alopecia areata is a microbacillus which also causes seborrhœa oleosa and acne vulgaris, and he goes so far as to regard this type of alopecia as a localised acute seborrhœa. This opinion has not yet been generally accepted.

Norman Walker[1] inoculated a large number of cases of alopecia areata on the medium which Sabouraud recommends for his microbacillus, and only in one case was he able to obtain the characteristic cultures of that micro-organism, though he invariably obtained cultures of a white coccus which he recognised as the Staphylococcus epidermidis albus of Welch. Pawloff of St. Petersburg claims to have produced alopecia areata in rabbits by rubbing cultures of this white coccus into the skin.

There are other cases of alopecia areata in which these evidences suggestive of parasitism are absent, where the patches are glossy and atrophic, and no congestion can be noted. Such cases have frequently been explained as the result of some nerve-disturbance; but as actual degenerations in the peripheral nerves supplying the affected areas have not been demonstrated, and as the patches do not usually correspond to the distribution of cutaneous nerves, such an explanation is hypothetical, though it must not be forgotten that functional changes may be present in nerves without gross degenerative lesions. It is not improbable that, at least in the great majority of cases of alopecia areata, there is an early stage, before the patches become white and atrophic, in which congestion and plugging of the hair-follicles are present; but it has yet to be proved that this is the direct result of the presence of micro-organisms, and that the latter are not simply harmless denizens of the sebaceous plug.

Affections of the Hair-Follicles.

The pilo-sebaceous follicles are the seat of origin of a large number of skin-diseases. This is largely due to the fact that the follicles form the easiest mode of entrance for micro-organisms to penetrate into the deeper layers of the skin. At the junction of the upper and middle thirds of the follicle, the stratum corneum, which extends from the surface to form a lining for the follicle, ceases, and micro-organisms, which readily collect in that situation, are no longer prevented by a horny barrier from penetrating into the epidermis. On the other hand, the contents of the sebaceous glands constitute a suitable medium for the growth of the various pyogenic organisms. For these reasons the follicles are the sites of least resistance in the skin, and readily become the seats of inflammatory and pustular lesions.

[1] *Scot. Med. and Surg. Journ.*, 1901, IX., p. 12.

I. **Staphylogenic Folliculitis and Peri-Folliculitis.**—

1. *Staphylogenic Impetigo* (*Impetigo of Bockhart*).—The disease known as the impetigo of Bockhart is the simplest example of a folliculitis due to the inoculation of the pilo-sebaceous follicles with pus-cocci. Each of the affected follicles becomes a small pustule, which is generally pierced by a hair. These impetiginous lesions are frequently found around a suppurating wound, are generally the result of secondary inoculation, and occur most readily where the follicles are most numerous, as on the extensor aspects of the limbs.

Sometimes the inoculation of pus-cocci results first in the formation of a vesicle which rapidly becomes purulent, as in the case of the impetigo contagiosa of Tilbury Fox. Bockhart believes, and his view is supported by Sabouraud,[1] that this form of impetigo is pustular from the first (*pustule d'emblée*), and that there is no preceding vesicular stage such as occurs in impetigo contagiosa.

Sections of an early lesion show the presence of cocci in the funnel of the follicle, between the hair and the follicular wall and about the mouth of the sebaceous gland. These cocci cause certain inflammatory changes in the papillary layer around the follicle, such as slight dilatation of the blood-vessels and an infiltration of leucocytes ; and in the prickle-cell layer around the neck of the follicle, such as œdema, infiltration of leucocytes, and the formation of a superficial pustule.

2. *Furuncle.*—A boil may be regarded simply as a further stage in the above folliculitis, in which the cocci have spread deeper into the follicle and acini of the sebaceous gland, have gradually passed through into the surrounding corium, and have set up a peri-follicular abscess. Furuncles occur much more readily in connection with lanugo hairs than with stiff hairs, because the follicular walls of the lanugo hairs are weaker, and cocci more easily penetrate through them into the corium.

3. *Coccogenic Sycosis Barbae.*—When the hard hairs of the beard-region become infected with pus-cocci, a persistent deep-seated folliculitis is set up. The sebaceous glands in connection with the hair-follicles of the beard are proportionately smaller than those of the lanugo hairs, and the cocci, passing down into the depths of the follicle, do not produce

[1] *La Pratique Dermatologique*, 1901, II., p. 856.

such active changes as they do when they collect in the large sebaceous glands. A more indolent type of folliculitis thus results, in which the wall of the follicle becomes transformed into an abscess, which occasionally, breaking through into the corium, sets up a peri-folliculitis.

The *sweat-follicles* also may be the seat of inoculation of pus-cocci. The folliculitis of the sweat-glands will be discussed in the chapter dealing with the sweat-apparatus.

II. **Folliculitis associated with the Presence of the Fungi of Ringworm and Favus.**—The variety of ringworm caused by the Trichophyton ectothrix is invariably associated with more or less folliculitis. These ringworms are generally believed to be exclusively of animal origin, and in a large number of instances this can be demonstrated. Certain writers consider that the trichophyton is capable of setting up the folliculitis and pustulation, while others as firmly believe that the pustulation is the result of a double inoculation with ringworm and pyogenic cocci. Pustulation may also occur in association with favus and with other forms of ringworm, such as those produced by the Trichophyton endothrix, and the microsporon. In most instances, if not invariably, the pustulation in these cases is due to the simultaneous inoculation of pyogenic cocci, and is not the result of any specific action of the fungus.

III. **Folliculitis due to Chemical Irritants.**—Chemical irritants such as croton oil and aconitine are capable of causing pustulation. A folliculitis may also occur after the ingestion of iodine or bromine (*iod-acne or brom-acne*) in those who have an idiosyncrasy to the drugs. In such cases it has not been definitely proved that the folliculitis is a primary affection of the follicle, and not the result of a secondary inoculation in a tissue whose resistance has been diminished by the elimination of these drugs.

IV. **Folliculitis secondary to Keratosis and Plugging of the Follicles** (*e.g.* **Acne Vulgaris**).—The formation of the pustules in acne vulgaris is secondary to the presence of a comedo blocking the follicle. By the plugging of the funnel of the follicle the sebaceous material is prevented from escaping, and the gland undergoes a cystic distension. In this retention-cyst pus-cocci readily proliferate. The action of these cocci results in the formation of a small abscess, which is generally peri-follicular, but which may begin in the wall of the follicle. The disturbance set up in the corium is more than a simple

inflammatory infiltration, for surrounding the speck of pus a dense mass of granulomatous cells forms, in which are plasma-cells, multinucleated cells (chorioplaques) and connective-tissue spindles. This cellular infiltration surrounding the abscess accounts for the nodular appearances in old cases of acne and for the difficulty in obtaining pus when the nodules are incised. Organisation frequently occurs in these granulomatous cells, and scarring may be produced.

Sabouraud[1] and Unna consider that the primary cause of the formation of the comedo is a microbacillus (*see* p. 351), and they also attribute the pustulation to the same organism. It has consequently been described as a "bacillogenic impetigo." The presence in the lesions of the ordinary pus-cocci is regarded as a secondary phenomenon. Other organisms, such as an oat-shaped bacillus and the "diplococci of seborrhoic eczema," have also been noted in this connection by Unna.[2]

V. **Folliculitis associated with Hypertrophy of the Peri-Follicular Connective Tissue (Example: Acne Keloid).**—Hypertrophy of the connective tissue not infrequently occurs in association with acneiform lesions. A peculiar disease, in which they are invariably concomitant, has been described under the heading of *acne keloid.* In this disease hypertrophic scar tissue develops round a deep-seated peri-follicular abscess. Clinically the lesions appear as nodules, which are dotted over with pustules and hair-tufts, and are generally situated about the back of the neck. The lesions, histologically, are neither those of acne nor true keloids, and consequently the name is unfortunate.

VI. **Folliculitis associated with Necrosis and Scarring (Example: Acne Necrotica).**—Though ordinary acne may be associated with scarring, the latter is not a marked feature of the disease. In *acne necrotica* we have a type of acne in which necrosis occurs, and which results in the formation of pitted scars not unlike those of small-pox. The pathology of this disease has recently been worked out by Sabouraud.[3] He considers it to be the result of the invasion of pus-cocci in a tissue infected with the microbacillus of acne. The presence of these organisms occasions an abscess-formation in the epidermis, in the sebaceous glands, and in the surrounding papillary

[1] *Maladies du Cuir Chevelu*, Paris, 1902.
[2] *Histo-Pathology* (Walker's Trans.), 1896, p. 361.
[3] *Ann. de Derm. et de Syph.*, 1899, X., p. 841.

layer. This abscess is limited, and the affected tissue undergoes necrosis ; the healthy epidermis grows under the necrotic area, so that the latter becomes encased in a capsule of stratum corneum, forms a crust, and gradually gets thrown off, leaving a pitted scar.

A type of folliculitis in which the hair-follicle and papilla are destroyed and a scar results is also occasionally met with on the scalp. Bald patches occur in which a few hairs are left, and these are surrounded by a slight halo of hyperæmia. The surface of the patch is scarred where previous lesions have been. This affection has been variously known as *Folliculitis décalvante*, *Alopecia follicularis*, and *Acne décalvante*. Its pathology is not fully understood, though it strongly suggests a coccogenic origin.

VII. **Folliculitis associated with Dermatoses, which do not directly involve the Hair-Follicles.**—Any form of dermatitis, by lessening the power of resistance of the affected skin, facilitates the entrance and action of pyogenic cocci, and is apt, in consequence, to be associated with a folliculitis. In rosacea, for example, where the skin is inflamed, and often œdematous, and the sebaceous follicles are large and active, secondary inoculation with pus-cocci readily occurs, giving rise to a pustular affection, to which the unfortunate hybrid name of acne rosacea is generally applied. The association of folliculitis with tuberculosis has already been referred to in connection with the tuberculides (*see* p. 192).

TABLE OF PATHOLOGICAL CHANGES AFFECTING THE HAIRS AND HAIR-FOLLICLES.

Hairs.

I. **Hypertrophy or Hypertrichosis.**—

1. Congenital : (*a*) Universal . . . "Hairy men."
   (*b*) Local . . . Nævus pilosus.
2. Acquired : Local or regional.

II. **Dystrophy.**—

1. Colour-defects . . . Whitening of the hair (leucotrichia).
   May occur in patches or be universal.
   Hairs may show patches or rings of white, or may be completely blanched.
2. Structural defects . . . (*a*) Dry and brittle . . . After wasting illnesses, etc., and in association with Pityriasis capitis, etc.
   (*b*) Trichorrhexis nodosa.

Atrophy.—

1. Partial . . . Monilithrix.
2. Total. (*a*) Congenital . . . Arrest in development.
   (*b*) Acquired : (i) Traumatic.
   (ii) Parasitic.
   (iii) Dependent on general morbid conditions.
   (iv) Dependent on morbid states of the scalp.
   (v) Alopecia areata.

Hair-Follicles.

I. **Hyperkeratosis of the Funnel of the Hair-Follicles** occurs in a large number of skin-affections, such as :

1. Comedones.
2. Hyperkeratosis follicularis et supra-follicularis (Unna), or Lichen pilaris (Bazin), Keratosis pilaris (Brocq), Lichen spinulosus (Devergie).
3. Ichthyosis.
4. Keratosis follicularis contagiosa (Brooke).
5. Psorospermosis follicularis vegetans (Darier).

II. **Atrophy of the Hair-Follicles.**—

1. Congenital . . . Arrest in development.
2. Acquired : (*a*) Traumatic . . . Scars.
   (*b*) Parasitic . . . Fungi of Ringworm and Favus, pyogenic cocci.
   (*c*) Scar-leaving diseases . . . Small-pox, Sclerodermia.
   (*d*) Dependent on general morbid conditions.
   (*e*) Dependent on morbid states of the scalp, as Alopecia furfuracea, or Pityrodes, Eczema, etc.
   (*f*) Alopecia areata.

III. **Folliculitis.**—

1. *Primary folliculitis.*—
   (i) Parasitic : (*a*) Staphylogenic folliculitis and perifolliculitis . . . Impetigo (Bockhart), Furuncle, coccogenic Sycosis barbae, etc.
   (*b*) Fungus of ringworm (ectothrix).
   (ii) Chemical irritants . . . Croton oil, iodide of potassium.
2. *Secondary folliculitis.*—
   (*a*) After keratosis and plugging of the follicle . . . Acne vulgaris.
   (*b*) Associated with hypertrophy of the perifollicular connective tissue . . . Acne keloid, Dermatitis papillaris capillitii (Kaposi).
   (*c*) Associated with atrophy, necrosis, and scarring . . . Acne necrotica, Acne décalvante.
   (*d*) Associated with skin-affections which do not directly involve the hair-follicle . . . Eczema.
   (*e*) Secondary to tuberculosis, Lichen scrofulosorum, and Acne scrofulosorum.

CHAPTER XXIV.

THE SEBACEOUS GLANDS.

THE sebaceous glands are small saccular or racemose glands which occur in the skin usually in connection with the hair-follicles, but also independently of hairs in such situations as the free borders of the lips, towards the angles of the mouth, on the labia minora, the areolae of the nipples and the caruncles of the eyes; in the latter positions it has been asserted that they have had an embryonic connection with hairs which they have lost.

Note on the Development of the Sebaceous Glands.—They appear first, about the fifth month of embryonic life, as small button-shaped outgrowths of the hair-rudiment, and are composed of cells of the same type as that structure. Gradually they acquire a pear-shape, the long axis of which is directed obliquely downwards. The central cells of the outgrowth undergo a fatty change, which, by spreading along the axis of the process, leads to the formation of a lumen; the latter opens into the space between the hair and the cornified lining of the funnel of the follicle. Fatty granules and *débris* collect in the lumen and in the space into which it opens. The original process buds to form a number of saccules, which are enclosed in a connective-tissue envelope continuous with that of the hair-follicle. As many as six glands may develop in connection with a single follicle, but as a rule there are not more than two. When there are several glands they usually form a collar round the middle third of the follicle.

The General Characteristics and Minute Structure.—The glands are generally situated on the oblique side of the hair-follicle in the angle between it and the arrector pili muscle.

The glands vary greatly in size; those connected with the stiff hairs of the beard and scalp are relatively small, while

those belonging to the lanugo hairs are large. As a rule they may be described as appendages to the follicles, but occasionally they are considerably larger than the follicles to which they are attached. The largest sebaceous glands are those about the nose, concha of the ear, scrotum and areolae of the nipple. The number of saccules which make up the gland also varies greatly; there may only be a single saccule or there may be a bunch of twenty or even more. The saccules open into a common duct, which pours its contents into the neck of the follicle to lubricate the hair. The glands unconnected with hairs, such as those of the nipple, open directly on the surface of the skin.

Histologically each saccule or acinus (Pl. XXVIII., Fig. 2) has a connective-tissue covering, inside which is a basement layer of flat cells, on which are built up layers of cubical cells with round or oval nuclei. Towards the centre these cells have undergone a fatty change, by which their hyaloplasm has become converted into small fat-droplets which lie in the meshes of their persistent spongioplasm. But not only has the hyaloplasm undergone a change, but the peripheral part of the cell and the spongioplasm have also become altered. The latter has become more resistant to acids, alkalies and digestive ferments than the spongioplasm of ordinary prickle-cells, and in this, as well as in the fact of their containing fat-granules, the cells of the gland present a close analogy to horn-cells, although they have no actual keratin.

Occasionally in the larger glands a thin coating of the stratum corneum of the funnel of the follicle spreads into the lumen of the sebaceous duct.

The fatty substance appears first in the cells of the acini as small white or yellow shining droplets. These run together to form globules, and the cell generally breaks down, but the fine droplets may be discharged from the cell without its disintegration. The fatty droplets finally collect in the lumen of the duct, forming a whitish mass. When the fatty droplets reach the hair-follicle they become mixed up with epithelial *débris* and partially solidify to form the sebum.

Sebum consists of fats (olein, palmitin, and stearin), fatty acids (oleic, palmitic and stearic acids), cholesterin crystals, chlorides and phosphates of the alkaline earths, organic salts, albuminoids, water and occasionally butyric or caproic acids.

Mixed up with these are epidermal nuclei, *débris* of cells, and a few horn-cells.

Schmidt[1] gives the following analysis of the contents of a sebaceous cyst:

	Parts per 1000.
Water	317
Epithelium or proteids	617·5
Fat	41·6
Fatty acids	12·1
Ash	11·8

No excito-excretory nerves have been demonstrated in connection with the sebaceous glands, though it has several times been asserted that the quality and quantity of the sebaceous output was dependent on nerve-influences.

It was once generally taught that the sebum was excreted mechanically by the contraction of the arrector pili muscle, squeezing the gland in the acute angle between it and the follicle. This view has been shown to be incorrect, and the muscular contraction seems to have little or no influence on the excretory process. It is now generally believed that the excretion is the result of the *vis-a-tergo* caused by the continuous evolution of fat by the sebaceous cells.

There are several other types of glands which may be regarded as modified sebaceous glands—for example, the *Meibomian glands* of the eyelids and the *Tysonian glands* of the prepuce. These structures are more elongated than the ordinary sebaceous glands, but have the same microscopical appearances.

For fuller information on the subject of sebaceous cells *see* Philippson's paper, *Monats. f. prakt. Derm.*, 1890, XI., p. 202.

Pathological Conditions affecting the Sebaceous Glands.

1. **Increased Activity: Seborrhœa or Steatorrhœa.**—It is almost impossible to make a definite distinction between an increased activity in the output of sebum and an actual proliferation of the sebaceous glands, as it seems very doubtful whether a decided seborrhœa can occur without a glandular hypertrophy. Associated with the increased elimination there is an alteration in the quality of the sebum, in which it becomes either more oily in consistence than usual, or through the loss of part of its fluid constituents forms a greasy mass. Thus two types of seborrhœa have been described — namely, *Seborrhœa oleosa* and *Seborrhœa sicca.*

Recently a great deal of careful research has been carried

[1] *Deutsche Archiv klin. Med.*, 1869, V., p. 522.

out on this subject, with which the names of Unna and Sabouraud are intimately connected. The conclusions arrived at by these observers differ materially. Unna[1] does not admit of a *Seborrhœa oleosa* in the strict sense of the term, and considers that the oily condition of the skin to which the name has been applied is the result of a hyper-excretion of fat by the coil-glands, and is in reality a *Hyperidrosis oleosa*. He also denies the existence of a true *Seborrhœa sicca*, since he believes that sebum is incapable of setting and forming with epidermal *débris* a greasy crust or scale. In spite of this, he incorporates dry seborrhœa, and provisionally pityriasis capitis, under the heading of *Seborrhoic eczema*, which, according to him, has no connection with the sebaceous glands. *Seborrhoic eczema* he regards as a definite superficial inflammation, or catarrh, of the skin, associated with an increased output of fat by the coil-glands, and due to the action of certain micro-organisms, among which are morococci, flask-shaped bacilli and another small bacillus.

Sabouraud,[2] on the other hand, regards *Seborrhœa oleosa* as an inflammatory affection involving the sebaceous glands, which is caused by a specific microbacillus, and believes that when this condition becomes complicated by a superficial dermatitis of the surrounding skin, a scaly, greasy seborrhœa is produced. The latter he definitely distinguishes from pityriasis simplex of the scalp and glabrous skin, which he considers to be due to a flask-shaped bacillus and a coccus producing a grey culture. Though Sabouraud's conclusions are simpler, and may seem at first sight to be more convincing than those of Unna, they have not as yet been universally accepted. Sebaceous material is an almost perfect medium for the growth of the bacterial flora of the skin, and, in the absence of more conclusive inoculation experiments, it has still to be proved that the microbacillus is other than a harmless denizen of the skin, which has proliferated abundantly, owing to a suitable environment.

The oily state of the skin associated with puberty is a true instance of *Seborrhœa oleosa*; it affects the sides of the nose, scalp, forehead, concha of the ears, and the other situations where the excretion of oily material is abundant, such as the intrascapular and inguinal regions. It is generally believed to be the result of a proliferation and

[1] *Brit. Journ. of Derm.*, 1894, VI., p. 257; *Deutsche med. Ztg.*, 1898, XIX., p. 427; *Histo-Pathology* (Walker's Trans.), 1896, p. 222.

[2] *Brit. Med. Journ.*, 1901, II., p. 858, and *Maladies du Cuir Chevelu*, Paris, 1902.

increased activity of the sebaceous glands at puberty, and can hardly be regarded as a pathological state. There are certain individuals also who possess during their whole life an oily condition of the skin or permanent *Seborrhœa oleosa*, in which the follicles are plugged; and minute oily drops can be expressed if the openings of them are squeezed. Such individuals are peculiarly liable to develop acne, greasy scaly conditions of the scalp, and not infrequently *Alopecia areata*. The association of *Seborrhœa oleosa* with these skin-affections is a singularly suggestive fact, and has gone far to strengthen Sabouraud's hypothesis. *Seborrhœa oleosa* may also occur pathologically in association with superficial inflammatory states of the skin, such as rosacea—an extreme consequence of which is the condition known as *rhinophyma*, in which the skin of the nose is hypertrophied through a proliferation of the sebaceous glands associated with an increased formation of the fibrous stroma around the glands.

Adenoma Sebaceum.—Adenoma sebaceum is a congenital affection of the sebaceous glands in which yellowish tumours appear, which are the result chiefly of a glandular hypertrophy.

2. **Diminished Activity and Atrophy.**—A diminution in the output of sebum is generally associated with more or less atrophy of the glands. It is found in all the dry atrophic states of the skin, such as xerodermia, ichthyosis, and senile skin, or when the glandular elements become atrophied as the result of continuous pressure, such as is caused by the hypertrophic fibrous stroma of scar tissue and sclerodermia.

3. **Malignant Proliferation of the Sebaceous Glands.**—Until recently it was believed that the sebaceous glands played an important *rôle* in the formation of the skin-carcinomata—a view which was based on the facts that so many carcinomata of the skin have a distinctly acinous appearance, and that the acinous groups of cells are not infrequently found in the situations of the glands. It is doubtful, however, if a purely sebaceous gland cancer exists, although enclosed glandular masses may frequently be found in the cancerous infiltration. There is no reason why a cancer should not develop from the mother-cells of a sebaceous gland any more than from any other epithelial cell, but the fully evolved sebaceous cell has undergone a fatty or degenerative change, which renders it incapable of proliferating.

4. **Cystic Tumours of the Sebaceous Glands.**—Sebaceous cysts, varying in size from a pin's head to a pea, may result

from the plugging of the sebaceous follicles; but they are comparatively rare. They occur in regions where the sebaceous glands are large, as about the nose, eyelids, and forehead, and form yellowish translucent structures which are easily enucleated, and on examination prove to be composed partly of sebaceous material and partly of more or less cornified epithelial cells. *Atheromata* or *wens* were until recently regarded as sebaceous cysts. The researches of Franke and Török [1] show that they are really the result of embryonic cellular inclusions, and are more allied to dermoids than to sebaceous cysts. By staining sections of atheroma with osmic acid, Török [2] showed that fatty sebaceous matter was, as a rule, absent, and that the inclusion contained in the centre a cornified mass mixed up with cholesterin and occasionally with calcareous salts.

TABLE OF PATHOLOGICAL CHANGES AFFECTING THE SEBACEOUS GLANDS.

I. **Increased Activity and Hypertrophy.**—

1. Seborrhœa oleosa or Steatorrhœa.
2. Rhinophyma.
3. Adenoma sebaceum.

II. **Diminished Activity and Atrophy.**—

. . . Xerodermia, Ichthyosis, Senile skin, etc.

III. **Malignant Proliferation.**—

Doubtful if a true sebaceous gland cancer exists.

IV. **Cystic Tumours.**—

Sebaceous cysts.

[1] *Archiv f. klin. Chir.*, 1887, XXXIV., p. 417, and *Wien. klin. Wochenschr.*, 1890, III., p. 696.

[2] *Monats. f. prakt. Derm.*, 1891, XII., p. 437.

CHAPTER XXV.

THE SWEAT-GLANDS OR COIL-GLANDS.

THE sweat-glands are simple tubular glands composed of a *body*, consisting of two or more turns of a tube, and forming a coil which is situated either in the reticular layer of the corium or in the subcutaneous tissue; and a *duct* which traverses the corium in a spiral manner, passes through the epidermis and opens on the surface of the skin at the sweat-pore.

Note on the Development of the Sweat-Glands.—The sweat-glands first make their appearance on the palms and soles between the fifth and sixth months of embryonic life, as small, conical down-growths of the epidermis. Similar gland-rudiments gradually form over the whole skin, being specially numerous in the situations where hairs are absent. As the gland develops the rudiment elongates, becomes constricted near the epidermis to form a narrow neck, and widens out at the lower end to form a club-shaped thickening. The rudiments develop from the interpapillary processes of the epidermis. They consist of polygonal, nucleated cells, surrounded by a layer of cubical cells continuous with the basal layer of the epidermis. Between the sixth and seventh months the central cells of the developing gland break down, and the first trace of an axial canal becomes noticeable. When the gland has grown down as far as the dense lower part of the reticular layer, it usually turns up, and becomes fixed, and any further elongation of it has the effect of increasing the number of turns and of forming the coil. Between the seventh and eighth months the sweat-pores form on the palms of the hands and soles of the feet, the gland being usually well developed before a sweat-pore can be detected.

Fat-globules have been noted in and between the cells of the coil before there is any distinct outlet for the sweat at the pore. This fat passes out from the cells of the coil into the lymph which bathes the gland, in the form of fine fatty granules, and these gradually become deposited in the

neighbouring connective-tissue cells to form fat-cells. The skin of the palms and soles possesses no sebaceous glands, so that the fatty constituents of the vernix caseosa of these regions is now generally believed to be derived from the coil-glands. Unna maintains that they act as lubricating glands for the fœtal skin, and that only after birth do they become sweat-excretory organs.

General Characteristics.

Situation.—Coil-glands are distributed over the skin of the whole body except that of the glans penis, margins of the lips and nail-bed. They are found also on the upper and lower surfaces of the cartilaginous portion of the external auditory meatus in the form of *ceruminous glands*, which differ only slightly from ordinary sweat-glands. On the palms and soles the glands are regularly arranged, and their pores form transverse depressions at regular intervals on the fine ridges of the skin. Round the anus the glands are large, and form an elliptical ring (*glands of Gay*). They are also distributed in a ring round the areola of the nipple. On the eyelids they differ slightly in structure from the ordinary coil-glands, and are known as the *glands of Moll.*

Number and Size.—According to their size, the sweat-glands are divided into two varieties, the *large glands* and the *small glands.* The large sweat-glands are met with in the axillae and groins, and around the anus, while the small variety are distributed generally over the skin. In the small glands the diameter of the coils averages ·3 mm. to ·4 mm. (v. Brunn[1]); in the large glands of the axillae and scrotum it may measure 1 mm. to 3 mm. (Kölliker[2]).

The glands vary greatly in number in different individuals. Krause[3] estimates that they average 2,800 per square inch on the palms of the hands, where they are three and a half times more numerous than on any other part of the body, except the soles of the feet.

Structure.—For convenience of description the sweat-apparatus may be divided into the *coil* or *body* and the *duct*; but it must not be forgotten that this division is purely arbitrary, as the gland structurally and developmentally is simply a continuous tube coiled at the lower end.

[1] *Bardeleben's Handb. der Anat. des Menschen*, 1897.
[2] *Handb. der Gewebelehre des Menschen*, Leipzig, 1889.
[3] *Quain's Anat.*, 1901, I., Part II., p. 429.

(*a*) *Coil or Body.*—The coil or body is a flattened or roundish structure, usually composed of two or three turns of the tube. The distal portion of it near the blind end consists of a single layer of cylindrical epithelial cells, with oval nuclei similar to those of the epidermis, but smaller. The spongioplasm of the cells is frequently arranged in such a manner that the base of the cell has a radially striated appearance, while the central portion is clearer and finely granular. Renaut[1] has noted that these cells present a different appearance when the gland is in the resting state from that when it is active. When the gland is at rest the cells are clearer and the nucleus is near the base of the cell, whereas, after secreting, the cells become more granular and the nucleus is to be found towards the centre. These cells are not in perfect contact with each other, and here and there a connective tissue cell may be found wedged in between two of them; this allows an interchange of the gland-contents with the lymph of the neighbouring tissue-spaces. Outside these epithelial cells, and flattened into their bases, involuntary muscle-cells are present, which are arranged longitudinally or spirally round this part of the gland. Outside the muscular layer a basement membrane has been described by Kölliker.[2] Czerny believes that this is not a homogeneous membrane, but a close network of cells arranged like an endothelium; and Klein[3] regards it as the product of the union of the bases or foot-plates of the cells.

From the fact that the muscle-layer lies within the so-called basement membrane, Ranvier[4] considered that the muscle-fibres were epiblastic structures, analogous to the myo-epithelial cells in cœlenterates. Other observers consider that the basement membrane is purely hypothetical, in which case such an explanation of the origin of the muscle-cells would not be required.

The lumen of this portion of the gland is wider than any other part of it, and consequently it has been named the ampulla. Towards the duct the character of the epithelium alters; it becomes more cubical in shape, and two or even three layers of cells may be present; and the muscle-cells disappear. Lining the lumen a thin homogeneous membrane or cuticle has been described by Heynold.

Occasionally brown or yellow pigment-granules may be

[1] *Ann. de Derm. et de Syph.*, 1894, V., p. 1101.
[2] *Handb. der Gewebelehre des Menschen*, Leipzig, 1889.
[3] *Atlas of Histology*, London, 1880.
[4] *Traité technique d'Histologie*, Paris, 1890.

present in the epithelial cells of the coil. These are secreted with the sweat, and may colour it. The pigment-granules frequently occur in dark races and in pigmented regions in white races.

(*b*) *Duct.*—The duct is made up of two well-defined portions, which differ entirely in their structure—namely, (1) the part in the corium, and (2) the channel through the epidermis.

1. *Portion of the Duct in the Corium.*—The part of the duct which passes through the corium like a corkscrew has a uniform calibre, and its lumen is stellate in section or forms a cleft. The epithelium is cubical in shape and similar to that of the coil, and consists of two or three layers of cells. Inside this a cuticle has been described, but its existence is not universally accepted. Outside there is no basement membrane, but the connective tissue and elastic fibres are condensed to form a fibrous coating. There is no muscular coat to the duct.

A plexus of blood-vessels surrounds the coil and extends up the duct, and small capillaries pass between the coils. It has been asserted by Tomsa, however, that the duct is supplied from the papillary vessels, while the vessels of the coil come from a deeper plexus. Small nerve-fibres pass to the muscle-cells of the coil.

2. *Channel through the Epidermis.*—On reaching the epidermis the duct proper may be said to end, for in this situation it is represented simply by a spiral cleft between the prickle-cells of an interpapillary process. Towards the surface the transitional layers and a thin lining of the stratum corneum dip down to form a funnel to the duct. Through the stratum corneum the duct forms a vertical or spiral channel between the horn-cells, which opens on the surface to form the sweat-pore.

Since the sweat-channel through the epidermis is a simple cleft between the cells, and not a specialised duct, the sweat is enabled to communicate freely with the inter-epithelial lymph, and on this account the epidermal juices find an exit with the sweat at the pores. Consequently much of the fluid constituents of the sweat may be obtained from the lymph of the epidermis. Between the prickle-cells surrounding the duct fat-granules have been detected ; these have in all probability been deposited there from the sweat.

Occasionally the sweat-duct opens into the mouth of a hair-follicle, as in the axillary and circum-anal glands.

The *large glands* of the axillae and anus differ only slightly in structure from the small sweat-glands. In the large glands the tubule of the coil tends to divide dichotomously into smaller tubules, which end in blind sacs. Both the lumen of the tubules and the duct are wider than those of the small glands. The coils of the large glands are situated in the subcutaneous tissue.

The *ceruminous glands* of the external auditory meatus are similar in structure, but differ slightly from the other large glands in that their cells are filled with fat-droplets and brown pigment-granules.

Physiology of the Excretion of Sweat.—The excretion of sweat is influenced by two sets of nerve-fibres:

1. Special secretory fibres, which cause an increased perspiration on being stimulated.
2. Nerve-fibrils supplying the involuntary muscle-cells, which by their contraction aid the expulsion of the sweat.

Special sweat-centres are present in the cord, which are in turn regulated by a centre in the medulla. These centres are stimulated directly by certain drugs, such as pilocarpine and strychnine, and by toxins, heat, and a venous state of the blood; they are reflexly stimulated by the irritation of the mucosa of the mouth by mustard and other pungent substances (Halliburton).

Composition of Sweat.—Sweat has normally an acid reaction, due to the presence of acid sodium phosphate (Hoppe-Seyler), but it becomes alkaline in excessive sweating.

The following table of the composition of the sweat is quoted by Halliburton from Charles [1]:

Water	98·88 per cent.
Solids	1·12 „
Salts	0·57 „
Sodium chloride	0·22 to 0·33 „
Other salts	0·18 „
(Alkaline sulphates, phosphates, lactates, and potassium chloride.)	
Fats	0.41 per cent.
(Including fatty acids and cholesterin.)	
Epithelium	0·17 „
Urea	0·08 „

[1] *Textbook of Chemical Physiology and Pathology*, London, 1891, p. 820.

Pathological Affections of the Sweat-Coils and Ducts.

It is customary to divide the pathological affections of the sweat-apparatus into two classes—namely, those which are, as far as we know, purely functional, and in which no very definite pathological changes have been detected microscopically, and those in which definite pathological lesions have been found.

Functional Diseases.—It will be out of place here to do more than mention a few of these, with the addition of a brief note on each.

(*a*) *Hyperidrosis or Excessive Perspiration.* — In this affection no pathological lesion has been found microscopically to account for its occurrence, and it has come to be regarded as the result of disturbed innervation.

(*b*) *Anidrosis or Defective Perspiration.*—This condition is also regarded as a nervous phenomenon.

(*c*) *Bromidrosis or Fetid Sweating.*—Fetid sweating is due to the action of the Bacterium fœtidum (Thin), which causes a disintegration of the sweat after it has been excreted, with the formation of caproic and other malodorous fatty acids.

(*d*) *Chromidrosis or Pigmented Sweating.*—The colours said to be assumed by the sweat are purplish blue (cyanidrosis), red, yellow, and occasionally green (chromidrosis). Colcott Fox[1] has reported a case of cyanidrosis in a female in which amorphous granules of a dark purplish colour were excreted, and caused the formation of dark patches around the orbits. Cases of apparent red sweating in the axillae have been reported, in which the appearance was due to a growth of the B. prodigiosus in zoogloea-like masses around the hairs.

The occurrence of true chromidrosis has been much disputed. Recently Hall[2] has shown that, apart from it, a blue discoloration of the skin may be produced by a blue anilin dye used in making cheap black stockings, which is dissolved by the acid sweat and stains the epidermis to some depth.

Indican has been said to be occasionally excreted by the sweat and to colour it, in cases in which it is found in the urine,

[1] *Clin. Soc. Trans.*, 1881, XIV., p. 211.
[2] *Brit. Journ. of Derm.*, 1902, XIV., p. 422.

such as in severe obstipation. Certain drugs may cause coloured sweating—for example, iodide of potassium has been known to colour the sweat pink and copper to give it a greenish tinge.

(*e*) *Hæmatidrosis.*—In hysterical women hæmorrhage has sometimes occurred in the ducts of the sweat-apparatus, with the result that the sweat was blood-stained; this condition has been described as a form of vicarious menstruation.

(*f*) *Phosphorescent Sweating.*—The sweat has been known to have a phosphorescent appearance from the ingestion of fish or phosphorus.

(*g*) *Uridrosis.*—In uræmia a marked increase in the normal amount of urea in the sweat may occur; this has been named "uridrosis."

Diseases of the Sweat-Apparatus in which Structural Changes may be Detected.

1. **Sweat-Cysts.**—Cysts may form either in connection with the sweat-duct proper or with the sweat-channel through the epidermis; but they rarely, if ever, occur in connection with the coils, though a simple dilatation of the latter may be observed.

In washerwomen, who suffer from excessive sweating, a non-inflammatory cystic formation of the sweat-duct which has been named *hydrocystoma*, has several times been reported. In this affection the duct widens out to form a cyst, lined with epithelium, and situated in the upper part of the corium. The cysts contain clear, sometimes viscid, acid sweat. A proliferation of the epithelium lining a dilated sweat-duct in the form of papillomatous masses has been reported by Elliot[1] and Rolleston.[2]

In association with hyperidrotic conditions, such as may occur in phthisis, rheumatism, and the like, small shiny vesicles, known as *sudamina*, frequently appear. These are situated superficially in the epidermis, and are due to an accumulation of sweat between the cells of the stratum corneum near the sweat-orifices. In the skin-affection named *miliaria* superficial vesicles also occur, but these differ from sudamina in being accompanied by more or less

[1] *Journ. of Cut. and Gen.-Urin. Dis.*, 1893, XI., p. 168.
[2] *Brit. Journ. of Derm.*, 1902, XIV., p. 83.

inflammation. Although the lesions of miliaria are associated with increased perspiration, the researches of Török [1] have shown that they are not definitely connected with the sweat-apparatus, and are possibly the result of an inflammatory condition, caused by some micro-organism not yet isolated. The vesicles in miliaria are not situated as superficially in the epidermis as those in sudamina. The vesicles which occur in the disease named by Hutchinson *cheiropompholyx*, and by Tilbury Fox *dysidrosis*, must also be referred to in this connection, since, as the latter name implies, the vesicles were until lately believed to be connected with the sweat-ducts. The observations of Santi [2] and Williams [3] disproved this view, and the balance of opinion is now in favour of regarding them as due to an inflammatory condition and independent of the sweat-apparatus; and Unna claims to have isolated a specific micro-organism.

2. **Adenomata.**—Adenomata arising from the epithelium of the sweat-coil or duct are rare, but have been described under such names as *adenoma sudoriparum* and *spiradenoma*, where the benign tumour develops from the coil; and *syringadenoma* (from *syrinx* = a duct), when it forms from the duct. In these tumours a regular layer of limiting cells and a central lumen may generally be detected. Many epithelial growths in the cutis may have a glandular arrangement simulating that of the sweat-coil; but unless a definite connection with the sweat-apparatus can be traced, the term "sweat-adenoma" should be avoided.

3. **Malignant proliferation** of the glandular epithelium has several times been reported. Under the title of *Hydradenitis destruens suppurativa*, Pollitzer [4] has described a rare affection in which inflammatory changes occur in the sweat-coil, which result in necrosis. The gland becomes replaced at first by a cellular infiltration derived from the connective tissue, in which numerous plasma-cells and occasional giant-cells may be found. By the organisation of this infiltration the scarring is produced. The possibility of this anomalous disease being a tuberculous affection is at present under consideration.

[1] *Monats. f. prakt. Derm.*, 1891, XIII., p. 436.
[2] *Ibid.*, 1892, XV., p. 93.
[3] *Brit. Journ. of Derm.*, 1891, III., p. 303.
[4] *Journ. of Cut. and Gen.-Urin. Dis.*, 1892, X., p. 9.

TABLE OF PATHOLOGICAL AFFECTIONS OF THE SWEAT-APPARATUS.

I. **Functional Disorders.—**

1. Excessive sweating . . . Hyperidrosis.
2. Diminished sweating . . . Anidrosis.
3. Fetid sweating . . . Bromidrosis.
4. Pigmented sweating . . . Chromidrosis and cyanidrosis.
5. Blood in the sweat . . . Hæmatidrosis.
6. Phosphorus in the sweat.
7. Increased urea in the sweat . . . Uridrosis.

II. **Structural Disorders.—**

1. Sweat-cysts: (*a*) Superficial . . . Sudamina.
   (*b*) Deep . . . Hydrocystomata.
2. Adenomata: (*a*) Of duct . . . Syringadenomata.
   (*b*) Of coil . . . Spiradenomata.
3. Proliferation of the epithelium of the coil or duct; may be malignant.
4. Inflammation followed by necrosis, possibly tuberculous. . . . Hydradenitis destruens suppurativa (Pollitzer).

CHAPTER XXVI.

THE MUSCLES OF THE SKIN.

THE muscles of the skin consist of the *Arrectores pilorum* and the *layers of involuntary muscular fibres*, such as are found in the areolae of the nipples and the dartos of the scrotum. In the forehead, cheeks and back, *diagonal muscular* fibres have also been described, which ascend obliquely in the corium, but have no connection with the hair-follicles. These, with the arrectores pilorum, have been designated by Unna the *oblique tensors of the skin*. Besides these involuntary muscles, *voluntary muscular fibres* also occur in the skin of the face in connection with the muscles of expression.

Arrectores Pilorum.—The arrector muscles of the hairs are involuntary muscles. They arise from the fibres of the papillae, and are inserted into the fibrous coat of the hair-follicle below the sebaceous gland. They are situated in the oblique angle of the follicle, so that on contracting they make the follicle more vertical, and so cause the hair to become erect. They have generally a single belly, which splits at each end into smaller bundles. They are enclosed in a fibrous sheath in which elastic fibres are present, and it is this sheath which forms the connection between the fibres of the papilla and the fibrous coat of the follicle. The elastic fibres of the muscle-sheath are continuous with the elastic network of the corium, so that the contraction of the muscle not only causes an erection of the hair, but also an increased tension of the corium in the neighbourhood, and consequently a dimpling of the skin. The condition known as "goose-skin," which results from the action of cold, is due to the contraction of these muscles. It is characterised by an erection of the hairs, a dimpling of the skin, and an anæmia from pressure on the capillaries. It was once generally taught that the contraction of the arrectores also caused an expulsion of sebum from the sebaceous gland, and the position of the gland in the angle between the muscle and the follicle lent

colour to this belief. This view is no longer admitted, however, and it is questionable if the contraction of the muscle causes any expulsion of sebum or even any marked pressure on the gland.

These muscles are most highly developed in connection with the hairs of the scalp, while they are only rudimentary in the lanugo hairs, and are absent in the hairs of the axillae, lips and eyebrows (Kölliker).

Muscular Layers or Membranes.—Involuntary muscle-fibres forming layers are found in the dartos of the scrotum, areolae of the nipples, and the eyelids. These bundles are arranged principally at right angles to the lines of cleavage of the skin; in the scrotum they are generally parallel to the median raphé; and in the eyelid (Müller's muscle) they radiate towards the free margin. They are concentrically arranged in the nipples and areolae. They are stimulated to contract by cold, and on contracting they cause a puckering of the skin.

Striated Muscle-Fibres of the Skin.—Striated muscular fibres pass from the platysma and from the muscles of expression of the face into the corium, so that when these muscles contract a wrinkling of the skin is produced.

Methods of Staining the Muscles.—The muscles can usually be easily distinguished in the cutis without specific staining, owing to the peculiar structure of their long tapering cells and their elongated nuclei (Pl. XXX., Fig. 4). The nuclei are stained red with picro-carmine, and the rest of the muscle has a yellowish tinge; hæmatoxylin stains the nuclei purplish and the muscular fibres greyish blue: but these stains do not sufficiently differentiate the muscle from the collagen. By v. Gieson's method the muscle is stained yellow and the collagen red.

Various specific staining methods have been suggested.

I. *After Unna* (*Monats. f. prakt. Derm.*, 1894, XIX., p. 533).—

(*a*) Stain the sections in polychrome methylene blue for half an hour or longer.

(*b*) Wash in water and dry.

(*c*) Counter-stain in a 1 per cent. spirituous solution of orcein for fifteen minutes.

(*d*) Absolute alcohol, bergamot oil, Canada balsam.

The muscle-protoplasm is stained bluish, the nuclei blue, and the collagen reddish brown.

II. *After the same Author.*—

(*a*) Stain the sections in polychrome methylene blue for ten minutes.

(*b*) Wash in water.

(*c*) Transfer for ten minutes to a 1 per cent. solution of potassium ferricyanide.

(*d*) Wash in water.

(*e*) Differentiate for ten minutes in acid alcohol (1 per cent. hydrochloric acid).

(*f*) Absolute alcohol, bergamot oil, Canada balsam.

The muscle-protoplasm is stained bluish violet, the nuclei violet, and the collagen is unstained.

III. *After Vignolo-Lutati* (*Archiv f. Derm. u Syph.*, 1901, LVII., p. 329).—

(*a*) Stain the sections from six to twenty-four hours in a 1 per cent. spirituous solution of orcein, with the addition of 1 per cent. hydrochloric acid.

(*b*) Rinse in 90 per cent. alcohol and then in distilled water.

(*c*) Stain for five minutes in hæmatoxylin.

(*d*) Wash in water.

(*e*) Absolute alcohol, xylol, Canada balsam.

The muscle-protoplasm is stained light brown, the nuclei deep blue, and the elastin an intense brown.

Pathological Changes in the Muscles of the Skin.—The only pathological change affecting the muscles of the skin which need be mentioned here is the formation of small involuntary muscular tumours or "*leiomyomata.*" Myomata do not appear to develop from the striped muscular fibres which occur in the skin. The commonest situations in which leiomyomata develop are the dartos of the scrotum and the labia. The tumours are usually solitary; they may be surrounded by a fibrous sheath, and there is generally an inflammatory cellular infiltration associated with them. Multiple leiomyomata may develop from the arrectores pilorum, and they are generally present on the extensor aspects of the arms or legs, and rarely on the trunk. About twenty such cases have been reported. These tumours may be composed partly of muscular and partly of fibrous tissue (fibromyomata), and new blood-vessels may form in connection with them (myoma telangiectodes: Virchow). They are generally accompanied by spasmodic pains, from the stretching of nerve-fibres over them.

CHAPTER XXVII.

THE BLOOD-VESSELS OF THE SKIN.

Distribution.—For purposes of description it is customary to divide the cutaneous blood-vessels into two sets, according as they are given off, (1) from a deep plexus situated about the junction of the corium and the subcutaneous tissue, or (2) from a superficial plexus in the subpapillary layer. From the deep plexus, branches pass down to the fat-lobules, sweat-coils, hair-follicles, and sebaceous glands; while from the superficial plexus branches are given off for the supply of the papillae, the upper portions of the hair-follicles, and the ducts of the coil-glands. Such a scheme as this, though convenient, is not absolutely accurate, for the arrangement of the cutaneous vessels is extremely inconstant, and varies to such an extent in different parts that a description like the above, if taken too literally, is apt to be misleading.

The cutaneous blood-vessels tend to be directed vertically in the corium, and pass either along the coil-ducts and hair-follicles or independently of those structures. Like the other constituents of the corium, the vessels are subjected to varying degrees of tension by the arrangement of the fibrous bundles and the elastic framework, and where the tension is marked the vessels may take a more horizontal course.

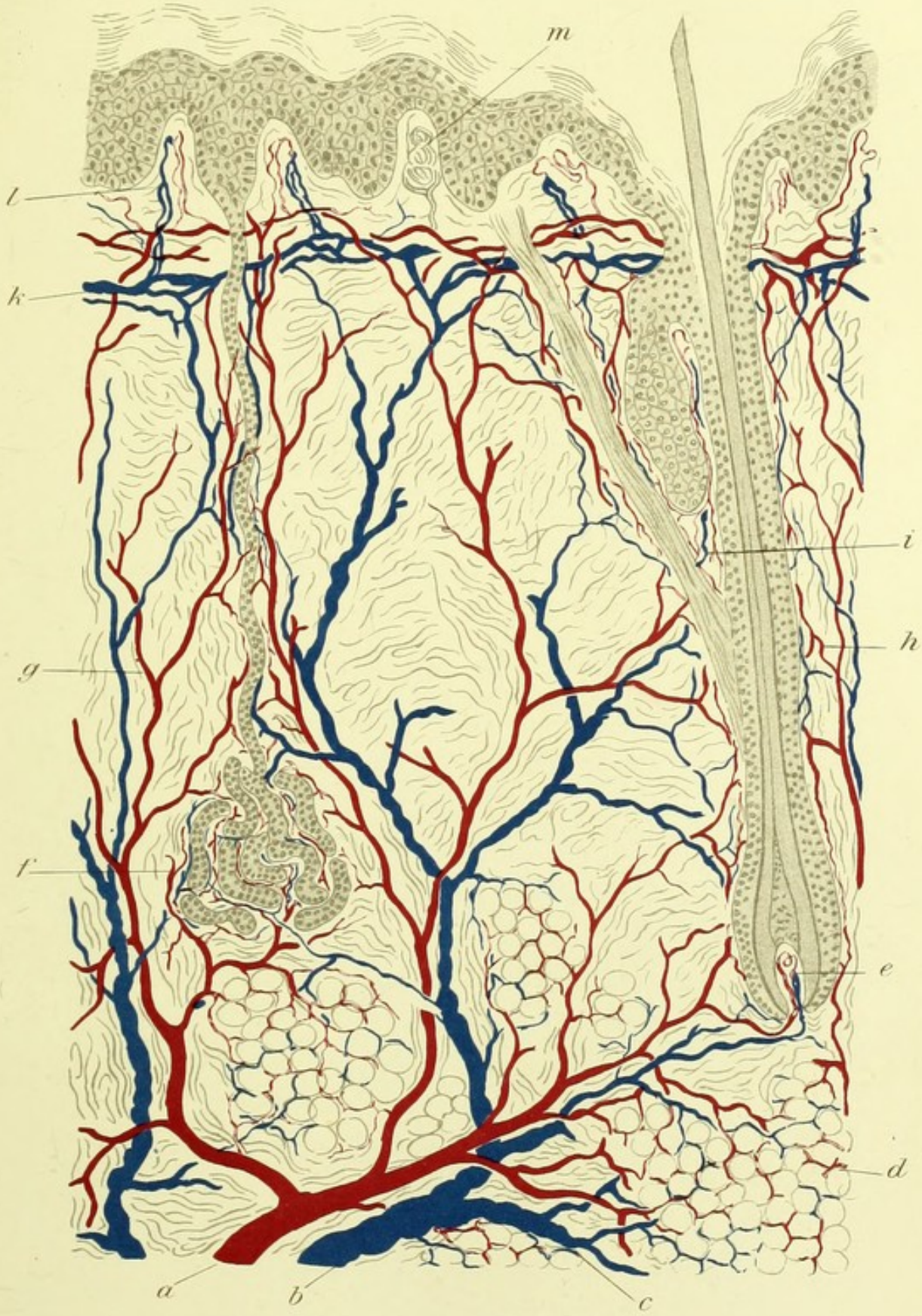
Beginning in the subcutaneous tissue and passing towards the surface, we find the following **systems of blood-vessels** in the skin (Pl. XXXI.):

(*a*) *The Blood-Vessels of the Subcutaneous Tissue.*—Large arterial branches with a well-developed muscular coat and an outer fibrous tunic course between the fat-lobes; from these, smaller branches pass between the fat-lobules, giving off capillaries which form a network between the fat-cells. The capillaries communicate with venous capillaries, which pour their blood into small venules between the lobules; these in turn empty into small veins situated in the interlobar septa.

PLATE XXXI.

Distribution of the Blood-Vessels in the Skin (Semi-Diagrammatic).

a. Large arterial branch in interlobar septum of subcutaneous tissue.
b. Large vein.
c. Interlobular vein.
d. Capillaries between the fat-cells.
e. Capillary-loop of hair-papilla.
f. Capillary-network between sweat-coils.
g. Vertical branches giving off twigs to sweat-duct.
h. Twigs to hair-follicle.
i. Twigs to sebaceous gland and arrector pili.
k. Sub-papillary plexus.
l. Capillary-loop to papilla.
m. Tactile corpuscle.



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(*b*) *The Blood-Vessels of the Sweat-Apparatus.*—From the arteries in the interlobar septa of the subcutaneous tissue branches are given off which ascend and break up into a network of capillaries around the coils of the sweat-gland. A few of these capillaries pass up with the duct, but the latter is chiefly supplied from the more superficial capillaries of the corium, which form an elongated network encircling it. The venules from the sweat-apparatus pass down to join those of the interlobar septa.

(*c*) *The Blood-Vessels of the Hair-Follicles, Arrectores Pilorum and Sebaceous Glands.*—A capillary loop, derived from the subcutaneous vessels, is present in the papilla of the hair-follicle, and branches of the superficial capillaries of the corium are distributed between the external longitudinal and inner transverse dermic coats. From the latter capillaries twigs are given off, which form a close network enveloping the acini of the sebaceous gland and ensheathing the arrectores pilorum. The venous capillaries have the same arrangement.

(*d*) *The Blood-Vessels of the Papillary Layer.*—Small vessels ascend from the subcutaneous tissue to the subpapillary layer, from which branches pass in a horizontal direction to form an elongated network, which gives off capillary loops to the vascular papillae. The arterial capillary to a papilla may be single or compound. It joins a venous capillary which is several times greater in diameter, and this in turn joins a corresponding subpapillary venous network. From this network venules descend, and, being joined by others from the glands and follicles, eventually pour their contents into the subcutaneous veins.

The blood-vessels of the skin of the face, palms of the hands and soles of the feet are exceptionally large, and they are larger and more numerous on the skin of the flexor than of the extensor aspects of the limbs.

In certain situations, such as the nail-bed, tips of the fingers and toes, lobes of the ears, nostrils and lips, the superficial venous capillaries open into venous sinuses lined with endothelium.

The blood-vessels of the corium are really capillaries in structure, in that they only possess an endothelial or inner coat; it is only when the subcutaneous tissue is reached that a muscular and an adventitious coat can be detected.

The Injection of the Cutaneous Blood-Vessels.—For the study of the distribution and the state of dilatation of the skin-vessels, both in health and in disease, it is often of service to inject the vessels before excising the skin for microscopical examination. In skin-affections where the vessels are dilated, beautiful specimens can in this way be obtained.

Mode of Procedure.—In a cadaver the artery supplying the area of the skin to be examined is dissected out, and into it a small cannula is tied. Through the latter the injection fluid is slowly forced at a uniform pressure, till it comes out at the vein. A well-made syringe, an india-rubber tube with a stop-cock on it and a cannula are all that are necessary for the operation. An elaborate apparatus has been devised for this purpose; but with a little practice the foregoing simple arrangement will be found to be adequate.

Injecting Fluids.—A *cold injection-fluid*, such as Kollmann's carmine and glycerin mixture, will generally suffice for the study of the distribution of the cutaneous vessels.

Kollmann's Fluid.—Dissolve 1 grm. of carmine in a little water, with 15 drops of strong ammonia and 20 c.cm. of glycerin: to this add a mixture of 30 c.cm. of glycerin and 1 grm. of sodium chloride; dilute the whole with an equal quantity of water.

But when sections of the skin are to be cut subsequently, it is necessary to employ a *warm injecting fluid*, which will solidify when cold. For this purpose the colouring matter is dissolved in gelatin, and injected at about 60° C. The piece of tissue to be injected must first be excised, so as to include the vessel, and the injection should be done in a water-bath. Ranvier's red or blue masses may be employed for this purpose.

Ranvier's Carmine-Gelatin Mass (*Traité Technique*, p. 116).—Soak 5 grms. of gelatin for half an hour in water; then drain and melt it in a test-tube over a water-bath. Add slowly a solution of carmine in ammonia to the melted gelatin ($2\frac{1}{2}$ grms. of carmine in a little water, with the addition of enough ammonia to render the solution transparent). Carefully neutralise the solution with glacial acetic acid. If too much acid be added, the carmine will be precipitated.

Or—

Prussian Blue Gelatin Mass (*Traité*, p. 119).—A soluble aqueous solution of Prussian blue is first made. This is

done by making a concentrated solution of sulphate of the peroxide of iron in distilled water, and pouring it gradually into a concentrated solution of yellow prussiate of potash. In this way a precipitate of Prussian blue is formed. The whole is then filtered through a felt strainer and a filter-paper in a glass funnel. By gradually pouring in distilled water the Prussian blue will dissolve and come through. Twenty-five parts of this are mixed with one part of solid gelatin. The gelatin is melted as above, and the Prussian blue, heated to the same temperature in a water-bath, is gradually added, the mixture being continuously stirred.

Fol has suggested the use of *meta-gelatin* in place of ordinary gelatin, since it is liquid when cold, and does not require to be injected warm. Meta-gelatin is formed by adding a slight proportion of ammonia to a solution of gelatin, and heating it for several hours. After injection, the preparations can be solidified in alcohol. The injected tissues are hardened in alcohol and imbedded and cut in celloidin or paraffin (*Lee's Vade-Mecum*, 1900, p. 298).

When a blue-coloured injection-mass has been employed the sections should be stained with safranin or carmine to give a contrast, while hæmatoxylin may be used with a red mass.

Anatomical and Physiological Considerations in Connection with the Cutaneous Blood-Vessels.

In connection with the blood-vessels of the skin there are several important anatomical and physiological considerations which it is advisable to keep in view, for though apparently trivial they have an intimate bearing on the production of anæmia, œdema, and the like. The most important of these are the following:

1. The blood-vessels of the skin, with the exception of a few twigs in the deepest part of the corium, belong to the category of *capillaries*. They are simply fine tubes, whose walls are composed of an endothelial layer, and have neither muscular fibres nor an outer fibrous coat. Owing to their structure, they are easily dilated by increased internal pressure, and are liable to be constricted by pressure from without and readily rupture. They are imbedded in a tissue in which a greater or less amount of tension is invariably present, owing chiefly to the intimate connection between the elastic framework and the muscles of the skin. Differences in tension readily

alter the calibre of the vessels, and when the skin is ruptured and its elastic framework broken, a gaping wound is produced, and the small vessels in the implicated area are generally torn.

2. The blood-vessels of the subcutaneous tissue and those of the corium in the immediate vicinity belong, on the other hand, to the category of *small arteries* or *veins*. They possess an outer fibrous coat and a middle muscular layer, the contraction and dilatation of which are regulated by nerve-impulses. On this account they differ from the remaining vessels of the skin, the state of which is only affected by the passive pressure of the blood from within or the tension of the surrounding stroma from without. Consequently, when a blanching of the skin occurs, it is the vaso-constrictor nerves of the subcutaneous arteries which are primarily affected ; these cause a constriction of the subcutaneous vessels, with the result that a diminution in blood-pressure takes place passively in the vessels throughout the corium.

The *vaso-constrictor* fibres are in excess of the vaso-dilators in the subcutaneous vessels, and, being constantly in action, they keep up the so-called tone of the vessels. The vaso-constrictor nerves leave the spinal cord in the dorsal and upper lumbar regions ; they pass out in the anterior root to the mixed trunk, leave the latter by its visceral branch, and join the sympathetic chain, losing their medullary sheath in the sympathetic ganglia, and pass to the subcutaneous tissue by means of the large peripheral nerves.

The chief vaso-constrictor centre is situated in the medulla ; subordinate centres, which are capable of independent action, are present at different levels of the spinal axis and in the sympathetic ganglia. Even if all three centres be cut off, the muscular fibres themselves appear to have an inherent power of contraction to stimulation.

The *vaso-dilator* nerves are supposed to pass out of the cord in its whole length and also from the medulla ; they pass along the anterior roots, and from them directly to the ganglion of the blood-vessels. The vaso-dilator centres are evenly distributed in the cord and medulla.

Circulatory Disturbances.

Anæmia.—

Generalised.—A *pallor* of the skin may be the result of an *alteration in the quality of the blood.* In chlorosis, for instance, we have an anæmic condition which is not the result

of deficiency of the blood in the skin-vessels, but is caused by a diminution of the colouring matter of the blood. An anæmia due to a similar cause occurs in a number of cachectic conditions such as are associated with tuberculosis and syphilis. An actual decrease in the number of red blood-cells, together with an increase in the number of leucocytes, occurs in the anæmia of leukæmia.

Another cause of generalised anæmia is a general *constriction of the skin blood-vessels.* The skin forms, as it were, a safety-valve or regulator for the general blood-pressure. After hæmorrhage, internal or external, a pallor of the skin occurs, owing partly to a reflex stimulation of the vaso-constrictor centres of the skin-vessels, and partly to a diminution in the blood-pressure from loss of blood. Toxins circulating in the blood may produce anæmia by stimulating the vaso-constrictor centres. Psychical disturbances of the nerve-centres, such as fear and anger, may produce a pallor of the skin by causing a general constriction of the deep blood-vessels.

Localised.—Local anæmias may be the result of a *local constriction of the small arteries*, such as may follow from the application of cold to the skin. A spasm of the small arteries is the cause of the "local syncope" of Raynaud's disease. Pressure locally on a set of blood-vessels will result in anæmia, as is seen commonly on pressing the blood from an erythematous patch. But localised anæmia may occur from internal pressure, such as is caused by the lymph in an urticarial wheal, or by a neoplasm pressing on the skin from underneath. Localised anæmia may also result from an *organic obliteration* of a certain set of vessels by (1) an embolus or thrombus, (2) a proliferation of the vessel-walls, as in *endarteritis obliterans*, and (3) a constriction of the vessels by the development of *sclerotic tissue around the vessel*, as in sclerodermia and keloid.

Hyperæmia.—In hyperæmia there is an increase in the blood-flow in the vessels of the skin. This may be associated either with a diminished resistance and an increased flow of blood (erythema), or with an increased resistance and a diminished flow (cyanosis). Hyperæmias are thus divided into two easily separable classes—active hyperæmia or erythema, and passive hyperæmia or cyanosis.

Generalised Active Hyperæmia or Erythema.—Erythema may result from an inhibition of the vaso-constrictor centre,

with a general diminution in the tone and a consequent dilatation of the blood-vessels of the skin. Psychical emotions, such as shame, fear, and the like, are capable of causing an inhibition of the constrictor centre and erythema. Poisons circulating in the blood may also produce erythema by acting on the constrictor centre, and the various roseolar eruptions are examples of this. In the generalised erythemata both the arteries and the veins are to some extent implicated.

Local Active Hyperæmia.—A local active hyperæmia is the cause of the erythematous macules and patches which so commonly occur in the skin. It is evident in the reaction after the application of cold, when the initial anæmia becomes replaced by a hyperæmia, due to the local inhibition of the constrictor nerves. Where the action of the cold is prolonged a temporary paralysis of the constrictor nerve may be set up and the condition known as chilblains be produced, or the severe hyperæmia which occurs in the "local asphyxia" of Raynaud's disease.

The hyperæmia may not be in the form of macules or patches, but it may assume a retiform or arborescent appearance, due to the arrangement of the blood-vessels of the skin, especially those of the papillary layer. The latter are arranged in cones or brushes of arterial capillaries, separated by areas, in which the arterial twigs are smaller and the venous capillaries begin. With mild degrees of congestion a retiform appearance is produced in the skin, in which a hyperæmic network encloses small areas the colour of the normal skin, which correspond to the bases of the cones. This mottled hyperæmic condition is frequently observed in babies' limbs from exposure to the cold, and in adults who suffer from a weak peripheral circulation, and in certain diseases of the skin, such as the rare persistent scaly affection known as parakeratosis variegata.[1]

Passive Hyperæmia or Cyanosis.—Passive hyperæmia, either general or local, is determined by some obstruction to the circulation, such as may be caused by an emphysematous lung, or by the local constriction of the vessels of the limb produced by a garter or a tumour pressing upon them from within. In passive hyperæmia the veins are chiefly implicated, and hence the bluish, livid colour of the affected skin. This type of hyperæmia readily goes on to actual hæmorrhage with

[1] Fox and MacLeod, *Brit. Journ. of Derm.*, 1901, XIII., p. 319.

the accumulation of blood-pigment in the affected skin, as in varicose dermatitis. It is also frequently associated with œdema.

Œdema.—By œdema is meant a collection of serous or plasma-like fluid in the areolar tissue of the skin. It is due to an interference with the proper relation of the entrance and exit of blood in the tissue. It has been experimentally proved that ligature or blocking of the arteries does not cause œdema, and that the lymphatics also may be blocked without increasing the amount of fluid in the tissue to any extent, since much of the lymph returns not by the lymph-channels, but through the veins. It is in a blockage of the veins that we have to seek for the chief cause of œdema.

It is customary to recognise two different types of œdema in the skin—namely, (1) an œdema which is mechanical in nature and due to a blockage of the veins, or the lymphatics and veins of the affected area; and (2) an œdema which occurs in association with inflammatory conditions.

Besides simple blockage and inflammatory conditions affecting the vessel-walls and the surrounding tissue, we have another undoubted factor in the production of œdema—*viz.* a want of nutrition of the vessel-walls, such as occurs in association with anæmia and states of general debility. The œdematous fluid varies in character according as the œdema is purely mechanical or is associated with inflammation. In the former condition the œdematous fluid is known as a transudate, and it has much the same composition as blood-serum, and contains very little albumen; while in inflammatory œdema the fluid is known as the exudate, and its constitution is similar to blood-plasma, being richer in albumen and white blood-cells than a transudate.

1. *Mechanical.—General œdema* or *anasarca*, due to a valvular defect, where the venous circulation is greatly impeded, gives rise to a collection of fluid in the tissues which is most marked in the regions where a loose areolar tissue is present, such as the lower eyelids, the backs of the hands, and the ankles.

Local œdema may occur mechanically from a tight bandage constricting the veins of a limb, or from a thrombus blocking a vein. Such œdemas are frequently preceded by a passive hyperæmia of the part. In this type of œdema, if it be in excess, the interepithelial lymphatics may participate, and vesicles or bullae may appear in the skin.

2. *Inflammatory Œdema.*—Inflammation in and around the walls of the blood-vessels of the skin may cause a constriction

of the latter, and determine an œdema. The œdema which occurs in erysipelas is an instance of this type. The condition is aggravated by the production of a hyperplasia of the fibrous elements in the affected area, which further constricts the vessels. Such an occurrence accounts for the marked œdema in "lymph scrotum," for though the presence of the "Filaria sanguinis hominis" blocking the lymphatics may be a factor in its production, it is largely due to the inflammatory changes set up in and around the vessel-walls. It is impossible to draw a hard and fast line between the inflammatory œdemas and those of angioneurotic origin. In fact, it is often maintained that many of the so-called angioneuroses are in reality the result of inflammatory conditions affecting the vessels.[1] A vaso-motor disturbance due to toxins acting locally on the skin or circulating in the blood, may cause the formation of a wheal, which evolves into a small acuminate papule or in severe cases into an actual vesicle. In skins where a predisposing irritability of the nerve-mechanism of the vessels exists, very slight causes may result in the formation of large wheals, such as occur in ordinary factitious urticaria and the "spastic œdema of Quincke." These effects are generally believed to be due to the toxin causing in the first instance a spastic contraction of the veins and a subsequent serous exudation in the neighbourhood of them; but it is undecided whether or not the toxin causes at the same time an inflammatory alteration in the walls of the vessels, facilitating the exudation of serous fluid.

Hæmorrhage into the Skin or Purpuric Conditions.—Instead of simple serous fluid, blood may be extravasated into the corium in greater or less amount, producing petechiae, ecchymoses, or raised tumours containing blood (hæmatomata). At first these lesions are bright red in colour, but owing to the breaking up of the red blood-cells and the deposition of pigment, they undergo alterations in colour, assuming a purplish, yellowish, and finally a greenish tinge.

Purpuras may occur in severe cases of the acute exanthemata; they may result from the ingestion of certain drugs, such as copaiba, chloral hydrate and iodide of potassium; they may be due to toxins, such as that of rheumatism, circulating in the blood; they may be caused by alkaloidal poisons, and be simply a further stage in the evolution of an urticarial lesion, and the result of an increased virulence of the poison or a special predisposition in the individual;

[1] Török, *Archiv f. Derm. u. Syph.*, 1900, LIII., p. 243.

they may be an evidence of profound alterations in nutrition, as in scurvy; or they may be due to a marked increase in the intra-vascular pressure, as in the purpura which may occur in high altitudes. Purpura is not so much a disease *per se* as a symptom, and it is one which has not yet been satisfactorily explained. Naturally a lesion such as the rupture of a vessel-wall will allow an extravasation of blood and the production of a hæmatoma; but in sections of the smaller purpuric lesions no vascular defect can as a rule be detected. It has been suggested that the red blood-cells may escape from the vessels by a process of diapedesis, like the leucocytes; but as they are not amœboid such an explanation is inadequate. Sack[1] maintains that a rupture of the vessel-wall is essential, and invariably occurs. This rupture is generally associated with some weakness of the vessel-wall, as occurs in the malnutrition of scurvy, in association with fevers, or as a congenital condition in hæmophilics. Watson Cheyne[2] has demonstrated the presence of bacilli blocking the small arteries in cases of purpura, and his observations have been confirmed by other observers. It would thus seem that certain cases of purpura are the result of the destructive action of micro-organisms on the vessel-walls. Such an explanation is far more satisfactory than either that of a simple proliferation of the intima of the blood-vessels, or a blocking of the small vessels by emboli. The part played by the nervous system in the determining of purpura is not decided.

Pathological Conditions affecting the Blood-Vessels.

Angiomata.—The angiomata are benign new-growths composed of blood-vessels. Of these there are three principal varieties—namely, (1) cavernous angiomata, (2) telangiectases, and (3) vascular nævi.

1. *Cavernous Angiomata.*—These small, soft, generally subcutaneous, lobulated tumours consist histologically of loculi situated in a framework of connective tissue, and communicating with the neighbouring vessels. Winiwarter[3] believes that they are developed in much the same way as the erectile tissue—namely, by a process of budding of solid

[1] *Monats. f. prakt. Derm.*, 1893, XVII., p. 49.
[2] *Brit. Med. Journ.*, 1883, II., p. 416.
[3] *Die Chirurgischen Krankheiten der Haut.*, Stuttgart, 1892.

vascular bodies from the walls of the veins, which become excavated and lined by endothelium. Other observers consider that a loose fibrous stroma develops first, and that its meshes become subsequently connected with the blood-vessels; while Virchow[1] holds the opinion that they arise simply from a dilatation of pre-existing blood-vessels.

There is another type of angioma, known as a "cirsoid aneurysm," which forms a bluish red tumour, varying in size from a bean to a walnut, and is usually situated about the head and neck. It results from a hyperplasia of the arterial capillaries in the corium and subcutaneous tissue, and rarely becomes cavernous.

2. *Telangiectases.*—These are acquired dilatations or new formations of capillaries, which appear most frequently on the face, and occur chiefly late in life. They are a frequent complication of various forms of skin-disease, such as rosacea, lupus erythematosus and xeroderma pigmentosum. The capillaries diverge as a rule from a central point. The telangiectasis results from a stagnation of blood in the venous capillaries, extending to the arterial capillaries. The skin around them is frequently converted into a cavernous tissue.

3. *Vascular Nævi.*—In this country the term "nævus" is generally restricted to the vascular anomalies of the skin which appear at birth, or soon after it. The vascular nævi may be small, as the familiar "spider nævi," or large, forming the "port-wine stains," and they occasionally pulsate.

The venous capillaries are chiefly implicated in the formation of vascular nævi (Virchow); these may become varicose, and occasionally new capillaries may form. The walls of the capillaries become thickened, owing to an endothelial proliferation, so that the capillaries resemble the veins of the subcutaneous tissue. It has been suggested that certain of these nævi are the result of intra-uterine pressure, and Unna noted the coincidence of a nævus on the forehead opposite one in the common situation about the posterior fontanelle—a fact which was extremely suggestive that the nævus had been caused by pressure.

Endarteritis may affect the vessels of the subcutaneous tissue and the corium. It occurs in late syphilides, in which case the endothelial proliferation may be so great as to block the vessel.

[1] *Die krankhaften Geschwülste*, Berlin, 1863.

Endophlebitis.—Phlebitis, emboli, and thrombosis are important factors in the production of a weakened resistance of the skin to micro-organisms, and in the formation of an inflamed œdematous skin, such as occurs in the so-called "varicose eczema." Recently Philippson[1] has given the title of *Phlebitis nodularis necrotisans* to a condition chiefly affecting the calves of the legs, in which indolent nodules occur, which gradually necrose and leave scars. Here the necrotic process is ushered in by an endophlebitis, or by a thrombosis, which may possibly be due to the presence of tubercle bacilli in the affected vein.

[1] *Archiv f. Derm. u. Syph.*, 1901, LV., p. 215.

CHAPTER XXVIII.

THE BLOOD IN ASSOCIATION WITH CERTAIN DISEASES OF THE SKIN.

TECHNIQUE IN CONNECTION WITH THE EXAMINATION OF THE BLOOD.

AS a knowledge of the technique in connection with the blood is of importance to the dermatologist, in view of the alterations which have recently been described in it in association with a number of skin-diseases, it will not be out of place to refresh the memory of the student regarding such technical proceedings as the enumeration of the blood-cells, the estimation of hæmoglobin, and the microscopical examination of the blood. It has also been considered advisable to describe briefly the various types of leucocytes.

Enumeration of Red Blood-Cells.—The red blood-corpuscles may be counted by means of Gowers' or Thoma-Zeiss' hæmocytometer. The latter is simpler to use, and the results obtained by it are sufficiently accurate.

The method of counting the red blood-corpuscles by the Thoma-Zeiss instrument is briefly as follows : The hæmocytometer consists of (1) a specially graduated pipette to suck up and dilute the blood ; (2) a special counting-slide, consisting of a central cell bounded by a rim of glass, in the centre of which is a circular platform not so high as the rim, ruled off in squares of $\frac{1}{400}$ square millimetre in area ; (3) a specially ground cover-glass which, when fitted on to the rim of glass, leaves a space of $\frac{1}{10}$th of a millimetre between its under surface and the platform ; and (4) a small lancet-shaped needle to draw the blood.

The blood should be taken from the lobe of the ear, and this should be cleansed previously with soap and water, dried with a clean cloth, and rubbed to render it hyperæmic. The tip of the lobule is sharply punctured till the blood flows freely, and the blood is slowly sucked into the pipette up to the mark ·5 upon it. The end of the pipette is then wiped on

a clean cloth, and diluting fluid is sucked into it till the mixture of blood and diluting fluid reaches the mark 101. The diluting fluid, which is the same for both instruments, consists of :

Sodium sulphate	104 grs.
Acetic acid	1 drm.
Distilled water	6 oz.

The pipette is then taken between the second finger and thumb, and shaken thoroughly to mix the blood and diluting fluid. The diluting fluid in the capillary part of the pipette, which is not mixed with blood, is blown out, and then a small drop of the mixed blood is transferred to the centre of the platform of the slide, and the cover-glass gently laid on with the help of a needle. The drop should be sufficiently large almost to cover the platform after the cover-slip has been applied; and, if it is properly applied, concentric rings of colour should appear between the cover-slip and the platform (Newtonian rings).

The red corpuscles should then be counted in three sets of sixteen squares, and the average number in one square calculated. In counting corpuscles on the line, only those on the upper and left lines should be counted. To obtain the number of corpuscles in a cubic millimetre, multiply the number in one square by 800,000 (since the square is $\frac{1}{4000}$th of a c.mm. and the blood was diluted 200 times).

Number: In an adult healthy male there are about 5,000,000 red blood-cells per c.mm., and in a female 4,500,000.

Enumeration of Leucocytes.—A special pipette is supplied for this purpose which gives a dilution of twenty times. The method employed is precisely similar to that described above. The diluting fluid employed is ·3 per cent. glacial acetic acid; to this a few drops of an aqueous solution of methyl green may be added to give the fluid a distinctly green tinge. This solution dissolves the red blood-cells and renders the leucocytes more clearly visible, and the methyl green stains the nuclei.

The leucocytes should be counted in 16 sets of 16 squares (256), and to obtain the number in 1 c.mm. divide the result by 256 and multiply by 80,000.

Number: The number of leucocytes in an adult in health is about 7,000 per c.mm.

Estimation of Blood-Platelets.—

After Hutchison ("*Clinical Methods*," 1898, p. 188).—"Place upon a slide a drop of a mixture of equal parts of glycerin,

which has been saturated with dahlia and a 2 per cent. salt solution. The use of the dahlia is to stain the platelets. Touch the drop of blood with this mixture and cover. Count with a $\frac{1}{12}$ oil-immersion lens in a succession of fields: (1) the platelets, (2) the red corpuscles. Continue until four hundred of the latter have been enumerated, and estimate the proportion of platelets to red corpuscles. Normally they should be as 1 : $8\frac{1}{2}$."

Estimate the number of red corpuscles, and in this way the number of platelets may be obtained in 1 c.mm. It is usually about 640,000.

Estimation of Hæmoglobin.—This is accomplished by means of Gowers' hæmoglobinometer. It consists of: (1) two small tubes of equal diameter placed on a stand,—one of which contains a solution of glycerin jelly and carmine representing the colour of healthy blood diluted one hundred times with water, and the other is empty and specially graduated; and (2) a pipette to contain 20 c.mm. The pipette is filled with blood and the contents blown into the graduated tube, into which have been poured a few drops of distilled water; more distilled water is then dropped in till the colour in the two tubes is the same. The height of the mixture is then read off in the graduated tube, and this gives the percentage of hæmoglobin.

Coagulability of the Blood.—In a healthy individual the blood coagulates in about four minutes at a temperature of 18·5° C. The "coagulation-time" is estimated by means of Wright's coagulometer.[1] This consists of a number of capillary tubes ·25 mm. in diameter. Into these the blood is aspirated to a distance of 5 cm., and blown out at different intervals to ascertain when it has coagulated. It is necessary to warm the tubes to blood-heat before filling them, and to keep them at that temperature during the process of coagulation. The time between the filling of the tubes and the coagulation is known as the coagulation-time.

Microscopical Examination of Blood.—Blood may be examined fresh in order to determine any deformities in the red blood-corpuscles. By placing a drop of a 2 per cent. solution of osmic acid on the skin before puncturing it, the blood, as it oozes out, is fixed and the size and shape of the corpuscles are better preserved than if this procedure be not adopted. The types of abnormal red blood-corpuscles which may occur are three in number: (1) small red blood-cells

[1] *Brit. Med. Journ.*, 1894, I., p. 237.

(microcytes); (2) large red blood-cells (megalocytes); and (3) irregularly shaped red blood-cells (poikilocytes).

For diagnostic purposes it is usually advisable to make what are known as blood-films.

The Preparation of Blood-Films.—The first essential in the making of a blood-film is to have an absolutely clean cover-slip.[1] It must be free from grease, otherwise it is impossible to get the blood to spread in a uniformly thin film. The requisite number of cover-slips are carefully dried by being passed through the flame, and are then propped up on their edges against a glass rod placed on a clean plate.

The following method of procedure is simple, and gives excellent results[2]:

A puncture is made in the cleansed lobe of the ear. A cigarette-paper is cut in strips slightly narrower than the breadth of the cover-slip. The edge of one of these strips is run along the drop of blood, so as to make an even mark on the paper about an eighth of an inch broad. A cover-slip is seized by the cornet forceps, laid flat on the plate, held there by pressing the forceps down on it, and the edge of the paper, moistened with blood, is laid on the cover-slip near the forceps and drawn gently across it. In this way a beautifully uniform thin film is produced. The procedure is repeated so that a series of films are obtained. The same paper will generally make several films, provided the slips are ready and the paper is drawn over the other cover-glasses without delay.

The films should then be covered to prevent dust collecting on them, and allowed to dry.

The Fixation of the Films.—

1. Place the dried cover-slips in a wide-mouthed jar containing equal parts of alcohol and ether. In a few hours they are ready for staining, but they may be left in the mixture for several days without injury to the films.

2. Another method which is strongly recommended is to keep the films in a hot-air chamber at 120° C. for thirty minutes.

Methods of Staining Films.—

I. *After Eyre.*—

(*a*) Stain for one minute in a 1 per cent. solution of yellow aqueous eosin.

[1] For the methods of cleaning cover-slips and slides *see* page 4.

[2] For this method I am indebted to Dr. J. W. Eyre, Bacteriologist to Guy's Hospital.

(*b*) Wash in water.

(*c*) Stain for two minutes in a 1 per cent. solution of methylene blue.

(*d*) Wash, dry slowly without heat, and mount in Canada balsam.

The nuclei are stained blue, the red blood-cells pink, and the acidophilic granules reddish pink.

II. *Jenner's Composite Stain* (*Lancet*, February 11th, 1899), consisting of 125 c.c. of a ·5 per cent. solution of eosin, and 100 c.c. of a ·5 per cent. solution of methylene blue in absolute methyl alcohol, also gives good results. It combines the processes of fixing and staining.

(*a*) Stain without fixing from one to three minutes in Jenner's stain, preventing the evaporation of the stain.

(*b*) Rinse well in distilled water.

(*c*) Dry without heat, and mount in Merck's dammar-lack in xylol.

The red blood-corpuscles are stained terra-cotta colour, the nuclei of the leucocytes blue, the acidophilic granules red, and the basophilic granules dark violet.

III. *Ehrlich's Triple Stain, after Reinbach* (*Zeit. f. wiss. Mik.*, 1894, XI., p. 259).—

Saturated aqueous solution of orange G. . .	120 c.c.
„ „ „ „ acid fuchsin .	80 „
„ „ „ „ methyl green .	100 „
Distilled water	300 „
Absolute alcohol	180 „
Glycerin	50 „

After the mixture has been made, it should never be shaken, but kept for some time to ripen, and the stain required should be drawn off from the middle of the fluid by a pipette. Stain films for five minutes in this mixture, wash, dry, and mount them in Canada balsam.

The red corpuscles are stained orange yellow, the nuclei greenish blue, the acidophilic granules red, the neutrophilic granules purple ; the basophilic granules are not stained.

The Varieties of Leucocytes.

Various types of white blood-corpuscles were distinguished more than half a century ago by Wharton Jones.[1] Other observers elaborated these differences ; but it is to the researches of Ehrlich that we are mainly indebted for our

[1] *Phil. Trans.*, 1846, p. 64.

knowledge of the different forms of leucocytes. Ehrlich[1] classified the leucocytes according to certain granules which they contained. These granules varied in shape, size, and distribution, but were specially distinguishable by their behaviour towards anilin dyes, since some of them attracted acid dyes (acidophilic granules), others basic dyes (basophilic granules), and a third variety neutral dyes (neutrophilic granules). In certain of the leucocytes he noted that the granules were uniformly coarse, and in others that they were invariably fine. On account of these differences he identified five varieties of granules, which he designated as α, β, γ, δ, and ϵ granules. Since Ehrlich's original publications, the researches of Sherrington,[2] Kanthack and Hardy[3] have proved that the so-called neutral dyes of Ehrlich are in reality acid dyes, and in this way have simplified the classification.

The following are the varieties of leucocytes usually described in the healthy blood:

1. **Small Lymphocytes.**—These are small corpuscles with a round nucleus which stains deeply with ordinary nuclear dyes, and a slight halo of protoplasm surrounding it. They are immature leucocytes. They are neither amœboid nor phagocytic. They vary in number, but may reach 30 per cent. of the leucocytes in normal blood.

2. **Large Lymphocytes or Hyaline Leucocytes.**—These are large corpuscles, with a large round or kidney-shaped nucleus which stains badly, and an abundant non-granular protoplasm. They are probably adult forms of the small lymphocytes, and are both amœboid and phagocytic. They form only about 2 per cent. of the leucocytes in normal blood, but are found in a much larger proportion in the peritoneal fluid.

3. **Coarsely Granular Oxyphiles or True Eosinophiles.**—The nuclei of these cells are kidney-shaped. The protoplasm contains numerous coarse refractive granules of an albuminoid nature (Weiss), which are stained deeply with eosin and other acid anilin dyes. They are amœboid, and most observers consider them to be non-phagocytic. They form 2 to 4 per cent. of the leucocytes in the blood, but form a large proportion of those in the peritoneal and serous fluids.

[1] *Zeit. klin. Med.*, 1880, I., p. 555, and "*Farbenanalytische Unters. z. Histol. u. Klin. des Blutes*," Berlin, 1891.
[2] *Proc. Roy. Soc.*, 1894, LV., p. 161.
[3] *Journ. of Path.*, 1894, XVII., p. 81.

4. **Finely Granular Oxyphiles (Neutrophile Cells of Ehrlich).**—These are smaller cells than the coarse oxyphiles, with a multipartite or branching nucleus, and small granules in the protoplasm which attract acid dyes faintly. They are the cells which are chiefly present in pus. In the normal blood they may form 70 per cent. of the total leucocytes. Stained by the eosin and methylene-blue method, the granules are stained pinkish and the nuclei blue.

Staining of Oxyphile Granules and Oxyphiles.—

I. Stain films for five to ten minutes in a deep-red solution of eosin in glycerin; then wash in water. Examine in glycerin, or dry and mount in balsam.

To stain the nuclei as well, methylene blue may be employed in the manner described on page 268.

II. *After Ehrlich:* "acidophilic mixture."

Indulin, aurantia, eosin	of each 2 parts.
Glycerin	30 „

Float the cover-glass preparations on to the stain.
Wash in water, dry, and mount in Canada balsam.

The nuclei are stained blue, the acidophilic granules red, and the red blood-corpuscles copper red.

5. **Coarsely Granular Basophiles (Mast-Cells).**—These cells have nuclei which stain faintly, and their protoplasm has large basophilic granules; according to Kanthack and Hardy, they are absent from the blood in health. They have similar staining reactions to the mast-cells of the corium, and are not phagocytic.

Staining of Coarsely Granular Basophiles.—

The "mast-cell granules" are stained by the ordinary basic anilin dyes, such as methylene blue, Bismarck brown, and dahlia.

After Ehrlich.—Stain for several hours in the following solution:

Glacial acetic acid	12·5 c.cm.
Absolute alcohol	50 „
Water	100
Dahlia to complete saturation.	

Partially decolorise under the microscope with alcohol, till the granules become noticeable, and mount in Canada

balsam. The basophilic granules are stained dark purple. The nuclei may be counter-stained with alum-carmine (*see* also stains for the mast-cells in the corium, p. 141).

6. **Finely Granular Basophiles.**—These are small cells with a tripartite nucleus, and a protoplasm with fine basophilic granulations. They are present in normal blood, forming ·5 per cent. of the leucocytes.

Table of the Varieties of Leucocytes and their Relative Numbers in Healthy Blood.

Small lymphocytes	25 per cent.
Large lymphocytes (hyaline cells)	2·5 „ „
Polynuclear leucocytes (neutrophiles or finely granular oxyphiles)	70 „ „
Eosinophiles (coarsely granular oxyphiles)	2 „ „
Basophiles[1]	·5 „ „

Changes in the Blood in Association with Certain Diseases of the Skin.

Alterations in the blood with regard to its cellular elements, degrees of alkalinity and coagulability, and the percentage of hæmoglobin have been from time to time recorded in association with skin-diseases. But as these changes vary so much in the same patient in the course of the disease, as well as in different cases, and since their significance is not yet fully understood, they cannot at the present time be regarded as of much diagnostic value.

I. Alterations in the Red Blood-Corpuscles or Hæmocytes.

In the *anæmia* which occurs in the cachectic conditions associated with leprosy, tuberculosis, and syphilis there is a distinct diminution in the number of the hæmocytes associated with a decrease in the percentage of hæmoglobin. In the eruptive stage of syphilis a similar diminution has been several times recorded (Jawein[2]), but such has not been noted in

[1] Ehrlich distinguished two varieties of basophiles: (*a*) basophiles with γ granules, coarsely granular, absent from the healthy blood (mast-cells); and (*b*) basophiles with δ granules, finely granular.

[2] *Dissertation*, St. Petersburg, 1896.

the initial stage of the disease previous to the generalisation of the virus. When syphilitic patients begin to take mercury the same observer has noted a marked increase in the number of red blood-corpuscles. Neumann and Konreid[1] assert that the red blood-corpuscles, though normal in number during the primary stage of syphilis, may become diminished to a third of the normal with the advent of the eruptive period.

II. Alterations in the Percentage of Hæmoglobin.

The percentage of hæmoglobin presents such distinct changes in syphilis as to be of diagnostic value. When the syphilitic virus becomes generalised, there is a marked diminution in the percentage of the hæmoglobin, and a steady increase occurs when mercury is prescribed (Neumann, Konreid, Jawein, and Justus[2]). The following are the conclusions which Justus has come to on the subject:

1. That syphilis, if untreated, produces a greater or less diminution in the hæmoglobin, according to the severity of the attack. This diminution is compensated as the affection undergoes spontaneous evolution.

2. If a syphilitic patient absorb a fairly large quantity of mercury in one dose, either by inunction or intramuscular injection, the quantity of hæmoglobin will sink rapidly and considerably.

3. This decrease of hæmoglobin will be restored in proportion to the gravity of the syphilitic manifestations, and the state of general nutrition of the hæmoglobin may again sink on repeating the injections. If treatment by mercury be continued, the amount of hæmoglobin will ultimately reach a much higher level than that observed before the commencement of treatment.

4. When the amount of hæmoglobin ceases to sink, on repeating the administration of the drug the syphilitic manifestations will be observed to remit. The reaction reappears during every relapse of the malady.

5. The rapid and characteristic sinking of the hæmoglobin (10° to 20° of Fleischl's hæmometer) after the administration of mercury is a specific phenomenon, and is not to be observed in the blood of healthy persons or in those affected with other diseases.

[1] *Wien. klin. Wochenschr.*, 1893, VI., p. 340.
[2] *Brit. Journ. of Derm.*, 1897, IX., p. 53.

III. Alterations in the Number and Relative Proportion of the White Blood-Cells or Leucocytes.

An increase in the number of leucocytes, or a "leucocytosis," has been noted in the blood in diseased conditions of the skin associated with intense irritation. A general increase of all the types of leucocytes is rare; one variety is generally specially implicated, and a polynuclear leucocytosis, a lymphocytosis, and an eosinophilia have all been described in connection with skin-affections.

1. **Polynuclear Leucocytosis.**—An increase in the number of the polynuclear leucocytes has been repeatedly noted in association with the acute exanthemata. It occurs at the beginning of the fever in scarlet fever (Steindler[1]), and increases with the onset of complications, such as otorrhœa. It is said to be absent in measles, and to be in consequence a diagnostic sign between these two exanthemata (Neisser and Jadassohn[2]). At the onset of an attack of erysipelas there is a marked polynuclear leucocytosis, which reaches its maximum with the acme of the fever, and steadily decreases as the fever declines; any increase signifies a relapse (Chantemesse and Rey[3]). It occurs also in variola, when the vesicles mature and become purulent (Pick[4]), and in the later stages of syphilis (Sorrentino[5]).

2. **Lymphocytosis.**—In *leukæmia of the "lymphatic type" of Ehrlich* a marked lymphocytosis is present, and the leucocytes, instead of having a proportion of 1 to 700 to the hæmocytes, may reach that of 1 to 10 (Osler[6]). The tumours which occur in the skin in association with this disease are simply lymphomatous masses due to the infiltration of the lymph-spaces of the skin by vast numbers of lymphocytes, which even push their way between the epithelial cells. Such tumours are exceptional.

In *lymphadenoma, or Hodgkins's disease*, a relative increase in the lymphocytes in the blood has been described. A decided lymphocytosis has been noted in *lymphodermia perniciosa* of Kaposi, and also in the premycotic stage of *mycosis fungoides* (Galloway and MacLeod[7]).

[1] *Allg. Wien. med. Ztg.*, 1897, XLII., p. 292.
[2] *Krankheiten der Haut*, Stuttgart, 1901, p. 235.
[3] *Presse Méd.*, 1899, No. 52.
[4] *Archiv f. Derm. u. Syph*, 1893, XXV., p. 63.
[5] *Giorn. intern. delle Scienze Med.*, 1899, No. 32.
[6] *Principles and Practice of Medicine*, London, 1898, p. 809.
[7] *Brit. Journ. of Derm.*, 1900, XII., p. 159.

Rille has described a lymphocytosis in measles in contradistinction to the polynuclear leucocytosis, which has already been referred to in scarlet fever.

In erysipelas the number of lymphocytes is said to be diminished during the fever (Chantemesse and Rey).

3. **Eosinophilia**.—An increase in the number and proportion of the coarse granular eosinophiles in the blood, or eosinophilia, has been so frequently observed in association with vesicular and bullous dermatoses that recently much prominence has been given to it in dermatology, and it has even been regarded as a sign of diagnostic importance. The percentages of the eosinophiles which have been recorded in various skin-diseases differ so greatly, however, that quotations of them are of comparatively slight value, and their significance is not fully understood. The discrepancy in the number of eosinophiles is the result of several causes: (1) the percentage not only varies in different individuals suffering from the same disease, but in the same individuals at different times; (2) until a universal method of preparing blood-films and of calculating the number of the leucocytes is adopted, the results are bound to differ widely; and (3) undoubtedly in some of the counts which have been recorded, the small granular oxyphiles have also been included.

In bullous dermatoses, such as *pemphigus*, eosinophilia not only occurs in the blood, but also in the contents of the bullae (Leredde, Kaposi, etc.). It has been stated that eosinophilia is never present in the contents of bullae artificially produced, and if this be true it would form a sign of undoubted value in distinguishing them from those of the various bullous affections of the skin. Bettmann[1] calculated that in a case of pemphigus there was an average of 14 per cent. of coarse granular eosinophiles in the blood, and 73 per cent. in the bullous fluid, while in bullae which resulted from cantharides there was only a slight increase of eosinophiles in the contents and no increase of them in the blood. He noted that the earlier the lesions the larger the number of eosinophiles.

Dermatitis herpetiformis (Duhring) is a vesicular affection associated with marked eosinophilia (Darier[2]). In the contents of the vesicles, Leredde and Perrin[3] noted 30 to 95 per cent., and in two cases I counted 11 and 14 per cent. respectively

[1] *Münch. med. Wochenschr.*, 1898, No. 39, p. 1229.
[2] *Soc. Française de Derm. et de Syph.*, June, 1896.
[3] *Ann. de Derm. et de Syph.*, 1895, VI., p. 452.

in the blood, and Gilchrist [1] found them in the dilated vessels and interepithelial lymphatics in sections of the skin. An eosinophilia has not yet, as far as I am aware, been demonstrated in erythema bullosum.

It has, however, been noted in *herpes zoster intercostalis* (Bettmann), *papular eczema* (Rille, Neisser [2]) and *urticaria* (Lazarus). In pruriginous conditions of the skin it has been frequently observed, and in these the degree of eosinophilia seems to depend rather on the size of the affected area than on the intensity of the itching (Canon [3]).

4. **Mast-Cells.**—These are rarely increased beyond their average of ·28 per cent., but in the myelogenous variety of leukæmia, which is associated with urticarial lesions in the skin, a distinct increase of mast-cells has been noted in the blood.

TABLE OF PATHOLOGICAL CHANGES AFFECTING THE BLOOD AND BLOOD-VESSELS IN ASSOCIATION WITH DISEASES OF THE SKIN.

Changes in the Blood.

I. **Hæmocytes.**—

Diminution . . . Cachectic states of Leprosy, Tuberculosis, etc. Eruptive stage of Syphilis (Jawein).

II. **Hæmoglobin.**—

Diminution . . . During the course of Syphilis and more marked when mercury is prescribed (Konreid, Justus).

III. **Leucocytes.**—

Increase in the Leucocytes, or Leucocytosis.—

1. Polynuclear leucocytosis . . . Scarlatina (Neisser and Jadassohn), Erysipelas, maturation of Small-pox.
2. Lymphocytosis . . . Leukæmia, Lymphodermia perniciosa (Kaposi), premycotic stage of Mycosis fungoides (Galloway and MacLeod), Measles (Rille).
3. Eosinophilia . . . Pemphigus, 14 per cent. in blood, 73 per cent. in bullae (Bettmann); Dermatitis herpetiformis, 14 per cent. in blood (MacLeod); Herpes zoster (Bettmann); papular Eczema (Rille); Urticaria (Lazarus).
4. Mast-cells increased in the blood . . . In myelogenous Leukæmia with urticarial lesions.

Circulatory Disturbances.

I. **Anæmia.**—

1. Generalised . . . Chlorosis, Leukæmia, etc.
2. Local . . . Spasm of small arteries, as in Raynaud's disease; local pressure; organic obliteration of a certain set of vessels by a thrombus, endarteritis, or sclerosis around them, as in Sclerodermia.

[1] *Johns Hopkins Hosp. Rep.*, 1896, I., p. 370.
[2] *Wiener med. Doktoren-Kolleg.*, December, 1891.
[3] *Deutsch. med. Wochenschr.*, 1892, XVIII., p. 206.

II. **Hyperæmia.**—
  1. *Active Hyperæmia or Erythema.*—
    (*a*) Generalised . . . Toxins circulating in the blood.
    (*b*) Local . . . Reaction after cold; local asphyxia of Raynaud's disease.
  2. *Passive* (*Cyanosis*).—Varicose veins.

III. **Œdema.**—
  1. Mechanical . . . Blocking of veins and lymphatics.
  2. Inflammatory . . . Erysipelas.
  3. Disturbances of nutrition of vessel-walls.
    (*a*) General . . . Anasarca, etc.
    (*b*) Local . . . Thrombosis, etc.

IV. **Hæmorrhage (Purpuras).**—
  1. Acute exanthemata when severe.
  2. Drugs . . . Copaiba, etc.
  3. Alkaloidal poisons . . . Further stage of urticaria.
  4. Nutritive disturbances . . . Scurvy.
  5. Increase in intravascular pressure . . . High altitudes, etc.

Changes affecting the Blood-Vessels.

I. **Dilatation, or New Formation, Angiomata.**—
  1. Cavernous and cirsoid aneurism.
  2. Telangiectases . . . Occurring alone or in association with certain skin-affections, such as Lupus erythematosus, Xeroderma pigmentosum.
  3. Vascular nævi . . . Spider-nævi and port-wine stains.

II. Endarteritis.

III. Endophlebitis . . . Varicose eczema, Phlebitis nodularis necrotisans (Philippson).

CHAPTER XXIX.

THE LYMPHATICS OF THE SKIN.

IN this connection not only the lymphatic vessels of the skin have to be considered, but also the lymph—or "juice-spaces" between the fibrous bundles and the epithelial cells.

1. **Lymphatic Vessels.**—By *lymphatic vessels* are meant vessels which possess a definite endothelial lining, in contra-distinction to lymph-spaces, which are simply spaces between the fibrous elements or the epithelial cells of the skin, which contain lymph, but have no distinct wall. There are comparatively few lymphatic vessels in the skin. They begin as blind ends or loops about the middle third of the papillae, and are best seen in the fingers and toes, where the papillae are largest. They pass down to a lymphatic plexus in the sub-papillary layer, from there they descend obliquely through the corium, accompanying the blood-vessels, and are collected into the interlobar lymphatics of the subcutaneous tissue. Into these interlobar lymphatics smaller interlobular branches, which communicate with the lymph-spaces between the fat-cells, pour their contents. The interlobar lymphatics possess a rudimentary muscular wall. The lymph from the tissue-spaces gains entrance into the lymphatic vessels either between the endothelial cells or through stomata in their walls (Klein). Some of the lymph is also taken up by the veins of the skin.

2. **Lymph-Spaces.**—These are simply spaces between the fibres and cells of the skin, which have no distinct structure, are not lined by endothelium, and pour their contents partly into the lymphatic vessels and partly into the veins.

Such spaces exist between the collagenous bundles of the corium, around the coils and ducts of the sweat-apparatus, and between the cells of the skin-glands and the hair-follicles. The arrectores pilorum are also surrounded by lymph-spaces, which enable the muscles to act easily. The spaces between the fibrous bundles are generally more or less continuously

lined by flattened connective-tissue cells, but there is no true endothelium. All these spaces can be injected through the lymphatic vessels of the subcutaneous tissue. The lymph-spaces form a network between the cells of the epidermis, which is best marked between the prickle-cells over the apices of the papillae. The researches of Key and Retzius[1] have demonstrated that the lymph circulates in the epidermis, passing in at the apices of the papillae and oozing back at the interpapillary process into the corium, or that it is eliminated at the sweat-pores. Beautiful specimens showing the lymphatic system of the epidermis may sometimes be obtained from a piece of inflamed negro-skin; for here the lymph-spaces are dilated, and the deposits of pigment, present between them, serve to map them out. These interepithelial lymphatic spaces can also be injected from the subcutaneous tissue.

Injection of Lymphatics.—This may be accomplished by puncturing the skin with a fine cannula, and injecting into the subcutaneous tissue in the manner already referred to in connection with the blood-vessels; the injection must be done slowly and at a uniform pressure, otherwise it will become too diffused.

Pathological Changes in the Lymphatics.

Lymphangioma or Lymphangiectasis.—It is difficult to draw a hard and fast line of distinction between the lymphangiomata or lymphatic new growths, and the lymphangiectases or simple dilatations of already existing lymph-channels. It has even been doubted whether a primary new growth of lymphatic tissue really exists, and whether we are not dealing, in cases which suggest a new growth, with a cellular proliferation secondary to a dilatation of the lymph-vessels. The majority of these lymphatic dilatations rapidly become varicose and finally cavernous. The explanation of these growths is still undecided. It would seem that blockage of the lymphatics alone will not cause stagnation of lymph, but that it requires a blockage also of the veins. It is as yet undetermined how this blockage is brought about,—whether it is the result of a proliferation of the endothelium and perithelium of the lymphatics and veins, or is due to an inflammatory process which causes a hyperplasia of the surrounding tissue and constricts the vessels.

[1] *Ziemssen's Handbook of Skin Disease*, 1885, p. 60 (quoted from Unna).

The best-known example of a lymphangioma affecting the upper layers of the corium is the *lymphangioma circumscriptum*, of which the first case was described by Drs. Tilbury and Colcott Fox.[1] It consists of clusters of vesicles slightly resembling warts, varying in size from a pin's head to a small pea. From these, on being punctured, a clear fluid containing albumen exudes. These cysts are found to be lined by endothelium, and are simply dilated lymphatics. Around them a cellular hyperplasia, with occasional giant-cells, has been described, and new blood-vessels have been noted. It is just possible that new lymphatics do form in this disease.

Another form of superficial lymphangioma, associated with a marked cellular hyperplasia in the corium, results in the formation of flat, raised patches, dotted over with deep-seated vesicles, which have been likened to frogs' spawn. The skin has a pinkish or yellowish tinge, and is much indurated. This condition is allied to elephantiasis. The name *pachydermia lymphangiectatica* has been suggested for it. Such patches have been known to arise after repeated attacks of erysipelas.

Solitary or multiple lymphangiomata may also occur in the subcutaneous tissue, and these give rise to variously-sized tumours. The single ones are as a rule congenital. In this situation cavernous lymphangiectases may form.

Lymphoid-Celled Tumours.—These form a somewhat rare group of tumours, in which lymphocytes are the predominant type of cell found in the hyperplasia. To this group belong the rare skin-growths which occur in leukæmia, where the minute structure of the tumour is that of a lymphomatous mass similar to a lymphatic gland. The tumours result from the dilatation of the lymphatic spaces in the corium and the invasion of these by lymphocytes. The connective tissue gradually atrophies, and an adenoid tissue is formed. The tumours which occur in the course of Hodgkin's disease, or pseudo-leukæmia, are sometimes included in this group. But since plasma-cells may be detected in the latter tumours, certain observers consider that they belong to a different category from the tumours of ordinary leukæmia, and are more nearly related to the granulomata (Unna,[2] Nékám,[3] Graham Little [4]).

[1] *Trans. Path. Soc. of London.*, 1879, XXX., p. 470.
[2] *Histo-Pathology*, Walker's Trans., 1896, p. 621.
[3] *Leukämische Erkrank. der Haut*, Hamburg, 1899, p. 37.
[4] *Brit. Journ. of Derm.*, 1902, XIV., p. 228.

CHAPTER XXX.

THE NERVE-TERMINATIONS IN THE SKIN.

In the skin both medullated and non-medullated nerve-fibrils are present. The *medullated fibrils* form plexuses in the corium, from the most superficial of which fine non-medullated fibrils pass up between the prickle-cells of the epidermis and between the cells of the corresponding layer of the hair-follicles. A few of the medullated fibres terminate in the special end-organs known as the tactile corpuscles, the touch-cells of Merkel, and the Pacinian bodies of the subcutaneous tissue. Our knowledge of the terminations of the *non-medullated nerves* is not so complete; they probably supply the muscular fibres of the arrectores pilorum, the sweat-coils, and the blood-vessels. The nerves of the skin are numerous in the palms of the hands and the soles of the feet, especially in the tips of the fingers and toes—regions where sensation is particularly acute. From the subcutaneous tissue the nerves pass up into the corium with the blood-vessels.

The Interepithelial Nerve-Fibrils. — The subepithelial plexus consists chiefly of nerve-fibres which have lost their medullary sheaths, and occasional groups of ganglia connected with them. Among the non-medullated fibres a few nerves may be detected which have retained their medullary sheaths, and these terminate in the special end-bulbs. The non-medullated nerves form a true plexus by branching and anastomosing again, immediately beneath the epithelium. From this plexus fine fibrils extend up between the prickle-cells as far as the stratum lucidum. According to Klein, these fibrils end in minute swellings between the prickle-cells; but Unna maintains that many of them pass into the cells, to terminate in swellings which are applied to the nuclear membrane.

The interepithelial nerve-fibrils occasionally present varicose swellings, the significance of which is disputed; but it is possible that they are only optical illusions. These

nerve-fibrils are sensitive to tactile impressions and to common sensation.

The Nerve-Fibrils of the Hair-Follicles.—Small medullated nerves pass down from the sub-epithelial plexus, have a circular course in the dermic coat of the hair-follicle, lose their medullary sheaths, and split into fibrils, which end between or within (Unna) the cells of the prickle-cell layer of the follicle.

Hoggan [1] states that the axis-cylinder of the nerve breaks up into from two to six forks between the inmost dermic layer and the prickle-cell layer of the follicle, and that these forks terminate in flattened spade-like bodies situated below the openings of the sebaceous glands. Beneath these nerve-endings Hoggan describes groups of branched nerve-cells; but as his researches were carried out in the tactile hairs of lower animals, it is not certain that they are applicable to human hairs.

The Special "Terminal Corpuscles."—

1. *Tactile Corpuscles or Meissner's Bodies.*—These end-bulbs are situated in the papillae, are very universally distributed, but are in greatest number where tactile sensations are most acute, as in the tips of the fingers. They are not present in all the papillae of the skin of the finger-tips, since the majority of the papillae are purely vascular. In shape they are oblong or spindle-shaped (Pl. XXXII., Fig. 1), and are generally placed vertically in the papilla. They occupy nearly the whole papilla if they be large; but if small, occasionally several may be present in the same papilla. They present a transversely striated or ridged appearance, owing to their being made up of superimposed layers of connective tissue with numerous nuclei. On entering the corpuscle the nerve loses its medullary sheath, and its axis cylinder splits into fibrils, which ramify between the layers in a somewhat spiral manner, and end in small swellings.

2. *Touch-Cells of Merkel.*—Merkel, Ranvier, and others have described peculiar small cells in the papillae, chiefly of the fingers and toes. These cells are round or pear-shaped, and are connected with the axis-cylinder of a nerve-fibril. It is said that they have a cell-membrane which is continuous with a prolongation of the primitive sheath of the fibril. Krause regards them as an unusual type of epithelial cell, and the

[1] *Journ. of Anat. and Phys.*, 1893, XXVII., p. 224.

majority of histologists doubt that they have any special sensory function.

3. *Pacinian Bodies, Corpuscles of Vater, or Lamellar Corpuscles.*—In unstained sections of the skin these structures appear as small, oval, milky specks when the section is held over a dark background. They are situated chiefly in the subcutaneous tissue of the palms of the hands, the soles of the feet, the fingers and toes, and elsewhere more sparsely. They are oval or elliptical in shape, and vary in length from 1 to 4 mm. In structure they are made up of a large cortical portion and a central core (Pl. XXXII., Fig. 2). The *cortex* is composed of from twenty to sixty (Kölliker) concentrically arranged capsules, like the sheaths of an onion, which give to the body on section a striated appearance. The capsules are the result of a swelling and splitting-up of the sheath of Schwann of the nerve. Each capsule or lamella is composed of a meshwork of collagenous and elastic fibres, with transversely arranged nuclei, and is lined by a layer of endothelium on its inner surface. The lamellae are thinnest near the periphery and centre, those intervening being swollen from the presence of a certain amount of lymph between their fibres. Occasionally small capillaries may be detected between the capsules. Immediately below the corpuscle the nerve with its sheath of Schwann forms the so-called *stalk*. The axis-cylinder of the nerve passes directly into the central core of the body. Occasionally a nerve may pass through one of these structures to end in a second one beyond. The *core* consists of an indefinite granular ground-substance in which the termination of the axis-cylinder is situated. It is limited externally by an endothelial layer. The axis-cylinder beyond the centre of the core splits up into several branches, which end in knobs or pear-shaped swellings, and are sometimes grouped together like a raspberry. The Pacinian bodies are believed to be sensory instruments for the appreciation of pressure and traction, which they are said to be able to do by the hydrostatic influences of the albuminous lymph of the cortex acting on the sensitive core.

Technique for Demonstrating the Peripheral Nerve-Endings.

Within recent years a great advance has been made in the technique for demonstrating the peripheral nerve-endings. The methods which are requisite for this purpose are as a rule

PLATE XXXII.

FIG. 1. TACTILE CORPUSCLE WITHIN A PAPILLA OF THE SKIN OF THE HAND.

Stained with chloride of gold (after Ranvier.)

a. Two nerve fibres passing to the corpuscle.
b. Terminal varicose ramifications of the axis-cylinder within the corpuscle.

FIG. 2. LONGITUDINAL SECTION OF A PACINIAN CORPUSCLE OF MAN (after Kolliker).

a. Indefinite granular core.
b. Termination of axis-cylinder of nerve.
c. Nerve entering the corpuscle, forming the "stalk."
d. Cortex made up of capsules arranged like the sheaths of an onion.
e. Transverse nuclei in section.

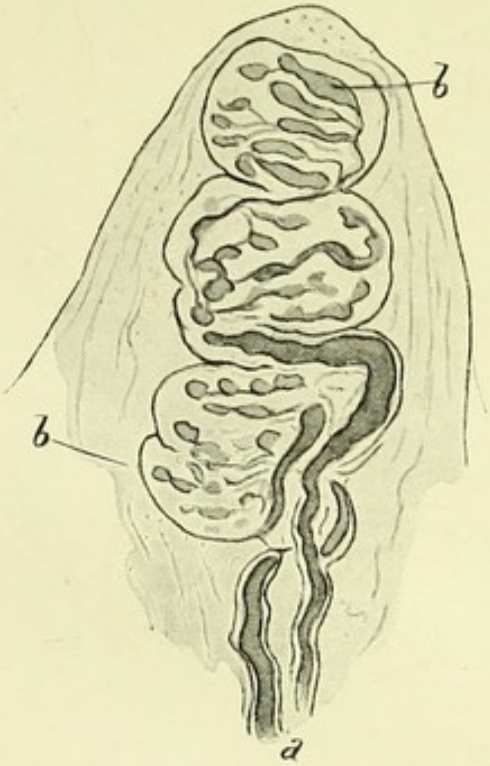

FIG. 1.

(*After* RANVIER.)

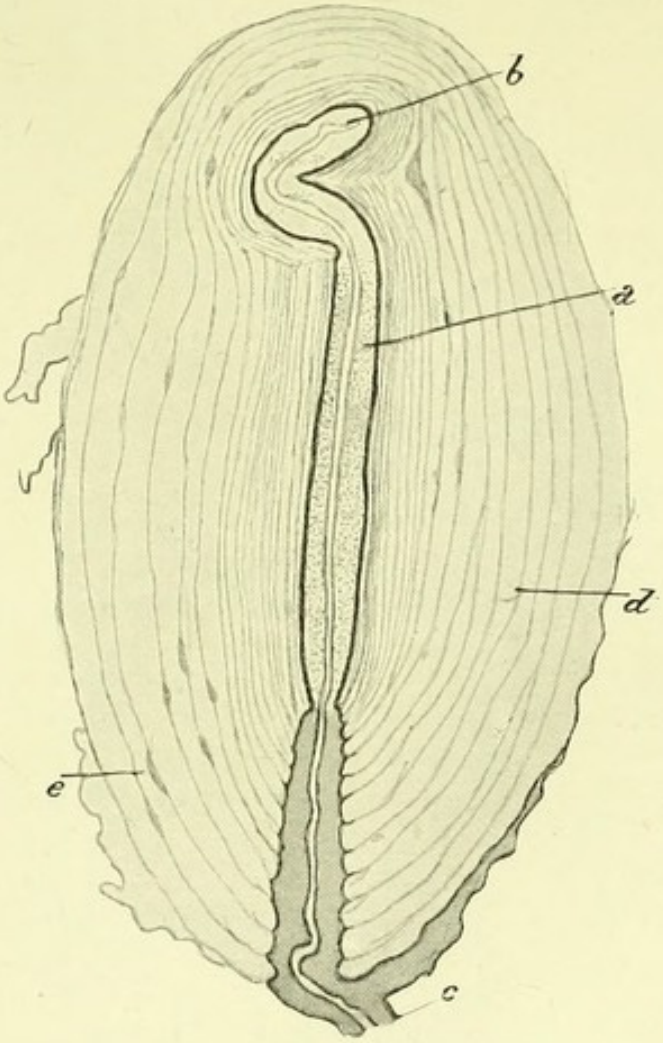

FIG. 2.

(*After* KÖLLIKER.)

complicated, and necessitate careful manipulation. It will be impossible here to do more than refer to a few of them, but I would earnestly recommend all those interested in the subject to study carefully the chapters bearing upon it in the latest edition of Lee's *Vade-Mecum*.[1]

For the demonstration of the peripheral nerve-endings it is absolutely essential to employ fresh tissue, since if the tissues be removed even a few hours after death, the nerve-endings are apt to be destroyed. The best results are obtained from tissues removed by a biopsy and at once placed in a suitable fixative.

Fixing-Agents for Nerves.—Of all the fixing fluids, Müller's bichromate solution seems to give the most satisfactory results. It has decided advantages over Flemming's aceto-chromo-osmic acid solution, alcohol, and corrosive sublimate.

Staining of Medullated Nerve-Fibres.—

I. *After Weigert* (*Deutsch. med. Wochenschr.*, 1891, XVII., p. 1184).—

(*a*) Fix small pieces of fresh skin for forty-eight hours in Müller's fluid.

(*b*) Transfer them for twenty-four hours into absolute alcohol, and then into thin and thick celloidin for forty-eight hours each.

(*c*) Make a celloidin block in the usual manner, and place it in the following solution for twenty-four hours in an incubator: Equal parts of cold saturated solution of neutral acetate of copper and 10 per cent. aqueous solution of potassio-tartrate of sodium.

(*d*) Transfer the hardened block for twenty-four hours into the cold saturated solution of acetate of copper in an incubator.

(*e*) Wash the block in water, leave it for twelve hours in 80 per cent. alcohol, and then cut sections.

(*f*) Stain the sections for twenty-four hours at room-temperature in the following solution, freshly prepared:

9 vols. :	Saturated solution of lithium carbonate	7 c.c.
	Water	93 c.c.
1 vol. :	Hæmatoxylin	1 grm.
	Alcohol	10 c.c.

(*g*) Wash in water.

[1] Lee's *Vade-Mecum*, 1900, Chaps XVII., XVIII., XXX.–XXXII.

(*h*) Differentiate in the following solution :

Borax	2 parts.
Potassium ferricyanide	1 part.
Water	200 parts.

(*i*) Wash in water.
(*j*) Dehydrate in alcohol.
(*k*) Clear in xylol and mount in Canada balsam.

By this complicated method the medullated nerve-fibres are stained a dark-blue colour, and the rest of the section is pink or rose-coloured.

II. *After Heller and Gumpertz* (*Allg. med. Centralzeitg.*, 1895, p. 548, and *Lee*, p. 406).—
(*a*) Fix a piece of fresh skin for forty-eight hours in Müller's fluid.
(*b*) Harden in alcohol and imbed in celloidin.
(*c*) Stain sections for twenty-four hours in 1 per cent. osmic acid in an incubator at 37° C.
(*d*) Transfer to pyrogallic acid till the nerves are black.
(*e*) Then to a violet-coloured solution of permanganate of potash till the sections are brown.
(*f*) And to a 2 per cent. solution of oxalic acid till they become greenish yellow.
(*g*) Wash, dehydrate in alcohol, clear in xylol, and mount in Canada balsam.

The medullated nerves are stained black.

III. *After Sahli* (*Zeit. f. wiss. Mikr.*, 1885, II., p. 1).—
(*a*) Fix in bichromate of potash, 5 per cent. solution.
(*b*) Harden in alcohol ; imbed and cut in celloidin.
(*c*) Stain the sections for several hours in a concentrated aqueous solution of methylene blue.
(*d*) Wash and counter-stain in a saturated aqueous solution of acid fuchsin.
(*e*) Wash, dehydrate in alcohol, clear in xylol, and mount in Canada balsam.

The medullary sheath of the nerve is stained blue, and the axis-cylinder red.

Staining of Degenerate Nerves.—
After Marchi (Lee's *Vade-Mecum.*, 1900, p. 404).—
(*a*) Fix the tissues for a week in Müller's fluid, then for several days in Müller's fluid (2 parts), osmic acid (1 part).
(*b*) Harden in alcohol, imbed in celloidin.

(*c*) Alcohol, xylol, Canada balsam.

The medullary sheath is stained yellowish; the degenerated portions are stained black.

Staining of Non-Medullated Nerves and Plexuses (Inter-epithelial).—

I. *After Strauss* (*Monats. f. prakt. Derm.*, 1893, XVII., p. 163).—

(*a*) Place pieces of fresh skin from two to seven days, according to size, in a 1 per cent. aqueous solution of palladium chloride, to which is added a few drops of hydrochloric acid, to render it more soluble.

(*b*) Harden in alcohol.

(*c*) Imbed and cut in celloidin.

(*d*) Clear in clove oil and mount in Canada balsam.

The nerves are stained black or grey. To counter-stain the fibrous elements of the tissue the sections may be stained for a few minutes in neutral orcein solution.

II. *After Golgi.*—Rapid method, with silver nitrate (abstracted from Lee's *Vade-Mecum*).—

(*a*) Put small pieces of fresh skin for several days—not longer than twelve—in the following mixture:

Bichromate of potash solution, 2 per cent.. .	8 parts.
Osmic acid, 1 per cent.	2 „

(*b*) Impregnate the tissue with silver nitrate. After the piece of tissue is sufficiently fixed and hardened by the bichromate mixture, it is transferred by a glass rod to a vessel containing a quantity of ·75 per cent. nitrate of silver solution. It is advisable to change the solution, as a precipitate of yellow chromate of silver forms. Keep the tissue in the silver nitrate solution from twenty-four to forty-eight hours. It is unnecessary to keep it in the dark. In winter it is advisable to warm it to obtain the reaction.

(*c*) Transfer to absolute alcohol, to wash out thoroughly the silver. Let it remain in the alcohol for several days, changing it daily.

(*d*) Cut the tissue between two pieces of lardaceous liver.

(*e*) Clear in creosote for a few minutes, then in oil of turpentine for fifteen minutes.

(*f*) Mount in dammar, without a cover-glass.

The non-medullated nerves are stained black. This method "has given brilliant results in the study of peripheral nerves and their terminations" (Lee).

III. *After Ramón y Cajal*, quoted from Meissner (*Archiv f. Derm. u. Syph.*, 1894, XXVII., p. 385), and Joseph and Loewenbach (*Derm.-Hist. Tech.*, 1900, p. 91).—

(*a*) Fix for seven days in the following solution in the dark at 30° C.:

Aqueous solution of osmic acid, 1 per cent.	1 part.
„ „ „ potassium bichromate, 3½ per cent.	4 parts.

(*b*) Wash in ¼ per cent. solution of silver nitrate.

(*c*) Transfer for twenty-four hours to ¾ per cent. solution of silver nitrate in the light.

(*d*) Harden in alcohol and cut in paraffin.

(*e*) Alcohol, xylol, Canada balsam.

The non-medullated fibres are stained black.

Staining of Tactile Corpuscles of Meissner.— The tactile corpuscles, being chiefly composed of connective tissue, stain readily by the ordinary connective-tissue stains; but these do not bring out sufficiently their connection with the nerve-fibrils.

The following special method is recommended:

I. *After Löwit, modified by Stöhr* (*Histology*, American ed., p. 204).—

(*a*) Shave off the fat from a piece of fresh skin removed from the finger-pulp.

(*b*) Impregnate for one hour in the dark in the following mixture of Ranvier:

Gold chloride, 1 per cent.	4 parts.
Formic acid	1 part.

(This solution should be boiled, then cooled.)

(*c*) Wash in distilled water.

(*d*) Transfer to a solution containing 10 c.c. of formic acid and 40 c.c. of distilled water. Expose to the daylight for twenty-four hours, to reduce the gold chloride, till the tissue becomes dark violet.

(*e*) Place it in 70 per cent. alcohol for twenty-four hours.

(*f*) And in 90 per cent. alcohol for eight days, or till the reduction ceases.

(*g*) Imbed the tissue in a piece of lardaceous liver, and mount the sections in dammar or glycerin.

Meissner's bodies are stained dark violet or black.

NOTE.—In all these manipulations it is necessary to avoid the use of metal instruments; and glass rods or porcupine quills should be employed. Stöhr recommends the same method for the demonstration of the nerve-endings in the muscles of the skin. For this purpose a piece of skin from the scalp should be chosen, since the arrectores pilorum are very large in that situation.

The Staining of Pacinian Bodies.—These structures can be seen with the naked eye in unstained sections over a dark background. The capsules, being composed of ordinary connective tissue, stain well with the usual connective-tissue stains, such as orcein and water-blue. To study the axis-cylinders fix a piece of skin in Müller's fluid, and cut in celloidin. Examine the section with the naked eye for Pacinian bodies, and, having found a suitable section, treat it under the cover-glass with a 1 per cent. osmic acid solution. The axis-cylinder and its prolongation in the central core are stained brownish black.

PATHOLOGICAL CHANGES IN THE PERIPHERAL NERVES OF THE SKIN.

Though nearly every form of dermatitis has at one time or another been attributed to a disorder of the nervous system, this assumption has in the majority of cases been largely hypothetical, and has only in rare instances been corroborated by the demonstration of definite pathological changes either in the central nervous system or in its peripheral terminations in the skin. Even in the large group of diseases which it is customary to classify as the angioneuroses, such as urticaria, erythema multiforme, and the like, actual nerve-lesions have not yet been conclusively demonstrated. Histologically the angioneurotic manifestations are indistinguishable from the earlier stages of inflammation; but from the rapidity with which they may develop it seems more than probable that they are associated with an instability in the muscular tone of the subcutaneous vessels due to the action of some toxin; and from the short time which they may take to involute, it seems equally likely that any disorder of the peripheral nerves which may precede them is functional in nature and not organic.

It has been definitely proved, however, that degenerative changes in the peripheral nerves are followed by lesions in the skin in the area of distribution of these nerves. These are the result of an interference with the trophic influences

which regulate the nutrition of the part and a diminution in the vaso-motor control of the blood-vessels. After an injury to the peripheral nerve, or in association with the various forms of peripheral neuritis, the skin in the area supplied by the nerve frequently becomes glossy and atrophic, and vesicles, bullae, ulcers, and even gangrene may develop.

Degenerative changes have been detected in the peripheral nerves in several skin-diseases. In Raynaud's disease[1] actual changes have been noted in the nerves of the fingers affected. Leloir[2] has reported a degeneration of the underlying nerve-fibres in pemphigus; and in association with vitiligo, a parenchymatous neuritis, in which the axis-cylinder disappears, the myelin sheath breaks down, and the nerve-fibre becomes transformed into an empty primitive sheath, the nuclei of which have proliferated. In the anæsthetic lesions of leprosy the nerves supplying the affected areas are thickened from a proliferation of their connective tissue and an inflammatory cellular infiltration due to the presence of Hansen's bacilli.

Ever since v. Bärensprung in 1861[3] stated that herpes zoster was of nervous origin, a certain section of dermatologists have clung to that explanation in opposition to the vascular or the parasitic theory. Recently the brilliant researches of Head and Campbell[4] have gone far to prove that this belief was well founded. In a large number of cases of zoster in which post-mortem examinations were obtained, Head has been able to detect inflammatory changes in the ganglia of the posterior root, in the posterior root itself, in the root-fibres of the posterior columns of the cord, and in the peripheral nerves. Degenerations in the nerve-fibres were traced as far as the piece of skin excised, but unfortunately have not been detected in the tissue itself.

Tumours of the Peripheral Nerves: Neuromata.—There are two types of neuromata—namely, true neuromata and false neuromata.

1. *True Neuromata* are new growths caused by a proliferation of nerve-tissue alone, and are extremely rare. They occur usually about the face, but they may develop in other situations after injury to a nerve. Histologically

[1] *Raynaud's Disease*, Monro, Glasgow, 1899, p. 190.

[2] *Recherches cliniques et anatomo-pathologiques sur les affections cutanées d'origine nerveuse*, Paris, 1881.

[3] *Charité Ann.*, 1861, p. 40.

[4] *Brain*, 1900, XXIII., p. 362.

they are made up of ganglion-cells, and medullated and non-medullated nerve-fibrils, supported by a connective-tissue stroma.

2. *False Neuromata* are so called because they consist, at least in part, of a proliferation of connective tissue. They are far more common than the former variety. They may be simply fibromata situated on a nerve-trunk, over which a few nerve-fibrils are stretched, or may result from a proliferation of the interstitial connective tissue and perineurium of the nerve, together with a new formation of nerve-elements.

These neurofibromata may occur along a peripheral nerve, like beads in a rosary, or they may assume a plexiform arrangement. They are usually painful, from inclosing sensory twigs. When these neuromata occur in the hypoderm they are known as *tubercula dolorosa*, and are frequently associated with paroxysmal attacks of excruciating pain, and the skin over them is generally violaceous in tinge. v. Recklinghausen[1] has carefully described a congenital affection in which multiple fibromata and pigmentary changes occur in the skin, associated with general nervous derangements, and almost invariably with a defective mental and physical development. In this disease, which now goes by his name, soft nodules, varying in size from a hemp-seed to a nut, appear in the skin. The largest of these are gelatinous to the touch and violaceous in colour. These tumours are said to be neurofibromata, and to develop in connection with the peripheral nerves, but this has not yet been definitely proved. The skin between these lesions is pigmented in patches, varying in size from small freckles to large irregular areas.

TABLE OF PATHOLOGIAL CHANGES IN THE PERIPHERAL NERVES OF THE SKIN.

Parenchymatous Degenerations.—

(*a*) After injury.
(*b*) Raynaud's disease.
(*c*) Pemphigus and Vitiligo (Leloir).
(*d*) Leprosy due to the presence of the bacilli of leprosy.
(*e*) Herpes Zoster. (Head and Campbell have traced degenerations in the peripheral nerves as far as the piece of skin excised, but not actually in it.)

Nerve-Tumours.—

1. True neuromata . . . Usually on face.
2. False neuromata or neurofibromata may occur as—
   (*a*) Beads on a rosary
   (*b*) Plexiform. } superficial and painful.
   (*c*) Deep-seated and painful . . . Tubercula dolorosa.

[1] *Ueber die multiplen Fibrome der Haut*, Berlin, 1882.

CHAPTER XXXI.

FAT IN THE SKIN.

THE SUBCUTANEOUS TISSUE.

THE subcutaneous tissue is derived from the same embryonic layer as the corium, and may be most simply regarded as a deeper layer of the same structure, many of the cells of which have become infiltrated with fat-globules and transformed into fat-cells. This layer serves three distinct purposes, namely:

1. It forms a protective pad by which injuries to the skin are prevented from doing harm to the more vital underlying structures.

2. Being a bad conductor of heat, it prevents too great loss of heat from the surface of the skin by radiation and evaporation.

3. It forms a protective framework supporting various delicate structures, such as the Pacinian bodies, nerve-trunks, coil-glands, blood-vessels, and lymphatics.

It varies in thickness in different situations, being specially thick on the palms and soles, and peculiarly thin where the skin is loosely attached to the underlying tissues, as in the eyelids; or strongly attached and immovable, as in the skin of the nose and auricle.

In structure the tissue consists of a coarse fibrous network of collagen and elastin, enclosing large groups of fat-cells, forming *lobes*; the fibrous walls enclosing the lobes are known as *trabeculae*. The lobes are broken up by fibrous septa into *lobules* composed of a varying number of fat-cells. The lobes, lobules, and individual fat-cells are richly supplied with blood-vessels. An arterial branch can be detected for each lobule, and this splits up into numerous capillaries which surround and to a great extent support the fat-cells. These capillaries pour their contents into small venules coursing between the lobules, which in turn open into the larger

veins of the subcutaneous layer. Around the lobules and between the fat-cells lymphatic spaces occur.

Besides the ordinary fat-lobules, fat-columns have been described, which pass up vertically from the fat-lobules to the ends of the hair-follicles and coil-glands in the corium (Unna). These are known as the *columnae adiposae* (Warren),[1] and accompany the larger blood-vessels, but they have no capillaries ramifying between the fat-cells which compose them.

The fat-cells of the subcutaneous tissue are large, oval, or round bodies, which become polygonal from pressure, and consist of a globule of fat encapsuled in a thin homogeneous mantle (Pl. XIV., Fig. 5). The latter is the remains of the protoplasm of the original cell, and at one side of it a flattened nucleus can generally be detected. These cells are the result of a fat-infiltration of the cells of the connective tissue. Granules of fat appear in the cells; these coalesce to form minute globules, which run together to form a fat-globe, which distends the cell. It has not been definitely settled which type of connective-tissue cell develops into a fat-cell. Klein asserts that it is the "granular cells" and the "amœboid vacuolated cells," while Schäfer believes that it may be the flat-branched cells and the granular cells.

If the fat be abstracted from the cells by ether, and the mantle and nucleus stained by a good nuclear and protoplasmic stain, such as polychrome methylene blue, several peculiarities can be detected in the fat-cells. In the nuclei one or more vacuoles which do not contain fat may be noted. These were carefully described by Sack,[2] and he observed that they were only present in fully developed fat-cells, and were absent in the embryo and in the fat-cells of the senile skin.

By staining the fat-cells with osmic acid, vacuoles may also be demonstrated in the fat-globes themselves. Solger[3] suggested that this appearance might be explained by the acid causing a chemical change in the fat, by which the more solid constituents tended to become deposited at the periphery of the cell, while the fluid constituents remained at the centre.

Other Situations of Fat in the Skin.

The fat is not confined to the lobules in the subcutaneous tissue, but is present in the corium and epidermis. It exists

[1] *Boston Med. and Surg. Journ.*, April, 1877.
[2] *Monats. f. prakt. Derm.*, 1895, XX., p. 621 (abstract).
[3] *Anat. Anzeiger*, 1893, VIII., p. 647.

in the epithelium of the sweat-apparatus and in the lumen of the sweat-coil and of the duct. It is present in the lymphatic spaces of the corium, in the walls and lumina of the arteries, and in the medullae of nerves. It also occurs in the epidermal cells, in their nuclear spaces, and in the interepithelial lymphatics. It is similarly distributed in the prickle-cell layer of the hair-follicles. It is also present in the cells of the stratum corneum.

Chemical Composition of Fat.—Fat is formed of three compounds of glycerin with the fatty acids (oleic, palmitic, and stearic acids), known as olein, palmatin, and stearin. It is soluble in alcohol, xylol, ether, and chloroform; hence it is useless to stain tissues for fat which have been hardened in alcohol, if they have not been previously fixed in some solution which would render the fat insoluble. Fat resists the action of weak acids, but even weak alkalies cause it to emulsify.

The Technique for Staining Fat—Fat is stained brown to black by osmic acid; yellow or orange by Sudan III.; rose red by alkannin; and blue by cyanin.

Before hardening tissue in alcohol, one or other of the following solutions should be employed for *fixing* the fat:

I. *Flemming's Solution (Strong Formula).*—

Chromic acid, 1 per cent.	15 parts.
Osmic acid, 2 per cent.	4 „
Glacial acetic acid	1 part.

II. *Hermann's Solution*, in which 1 per cent. platinic chloride is substituted for the chromic acid in Flemming's solution.

III. *Müller's Fluid.*—

Potassium bichromate	2·5 per cent.
Sodium sulphate	1 „ „
Distilled water	100 „ „

IV. *Unna's Solution.*—

Picric acid	1 part.
Tannic acid	1 „
Nitric acid	0·1 „
Acetic acid	5 parts.
Water	100 „

All these fluids tend to coagulate the cell-protoplasm, and cause more or less shrinkage; and Müller's fluid has the additional disadvantage of causing the fat-granules to run together to form drops.

After fixing in one of these solutions the tissue is *hardened* in alcohol and cut in celloidin.

Staining in Osmic Acid.—

I.—

(*a*) Fix from one to four days in Flemming's solution.

(*b*) Wash for twelve hours in running water.

(*c*) Harden in increasing strengths of alcohol.

(*d*) Imbed and cut sections in celloidin.

(*e*) Stain the sections for twenty-four hours in a 1 per cent. aqueous solution of osmic acid, or fix the section to the slide and place it over the uncorked bottle containing the osmic acid solution for twelve hours, thus allowing the vapour of the osmic acid to act on the fat, as it acts more strongly than the solution.

(*f*) Wash in water and examine in glycerin.

(*g*) The section may be counter-stained by hæmatoxylin or safranin to demonstrate the nuclei.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1898, XXVI., p. 601).—

(*a*) Fix in Unna's solution for twenty-four hours in an incubator at 37°C.

(*b*) Wash, harden in alcohol, and imbed in celloidin.

(*c*) Stain the sections for four hours in the following solution:

Alum	1 part.
Osmic acid	1 „
Water	100 parts.

(*d*) Wash in water and examine in glycerin.

III. *After Marchi* (quoted from Joseph and Loewenbach's *Derm.-Hist. Technique*, 1900, p. 94).—

(*a*) Fix for two days in Müller's fluid in an incubator at 37°C.

(*b*) Stain the tissue in bulk for the same time in:

Müller's fluid	2 parts.
Osmic acid, 1 per cent.	1 part.

(*c*) Wash in water.

(*d*) Harden in alcohol, imbed and cut in celloidin.

(*e*) Alcohol, xylol, Canada balsam.

Sudan III. *After Daddi* (*Archiv. Ital. Biol.*, XXVI., 1896, p. 143; *Lee*, p. 437).—

(*a*) Stain sections in a concentrated alcoholic solution of Sudan III. from five to ten minutes.

(*b*) Differentiate for the same time in alcohol.

(*c*) Dry with blotting-paper and examine in glycerin.

The small fat-globules are stained yellow, and the large ones orange.

Cyanin or Chinolin Blue. *After Unna* (*Histo-Pathology*, Walker's Trans., p. 611).—

(*a*) Stain the sections slowly overnight in a 1 to 2 per cent. spirituous solution of cyanin.

(*b*) Differentiate in a 1 per cent. aqueous solution of soap.

(*c*) Examine in levulose.

The fat is stained an intense blue.

Alkannin: *Extract of Alkanna Root* (*after Unna*).—"Fill a small flask with pieces of alkanna root, and fill it up to the neck with diluted spirit. A piece of wool is then pushed in which acts as a filter, and on it a piece of silk paper is placed. The sections are placed on this paper to preserve them from the fibres of the wool. The flask is then filled full with diluted spirit, corked, and placed upside down overnight. The deeply stained sections are then freed from free fat and precipitates, by a 1 per cent. aqueous solution of soap; they are then treated with chlorine water and mounted in levulose." The fat is stained rose red.

A simpler method than those described is to cut the sections, without hardening, by a freezing microtome, to stain them by osmic acid or Sudan III., and to wash and examine them in glycerin.

The Origin of Fat in the Skin.

The origin of the fat in the skin and the subcutaneous tissue has been much disputed, and the various possibilities have all been more or less supported; of these only four need be referred to—namely:

1. That the skin-fat is a product of degeneration of cell-protoplasm.

2. That it is a product of secretion of the cell-protoplasm.

3. That the subcutaneous fat and that which occurs in the lymphatics of the skin are derived from the coil-glands.

4. That the epithelial fat comes from the sebaceous glands.

It is generally conceded that the *fat of the sebaceous*

glands is a product of degeneration of the sebaceous cells. Its function is simply that of a lubricant for the hair. It is unable to permeate the epidermis of the funnel of the hair-follicle along which it passes, since the funnel is lined by a layer of stratum corneum, continuous with that on the surface of the skin, and since the cells of this horny layer are themselves more or less filled with fat, which, like the sebaceous fat, is a product of degeneration of the cells.

But another explanation is necessary to explain the formation of the *subcutaneous fat* and that of the rest of the skin. From the fact that the subcutaneous fat-cells are not dead, but rather highly specialised structures, it is improbable that the fat which they contain is a product of degeneration. Of the various theories which have been put forward regarding the origin of the subcutaneous fat, the most likely one is that it is derived from the coil-glands. A large number of observers have testified to the presence of fat in the sweat-glands. Krause in 1844 proved that fat was secreted by the sweat-glands of the palms of the hands and the soles of the feet; and Meissner and Kölliker corroborated this observation. Henle detected fat-droplets in the lumen of the coil-gland and fat-granules in the epithelium, and he considered that altered innervation was capable of causing the gland to excrete a watery fluid instead of fat. Unna[1] strongly advocates this theory, and cites the following simple experimental proof of the presence of fat in the coil-glands of the palmar aspects of the fingers:

Thoroughly wash the fingers with soap, and then rub them with ether, to remove the fat from the surface. After ten minutes, press down the finger-tip on a clean glass slide so as to make an impression of the lines on the finger. Then expose this to the vapour from an open bottle containing 2 per cent. osmic acid for twenty-four hours. On examining the slide, rows of fine black dots will be seen on the slide; these are due to fat, and correspond to the sweat-pores.

He describes the formation of the subcutaneous fat from the coil-gland as follows:

In about the eighth month of fœtal life, when the coil-glands and subcutaneous fat develop, the fat-cells are found to be most numerous around the coil-glands, especially where these are largest and most deeply seated, as on the palms of the hands and the soles of the feet. Where the coils are situated in the pars reticularis of the corium they are not surrounded

[1] *Brit. Journ. of Derm.*, 1894, VI., p. 257, and *Monats. f. prakt. Derm.*, 1898, XXVI., p. 601.

by fat-cells, but from them columns of fat-cells (*columnae adiposae* of Warren) pass down to the fat-lobules. The lymph which bathes the coil is said by Unna to be loaded with fat. It passes as a rule into the small venules, and in so doing is filtered, and the fat is deposited. The latter accumulates in columns around the blood-vessels and in the subcutaneous tissue, and is taken up in the form of fine droplets by branching connective-tissue cells ; fat-cells are produced by the infiltration and coalescence of these droplets.

In short, the fat which is present in the lymphatic spaces of the corium, in the interepithelial lymphatics, and in the prickle-cells, is carried there from the coil-glands. The fat of the stratum corneum and sebaceous glands is the result of a fatty degeneration of the protoplasm of the cells.

Pathological Changes Invoving the Fat.

General Increase.—In obesity there is an enormous increase of the panniculus adiposus. The fat-lobules are not only increased in number, but also in size, owing to a more active production of fat.

Local Increase.—

1. At *puberty* there is frequently a decided increase in the surface lubricant of the skin. This is generally regarded as a seborrhœa oleosa, and is due to a hyperactivity of the sebaceous glands. In this condition oily beads make their appearance about the face, scalp, sternal region, groins, and axillae.

2. *Lipomata* are fatty tumours due to a localised accumulation of fat. Their mode of origin is disputed, but they are generally regarded as the result of a fatty infiltration of the connective-tissue cells. It has been asserted, on the one hand, that any of the connective-tissue cells are capable of being infiltrated with fat to form fat-cells ; and on the other that it is only a special type of cell which possesses this capacity.

A local stagnation of lymph is believed to be the initial cause, and it is thought that the fat is taken up from the stagnant lymph. As a clinical argument in favour of this view, Unna has pointed out the fact that lipomata readily arise in the seats of pressure where the flow of lymph is apt to be impeded.

A fatty degeneration not infrequently attacks nævi, and the so called lipomatous nævi result.

3. *Xanthoma.*—Under the heading of xanthomata are grouped a number of orange or yellow, plane or tuberous lesions of the skin which, though differing considerably in shape, size, and colour, have the common histological characteristic of a fatty infiltration of the connective-tissue cells and a deposition of free fat in the lymphatics of the corium. At the present time the literature on the subject gives evidence of the confusion which now exists both with regard to the clinical types of xanthoma and their histology; for while certain writers are inclined to regard the different forms of xanthoma simply as variations of one morbid process, others believe that several totally different pathological conditions are included under the one heading.

Xanthoma may occur in the eyelids in localised patches, scarcely, if at all, raised above the level of the skin (*Xanthoma planum*); or it may become more generalised and form multiple nodules or tumours, frequently situated about the elbows, knees, palms of the hands, and soles of the feet (*Xanthoma tuberosum multiplex*). It may occur in apparently healthy individuals or in association with disturbances of the liver and jaundice. Xanthomatous nodules are also frequently present in association with diabetes (*Xanthoma diabeticorum*). In their *histology* these lesions present the following characteristics:

As a result possibly of a chronic inflammatory process, a cellular hyperplasia occurs in the corium, consisting of oval and spindle-shaped connective-tissue cells and nuclei, and a moderate number of leucocytes. The fibrous elements between these cells become attenuated and tend to disappear. Some of these cells become swollen, and fat-granules appear in the meshes of their spongioplasm. By the rupture of these cells fat-granules become deposited in the lymphatic spaces of the corium. In sections of xanthoma, suitably fixed and stained, the fat-granules or droplets are chiefly found lying free in the lymphatic spaces, but they may also be detected in the various cellular elements of the corium.

Giant-Cells have from time to time been noted in the lesions. Radcliffe-Crocker[1] found that they were more common in xanthoma tuberosum multiplex than in xanthoma diabeticorum, and Norman Walker[2] failed to find

[1] *Brit. Journ. of Derm.*, 1892, IV., p. 256.
[2] *Ibid.*, 1897, IX., p. 461.

them in his case of xanthoma of the latter type. The fatty change in xanthoma is more in the nature of an infiltration than a degeneration, since the tissue is not destroyed by the presence of the fat, and the cells seem capable of regeneration. In long-standing cases of xanthoma the fatty infiltration tends to disappear and to be replaced by a connective-tissue hyperplasia, with the formation of new fibrous tissue.

Unna has described a case in which the xanthomatous masses were enclosed in hypertrophied fibrous tissue, and named it *fibro-xanthoma*; in it numerous giant-cells were detected. The same writer has carefully described the histology of xanthoma of the eyelids, which he considers to be different from that of the more generalised type of the disease, in that the fatty substance is arranged in cord-like masses lying parallel to the fibres of the orbicularis muscle. In these masses there are fatty clumps with nuclei which have been named *xanthoma cells*; but they are simply nuclei surrounded by free fat, and are not the result of the fatty degeneration of a connective-tissue cell.

Balzer [1] has described a type of xanthoma in which the elastic fibres are thickened, and some of them are broken down into irregular fragments (*Xanthoma elasticum*). It is doubtful whether these lesions, though chemically suggesting xanthoma, should be classed as such; and Darier [2] was unable to detect any of the specific characters of xanthoma in the tissue, and named the condition *pseudo-xanthome élastique*.

An apparent increase in the elastin was also observed by Payne [3] in a case of xanthoma diabeticorum, but he believed that the increase was merely relative to a destruction and diminution of the collagen.

Diminution of Fat.—

(*a*) *General.*—A general decrease in the panniculus adiposus occurs in the emaciation from wasting diseases, and in senile skin.

(*b*) *Local.*—A localised or regional decrease occurs in association with wasting of the limbs from interference with the trophic nerve-influences to the part by injury or degeneration. It also is an accompaniment of scar-leaving lesions, such as breaking-down gummata, lepromata, and the like.

[1] *Archiv. de Physiol.*, 1886, XVIII., p. 93.
[2] *Trans. of Third Internat. Dermat. Congr.*, London, 1896, p. 289.
[3] *Brit. Journ. of Derm.*, 1893, V., p. 333.

PATHOLOGICAL CHANGES IN THE FAT IN THE SKIN AND SUBCUTANEOUS TISSUE.

I. **Increase of Fat.—**

1. General . . . Obesity.
2. Local : (*a*) Lipomata.
   (*b*) Xanthomata.
   (*c*) Regional increase of fat at puberty.

II. **Diminution of Fat.—**

1. General . . . Emaciating diseases.
   Senile skin.
2. Local or regional . . . In wasting limbs from interference with a trophic nerve, breaking-down gummata, etc.

CHAPTER XXXII.

PIGMENT IN THE HEALTHY SKIN.

In white races very little pigment is present in the skin, except in the pigmented regions, such as the areolae of the nipples, axillae, scrotum, around the anus, and in the hairs. The colour of the skin is, as a rule, more dependent on the subcutaneous fat and the degree of vascularity than on pigment. Apart from the colour caused by the vascularity of the skin, the stratum corneum has a greyish or ground-glass tinge, while the Malpighian layer has a more yellowish colour. Pigment, except in the hairs, does not usually appear till after birth. It has been frequently asserted that the pigment does not appear in the negro-skin till a month after birth, but this is not invariably the case, and recently Thomson[1] has detected pigment-granules in the skin of a five-months negro fœtus.

The Situation of the Pigment-Granules in the Healthy Skin.

The pigment-granules in white races are situated chiefly in the epithelial cells of the basal layer of the epidermis. They are generally confined to the periphery of the cell, while the nucleus and the zone immediately around it are free from pigment. They may also occur in the interepithelial lymphatic spaces, where they form branching figures, sometimes surrounding a leucocyte and suggesting a pigmented cell with a nucleus. These figures have frequently been described as the branching pigment-cells of the epithelium. Pigment-granules are sometimes present in the deeper prickle-cells of the Malpighian layer, and more rarely in the fusiform connective-tissue cells of the papillary body.

In dark races the pigment extends up as far as the transitional layers of the epidermis, and is present in some of the connective-tissue cells of the superficial portions of the corium.

[1] *Journ. of Anat. and Phys.*, 1891, XXV., p. 282.

Nature of the Pigment. — The true pigment of the skin consists of a substance called *melanin*. A pathological increase of pigment may not only result from an increase of melanin, but may also be produced by the presence of blood-pigments in the skin, or the deposition of particles of soot, dust, or other extraneous substances, such as silver.

Melanin.—Melanin occurs in the form of more or less fine irregular granules, of a brownish or brownish black colour. It is never in the form of crystals. Chemically it contains no iron, or only a negligible quantity, which cannot, in the majority of cases, be detected by the tests for iron. It contains C.H.O and N. and S. in various proportions in different situations. It is soluble in ether, acids, weak alkalies, and hydrogen peroxide, and is bleached by chlorine.

Dressler's Analysis of Melanin.—

C=51·73, H=5, O=7, N=13·24. Ash 1·47.

The Blood-Pigments.—The presence of blood-pigments gives to the skin the various tints, from livid purple to greenish yellow, which are so familiar in connection with bruises and other extravasations of the blood in the skin. This coloration is directly due to products of the hæmoglobin. After blood has become extravasated and formed a clot in the tissue, numerous golden yellow to ruby-coloured amorphous granules, crystals, or rhombic plates become deposited in the centre of it, and are one source of the pigmentation. These granules or crystals consist of an iron-free substance known as *hæmatoidin*, which is identical with bilirubin, and gives the same play of colours with impure nitric acid (Gmelin's test); its formula is C_{16},H_{18},N_2,O_3.

At the edge of the clot another coloured product of hæmoglobin is present—namely:

Hæmatin.—This is in the form of coarse amorphous granules, brownish black in colour and containing much iron. It is formed from hæmoglobin by the oxidising action of the tissues. Its percentage-composition is estimated at C_{68}, H_{70}, N_8, Fe_2, O_{10} (Hoppe-Seyler).

Extraneous Pigments, such as particles of soot or dust, which may occur about the openings of the hair-follicles and sweat-ducts, are usually in the form of spicules or scales, instead of being granular, and are distinguished from melanin by not being bleached by chlorine and by being insoluble in weak alkalies.

Technique and Chemical Reactions of Pigment in the Skin.

The most important technical problems in connection with pigment in the skin are: (1) the distinguishing of true pigment or melanin from blood-pigments, and (2) the methods of depigmentation. The latter are frequently requisite in order to demonstrate the finer architecture of a deeply pigmented tissue.

I. Methods of differentiating Melanin from Hæmatogenous Pigments.—

1. *Morphology.*—Melanin granules are always amorphous. Hæmatoidin is frequently in the forms of plates or crystals. For the study of the morphology of pigment-granules the sections need not be stained; but as the melanin invariably presents some tinge of colour from yellow, through brown, to black, it may be a help to stain the sections with some dye, such as a weak solution of water-blue, which would give a contrast to the colour of the pigment.

2. *Chemical Tests.*—Melanin is an iron-free pigment; the hæmatin or hæmosiderin of blood-pigment contains much iron. This fact gives a reliable chemical means of distinguishing between melanin and ordinary hæmatogenous pigments. The ferrocyanide of potassium test for iron is the most generally employed in this connection.

After Stieda.—

(*a*) Stain the sections in lithium carmine for several hours.

(*b*) Wash in distilled water.

(*c*) Stain for four hours in a 2 per cent. aqueous solution of potassium ferrocyanide.

(*d*) Decolorise for twelve hours in acid alcohol (1 per cent. hydrochloric acid).

(*e*) Wash in water, dehydrate in alcohol.

(*f*) Xylol, Canada balsam.

Iron-containing pigment is stained blue; the colour of melanin is not affected; the rest of the section is stained yellowish pink, and the nuclei red.

After Perls (*Virchow's Archiv*, 1867, XXXIX., p. 42).—

(*a*) Stain for one hour in a watch-glass of lithium carmine, to which has been added a few drops of a 2 per cent. aqueous solution of potassium ferrocyanide.

(*b*) Differentiate for four hours in acid alcohol (1 per cent. hydrochloric acid).

(*c*) Wash in water.

(*d*) Alcohol, xylol, Canada balsam.

This method gives results similar to Stieda's, but is more rapid.

NOTE.—It is absolutely necessary to avoid using iron or other metallic instruments in the manipulation of the above tests, as with them the results will be vitiated.

Alum-Carmine Method.—

(*a*) Stain the sections for an hour in a 2 per cent. aqueous solution of potassium ferrocyanide.

(*b*) Differentiate in glycerin, to which has been added ½ per cent. of hydrochloric acid.

(*c*) Wash in water.

(*d*) Stain in alum-carmine for an hour or longer.

(*e*) Wash in water.

(*f*) Alcohol, xylol, Canada balsam.

The alum-carmine gives a more brilliant counter-stain than lithium carmine. Iron-holding pigment has a greenish tint.

Ammonium Sulphide Method.—

(*a*) Place the sections for ten minutes in a freshly prepared solution of ammonium sulphide till they are dark green or black in colour.

(*b*) Thoroughly wash them in water.

(*c*) Alcohol, xylol, Canada balsam.

Iron-containing pigment is stained greenish black in colour. Pigments containing silver and lead are also stained.

Differentiation by Staining.—

After Unna (*Monats. f. prakt. Derm.*, 1895, XXI., p. 1).—Unna is able to differentiate between melanin and hæmatogenous iron-holding pigment by certain colour-reactions with anilin dyes. He finds that basic dyes, such as carbol-fuchsin and safranin, stain the iron-holding pigment more vividly than they do melanin. He finds also that with polychrome methylene blue the hæmosiderin is not only stained a deeper blue than melanin, but resists decoloration with tannic acid longer after staining.

(*a*) Stain the sections for two minutes in polychrome methylene blue.

(*b*) Wash in water.

(*c*) Decolorise in concentrated tannic acid solution for two minutes.

(*d*) Wash in water.

(*e*) Alcohol, bergamot oil, Canada balsam.

Melanin is stained emerald green, and iron-holding pigment blackish blue.

II. **Methods for Depigmentation.**—The simplest method is to place the sections for twenty-four hours or longer in freshly prepared *peroxide of hydrogen.*

Chlorine Method, after Mayer (Lee's *Vade-Mecum*, 1900, p. 327).—

(*a*) Soak the sections for several hours in 70 per cent. alcohol to harden them slightly.

(*b*) Into a test-tube put a few granules of potassium chlorate. Add to this a few drops of hydrochloric acid, and when the green colour of the evolving chlorine appears, fill the tube a quarter full with 70 per cent. alcohol. Now put the sections into the tube, and they will be bleached in about a quarter of an hour.

Potassium Permanganate Method, after Alfieri (*Monitore Zool. Ital.*, 1897, VIII., p. 57).—

(*a*) Put the sections for twenty-four hours in a 1 to 2000 aqueous solution of potassium permanganate.

(*b*) Transfer them for a few hours to a 1 in 300 aqueous solution of oxalic acid, when they will be completely depigmented.

Origin of the Melanin in the Skin.—In spite of the profusion of the literature on the subject of the origin of melanin, the problem is still *sub judice.* A great deal of careful research has within late years been carried out on this subject, especially in cold-blooded animals such as the frog and other amphibians. The power of changing the colour of the skin according to the environment, which the chameleon possesses to a marked degree, suggested the possibility of solving the question of the origin of the pigment by studying the skin of various amphibians. In these animals peculiar pigment-carrying cells (chromatophores) have been from time to time described, and on the

assumption that these also must occur in the human skin one of the theories explaining the origin of the pigment has been based. Unfortunately no cells definitely corresponding to the chromatophores of the frog have been found in the human skin ; but because their presence would clear up this problem so easily, the "fixed idea" that they must be there seems to have arisen. Consequently different observers have seen in the branched or fusiform pigmented connective-tissue cells or the stellate pigment-figures between the epidermal cells the pigment-carriers which they sought for, while others have regarded the leucocytes as chromatophores. Briefly stated, the two leading views regarding the origin of melanin are: (1) that melanin is a further degeneration-product of hæmoglobin than hæmosiderin, and (2) that it is a separation- or secretion-product of the protoplasm of pigmented cells.

(*a*) **Melanin is a Degeneration-Product of Hæmoglobin.**—Schmidt,[1] who strongly supports this view, asserts that the coarse brown granules of hæmosiderin break up into fine blackish granules of melanin containing no iron, which are carried by chromatophores from the blood-vessel to the epithelium, and that the chromatophores are leucocytes. After obtaining the melanin from the red blood-cells, the leucocytes carry it to the interepithelial lymph-spaces; there they break down and deposit their granules, which are gradually absorbed by the epidermal cells.

Karg [2] and Kölliker [3] both support the view that melanin is derived from the hæmoglobin, but consider that it is built up from the blood by the connective-tissue cells. It has been stated that the connective-tissue cells in which the pigment collects are capable of amœboid movement. Ehrmann [4] maintains that the pigment-bearing cells are neither ordinary connective-tissue cells nor leucocytes, but peculiar structures derived from the mesoderm, which he calls *melanoblasts*.

One of the strongest arguments in favour of this theory is the fact that Karg has proved that the transplanting of a piece of white skin on to a negro is soon followed by a pigmentation of that piece of skin, and that if a piece of

[1] *Virchow's Archiv*, 1889, CXV., p. 397.
[2] *Archiv f. Anat. u. Physiol.*, 1888, p. 369.
[3] *Zeitschr. f. wissensch. Zoolog.*, 1887, XLV.
[4] *Vierteljahrsschr. f. Derm. u. Syph.*, 1886, XIII., p. 57.

negro-skin be grafted on to a white man the result is a rapid depigmentation of it.

(*b*) **Melanin is elaborated by the Cells, and is not derived from the Blood-Pigment.**—Delépine[1] considers that melanin is elaborated in certain epithelial cells like other products of glandular activity, and is not a derivative of hæmoglobin, and that an antecedent variety or derivative of melanin passes from the deep layers of the epithelium into the lymphatics. When a pigmented region such as the areola of the nipple is irritated it becomes more deeply pigmented, and melanin granules are found to have accumulated not only in the epithelial lymphatics, but also in the lymphatics of the corium, and if any obstruction occurs to them this may go on to a natural injection of the lymphatics with pigment. The action of the sun's rays in the same way is said to cause a pigmentation by stimulating the elaboration of melanin by the deep epidermal cells. In support of this view Jooss[2] cites the negative facts that melanin granules are rarely found in the blood, that pigmentation is not most marked near the blood-vessels, and that it is localised in certain regions, instead of being generally distributed, as it would be were it merely a hæmatogenous pigment deposited in the epithelial cells.

Pathological Anomalies of Pigmentation.

I. **Pigmentation due to Hæmatogenous Pigment.**—The deposition of hæmatoidin and hæmosiderin in the corium produces in the skin various depths of staining, from purplish to green. This may follow hæmorrhages, or result from chronic venous stagnation, or occur in association with vaso-motor disturbances, such as Raynaud's disease.

II. Disorders of Pigmentation connected with Melanin.

Hyperpigmentations or Melanoses.—An increased formation of melanin occurs in association with a number of diseases, and may result from a large variety of causes. Of these the following are the most important:

(*a*) *Melanosis from Exposure to Light-Rays.*—The exposure of the skin to strong sunlight causes melanosis, which may take the form of freckles or a more diffuse sunburn, and it is

[1] *Proc. of the Physiol. Soc.*, 1890, VI., p. 23.
[2] *Münch. med. Abhandl.*, I., *Ht.* XVI.

the primary cause of the dark complexions of the inhabitants of sunny climates. This pigmentation has been described as a provision of nature against the penetration and harmful action of the sun's rays. It is due to the actinic or chemical rays of the spectrum—namely, the violet, ultra-violet, and blue rays, and not to the red heat-rays. In it the melanin granules are increased in and between the cells of the epidermis, and pigmentation appears in regions where it is not generally present.

(*b*) *Melanosis from the Ingestion of Toxins.*—The increased pigmentation of the skin which occurs in arsenical poisoning is a familiar instance of a toxic melanosis. This chiefly affects the pigmented regions, but may also attack other situations on the body; it is frequently determined by the irritation and pressure of garters, corsets, and the like. The arsenic causes a mottled brownish discoloration in which there may be points of sepia-brown colour on an earthy pigmented base, or in which small unpigmented areas may occur in the midst of a deeply pigmented patch. It varies greatly in different cases. The pigment, in the form of small melanin granules, is present in and around the epithelial cells, extending to the most superficial scales of the epidermis, only a small quantity being found in the cells of the corium. It contains neither iron nor arsenic.

A satisfactory explanation of the increased pigmentation due to arsenic is still wanting.

Brooke and Leslie Roberts[1] give the following chemical characteristics for the pigment in arsenical poisoning. It is amorphous, brownish yellow in colour, and discharged by reducing agents. It is insoluble in absolute alcohol, but rapidly soluble in anilin-oil and clove-oil, and partially soluble in peroxide of hydrogen. As to whether the pigment contains iron their investigations did not definitely decide.

(*c*) *Melanosis in Association with Certain General and Cutaneous Diseases.*—Hyperpigmentation occurs in Addison's disease, and in it is most evident in the regions in which pigmentation is usually present, but is also found in other situations in the skin and in the mucous membranes. The melanin is increased in the basal layer, and is present in the epidermis as far as the transitional layers. It has also been found in the connective-tissue cells of the corium, in the leucocytes and around the blood-vessels.

[1] *Brit. Journ. of Derm.*, 1901, XIII., p. 121.

A mottled pigmentation not infrequently occurs in syphilis in unpigmented regions, such as the neck, producing the characteristic *café-au-lait* patches. The mottled appearance is the result of an absorption of pigment in patches in an already diffusely pigmented area.

Increased pigmentation is also found in association with pregnancy and uterine disorders, (*Chloasma uterinum*), diabetes, (*diabète bronzé*) and in cirrhosis and other diseased states of the liver. In these various conditions there is an increase of melanin in the epidermis and in the connective-tissue cells.

In the *pigmented nævi* there is a great increase of melanin in the deeper layers of the epidermis. The presence of the pigment seems to make the prickle-cells lose their fibrillated structure, and consequently produces a state of instability, in which they readily assume malignant characters.

Hyperpigmentation also occurs in association with multiple fibromata (v. Recklinghausen's disease). This has been explained by the French school as the result of a lesion of the nerve supplying the affected area.

Pigmentation may also follow a number of chronic dermatoses, such as lichen planus, eczema, and psoriasis.

III. Pigmentation of the Skin due to the Deposition of Metallic Substances or Extraneous Pigments.—The general slate-colour or bronzing of the skin which occurs from the ingestion of silver, and is known as "argyria," is caused by the actual deposition of fine particles of silver in the connective tissue.

It usually follows the taking of large doses of silver nitrate over a prolonged period for epilepsy. It is invariably extracellular. The pigment presents the following chemical reactions which distinguish it from melanin:

1. It is insoluble in weak acids or alkalies, and in peroxide of hydrogen.
2. Strong nitric acid dissolves it, but it is again precipitated by the addition of ammonium sulphide in the form of black granules.

The extraneous pigments, such as soot, particles of dust, and the like, have already been referred to.

IV. Atrophy or Decrease of Pigmentation.—Diminution in the normal pigmentation of the skin may occur as a hereditary condition in "albinism," or it may be congenital or acquired. The disease of the skin known as *vitiligo* is an example of

an acquired diminution of pigment. In it white areas occur surrounded by deeply pigmented patches. It begins as a hyperpigmentation in spots which coalesce to form polycyclical areas. In these the pigment becomes absorbed in the centre, leaving white patches.

In the depigmented areas the pigment is absent even from the hairs, while in the surrounding pigmented patches it is present in increased quantity in the epidermis, in the connective-tissue cells, around the blood-vessels, and about the hair-follicles.

The explanations which have been put forward to explain this curious anomaly of pigmentation are as yet purely hypothetical.

ANOMALIES OF PIGMENTATION.

I. **Hyperpigmentation.**—

1. *Blood-Pigment* (*Hæmatoidin and hæmosiderin*) occurs in hæmorrhages, venous stagnation, etc.
2. *Melanin* (*Melanosis*) may be the result of—
   - (*a*) Exposure of the skin to the actinic rays of light.
   - (*b*) Ingestion of toxins . . . Arsenic, etc.
   - (*c*) Certain general diseases—Addison's disease, Chloasma, Diabetes (*diabète bronzé*), and Syphilis (*café-au-lait* spots).
   - (*d*) Certain skin-affections:
     Chronic dermatoses . . . Lichen planus, Eczema, etc.
     Neurofibromata (v. Recklinghausen).
     Pigmented Nævi, Sarcomata.
3. *Extraneous Substances.*—
   - (*a*) Deposition of metallic substances in the skin . . . Argyria, etc.
   - (*b*) Other foreign substances . . . Soot, etc.

II. **Depigmentation or Atrophy of Pigment.**—

1. Hereditary . . . Albinism.
2. Acquired . . . Vitiligo.

CHAPTER XXXIII.

THE NAIL.

A COMPARATIVELY slight knowledge of the mode of development of the nail is a valuable aid in the understanding of its structure, as well as of a number of pathological processes which may affect it.

NOTE ON THE DEVELOPMENT OF THE NAILS.

Though the nail does not begin to form till about the fourth month of fœtal life, as early as the second month, in the skin of the dorsal aspect of the ungual phalanges, changes have been noted, in which it becomes shiny and more firmly attached to the underlying tissue; these changes are the precursors of the nail-formation. At the beginning of the fourth month a distinct differentiation takes place on the dorsum of the ungual phalanges by the formation of a horse-shoe-shaped groove curved backwards. The anterior ends of this groove are joined by a transverse ridge, in front of which there is a shallow groove. The area enclosed by the groove and the transverse ridge is known as the *nail-field.* Outside the groove a similarly shaped ridge forms the first indication of the *nail-wall.* A longitudinal section, including the curved end of the groove, shows that at the bend of the groove the prickle-cell layer of the surface dips downwards and backwards towards the proximal end of the phalanx to form what is called the *posterior nail-fold.* This structure corresponds to the hair-follicle, for in it the nail develops. The prickle-cell layer, after dipping down, spreads over the nail-field, forming the *nail-bed.* Beneath the prickle-cell layer of the nail-bed there is a dense fibrous layer connecting it with the underlying cartilaginous phalanx (Pl. XXXIII., Fig. 5).

The stratum corneum, according to some observers, passes over the nail-bed without dipping into the nail-fold; others believe that it ends at the nail-fold, and that the horny layer

over the nail-bed is derived from the epitrichium, and it has been named in consequence the eponychium (*see* p. 51); and it has also been suggested that both the epitrichium and a continuation of the stratum corneum are present over the nail-bed. In front of the anterior ridge of the nail-bed a number of swollen glistening cells may be noted. These are the "bladder cells" of Zander,[1] and are believed to be the remains of the epitrichium.

In the posterior nail-fold a crescent of large granular cells appears, and this forms the matrix from which the nail-plate grows. The nail-plate grows forwards horizontally over the prickle-cell layer of the nail-bed, being bound down at first by the overlying horny layer. Granules appear in the cells of the matrix, which give to the lunule of the nail its milky, opalescent character.

The blood-vessels of the nail-bed begin to form about the seventh month by the appearance of two lateral arteries, giving off two anastomosing loops, which pass transversely in the posterior nail-fold and in the anterior groove. From these loops a fine arterial plexus forms in the corium of the nail-bed, whose capillaries empty themselves into minute venous sinuses, and these in turn into lateral veins.

About the time when the circulation in the nail-bed is complete the nail has grown forward as far as the anterior ridge, and has ruptured the overlying horny layer. The nail has as yet no free edge, but is thinned out into a fine plate, which bends over the ridge and is adherent to it. By this time changes have taken place in the nail-bed by the formation of rows of papillary processes in the underlying corium. These rows are horseshoe-shaped, like the original groove, are six or seven in number, and have a concentric arrangement. Corresponding to these papillary ridges, the prickle-cell layer of the nail-bed forms rows of interpapillary processes. Before birth the horny anterior ridge breaks down, and the nail projects forward as a delicate plate with a free border.

From the matrix a single nail grows, which usually persists during life. At birth the vessels of the pulp of the finger begin to anastomose with the vessels of the nail-bed. Small venous capillaries form in the corium, and into these a few of the arteries pour their blood; but the greater number of them open into the venous sinuses. These sinuses are lined with an endothelium, and are similar to those of erectile tissue. The nail-bed thus forms a safety-valve to relieve any sudden increase in blood-pressure.

[1] *Archiv f. Anat. u. Physiol.*, 1886, p. 273.

General Description of the Nails.

The nails are inelastic, translucent, horny plates, situated on the dorsum of the distal phalanges of the fingers and toes. In shape they are generally oblong, the long axis being longitudinal on the fingers and transverse on the toes. They have a posterior border, which is slightly concave; two almost parallel lateral borders, and a convex "free edge." Their upper surface is convex transversely and to a less extent longitudinally.

For purposes of description it is customary to divide the nail into—

(*a*) A posterior part, which can only be seen when the posterior wall is removed, and which is known as the root;

(*b*) A middle portion, or body; and

(*c*) An anterior portion, or free edge.

On the body of the nail the whitish semilunar area occupying the posterior fifth is called the *lunule*. Its opalescence is due to the presence of the granules in the cells of the underlying matrix. The nails are bounded posteriorly and laterally by the *posterior and lateral nail-walls.*

From the posterior wall a thin crescentic membrane passes over the lunule for a short distance; this is the remains of the eponychium. The lateral walls are parallel, or slightly divergent, and have a distinctly rolled-over appearance. The nail-plate passes to a slight extent beneath the lateral walls, and to a far greater extent under the posterior wall, to form the root which lies in the nail-fold.

Minute Structure.—A description of the minute structure of the nail may be conveniently divided under the following headings:

1. The nail-fold.
2. The nail-matrix.
3. The nail-bed.
4. The nail-plate.

1. *Nail-Fold* (Pl. XXXIII., Fig. 2).—The nail-fold is split horizontally by the root of the nail into an upper portion which forms a roof to the root of the nail, and a lower portion corresponding to the nail-matrix. The various layers of the epidermis spread down from the surface and compose the roof; but the prickle-cell layer, instead of being wavy, is flattened and even. The stratum corneum of the roof is in contact with the upper surface of the nail-root, but is not

PLATE XXXIII.

IG. 1. TRANSVERSE SECTION OF A NAIL ABOUT THE MIDDLE OF THE NAIL-PLATE (SEMI-DIAGRAMMATIC).

a. Nail-plate.
b. Lateral wall.
c. Longitudinal ridges on the under surface of the nail-plate.
d. Longitudinal papillary ridges.

FIG. 2. LONGITUDINAL SECTION OF THE POSTERIOR PART OF THE NAIL AND THE NAIL-FOLD (SEMI-DIAGRAMMATIC).

a. Stratum corneum.
b. Stratum granulosum.
c. Stratum Malpighii.
d. Remains of the eponychium stretching over the lunule.
e. Fat-lobes.
f. Upper portion of the nail-fold forming a roof to the root of the nail.
g. End of the nail-fold.
h. Lower portion of the nail-fold forming the nail-matrix.
i. Layers of granular cells.
k. Nail-bed; no papillae beneath it.
l. Nail-plate.

FIG. 3. LONGITUDINAL SECTION OF THE ANTERIOR PORTION AND FREE BORDER OF THE NAIL (SEMI-DIAGRAMMATIC).

a. Nail-plate.
b. Stratum corneum and granular layer of the pulp passing up to come in contact with the under surface of the nail-plate.
c. End of the nail-bed.

FIG. 4. NAIL-CELLS. (× about 1000.)

Macerated from a piece of nail soaked for a week in potash solution.

a. Cells showing facets, seen from the surface.
b. Cells seen from the side.

FIG. 5. DEVELOPING NAIL FROM FINGER OF A HUMAN EMBRYO OF BETWEEN FOUR AND FIVE MONTHS.

The section shows a group of granular cells and the first indication of the nail-plate.

a. Posterior groove.
b. Eponychium.
c. Anterior groove.
d. Heaping up of the stratum corneum in front of the anterior groove, with a layer of bladder-cells of Zander near the surface.
e. Basal layer; no papillae under the eponychium.
f. Nail-fold.
g. Granular layer and commencing nail-plate.
h. Nail-matrix.
i. Nail-wall.
k. Nail-bed.
l. Ungual phalanx.
m. Dense corium.
n. Looser corium.

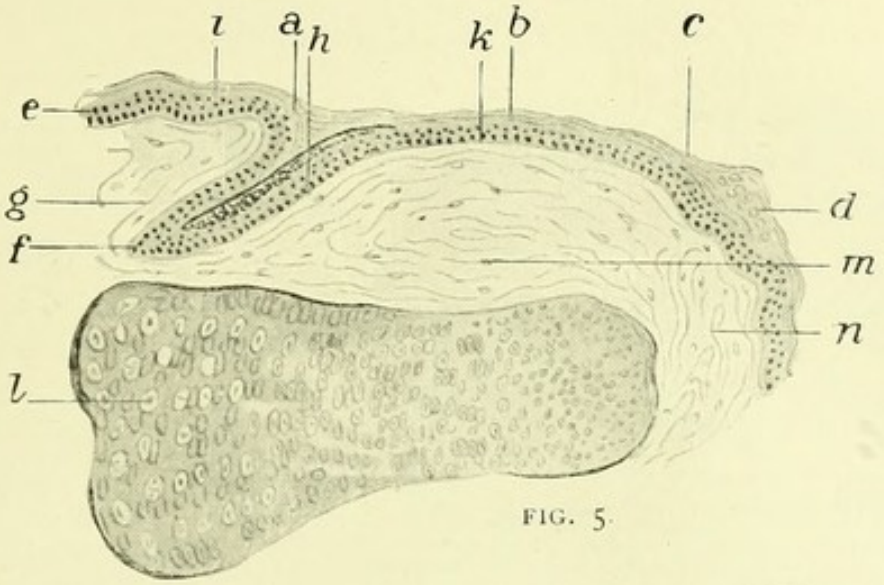

FIG. 5.

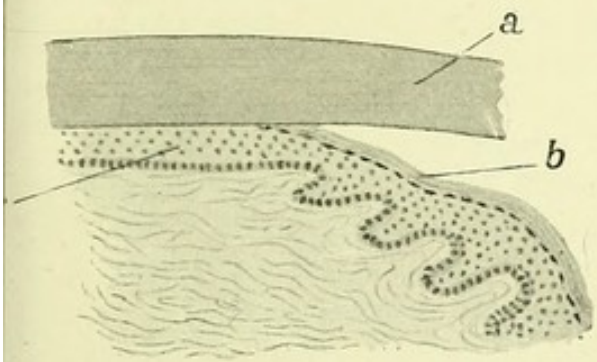

FIG. 3.

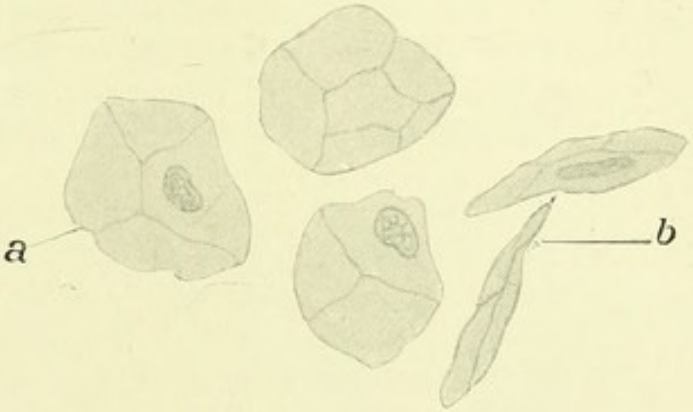

FIG. 4.

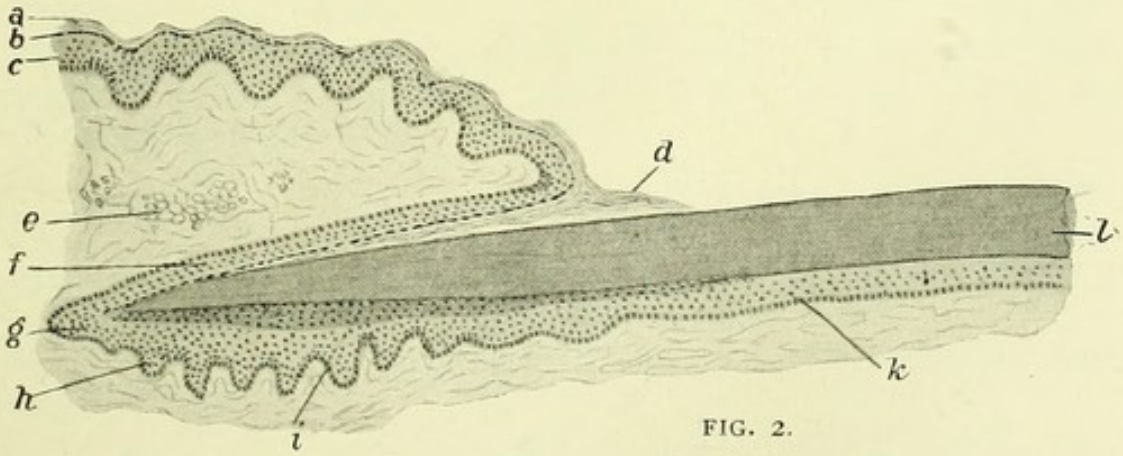

FIG. 2.

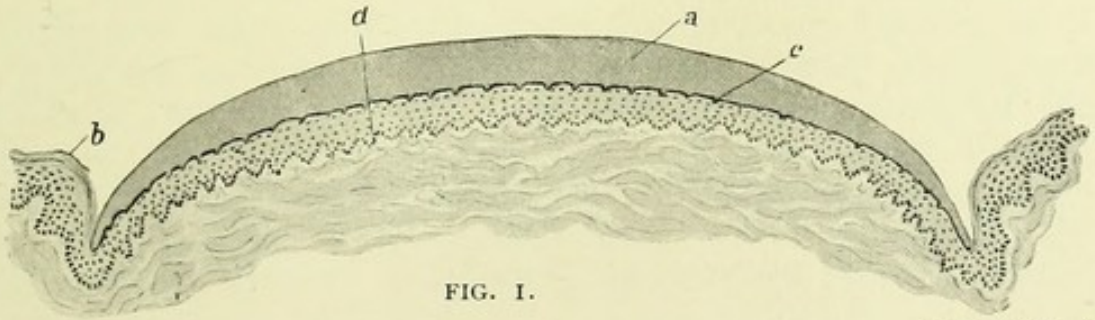

FIG. 1.

J. M. H. M., del.

in organic connection with it. The only function possessed by the upper portion of the nail-fold with regard to the growth of the nail is that of causing a certain amount of pressure to keep the nail-plate horizontal.

2. *Nail-Matrix.*—This important structure corresponds with the lower portion of the nail-fold, and extends from the posterior extremity of that structure as far forwards as the anterior margin of the lunule. It is composed of a prickle-cell layer, continuous behind with that of the roof and in front with that of the nail-bed. The prickle-cells composing this layer of the matrix are larger than those of the other situations mentioned. In longitudinal sections the lower surface of the layer is wavy, from the presence of interpapillary processes, which are most marked posteriorly. In the anterior part of the matrix, interpapillary ridges are also noticeable in transverse sections.

The matrix is composed of from three to ten layers of polygonal cells, situated on a basal layer of regular cylindrical cells. Above these there are several rows of flat cells, packed more closely together, with shrivelled nuclei, and containing fine granules. Above this layer the true nail-cells begin to form. The granules in the transitional layer beneath the nail are finer than keratohyalin granules generally are. Ranvier believes them to be of a different nature from keratohyalin, and named them *onychogène.* Recently Okamura[1] described them as keratin granules within the cells. It has also been suggested that the granular appearance is brought about by shrunken prickles seen "in relief."

The *lunule* is the "macroscopical expression of the nail-matrix." Its colour is not the result of a diminished blood-supply, but is due to the existence of these partially cornified cells, which appear, for some undetermined reason, to be more opaque than either the prickle-cells or the homogeneous cornified cells.

3. *Nail-Bed.*—The nail-bed extends forwards from the matrix to the free edge, and on it the nail-plate rests; but there is no organic connection between the two. It does not extend quite to the free edge of the nail, for the horny layer of the pulp of the finger passes upwards and comes into contact with the nail immediately behind the free edge, and limits the extent of the nail-bed; this fact can be demonstrated by pressing the pulp of the finger against any resistant body,

[1] *Archiv f. Derm. u. Syph.*, 1900, LII., p. 223.

when this line of junction will appear as a yellowish curved band behind the free edge. In longitudinal sections the prickle-cell layer presents an even under-surface, with a basal layer of cylindrical cells; but in transverse sections inter-papillary processes are present, showing that here, as well as in front of the matrix, the papillae are arranged in longitudinal ridges. Above the basal layer are two or three rows of polygonal cells, which become flatter superficially, and these cells are in contact with the nail-plate.

4. *The Nail-Plate.*—The nail itself is made up of flat cells or squames arranged in lamellae. These can only be detected near the matrix, for towards the free border the cells become so closely welded together that they form an almost homogeneous plate. The cells can, however, be separated by maceration with caustic potash, when they are found to be flat, cornified cells, in which the remains of the nucleus persists (Pl. XXXIII., Fig. 4). In this way they differ from ordinary horn-cells, in which the nuclei completely disappear. The shape of the lamellae is dependent on that of the matrix. The presence of lamellae gives rise to "the lines of stratification" (Unna) of the nail. In a longitudinal section of the nail the lamellae will be indicated by parallel lines of stratification directed forwards and slightly downwards. If the matrix be irregular in shape and curved slightly round at the posterior extremity, irregular curved lamellae and lines of stratification will result. New lamellae are always being added by the matrix from beneath, and so it comes about that the upper surface of the nail is that which has been produced by the posterior part of the matrix, while the lower surface develops from the anterior portion. The under surface of the nail-plate is uneven, owing to the presence of a number of fine longitudinal ridges; these ridges fit into corresponding furrows in the underlying prickle-cell layer of the nail-bed, and it is on their account that some difficulty is experienced in separating the two structures.

Towards the middle line the ridges are small, but they increase in size and become more irregular near the sides of the nail.

The type of cornification by which the nail-plate is produced is not fully understood; it differs from the cornification of the surface epidermis in that (1) neither keratohyalin nor eleidin occurs in the transitional layer of the matrix, and (2) in the production of a harder horny structure than the stratum corneum and one in which the nuclei or nuclear *débris* persist.

The Corium underlying the matrix and nail-bed has several peculiarities. In it the collagenous bundles are arranged in two sets, and with greater regularity than is elsewhere met with. The one set of bundles radiates vertically from the periosteum of the phalanx to the epidermis of the nail-bed, tightly binding down the latter structure; and the other set of bundles tends to have a horizontal direction. The elastic fibres are diminished beneath the nail-bed, but are present in greater number below the matrix. In the meshes of the fibrous network, blood-vessels, lymphatics, and a certain amount of fat are present. The papillary body underlying the nail-matrix and nail-bed has been carefully described by Hans v. Hebra.[1] By maceration in boiling water he was able to remove the nail and study the arrangement of the papillae. He found that the papillary layer under the matrix may be divided into three portions: a posterior, a somewhat broader middle, and an anterior region which corresponded roughly with the lunule. In the posterior portion there are about six rows of small isolated papillae. In the middle region there is a series of ridges, slightly curved at the sides, but in the centre parallel to the long axis of the nail. Rows of papillae are present on the edges of the ridges, giving the latter somewhat the appearance of cocks' combs. In the anterior third no papillae are present, and the ridges become gradually flattened towards the nail-bed. The papillary body of the nail-bed consists of about sixty ridges parallel to the longitudinal axis of the nail. In front of these ridges are the ordinary papillae of the skin of the pulp of the finger or toe (Pl. XXXIII., Fig. 1).

In the papillae and ridges the blood-capillaries of the vascular nail-matrix and nail-bed are distributed. Beneath, there is a rich sub-papillary plexus, on which large venous sinuses are present, which are lined with endothelium. Into these sinuses not only the capillaries of the papillary layer pour their contents, but the small arteries of the pulp may also open directly into them. They form a sort of erectile tissue, and act as a safety-valve to relieve sudden increases in arterial pressure. The mode of termination of the nerves in the cells of the matrix and nail-bed is not known, and no Meissner's corpuscles have been detected. The nerves appear to lose their medullary sheath in the corium and run vertically to the surface.

Growth of the Nail.—If left uncut, the nail will not grow indefinitely, but some distance beyond the finger the edge thins

[1] *Wiener Med. Jahrb.*, 1880, p. 59.

and desquamates, and so a definite length is preserved. This thin edge is wedge-shaped in longitudinal sections, and its acute angle is the same as that of the root.

In certain Oriental races, such as the Chinese, the nails being left uncut may grow more than two inches in length. The nail is as a rule kept pared, and in this way it has the same thickness from the free edge till the root begins to taper. The nail-matrix, unless the nail has been destroyed, only produces one nail. During life the nails are constantly growing. They grow faster on the fingers than on the toes, the rate having been estimated at ·08 mm. on the fingers and ·04 mm. on the toes in twenty-four hours (Krause); and on the fingers they require for their growth from the lunule to the free edge a hundred and eight to a hundred and sixty-one days (Berthold).[1] In summer they grow faster than they do in winter, and their growth is more rapid in children than in adults.

Technique in Connection with the Nail.

The Separation of the Cells composing the Nail-Plate.—The cellular elements of the nail may be dissociated by soaking parings of it for a few days in a 40 per cent. solution of caustic potash, or in concentrated sulphuric acid. The action of the alkali may be increased and the time shortened by heating the parings in the solution. In scleronychia—a condition in which the nail-substance is particularly hard—the separation of the cells takes several days longer than it does in healthy nails; while in the brittle, badly formed nails associated with psoriasis and eczema dissociation occupies a shorter time.

Examination of Sections of the Nail.—For the study of the nail and its relation to the surrounding parts, Heller (*Die Krankheiten der Nägel*, Berlin, 1900) recommends the following procedure:

An ungual phalanx is removed from a cadaver, and treated as follows:

1. It is fixed for a few days in Müller's fluid, and then thoroughly washed.
2. It is next decalcified from four to six days in a solution of nitric acid in water (1 in 3).
3. It is then washed, hardened in alcohol, and thoroughly imbedded in celloidin for eight to ten days.

[1] Duhring, *Cutan. Med.*, 1895, I., p. 52.

4. A celloidin-block is made in the following manner: The phalanx is fixed to a wooden block with a pin in the desired position for cutting; a paper collar is fitted round the block, and thick celloidin poured in to cover the tissue; the block is then transferred to an air-tight dish, and the celloidin is allowed to harden slowly; the block is then placed for at least a night in 80 per cent. alcohol.

By this means satisfactory longitudinal or transverse sections of the ungual phalanx may be obtained. Instead of imbedding in celloidin, the decalcified tissue may be imbedded in mucilage and cut with a freezing microtome, but by this method the sections are usually so friable that they are difficult to manipulate.

The Staining of Sections of the Nail.—The nail-substance may be readily stained by any of the dyes in use for horn-cells, such as safranin, gentian violet, picro-carmine, and hæmatoxylin.

Special Methods for Staining Sections of the Nail to demonstrate its Structure and the Presence of Micro-Organisms.—

I. *After Echeverría* (*Monats. f. prakt. Derm.*, 1895, XX., p. 78).—Remove the celloidin by alcohol-ether.

(*a*) Stain the sections for five minutes in a 1 per cent. aqueous solution of eosin.

(*b*) Wash thoroughly.

(*c*) Stain for one minute in anilin gentian violet.

(*d*) Wash in water, then decolorise in potassium iodide[1] and hydrogen peroxide solution.

(*e*) Dry with filter-paper and differentiate in picro-anilin solution[2] (1 per cent.).

(*f*) Clear in xylol and mount in Canada balsam.

By this method the cells are stained yellowish red, and the contour of the cells is well brought out, while micro-organisms are stained violet.

[1] Iodine . . . . . 1 part
Pot. iodide . . . . . 2 parts
Hydrogen peroxide . . . . . 300 „

[2] Anilin oil, to which sufficient picric acid has been added to give it a yellow colour.

II. *After the same Author.*—

(*a*) Stain the sections for ten minutes in an aqueous solution of gentian alum.[1]

(*b*) Wash in water.

(*c*) Decolorise in the iodine solution.

(*d*) Dry with a piece of filter-paper.

(*e*) Differentiate in picro-anilin solution.

The nail-substance is stained yellowish and the micro-organisms violet.

III. **Special Method for Staining the Medullated Nerves in the Nail-Bed.**—

After Heller (*Die Krankheiten der Nägel*, Berlin, 1900).—

(*a*) Stain the sections in 1 per cent. osmic acid for twenty-four hours in an incubator at 36°C.

(*b*) Wash, reduce in a photographic developer, and oxidise in a weak solution of permanganate of potash.

(*c*) Wash.

(*d*) Transfer to a 2 per cent. oxalic acid solution.

(*e*) Wash, dehydrate in alcohol.

(*f*) Bergamot oil, Canada balsam.

The nerves are stained deep black on a clear yellow background.

Pathological Changes in the Nails.

I. **Simple Hypertrophy (Onychauxis).**—Simple hypertrophy of the nail-substance is a rare condition. It is the result either of an over-activity or an increase in size of the nail-matrix. The nail-plate is enlarged and thickened, and, owing to a closer adhesion of its component cells, is harder than usual. Simple hypertrophy of the nail occurs in acromegaly and gigantism. Acceleration in the growth of the nail is not necessarily hypertrophy, for this may be caused by a narrowing of the posterior nail-fold with the production of a thinner nail.

II. **Hypertrophy with Deformity (Onychogryphosis).**—The ingrowing toe-nail, claw-nail, and ram's-horn-nail are all instances of hypertrophy with deformity. In them the nail-substance is peculiarly hard and opaque, and presents

[1] A 1 per cent. aqueous solution of gentian violet, with the addition of 1 per cent. alum.

a dirty yellowish grey colour, and the surface is generally uneven and traversed by longitudinal wavy and transverse ridges. The graphic names which have been applied to the various degrees of deformity sufficiently indicate their clinical appearances.

The pathology of these affections has been variously explained. Virchow[1] taught that they were due in the first instance to pressure or trauma causing a widening of the posterior nail-fold, and, in consequence, the growth of a thicker nail. At the same time, by a horny thickening of the nail-bed in front, a barrier is formed which interferes with the forward growth of the nail and lifts it up, and according to the amount of this horny accumulation at the front of the nail-bed the degree of deformity is determined.

The presence of dirt beneath the free edge of the nail is liable to cause such a horny accumulation, and occasionally a corn or wart in the same situation may have a like result. The barrier to the growth of the nail which is thus formed causes it to press laterally on the soft parts; in this way a state of weak resistance is set up, in which slight lacerations become readily inoculated with pyogenic organisms, and suppuration is apt to take place; the latter may be followed by œdema and even gangrene. The cells composing these diseased nails are peculiar, in that they have completely lost their nuclei, except in the centre of the nail, where the cells are softer.

III. **Atrophy.**—Atrophy of the nails, complete or partial, may be congenital or acquired.

1. *Congenital* absence (*anonychia*) of one or more nails is rare, and is usually found in connection with other maldevelopments.

2. *Acquired.*—The pathological conditions which may cause a partial atrophy or total loss of the nail are numerous. They depend on a more or less complete solution of the continuity between the nail-plate and the nail-matrix. As the nail-bed is not in organic union with the nail-plate, pathological changes in the former alone do not lead to the shedding of the nail.

The following are the chief causes of atrophy of the nail:

(*a*) *Traumata.*—Injuries to the nail by causing a rupture of the blood-vessels beneath the matrix and an effusion of blood into the nail-fold frequently result in the disintegration

[1] *Verhandl. der Würzb. Ges.*, 1885, p. 83.

of the matrix and a shedding of the nail. As a rule the matrix recovers and a new nail forms in the course of four or five months. Slighter injuries may cause an interference with or a temporary arrest in the growth of the nail, with the production of a thin friable nail.

(*b*) *Nervous Diseases.*—In association with cerebral paralysis and tabes dorsalis, and after the division or degeneration of peripheral nerves from the vaso-motor disturbance so occasioned, a bleeding into the posterior nail-fold may occur with shedding of the nails; it has also been suggested that the interference of the trophic nerve-impulses to the matrix may cause an atrophy independent of gross lesions in the nail-fold.

(*c*) *Blood-Stasis.*—In cyanotic conditions of the extremities due to cardiac lesions and other affections associated with a weak peripheral circulation, the venous stagnation is frequently accompanied by atrophic changes in the nails. In such cases the nails become grey, opaque, thin, and friable, and lose their lustre.

(*d*) *Pyogenic Infections* (*Purulent Perionychia*).—Pus-inoculation about the nail-fold, such as occurs in whitlows, and not infrequently in association with syphilis and leprosy, may readily affect the nail-matrix and cause an atrophy or loss of the nail.

(*e*) *Scar-Leaving Conditions.*—The occurrence of pustular syphilides, especially of breaking-down gummata about the nail-matrix, occasionally causes a complete destruction of the matrix, with subsequent scarring, and renders future growth of the nail impossible.

The above headings will serve to indicate the conditions in which atrophy is liable to occur.

IV. **Dystrophies.**—When the function of the nail-matrix is interfered with by any condition which is insufficient to cause its destruction, imperfect nail-formation takes place, and the nails become opaque, discoloured, brittle, and fissured. A wedge-shaped, soft, opaque mass frequently appears in the region of the lunule, in which, through imperfect cornification, the cells are swollen and moist. When these cells dry, a distinct depression or cupping is produced. Occasionally the individual papillae of the matrix are affected, and in place of a soft mass, whitish opaque spots of soft nail-substance

appear, which, when they dry, give to the surface of the nail the appearance of being punctured over with a pin. Lines and furrows may form across the nail from a temporary interference with the process of cornification during an acute general illness, and in recurrent attacks several of these may occur in one nail. Vertical ridges and furrows are also due to irregularities in the nail-production at the matrix. The white discolorations of the nails, which occur as white specks (*flores unguium*), or striae and patches (*leuconychia*) are due to the presence of air between the nail-cells, owing to a shrinkage of the soft, imperfectly cornified cells.

V. **Derangements of the Nails may occur in Association with a Large Number of Chronic Skin-Diseases.**—Of these, psoriasis, eczema, syphilis, and pityriasis rubra pilaris are most frequently associated with nail-affections. The nails show atrophic changes such as puncta, worm-eaten, white or brown discolorations, and ridges and furrows. Deformities of shape supervene, and the nail gets lifted up and possibly loosened from the nail-bed by an accumulation of horny material beneath its anterior edge. Secondary inoculation of pus-organisms may occur, and a perionychia be set up. There do not seem to be any definite groups of appearances which are constant enough to warrant the diagnosis of psoriasis, eczema or syphilis of the nails, without the presence of corroborative lesions elsewhere.

Parasitic Diseases of the Nails (*Onychomycosis*).

The nail and the nail-bed are not infrequently attacked by the fungi of ringworm and favus, and occasionally pediculi and the acari of scabies may cause disturbances in the nail by passing in below it, and there setting up a pustular dermatitis.

Virchow and Unna have described two types of affections of the nail resulting from favus—a common type in which the nail becomes yellow and opaque, and is raised up by a horny accumulation in front, and a rarer variety in which scutula form beneath the nail, and dead-looking areas appear in the overlying nail-substance, which finally disintegrates, leaving the nail-bed exposed.

Ringworm of the nails, like favus, presents no very definite characteristics. The affected nail becomes dirty brownish or black, is frequently ridged and friable, and occasionally is raised up and may be shed.

For the purpose of diagnosing either of the above parasitic affections a microscopical examination is essential. Scrapings of the affected nail should be heated for at least fifteen minutes in a 40 per cent. solution of caustic potash. This causes the nail-cells to become dissociated, and on examining the specimen the spores and mycelial threads can be detected. It is the large-spored variety of ringworm which usually attacks the nails, but in children it may be the microsporon.

Certain authorities—for example, Besnier and Doyon—consider that ringworm of the nail never occurs unless the nail is previously softened by being attacked by eczema or psoriasis.

TABLE OF PATHOLOGICAL CHANGES AFFECTING THE NAILS.

I. Hypertrophy.—

1. Simple hypertrophy (*Onychauxis*) . . . Acromegaly, gigantism, etc.
2. Hypertrophy with deformity (*Onychogryphosis*) . . . Ingrowing nail, claw-nail, ram's-horn-nail.

II. Atrophy and Absence of the Nails.—

1. Congenital absence (*Anonychia*).
2. Acquired atrophy . . . May occur in association with—
   - (*a*) Traumata.
   - (*b*) Nervous diseases.
   - (*c*) Blood-stasis.
   - (*d*) Pyogenic affections.
   - (*e*) Scar-leaving conditions.

III Dystrophies.

1. Opaque and discoloured nails.
2. White spots (*Flores unguium*) or patches (*Leuconychia*).
3. Nails with ridges and furrows.
4. Pitted nails.
5. Brittle and fissured nails.

   These may occur in association with—
   - (*a*) Chronic skin-affections implicating the nail-matrix and the nail-bed, such as Psoriasis and Eczema.
   - (*b*) Pyogenic affections affecting the same regions.
   - (*c*) Vesicular affections affecting the same regions.
   - (*d*) Disturbances of the general nutrition.
   - (*e*) Parasitic affections—*e.g.*, presence of the fungi of ringworm and favus (*Onychomycosis*) and the acari of scabies and pediculi.

CHAPTER XXXIV.

PARASITIC DISEASES OF THE SKIN.

General Introduction.—As our knowledge of dermatology becomes more exact the greater is the *rôle* which micro-organisms are found to play in its etiology. Within recent years a large number of skin-diseases which had previously been vaguely considered to be due to diathesis, idiopathy, and the like, have been definitely proved to be of parasitic origin. Still, our knowledge of the "flora dermatologica" is far from complete. Sabouraud has aptly compared it to an ancient map in which the large countries alone are mapped out, while all within the lines enclosing them is blank and unknown. At one time or another any micro-organism may become deposited in the skin, so that a complete knowledge of this subject would include a study of almost every known micro-organism; but fortunately, in the great majority of instances, the presence of these organisms in the skin is not harmful.

The skin furnishes two distinct lines of defence against the entrance of micro-organisms from without. The first and the more important of the two is the stratum corneum, which, by its closely-welded keratinised cells containing fat, forms an almost impermeable barrier to the invasion of harmful microbes; and the second of them is constituted by the inflammatory reaction which the presence of virulent micro-organisms invariably occasions in the skin, and which leads to their destruction.

The facility with which micro-organisms reach the deeper parts of the skin, and there set up various degrees of dermatitis, is influenced by several general considerations. The most important of these are the following:

(*a*) The healthy skin in different regions of the body presents varying degrees of resistance to the entrance of micro-organisms. This power of resistance is at its maximum where the skin is thick and where the sebaceous glands are

small and few in number, and at its minimum where the skin is thin and the sebaceous glands are large and numerous, and where moist folds occur in which micro-organisms readily collect and proliferate.

(*b*) The resistance of the skin seems to vary at different ages. It is feeble in infancy and childhood ; it increases up to puberty, when it again undergoes diminution on account of the rapid growth of the pilo-sebaceous follicles, which occurs at that age ; it increases again up to the end of middle life, and as a rule it diminishes in old age.

(*c*) In states of enfeebled health every organ in the body, the skin included, is in a state of weak resistance, and at such times micro-organisms not only more readily gain entrance, but are capable of causing a more profound disturbance than in health, as the inflammatory reaction which they set up is relatively weak.

(*d*) The resistance of the skin may be diminished locally by injuries, lacerations, and local inflammatory conditions, and the entrance of micro-organisms facilitated in the affected areas. But not only may micro-organisms reach the skin from without, but by circulating in the blood they may become deposited in the deeper layers of the skin, and there set up a deep-seated dermatitis, such as is produced by the bacilli of tuberculosis and leprosy.

The study of the micro-organisms of the skin is complicated by the fact that the skin, and especially the moist folds and unexposed regions, forms the habitat for a large number of micro-organisms, some of which are merely accidentally deposited there, while others are usual denizens, and, though under ordinary circumstances they lead a harmless existence, are capable of becoming pathogenic under altered conditions. For example, the most constant of all the denizens of the skin—the Staphylococcus epidermidis albus of Welch—though as a rule innocuous, may assume virulent properties which are indistinguishable from those of the Staphylococcus pyogenes albus. This increase in the virulence of previously harmless microbes may possibly occur in the skin, owing to some pathological change in it. On the other hand, the same micro-organism, according as it acts superficially or deeply in the skin, may produce very dissimilar clinical appearances. The Staphylococcus pyogenes aureus, for example, is responsible not only for a superficial folliculitis, but also for a deep-seated furuncle. Several factors are at work in causing this difference in the type of lesion which results from the action of the micro-organism, such as the state of the resistance of the skin, the

position of the micro-organism in the skin, and possibly its combined action with some other microbe (symbiosis).

Before a micro-organism can be regarded as specific for any disease, it is absolutely essential that it should fulfil all Koch's postulates—namely:

1. It should be invariably present in the diseased tissues.
2. It should be capable of reproducing the disease in a susceptible animal.
3. It should be recoverable from the tissues of the animal and capable of cultivation on artificial media.
4. It should be capable of reproducing the disease when inoculated on a fresh animal.

I specially refer to this as, recently, in connection with a number of skin-affections, micro-organisms have been minutely described which fulfil only the first of these postulates and part of the third; and these micro-organisms have been put forward as specific for the disease in which they were found—an assumption which is wholly unwarranted. There has also been of late years a tendency to ascribe specific characters to microbes detected in sections of skin-lesions; this is equally fallacious, since the recognition of new types of micro-organisms in sections alone, especially in the case of the smaller microbes, such as cocci and microbacilli, is practically impossible.

At the present time the subject of the parasitic diseases of the skin, and more especially those caused by bacteria, is in a state of chaos. This confusion is to a great extent the result of the endeavours on the part of several observers to refine, by attempting to establish specific characters in a large variety of micro-organisms, and on the part of others to simplify, by regarding many of those which have been described not as different varieties, but as the result of different degrees of virulence and of the polymorphism of a few micro-organisms.

Classification of the Skin-Fungi.—The more common micro-organisms which occur in the skin will be discussed under the following classification, after Flügge (*Die Mikro-Organismen*, Leipzig, 1886).

I. *Schizomycetes — Fission-Fungi — Bacteria* (*including Bacilli, Cocci, Spirilla*).

II. *Streptotricheae.*

III. *Blastomycetes or Yeasts.*

IV. *Hyphomycetes or Moulds.*

NOTE.—It has been considered advisable to describe the schizomycetes of the skin under the diseases with which they are associated, and to arrange the latter in alphabetical order, and before describing the pathogenetic organisms to refer briefly to some of those which lead a harmless existence on the skin, but are capable of assuming virulent properties.

CHAPTER XXXV.

SPECIAL TECHNIQUE FOR THE DEMONSTRATION OF THE SKIN-PARASITES.

ONLY the special methods of bacteriological technique bearing on dermatology need be referred to here. The general bacteriological technique, such as the making of nutrient media, their standardisation, the methods of inoculation, the making of ordinary cover-slip preparations and impression-preparations, and the like, can best be acquired under the supervision of an expert teacher in a bacteriological laboratory.

Media.—The following media are generally employed in growing the parasites of the skin: Bouillon, glucose-bouillon (1 per cent. glucose), gelatin, glucose-gelatin, beer-wort gelatin, glycerin-agar, glucose-agar, beer-wort agar, potato.

The Microscopical Examination of Contents of Vesicles or Bullae for Micro-Organisms.—With a sterilised needle-loop transfer a drop of distilled water to a clean cover-slip; then mix gently with a drop of fluid from the vesicle or bulla. Allow it to dry in the air, but cover up the slide to prevent the dust being deposited upon it while it is drying. Fix by passing three times through the flame, and then stain.

The Microscopical Examination of Crusts, Scales, and Scrapings from the Skin.—Place a scale or piece of crust in a drop of acetic acid in the centre of a cleaned slide, and gently warm it over the flame. Hold the slide at one end with the finger and thumb of the left hand. Take another slide in the right hand, cross the slides, and triturate the moistened crust or scale till a fine pulp or *débris* results. Draw the slides apart, dry, and fix both films in the flame. Allow a drop of alcohol-ether to run over the slide to remove the acid and fat. Wash in water and stain.

The Technique for taking Cultures from Vesicles or Pustules in the Skin.—Before puncturing the vesicle or bulla it is

necessary to sterilise the skin. This may be done by gently washing the surface with soft soap and hot water, and then rubbing it over with 95 per cent. alcohol or with 1 in 1000 sublimate solution by means of a sterilised pledget of cotton-wool. The vesicle is then pierced with a sterilised tenotome, a platinum loop is inserted, and a tube inoculated. Gilchrist[1] employed this method in a large number of observations with satisfactory results. In the case of crusts the edge of the latter should be lifted up by a sterilised pair of forceps, and the platinum loop inserted beneath the crust. Sabouraud[2] advocates his pipette-method for growing cultures of streptococci. He employs sterile pipettes, containing 1 c.c. of ascitic fluid. Into these a drop of the contents of the vesicle is aspirated, and the tube inoculated at 37°C. Streptococci may be detected in the medium in about forty-eight hours. The inoculation may also be done by means of a sterile hypodermic syringe. After sterilising the surface, as already described, the syringe is pushed into the vesicle, a drop of the contents drawn in, and the latter expressed on to the medium.

The Staining of Films for Micro-Organisms.—There are two classes of stains or methods of staining micro-organisms—namely, *simple stains*, where the dye is poured on the film and the superfluity washed off in water; and *compound methods of staining*, such as the Gram-Weigert and Ziehl-Neelsen methods, in which the technique is more complicated.

I. **Simple Stains.**—The following are the simple stains and the time required by each in staining:

(*a*) Löffler's alkaline methylene blue, ten minutes (30 c.c. of a saturated alcoholic solution of methylene blue and 100 c.c. of a 1 in 10,000 solution of potash).

(*b*) Sahli's borax methylene blue, ten minutes (5 per cent. aqueous solution of borax, sixteen parts; concentrated aqueous solution of methylene blue, twenty parts; water, twenty-four parts.

(*c*) Carbol-fuchsin, two minutes.

(*d*) Anilin-water gentian violet, two minutes.

The stain is filtered, and sufficient is poured on to cover the slip. After the requisite time the slip is washed in water, the superfluous water removed by blotting-paper, and the drying completed above the flame.

[1] *Trans. American Derm. Assoc.*, 1900, p. 87.
[2] *Ann. de Derm. et de Syph.*, 1900, XI., p. 62.

II. **Compound Staining-Methods.**—Of these the most important is Gram's method. In it certain micro-organisms are decolorised by Gram's iodine solution, while others are unaffected by it (*iodfeste bacterien*). This compound method of staining micro-organisms is consequently of diagnostic value.

Gram's Method.—

(*a*) Stain from one to five minutes in anilin-water gentian violet mixture. Shake up 5 c.c. of anilin oil in 100 c.c. of distilled water, and filter. To 100 c.c. of this saturated anilin water in a test-tube add 10 c.c. of a saturated alcoholic solution of gentian violet. Prepare the anilin-water gentian violet solution freshly each time. Pour a few drops on the film. Instead of this the anilin water may be dropped on the slide, and a drop of the gentian violet solution added.

(*b*) Without washing off the stain, pour on freshly prepared iodine solution for two minutes (iodine, 1 ; pot. iodide, 2 ; water, 300).

(*c*) Dry with filter-paper, and differentiate in alcohol till the colour ceases to come off.

(*d*) Wash in water, dry, and mount in Canada balsam.

Weigert employs the following Modification: After the iodine solution has acted sufficiently, anilin oil is used to differentiate instead of alcohol. The anilin oil is discoloured by the gentian violet, and fresh anilin is poured on till no more colour comes off. The anilin is then removed by xylol, and the specimen mounted in Canada balsam.

By these methods the micro-organisms alone are stained and are coloured deep violet.

Bacteria which are not decolorised by Gram's Method.—The following bacteria which occur in the skin are not decolorised by Gram's method :

Staphylococcus pyogenes aureus, albus, and citreus.

Staphylococcus epidermidis albus.

Streptococcus pyogenes.

Microbacillus of Sabouraud, Unna, etc. Bacillus acnes (Gilchrist).

Bacilli anthracis, tuberculosis, leprae, diphtheriae.

Bacillus asciformis or flask-shaped bacillus.

Streptothrix actinomycosis and S. Madurae.

Blastomycetes.

Hyphomycetes of ringworm and favus.
Demme's bacillus of erythema nodosum.

Bacteria which are decolorised by Gram's Method.—
Bacterium septicæmiae hæmorrhagicum.
Bacillus mallei.
Gonococci.
Friedländer's pneumo-bacillus.
Bacillus of malignant œdema.
Streptobacillus of ulcus molle of Ducrey.
Bacillus of rhinoscleroma of v. Frisch and Paltauf.

Staining of Micro-Organisms in Sections of the Skin: by Simple Stains.—

(*a*) Stain the sections from ten to fifteen minutes in filtered Löffler's blue or Sahli's blue.
(*b*) Wash and dry with blotting-paper.
(*c*) Dehydrate and differentiate in alcohol.
(*d*) Xylol, Canada balsam.

The organisms are stained deep blue.
The tissues may be counter-stained by one or other of the following methods:

I. *After Unna* (*Monats. f. prakt. Derm.*, 1895, XXI., p. 533).—
(*a*) Polychrome methylene blue, five minutes.
(*b*) Wash in water.
(*c*) Orange-tannin mixture (Grübler),[1] one minute.
(*d*) Wash in water.
(*e*) Absolute alcohol, bergamot oil, Canada balsam.

By this method the micro-organisms are stained dark purple, the nuclei faintly blue, and the tissues yellowish. This is an extremely useful method, and stains a great variety of micro-organisms.

II. *After Semenowicz and Marzinowsky* (*Centralbl. f. Bact. u. Parasit.*, 1897, XXI., p. 874).—
(*a*) Carbol-fuchsin (1 part of a concentrated aqueous solution to 2 parts of water), five minutes.
(*b*) Wash in water.
(*c*) Löffler's blue, five minutes.
(*d*) Absolute alcohol, xylol, Canada balsam.

[1] Tannin, 33; gold orange, 2; distilled water, 65.

By this method the micro-organisms are stained blue, the nuclei blue, and the tissue red.

By Compound Stains.—

I. *After Gram* ("Colourless Method").—

(*a*) Sections in celloidin are transferred to alcohol before staining.

(*b*) Stain in anilin gentian violet solution for ten minutes.

(*c*) Fix in Gram's iodine solution.

(*d*) Transfer to alcohol, previously drying the section on a section-lifter; or, if it is a paraffin section, by pressing filter-paper on it. Decolorise it by means of the alcohol.

(*e*) Xylol, balsam.

The organisms alone are stained; the tissue is colourless.

If a counter-stain be desired, eosin (5 per cent. solution in water) may be employed. The procedure is the same as above from (*a*) to (*d*).

(*f*) Wash in water and stain in eosin for ten minutes.

(*g*) Absolute alcohol, xylol, balsam.

II. *After Unna* (*Monats. f. prakt. Derm.*, 1895, XXI., p. 543).—

(*a*) Stain for half an hour in picro-cochineal solution (Grübler):

Cochineal	3 parts.
Alum	5 „
Picric acid	5 „
Water	200 „
Boil down to	100 „

(*b*) Wash thoroughly in water on the slide.

(*c*) Anilin gentian violet solution, two minutes.

(*d*) Wash in water and dry with filter-paper.

(*e*) Fix in a solution of iodide of potassium and hydrogen peroxide in water (add to a watch-glass of water a crystal of KI and a few drops of H_2O_2), one minute.

(*f*) Dry with filter-paper.

(*g*) Anilin oil, five minutes.

(*h*) Xylol, Canada balsam.

The micro-organisms are stained blue, the tissue yellow, and the nuclei brownish red.

Staining of Micro-Organisms in the Stratum Corneum: Special Methods.—

I. *After Waelsch* (*Archiv f. Derm. u. Syph.*, 1895, XXXI., p. 49).—

(*a*) Stain sections for ten minutes in carmine, and wash.

(*b*) Stain for ten minutes in anilin gentian violet solution (anilin water, 2 parts, alcoholic solution of gentian violet, 1 part).

(*c*) Transfer for three minutes to a 5 per cent. aqueous solution of iodide of potassium and an equal volume of hydrogen peroxide.

(*d*) Differentiate from two to eight hours in acidulated anilin oil (three drops of hydrochloric acid to a watch-glass of anilin oil).

(*e*) Alcohol, xylol, Canada balsam.

The micro-organisms are stained blue and the nuclei red.

II. *After Boeck and Unna* (*Monats. f. prakt. Derm.*, 1891, XIII., p. 228).—

A. (*a*) Stain sections for five minutes in borax methylene blue (borax, 1 ; methylene blue, 1 ; water, 100).

(*b*) Wash in 1 per cent. acetic acid for ten seconds.

(*c*) Wash in water.

(*d*) Alcohol, bergamot oil, Canada balsam.

B. (*a*) Stain sections for five minutes in borax methylene blue.

(*b*) Transfer to a 5 per cent. aqueous solution of resorcin for two minutes.

(*c*) Then to a 1 per cent. oxalic acid solution for twenty seconds.

(*d*) Wash in water.

(*e*) Alcohol, bergamot oil, Canada balsam.

The micro-organisms are stained blue.

III. *After Unna* (*Monats. f. prakt. Derm.*, 1891, XIII., p. 310).—

A. (*a*) Stain sections in borax methylene blue for two minutes.

(*b*) Wash in water.

(*c*) Decolorise in glycerin-ether mixture for two minutes.

(*d*) Wash in water.

(*e*) Alcohol, xylol, Canada balsam.

Or—

B. (*a*) Stain in borax methylene blue for two minutes.

(*b*) Wash in water.

(*c*) Decolorise in orange spirit till the section has a greenish colour (1 per cent. alcoholic solution of orange).

(*d*) Alcohol, xylol, Canada balsam.

The micro-organisms are stained blue, and the tissues orange or greenish.

NOTE.—The above methods are also applicable for film-preparations of crusts and scales, a shorter time being necessary in the various stains than with sections.

CHAPTER XXXVI.

THE BACTERIA PRESENT IN THE HEALTHY STRATUM CORNEUM.

A LIST of the bacteria which may be present in the healthy stratum corneum, and which are, as a rule, harmless, owing to their occurring in small numbers or being in a state of diminished virulence, would of necessity be a large one. Only a few of the most common of these need be mentioned.[1]

Staphylococcus epidermidis albus (*Welch*[2]).—This microbe is a constant denizen of the epidermis. It closely resembles the Staphylococcus pyogenes albus, except that it liquefies gelatin and coagulates milk more slowly than the latter coccus. It is generally regarded as a less virulent stage of the Staphylococcus pyogenes albus.

Cedercreutz[3] has described a "**polymorphic coccus**" which he believes to assume different appearances according to its state of evolution. He asserts that it is the morococcus of Unna, the Staphylococcus cutis communis of Sabouraud, and the Staphylococcus epidermidis albus of Welch. He maintains that this organism in different states of evolution has been variously described by Demme (1886), Claessen (1893), Bulloch (1895), Whippam (1896), Class (1899), Berholm (1900), and Whitfield (1900). This observation of Cedercreutz, if it be corroborated, will go far to simplify the subject of the bacteriology of the skin.

The variations in this polymorphic coccus may be determined by varying the media of cultivation and passing it through different animals. On ordinary agar "all tints from milk-white to a golden-yellow, and on gelatin a canary-yellow,"

[1] For a more extended list *see* Galloway's article on "The Bacteria of the Skin," in Allbutt's *System of Medicine*, 1899, VIII., p. 900, to which the writer is indebted for much assistance in preparing this chapter.

[2] *Internat. Journ. of Med. Sci.*, 1891, CII., p. 441.

[3] *Investigations on a Polymorphic Coccus*, Paris, 1901.

may be obtained on cultivation. It prefers slightly acid or neutral media. Galloway,[1] in his review of Cedercreutz' monograph, notes the following characteristics :

"The best temperature for its growth is from 30° to 40°C. It grows slowly at the ordinary laboratory temperature, and ceases growth at a temperature beyond 60°C. The cultures develop slowly on gelatin at a temperature of 20° C. Gelatin is not liquefied under these conditions. Sown in gelatin, which is maintained in a liquid condition in the incubator, the coccus usually produces the effect that the medium does not solidify when it is brought to the ordinary laboratory temperature, even after a considerable lapse of time. The coccus does not coagulate milk, or does so only after some time. In broth under anaërobic conditions it does not produce visible growth, but maintains life for a long time in this medium. The coccus shows a considerable variation both in size and in magnitude, varying from distinct spheres to various flask-shaped elements. The diplococcus form is not infrequently assumed. The large variety of the organism developed under favourable conditions of growth appears to possess greater powers of resistance than the others. Examined in the suspended drop, no movement is observed except the ordinary Brownian movements. In preparations made from young cultures the organisms are not decolorised by Gram's method. The organism has very slight pathogenic effects upon guinea-pigs, mice, and rabbits. When inoculated into the hair-follicles of the human subject it produces folliculitis, which rapidly heals. In the pus of these lesions the cocci are usually surrounded by leucocytes, and under those circumstances are decolorised more or less quickly by Gram's method. The relations existing between this coccus and the staphylococcus aureus cannot yet be sharply defined. The morococcus of Unna (the Staphylococcus cutis communis of Sabouraud) is either this polymorphic coccus or is the result of an extraordinarily close symbiosis between this coccus and a small coccus producing white cultures (staphylococcus ?)."

Staphylococcus flavescens.—Obtained by Damman[2] from the toes, the scrotal region, and the prepuce. Forms yellowish colonies. Begins to liquefy gelatin in from three to six days.

Micrococcus flavescens subsidens.—Micrococci in irregular groups or short chains. Forms pale, creamy yellow colonies. Sinks in gelatin, but does not cause liquefaction.

[1] *Brit. Journ. of Derm.*, 1902, XIV., p. 315.
[2] *Brit. Med. Journ.*, 1892, II., p. 122.

Bacillus epidermidis capsulatus.—Obtained by Damman from the scrapings of the skin between the toes. Motile bacillus with rounded ends, occurring mostly in pairs. On gelatin it forms irregularly shaped bluish colonies, which emit a peculiar odour. Gas is formed deep down in stab-cultivations.

Bacillus fluorescens epidermidis.—Obtained by Damman from the tip of the finger after thoroughly washing with absolute alcohol. It is a motile bacillus usually arranged end to end in pairs. It liquefies gelatin rapidly, with fluorescence, the liquefied gelatin showing an upper green layer and a lower colourless one. It resembles the Bacillus fluorescens liquefaciens of Flügge and the Bacillus fluorescens liquefaciens minutissimus of Unna.

Bacillus gelatinosus.—Obtained from the skin between the toes (Damman). The bacilli are fine, slender, and motile, with a distinct capsule. They are often beaded like tubercle bacilli. Gelatin cultivations produce a colourless, transparent, gelatinous material, which surrounds and is incorporated with the purely chromogenic organism, giving it a coarsely granular or mottled appearance. Plate colonies are rusty brown in colour on microscopical examination, and yellowish to the naked eye.

Bacillus epidermidis (Bordoni-Uffreduzzi[1]). — Obtained from epidermic scales. Bacilli 2·8 μ to 6·3 μ in length, and 0·3 μ in breadth. Do not liquefy gelatin.

Bacterium graveolens (Bordoni-Uffreduzzi).—Short bacilli. Liquefy gelatin, and give off a fœtid odour like that from the feet. Isolated from between the toes.

Bacillus aureus.—Slightly bent bacilli, 1·5 to 4 $\mu \times 0{\cdot}5$ μ, arranged parallel in pairs or in groups. They give on gelatin irregular white to yellowish colonies, which become golden yellow and do not liquefy.

Tommasoli[2] has described ten cocci, six bacilli, and six yeasts, which may occur in any scale from the epidermis. These are the following:

[1] *Fortschr. der Med.*, 1886, IV., p. 157.
[2] *Monats. f. prakt. Derm.*, 1889, IX., p. 49.

Cocci.—

1. Micrococcus cereus flavus.
2. „ flavus tardigradus.
3. „ versicolor.
4. „ cereus albus.
5. Diplococcus albicans tardissimus.
6. „ „ tardus.
7. Micrococcus flavus liquefaciens.
8. Diplococcus subflavus.
9. „ citreus liquefaciens.
10. „ liquefaciens tardus.

Bacilli.—

1. Bacillus minutissimus.
2. „ aureus.
3. „ spiniferus.
4. „ albicans pateriformis.
5. „ ovatus minutissimus.
6. Asco-bacillus citreus.

Yeasts.—

1. Saccharomyces rosaceus.
2. „ albus.
3. „ flavus.
4. „ albus villosus.
5. „ reticulosus.
6. „ multiformis.

CHAPTER XXXVII.

SCHIZOMYCETES.

THE BACTERIA ASSOCIATED WITH VARIOUS DISEASES OF THE SKIN, THE LATTER ARRANGED ALPHABETICALLY.

Acne vulgaris.—The formation of the acne pustule is always preceded by the plugging of the pilo-sebaceous follicle with a comedo.

I. In the **comedo** the following bacteria have been described:

(*a*) *Microbacilli of Sabouraud and Unna*,[1] *or B. acnes of Gilchrist.*—

Gilchrist[2] gives the following description of the *B. acnes*: It grows slowly on glycerin-agar, the colony at first being creamy white, and later turning pinkish. It grows on glucose-agar, bouillon, and blood-serum, but not on milk. It does not decolorise with Gram's stain. It is motile and has branches, but no capsule. It is pathogenic to mice and guinea-pigs. For a further description of this microbe *see* p. 351. This micro-organism was stated by Sabouraud[3] to be the cause of the comedo, and Unna asserts that it not only causes the comedo, but is also responsible for suppuration. Gilchrist agreed with Sabouraud and disputed Lomry's[4] assertion that it was a variety of the *Bacillus coli communis*.

(*b*) *Flask-Shaped Bacilli.*—Situated about the "head" and "mantle" of the comedo (*see* p. 344).

(*c*) *Diplococci.*—In the same situation as the flask-shaped bacilli.

[1] *Histo-Pathology* (Walker's Trans.), 1896, p. 361.
[2] *Trans. American Derm. Assoc.*, 1900, p. 87.
[3] *Maladies du Cuir Chevelu*, Paris, 1902.
[4] *Derm. Zeitschr.*, 1896, III., p. 446.

PLATE XXXIV.

A Few of the more Common Micro-Organisms which occur in the Skin. (× about 1000.)

Fig. 1. Staphylococcus Pyogenes Aureus.

Drawn from a film-preparation of a culture obtained from a pustule.

Fig. 2. Flask-Shaped Bacilli.

Drawn from a preparation from Pityriasis of the scalp.

Fig. 3. Staphylococcus Epidermidis Albus (Morococcus).

Cocci arranged in pairs. Drawn from a section of eczema. The cocci were present in the stratum corneum and in the vesicles.

Fig. 4. Streptococcus Pyogenes.

Drawn from a film-preparation of a culture from a vesicle of Impetigo contagiosa.

Fig. 5. Microbacilli.

Drawn from a preparation made from an oily plug expressed from the scalp in Seborrhœa oleosa.

Fig. 6. Microsporon Minutissimum of Erythrasma.

Shows mycelial threads branching dichotomously, and consisting of irregularly segmented filaments like bacilli or cocci, and spores in dense clusters. (Drawn from an excellent specimen kindly lent by Dr. Colcott Fox.)

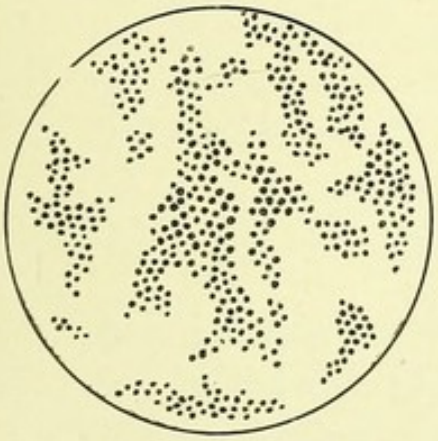

FIG 1.

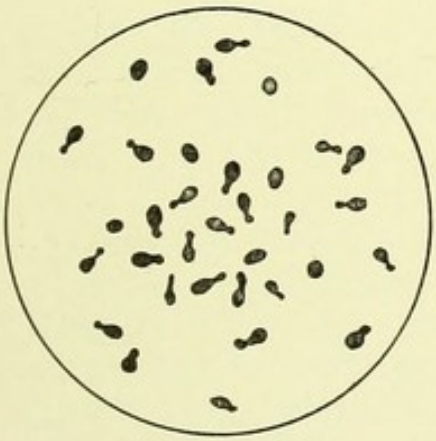

FIG. 2.

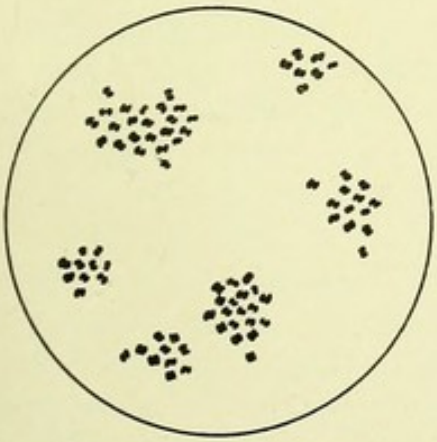

FIG. 3.

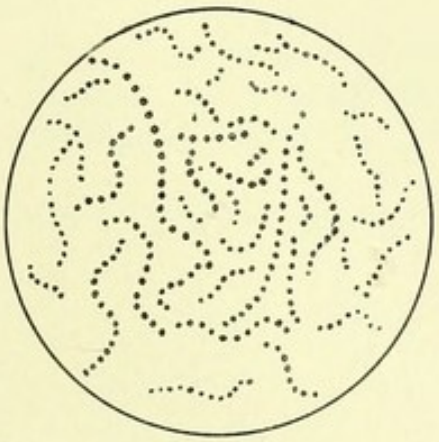

FIG. 4.

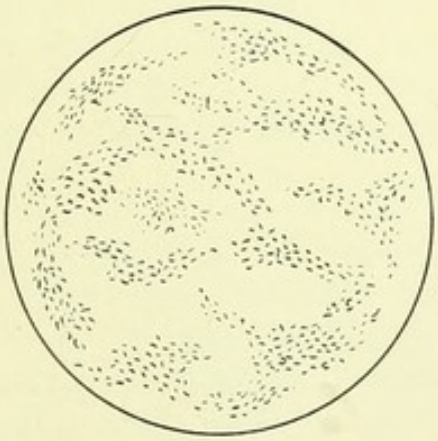

FIG. 5.

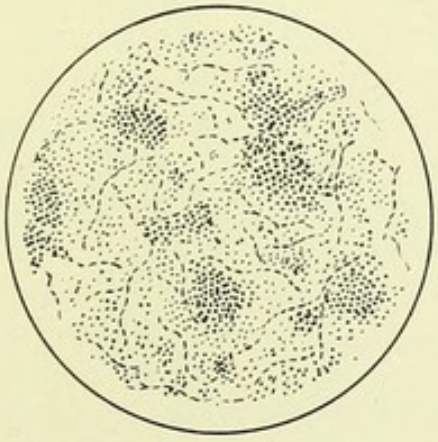

FIG. 6.

J. M. H. M., del.

(*d*) Small *cocci* which do not liquefy gelatin.

(*e*) Large *cocci* which liquefy gelatin.

(*f*) *Micrococci.*—Arranged as staphylococci, which in conditions of increased virulence may assume the characters of *S. pyogenes albus* and *aureus* (*S. epidermidis albus*).

II. In the **Acne Pustule** *Staphylococci pyogenes albus* and *aureus* and various *torulae* occur.

Acne necrotica seu varioliformis.—

(*a*) *Microbacilli* (Sabouraud).

(*b*) *Staphylococcus pyogenes aureus.*

The microbacilli, according to Sabouraud,[1] are only present in the initial stage of acne necrotica, and disappear when the lesions are fully evolved. The peculiar necrotic pustule he believes to be due to the symbiosis of these two micro-organisms. The staphylococci exist singly, in pairs, or in "mulberry" masses, and vary in diameter from ·5 μ up to 1·5 μ.

Alopecia areata.—The possibility of at least one type of alopecia areata being parasitic in origin has recently been strongly advocated—namely, the type, or possibly stage, in which the lesions appear at first as small pinkish patches, dotted over with seborrhoic plugs in the mouths of the follicles, and frequently associated with Pityriasis capitis.

Sabouraud [2] regards this type as an acute localised seborrhoic dermatitis of the scalp. He has isolated from one case fifteen species of micro-organisms, one of which, the *microbacillus*, he considers to be specific. It will be noted that this observer believes the same micro-organism to be specific for acne, seborrhoic dermatitis, and the "patchy type" of alopecia areata. One of the most constantly occurring micro-organisms in the plugs in alopecia areata is the *S. cutis communis*, or *S. epidermidis albus.* Walker has found it in seventeen cases. Sabouraud regards its occurrence as purely accidental, while Pawloff, of St. Petersburg, claims to have produced bald patches by inoculating it on rabbits. Hypodermic inoculations with cultures of the flask-shaped bacilli have also been said to have produced diffuse alopecia in a guinea-pig.

[1] *Ann. de Derm. et de Syph.*, 1889, X., p. 841.
[2] *Ibid.*, 1896, VII., p. 255.

Anthrax (**Malignant Pustule**), due to the Bacillus anthracis (*see* text-books on bacteriology).

Carbuncle, due to the micro-organisms of suppuration :

Staphylococcus pyogenes aureus.
" " *albus.*
" " *citreus.*
Streptococcus pyogenes (*see* text-books on bacteriology).

Chancroid (**Ulcus molle**).—Ducrey[1] has described a streptobacillus which he believes to be specific of chancroid.

Ducrey's Streptobacillus.—It is a short bacillus, 1·48 μ long by ·5 μ broad, with rounded ends. It is generally arranged in chains of varying length, and is situated in the lymph-spaces between the leucocytes, but not within them. It stains readily by fuchsin, methyl violet, and methylene blue, but is decolorised by Gram's method. It grows on a mixture of human blood-serum and agar (Petersen[2]) and on blood-agar (Bezançon, Griffon, Le Sourd[3]). The blood-agar is a mixture in sterilised tubes of one part of rabbit's blood and two parts of agar, melted at 50°C. and allowed to cool. If it be incubated at 37°C. in twenty-four to forty-eight hours, round shining whitish colonies appear, varying from 1 to 2 mm. in diameter. Experimental inoculation of four cases by Bezançon gave positive results, and soft sores formed. Unna has also described a specific *streptobacillus* which closely resembles, if it is not identical with, Ducrey's bacillus. Other observers deny that this organism is the specific virus.

The usual cocci of suppuration are also present, and probably give rise to the adenitis which is so characteristic an accompaniment of the chancroid.

Dysidrosis or Cheiropompholyx.—Certain authorities consider that the vesicles and bullae of this affection are the result of a blocking of the sweat-orifices and a consequent retention of sweat, but the more generally accepted view is that they are inflammatory and possibly parasitic. In this connection Unna has described a *bacillus* situated chiefly about the roof of the vesicles and in the exudation. This bacillus flourishes readily in sweat, and occurs in large numbers in conditions of hyperidrosis.

[1] *Monats. f. prakt. Derm.*, 1889, IX., p. 387.
[2] *Centralbl. f. Bacteriol. u. Paras.*, 1893, XIII., p. 743.
[3] *Ann. de Derm. et de Syph.*, 1901, XII., p. 1.

Unna's Bacillus.[1]—It is about the size of the tubercle bacillus, being 2·5 μ to 3·5 μ in length, and 0·5 μ in breadth. It is arranged singly, in bundles of two or three, in groups of four or six, or in short threads.

Ecthyma is an old term applied to a severe type of deep-seated pustule which terminated in a superficial cicatrix. It is now believed to be the effect of the inoculation of the usual organisms of suppuration in badly nourished subjects. In infants a type of gangrenous dermatitis may exist which the French call *Ecthyma térébrant*; but it is more generally known as *Dermatitis gangrænosa infantum.* Various micro-organisms have been isolated from the lesions, such as streptococci, staphylococci, and the Bacillus cyaneus. Recently Veillon and Hallé [2] detected a peculiar bacillus from a case of disseminated gangrene in an infant.

Bacillus of Hallé and Veillon.—About the shape and size of the larger forms of the bacillus of diphtheria. Straight or slightly curved. Often grouped in pairs, arranged like a V or Y. Immobile and anaërobic. Does not grow on gelatin. Forms greyish white colonies on agar, which emit a sour smell. Inoculated in the skin of animals, it caused gangrenous abscesses. Same as the Bacillus ramosus of Veillon and Zuber.[3]

The association between this type of gangrene and varicella has been frequently noted, and its possible connection with tuberculosis is at present under consideration.

Eczema.—The problem of the nature and origin of eczema is one which is at present so much under discussion and the solution of which is so beset with difficulties that only a brief reference to it will be advisable here. Indeed, until the term "eczema" is more definitely defined the discussion of the subject is more or less futile, for certain writers are inclined wrongly to limit the term to a disease which in one stage at least in its course is a papulo-vesicular eruption tending to ooze and to form crusts; while others include under this heading not only dry forms of eczema, but also the various types of seborrhoic dermatitis.

There are two opposing views regarding the origin of eczema. These may be named the *amicrobic* and the *microbic* theories.

[1] *Histo-Pathology* (Walker's Trans.), 1896, p. 179.
[2] *Ann. de Derm. et de Syph.*, 1901, XII., p. 401.
[3] *Archiv. de Méd. Expér.*, 1898, X., p. 517.

1. *Amicrobic Theory.*—The supporters of this hypothesis believe that the vesicles of papulo-vesicular eczema are sterile at first, and that they only become secondarily invaded by pyogenic micro-organisms. They grant, however, that the latter play an important *rôle* in the evolution of the lesions. This belief is supported by Neisser, Jadassohn,[1] Sabouraud,[2] Veillon,[3] and others.

2. *Microbic Theory.*—According to this view, eczema is a local parasitic disease due to one or a number of micro-organisms. The idea that eczema was caused by a single specific microbe is now almost entirely abandoned. Its chief advocate was Unna,[4] who believed it to be due to a peculiar type of coccus which tended to be arranged in groups like mulberries, and which he called in consequence the "morococcus." This organism was found in large numbers in the skin in eczema. Lately Unna has given up this view, and the "morococcus" is now generally regarded as identical with the *S. epidermidis albus* (a less virulent form of *S. pyogenes albus*), and not as a peculiar type of coccus.

Those who uphold the parasitic theory consider rather that several of the micro-organisms which may be isolated from the skin in eczema are pathogenic. Certain observers distinguish a large variety of micro-organisms, while others try to simplify the subject by regarding many of these slightly different microbes simply as variations of the same micro-organism, exhibiting different degrees of virulence. They believe that as many of the characters of a micro-organism, such as its appearance on cultivation and its power of coagulating milk and liquefying gelatin, may be altered in a laboratory by growing it under different conditions of temperature and atmosphere, similar alterations may occur in it in the skin.

The following recent experiments and deductions of Bockhart,[5] Bender, and Gerlach[6] in this connection are at least suggestive, if not absolutely conclusive.

They inoculated on the human skin :

1. Pure cultures of virulent staphylococci (albus and aureus).

2. The filtrate from a bouillon culture of staphylococci.

[1] *Compt. Rend.*, XIII., Congr. Internat. de Méd., Paris, 1900, p. 20.
[2] *Ann. de Derm. et de Syph.*, 1899, X., p. 305.
[3] *Ibid.*, 1900, XI., p. 683.
[4] *Monats. f. prakt. Derm.*, 1899, XXIX., p. 106.
[5] *Ibid.*, 1901, XXXIII., p. 421.
[6] *Ibid.*, 1901, XXXIII., p. 149.

After the inoculation on the arm of a virulent culture of staphylococci, a simple pyodermia resulted, the living cocci and their poisonous constituents ("staphyloplasmin") having caused a pustulation by a process of chemotaxis. When, however, the filtrate from a bouillon culture, containing no cocci, but only an excretion-product of the cocci ("staphylotoxin") was inoculated, an eruption of ordinary papulo-vesicular eczema followed.

The staphylotoxin is said by these observers to cause a serotaxis (a negative chemotaxis in which the leucocytes are repelled and only the serum attracted), and so a vesicle instead of a pustule is produced. Bockhart describes eczema as "an infectious inflammation of the epidermis caused by staphylococci." He admits a predisposition, and observes that the sound follicles of a predisposed individual have numerous quiescent staphylococci about them. From some internal or external cause these cocci become active and excrete the staphylotoxin. The latter passes out of the follicle into the lymph-spaces of the epidermis in the neighbourhood, and there sets up a serotaxis, which results in the formation of a vesicle. The vesicle may be sterile at first, but gradually the staphylococci make their way in increasing numbers into it, a positive chemotaxis results by which leucocytes are attracted, and the contents of the vesicle become seroleucocytic. If the cocci are particularly virulent, their staphyloplasmin potently attracts the leucocytes, and the pustulation becomes marked. Whitfield[1] has recently isolated a coccus with white and yellow varieties, corresponding to the S. cereus albus and flavus, from the dry eczema of the face of children.

Unna[2] has described twenty-three different varieties of *cocci* in a case of eczema. These he separates into groups, according as in their mature state they are arranged singly (monads), as diplococci (dyads), or as tetrads or octads. Twelve of these are harmless, eleven are pathogenic, two having proved themselves capable of producing eczema when inoculated on the skin in man. These two he names "Neufang" and "Traubel-Paas" cocci, after the patients from whom they were first isolated.

1. *Neufang.*—Cocci ·5 μ to ·7 μ in diameter, with capsules. Grow best at 37°C. on faintly acid media. On acidulated agar they appear as greenish yellow colonies, and they liquefy gelatin completely in fourteen days.

[1] *Brit. Journ. of Derm.*, 1900, XII., p. 406.

[2] *Monats. f. prakt. Derm.*, 1900, XXXI., p. 65 (Moberg and Unna), and *Ibid.*, 1900, XXXI., p. 213.

2. *Traubel.*—Cocci, with capsule, ·5 to ·8 μ diads. Grow best about 37°C.

On acidulated agar they produce a yellowish chamois-coloured culture. They liquefy gelatin slowly, completely liquefying Koch's gelatin in about fifteen days.

Paas forms a variety of the above, which only grows a faintly chamois-tinted colony on acid agar, while in alkaline Koch's agar it gives a pure white colony.

Besides cocci, the *flask-shaped bacillus* is frequently present in cases of eczema. It invariably occurs in association with the Staphylococcus epidermidis albus, and it has been suggested that it is a degenerated involuted form of this staphylococcus or of some other coccus.

Flask-Shaped Bacillus (*B. Asciformis*).—*Balloon bacillus* (Hodara), *Bacille bouteille* (Sabouraud). It varies considerably in shape, but its most usual form is that of a gourd or flask with a large spherical portion surmounted by a small roundish process. It may, however, be ovoid, round, barrel-shaped, or thread-like with a clubbed extremity. In size it may reach a length of 5 μ or longer. It is occasionally arranged singly, but is usually in groups.

It is stained by the usual dyes, and is not decolorised by Gram's iodine solution.

It grows in ordinary media. Sabouraud recommends the following special medium for its growth :

"Must" of potato	200 grms.
Human urine	500 „
Acetic acid	q.s.
(to avoid precipitating urinary salts)	
Glycerin	40 grms.

In fluid media it forms a deposit like fine sand ; in solid media it forms small radiate colonies.

Erysipelas.—Due to the *Streptococcus erysipelatis* of Fehleisen (*see* text-books on bacteriology).

Erythema multiforme.—In the vesicular and bullous lesions of this disease various *cocci* have been detected, but these do not seem to have any etiological relation with the disease.

Erythema nodosum.—*Demme's bacillus*[1] and various *cocci* have been detected in the blood in erythema nodosum.

[1] *Fortschr. der Med.*, 1888, VI., p. 241.

Demme's Bacilli.—Short bacilli with rounded ends, 2·2 μ to 2·5 μ in length, and ·5 μ to ·7 μ in breadth. Stained by ordinary dyes, and were not decolorised by Gram's iodine solution. Inoculated on the skin of guinea-pigs or injected into the blood, they produced an eruption resembling erythema nodosum, which was followed by gangrene.

Frambœsia.—*See* Yaws, page 354.

Furunculosis.—Due to the ordinary pyogenic cocci. Other micro-organisms have been isolated, such as the Bacillus pyocyaneus.

Gangrene.—Several micro-organisms have been described in the various forms of gangrene.

(*a*) *Disseminated Gangrene of the Skin in Children.*—Veillon and Hallé have isolated a *bacillus* from the pus of an unopened abscess.

Veillon and Hallé's Bacillus.—Identical with the Bacillus ramosus of Veillon and Zuber (*see* p. 341).

(*b*) *Hospital Gangrene.*—A *bacillus* somewhat similar to, if not identical with, the above has been described in hospital gangrene by Matzenauer.[1]

Matzenauer's Bacillus.—Short bacillus, 3 μ to 5 μ long by ·3 μ to ·5 μ broad. Frequently arranged in groups, but generally in pairs. Presents a powdery appearance after two or three days in a sugar-agar stab-culture. No gaseous formation. Inoculation-experiments were inconclusive.

Matzenauer detected a similar bacillus in noma.

Other micro-organisms, such as *streptococci*, *staphylococci*, and *Bacillus pyocyaneus*, are generally present in gangrenous conditions.

Glanders.—Due to the *Bacillus mallei* (*see* text-books on bacteriology).

Impetigo.—The term "impetigo" is a loose one. Two conditions only should be included under it—namely, the impetigo of Bockhart[2] and the impetigo contagiosa of Tilbury Fox. The so-called simple impetigo which results from the inoculation of pyogenic micro-organisms on any

[1] *Compt. Rend.*, XIII., Congr. Internat., Paris, 1900, p. 734.
[2] *Monats. f. prakt. Derm.*, 1887, VI., p. 450.

abraded or weakly resistant portion of the skin is only a pus-inoculation or pyodermia, and is better to be classed as such.

(*a*) *Impetigo of Bockhart* is a follicular disease due to the inoculation of the pilo-sebaceous follicles with pyogenic cocci. It is asserted by Bockhart that the lesions are pustules from the first (*pustule d'emblée*).

(*b*) *Impetigo contagiosa of Tilbury Fox* is a type of impetigo in which the initial lesion is a small vesicle. Cultivations from these vesicles generally give staphylococci, but Sabouraud[1] has shown that if the inoculations be made on liquid media such as bouillon or ascitic fluid, pure cultures of the *Streptococcus pyogenus* may be obtained. These fluid media are particularly suitable for growing streptococci. He recommends the following procedure:

Partially fill a sterilised pipette with the medium, pierce an intact vesicle of impetigo with the pipette, and suck up some of the contents into it. The pipette is then incubated, and chains of pure streptococci may be detected in twenty-four hours. Griffon and Balzer[2] originated this view, and Gilchrist,[3] Leroux,[4] and others have corroborated it.

Herpes simplex.—The *Bacillus viridans* has been isolated from herpes labialis, and in cases occurring in association with pneumonia the pneumococcus has been found; but the causal connection between these micro-organisms and the herpes has not yet been established.

Leprosy is most probably due to the *Bacillus leprae* of Hansen.[5] It is found in enormous quantities in the granulomata of leprosy and in nearly all the tissues except the muscles, spinal cord, and joints. The bacilli are found also in the older lesions of macular and anæsthetic leprosy (Hansen and Looft). According to Hansen, the bacillus is 5 μ to 6 μ in length and 1 μ broad. It closely resembles the tubercle bacillus, but is less curved and more pointed at the ends than the latter. It stains by the same methods as the tubercle bacillus, and is not decolorised by Gram's method. Cultivation and inoculation experiments on animals have been

[1] *La Pratique Dermatologique*, 1901, II., p. 878.
[2] *Presse Méd.*, 1897.
[3] *Trans. American Derm. Soc.*, 1900, p. 89.
[4] *Ann. de Derm. et de Syph.*, 1892, IV., p. 290.
[5] *Norsk Magazin for Laegevidenskab*, IX., and *Archiv f. path. Anat.*, 1880, LXXIX., p. 32.

unsuccessful except in a few doubtful instances (Bordoni-Uffreduzzi,[1] Ducrey,[2] Campana[3]). Most authors consider that the majority of the bacilli which appear in stained sections are dead.

So closely does the lepra bacillus resemble that of tuberculosis that they have from time to time been regarded as identical. Spiegel[4] formulates the following points of distinction between them:

1. Lepra bacilli are very numerous in the skin; tubercle bacilli are scarce.

2. Lepra bacilli are frequently arranged in clumps or like bundles of cigarettes; tubercle bacilli are generally separate or occasionally form irregular clumps.

3. Lepra bacilli are straight and plump; tubercle bacilli are bent and more slender.

4. Lepra bacilli contain coarse granules; tubercle bacilli have fine granules.

It may also be added that tubercle bacilli are easily cultivated and are pathogenic in animals, while lepra bacilli are not.

For the arrangement of the bacilli in the skin *see* p. 197.

Methods of Staining Lepra Bacilli and Tubercle Bacilli in Sections.—

I. *After Ziehl-Neelsen (modified).—*

(*a*) Stain sections for twenty-four hours in carbol-fuchsin in an incubator at 37°C., or heat over a flame in a watch-glass till steam comes off (saturated 5 per cent. aqueous solution of carbolic acid in a concentrated alcoholic solution of fuchsin).

(*b*) Decolorise for five minutes in 25 per cent. sulphuric acid.

(*c*) Wash in 70 per cent. alcohol till the sections assume a pink colour.

(*d*) Counter-stain for one minute in an aqueous solution of methylene blue, then wash in water.

(*e*) Absolute alcohol, xylol, Canada balsam.

The above method is used for tubercle bacilli. For lepra bacilli staining for five minutes in the steaming carbol-fuchsin will suffice.

[1] *Zeitschr. f. Hygien.*, 1887, III., p. 178.
[2] *Giorn. ital. d. mal. ven. e della pelle*, 1892, XXVII., p 76.
[3] *Centralbl. f. Bacter. u. Parasit.*, 1894, XVI., p. 375.
[4] *Monats. f. prakt. Derm.*, 1896, XXIII., p. 221.

II. *After Gabbet-Ernst* (quoted from Joseph and Loewenbach's *Dermato-Histolog. Technique*, 1900, p. 109).—

(*a*) Stain the sections without heating in the following solution of carbol-fuchsin for two minutes:

Fuchsin	1 grm.
Alcohol	10 c.c.
Carbolic acid, 5 per cent.	100 c.c.

(*b*) Wash in water.

(*c*) Decolorise and counter-stain in

Methylene blue	2 grms.
Sulphuric acid, 25 per cent.	100 c.c.

(*d*) Wash in water.

(*e*) Absolute alcohol, xylol, Canada balsam.

This is a simple and practical method. By it the bacilli are stained red and the tissue blue.

Alcohol decolorises the lepra bacilli much more readily than the tubercle bacilli, and this fact should be borne in mind in the staining process.

III. *After Unna for Lepra Bacilli.*—

(*a*) Stain from ten minutes to several hours in polychrome methylene blue solution.

(*b*) Wash in water.

(*c*) Differentiate in 33 per cent. aqueous solution of tannic acid for five minutes.

(*d*) Wash in water.

(*e*) Absolute alcohol coloured with orange, bergamot oil, Canada balsam.

The bacilli are stained red. The mucus surrounding the lepra bacilli and the glœa are stained blue.

IV. *After Unna* (*Monats. f. prakt. Derm.*, 1898, XXVI., p. 22).—Fix very small pieces of skin in a 1 per 1000 solution of nitric acid, harden in alcohol, and imbed and cut in celloidin. Remove the celloidin from the section before staining.

(*a*) Stain sections on the slide for one hour in carbol-fuchsin (Ziehl).

(*b*) Wash in water containing 3 per cent. nitric acid till the section is pink in colour.

(*c*) Stain in polychrome methylene blue for half an hour, and wash in water.

(*d*) Stain the collagen for half an hour in a 1 per cent. neutral alcoholic solution of orcein.

(*e*) Absolute alcohol.

(*f*) Further decolorise in anilin oil with 1 per cent. nitric acid.

(*g*) Anilin oil, xylol, Canada balsam.

The live bacilli are stained red, the glœa and the dead bacilli bluish.

When tubercle and lepra bacilli are stained with osmic acid they appear as black rods, and in unstained sections of tissue which has been fixed in Flemming's solution the bacilli may have a dark granular appearance and the surrounding tissue may be brownish in colour. The darkening which occurs with osmic acid is due to the presence of fat within the bacilli (Unna).[1]

Mycosis fungoides.—Numerous cocci and bacilli have been found in the breaking-down tumours of this disease, but these have probably no causal relation with it.

McVail, Murray, and Atkinson[2] isolated a *bacillus* with the following characteristics: Short bacillus with rounded ends, 1 μ to 2·5 μ in length, 0·75 μ in breadth. Single or in pairs. Sluggishly motile. Aërobic; with difficulty anaërobic. On agar it grows in twenty-four hours in the form of creamy white round colonies, from the margin of which short fine hair-like rays penetrate into the medium. It liquefies gelatin. It stains by ordinary anilin dyes, and is not decolorised by Gram's iodine solution.

Subcutaneous injection in rabbits caused death in from twelve to sixteen days, the bacilli being found in the enlarged lymphatic glands.

This bacillus has not been found in subsequent cases.

Pemphigus: Acute Pemphigus.—Demme,[3] Bulloch, and Pernet[4] have isolated a diplococcus from the bullae. The *diplococcus* is one-half to two-thirds larger than the gonococcus. Grows on blood-serum with characteristic colonies at a temperature of 35° to 37°C., and is pathogenic to rabbits, causing pneumonic patches in which cocci were found.

[1] *Deutsch. med. Zeit.*, 1896, No. 99.
[2] *Glasgow Hosp. Rep.*, 1898, I., p. 53.
[3] *Verhandl. d. Congr. f. inn. Med.*, Wiesb., 1886, p. 336.
[4] *Brit. Journ. of Derm.*, 1896, VIII., p. 214.

Identical diplococci have been found in chronic pemphigus by Dähnhardt.

Pemphigus neonatorum. — No specific cocci have been isolated. The ordinary pyogenic cocci are present in considerable numbers.

Purpura.—Numerous micro-organisms have been described in the dilated vessels of the skin in purpura hæmorrhagica, such as *streptococci*, *pneumococci*, and *Bacilli coli communis*. In a fatal case of purpura hæmorrhagica, Kolb[1] described a *Bacterium hæmorrhagicum* which occurred in the blood-vessels of the skin as well as in the lungs and kidneys, and in another case of the same disease Klein[2] described a Staphylococcus hæmorrhagicus. It is a short oval bacillus, ·8 μ to ·5 μ in length, by ·4 μ to ·8 μ in breadth. Generally arranged in pairs. It is immobile, anaërobic, and stains badly. Grows slowly on gelatin without liquefying it, forming whitish colonies, and produced purpuric lesions when inoculated on mice, guinea-pigs, and dogs.

Pyodermia.—The organisms which produce pus in the skin are the same as those producing pus elsewhere in the body. They are the Staphylococcus pyogenes aureus, albus, citreus, cereus albus, and cereus flavus, and the Streptococcus pyogenes. Occasionally the Bacillus coli communis and Bacillus pyocyaneus may be the cause.

By the inoculation of one or more of these micro-organisms on the lesions of various skin-diseases, pustulation and the formation of purulent crusts result, and these greatly alter the original appearance of the dermatitis.

Rhinoscleroma.—v. Frisch[3] first described the bacillus which is invariably present in this disease.

v. Frisch's bacillus is short, 2 μ in length by ·5 μ in breadth, with rounded ends. Enclosed in a gelatinous capsule. Arranged singly,[4] in pairs, or in characteristic groups lying in a glœa and situated in the protoplasm of the Mikulicz cells or free in the lymph-spaces. Grows on gelatin in the form of greyish, shiny pinhead-sized colonies, and does not liquefy it. Closely resembles the pneumococcus of Friedländer

[1] *Arbeit aus dem kaiserlichen Gesundheitsamt*, VII., p. 60.
[2] *Brit. Med. Journ.*, 1897, II., p. 385.
[3] *Wien. med. Wochenschr.*, 1882, XXXII., p. 958.
[4] For a description of the arrangement of the bacilli, *see* page 201.

both in its morphology and cultivation. Pathogenic in mice and guinea-pigs, causing abscess-formation and pleurisy, but never reproducing rhinoscleroma.

Seborrhœa oleosa.—Sabouraud[1] believes that his *microbacillus* is responsible for seborrhœa oleosa.

Microbacillus of Sabouraud.—
Two forms : (1) young and (2) old.

1. *Young Bacilli.*—Punctiform, oval, or barrel-shaped. Less than 1 μ in breadth. Have an envelope which stains by gentian violet. Superficially resemble cocci.

2. *Old Bacilli.*—Longer, sigmoid-shaped. Single or united in chains or arranged in bundles. Have a slight resemblance to tubercle bacilli. Found in the fatty plug which oozes from the seborrhoic follicles when they are squeezed.

Staining of Microbacilli.—Stain readily with basic anilin dyes. Gentian violet is a good stain for the capsule, but does not readily stain the protoplasm. Thionin stains the protoplasm.

Gram-Weigert's method for the bacilli, with carmine as a counter-stain for the tissues, is recommended by Sabouraud.

Method of Cultivating the Microbacilli.—Clean the affected skin with soap and hot water ; dry and rub with ether. Express from the skin one of the seborrhoic plugs from a follicle. Transfer it by a sterilised needle to a sterilised slide, and with a sterilised knife cut off the ends. Inoculate the medium with the central portion of the plug.

Medium.—Sloped tube of

Agar-agar	15 grms.
Peptone, granulated	20 „
Glycerin, neutralised	20 „
Glacial acetic acid	5 drops.
Distilled water	1 litre.

And incubate at 37°C.

Colonies of microbacilli begin to develop on the fourth day, and after twenty hours they take the form of a cone or button, 1 to 3 mm. above the surface, and generally extending a similar distance into the medium. They are brownish or brick-red in colour, and continue to grow for five weeks.

[1] *Maladies du Cuir Chevelu*, Paris, 1902, p. 33. For a discussion on the subject of seborrhœa *see* page 236.

Frequently in association with these colonies of microbacilli, colonies of a coccus with a grey culture (Unna's morococcus) develop. These appear about the second day. The brick-red culture of microbacilli may develop in the centre of the grey colony of cocci. In twenty-eight days the grey culture dies and the culture of microbacilli remains pure.

Inoculations from cultures of microbacilli on the surface of the skin of the horse and dog gave negative results; subcutaneous inoculations caused baldness.

Syphilis.—A number of micro-organisms have been put forward as specific for syphilis, but none of them has as yet been established. Bacilli have been described by Lustgarten,[1] Jullien, v. Niessen,[2] and others; cocci by Disse and Taguchi. Of these the best known is Lustgarten's bacillus.

Bacilli of Lustgarten.—Straight or curved. Ends often clubbed; 3·5 μ to 4·5 μ in length by 0·28 μ to 0·3 μ in breadth. Not free in the tissues, but lying in cells about double the size of leucocytes; stained by Ziehl-Neelsen's method, but decolorised by 25 per cent. sulphuric acid. It is similar in size and general appearance to the tubercle bacillus; it also resembles the smegma bacillus.

Lustgarten's Stain for the Bacillus.—
(*a*) Stain in anilin gentian violet solution.
(*b*) Differentiate in alcohol.
(*c*) Fix for a few seconds in 1·5 per cent. solution of potassium permanganate.
(*d*) Decolorise the surrounding tissues in sulphurous acid, then in alcohol.

The micro-organism was found chiefly in syphilitic ulcers and in gummata. It has not been cultivated outside the body.

Trichorrhexis nodosa.—Hodara[3] has demonstrated peculiar bacilli in a type of this disease of the hair prevalent in women in Constantinople; and Spiegler[4] has found similar bacilli in the shafts and follicles of beard-hairs.

[1] *Wien. med. Jahrbüch.*, 1885.
[2] *Wein. med. Woch.*, 1899, No. 11, p. 490.
[3] *Monats. f. prakt. Derm.*, 1894, XIX., p. 173.
[4] *Archiv f. Derm. u. Syph.*, 1897, XLI., p. 67.

Hodara's Bacillus (*Bacillus multiformis of Trichorrhexis*).—Bacillus with rounded ends. Varies greatly in length from 1 μ to 6 μ or larger, and ·3 μ in breadth. It is stained by the methods which serve for staining the fungi of ringworm and favus in the hair.

Before *staining* the hairs for the bacilli, remove the fat by placing them in alcohol-ether, and the hair-pigment by soaking them in hydrogen peroxide.

(*a*) Stain the hairs for four minutes in a freshly prepared solution of anilin gentian violet.
(*b*) Wash in water and fix in Lugol's iodine solution.
(*c*) Wash in water, dry.
(*d*) Differentiate in anilin oil.
(*e*) Xylol, Canada balsam.

Or—

(*a*) Stain for three minutes in Löffler's blue.
(*b*) Transfer to a ·5 per cent. aqueous solution of resorcin for a few minutes.
(*c*) Dry and decolorise in anilin oil.
(*d*) Bergamot oil, Canada balsam.

It grows readily on agar-agar, the following procedure being recommended for *cultivating* it:

Put the diseased hair for five or six days in absolute alcohol to kill the cocci, and plant it on agar-agar. After twenty-four hours the medium for about 1 cm. around the hair becomes cloudy, and is surrounded by a raised whitish grey border. From the border a sub-culture is made, and this gives small, round whitish grey colonies, which tend to become confluent. The bacilli have the effect of rapidly making the agar cloudy. They liquefy gelatin slowly.

Inoculations of the culture are said to have produced trichorrhexis nodosa in previously healthy hairs.

Raymond has also described a diplococcus on the affected hairs. Other observers deny that the condition is the result of the action of specific bacteria.

Tuberculosis Cutis.—Due to Koch's *Tubercle bacilli*. These have been found in lupus vulgaris, tuberculosis verrucosa cutis, erythema induratum (Bazin), etc. (*see* p. 189).

For method of staining, *see* p. 347; and for a description of the bacillus, *see* any of the text-books on bacteriology.

Yaws.—Several micro-organisms have been described in association with the lesions of yaws, which have been regarded by their discoverers as specific; but none of these have been as yet definitely established. These are a *yeast* (Powell),[1] a *bacillus* (Breda),[2] and a *micrococcus* (Nicholls[3] and Watts).

[1] *Brit. Journ. of Derm.*, 1896, VIII., p. 457.
[2] *Archiv f. Derm. u. Syph.*, 1895, XXXIII., p. 3.
[3] *Twentieth Century Practice of Med.*, 1899, XVI., p. 306.

CHAPTER XXXVIII.

STREPTOTRICHEAE AND BLASTOMYCETES.

STREPTOTRICHEAE.

Actinomyces.—The lesions which occur in the skin in actinomycosis may be primary, but as a rule they are secondary to deep-seated lesions, and occur round the openings of sinuses. In the pus which escapes from these sinuses lemon-yellow bodies about the size of a pin's head are present. These are small masses of the "ray-fungus" or actinomyces, which is the cause of the disease. (For a description of the actinomyces, *see* the text-books on bacteriology.)

Streptothrix Madurae is the organism of madura foot, a disease which occurs in India, Morocco, Algeria, America, Italy, and other foreign countries. The fungus is very similar to the actinomyces, and at one time was considered to be identical with it. (*See* text-books on bacteriology.)

Several other types of streptotriches have been identified in the human skin and subcutaneous tissue, such as:

Streptothrix asterroides of Paxton.—Found in the pus of an abscess in the neck.

Streptothrix pseudo-tuberculosa of Flexner.[1]—Found in the subcutaneous tissue in association with diseases of the lung.

Streptothrix of Foulerton.[2]—Somewhat similar to actinomyces; found in the neck of a woman (Foulerton's case).

Leptothrix of Paxton.—Occurring around hairs either as a sheath or in nodes at irregular intervals, and causing a brittle dry condition of the hairs.

Sporothrix of Schenck.[3]—Found in a subcutaneous abscess.

[1] *Journ. Exper. Med.*, 1898, III., No. 4, p. 435.
[2] *Brit. Journ. of Derm.*, 1899, XI., p. 417.
[3] *Journ. of Exper. Med.*, 1900, V., p. 77.

Blastomycetes or Yeasts.

Saccharomyces subcutaneus tumefaciens of Curtis. — This was the name given by Curtis[1] to a yeast which he isolated from a myxomatous tumour situated in the skin of the thigh in a man.

Yeast.—Spherical bodies, 16 μ to 20 μ in diameter, having a doubly-contoured envelope, including the mother-body and one or more daughter-cells. Grows easily on slightly acidulated ordinary media at about 37°C., and is aërobic. Forms a dense creamy culture on solid media. Inoculations in the mouse and rat caused the formation of myxomatous tumours, from which the yeast was again isolated.

Blastomyces of Gilchrist and Stokes[2] of Blastomycetic Dermatitis.—

Yeast.—Unicellular, 10 μ to 20 μ in diameter. Has a doubly-contoured membrane, enclosing a fine granular protoplasm with sometimes a vacuole. No mycelium or hyphae are present in the tissues. Parasites are outside the cells of the tissue; a few occur in giant-cells. Grows freely on ordinary media, especially potato and beer-wort agar, and there is little or no mycelium in the cultures. Stains readily with Löffler's methylene blue, carbol-fuchsin, and polychrome methylene blue. On glycerin-agar, in about seven days, fine greyish white colonies appear, which become white, and which show numbers of minute prickles over them. Reproduction takes place by budding or by lateral conidia on hyphae. A successful inoculation was performed in a dog by injecting 1 c.c. of teased colonies from a growth into the external jugular vein. The dog died, and nodules were found in lungs, from which the fungus was again cultivated. Successful inoculations were also performed in a horse, a sheep, and in guinea-pigs. Mycelium was not found in the tissues of any of these animals inoculated. Successful inoculations have been done also by Curtis,[3] Hyde and Hektoen,[4] and Montgomery and Ricketts.[5]

"Cancer-Bodies" are considered by several observers to be *blastomycetes*, and may conveniently be referred to under this

[1] *Ann. de l'Instit. Pasteur*, 1896, p. 449.
[2] *Journ. of Exper. Med.*, 1898, III., p. 53.
[3] *Ann. de l'Instit. Pasteur*, 1896, X., p. 449.
[4] *Brit. Journ. of Derm.*, 1899, XI., p. 264.
[5] *Journ. of Cut. and Gen.-Urin. Dis.*, 1901, XIX., p. 26.

heading. Other observers maintain that they are protozoa; while a third group hold that they are not parasitic, but simply forms of cellular degeneration.

Description of the So-Called "Cancer-Bodies."—They are usually round or oval structures, varying in size from ·004 mm. to ·04 mm. in diameter, or more (Plimmer).[1] When stained, they present a homogeneous endoplasm enveloped in a darkly stained capsule, and in the centre a darkly stained mass, which has been provisionally designated the "nucleus," but which has neither the staining reactions nor the appearances of an ordinary nucleus. The "nucleus" may present a number of different forms, and occasionally it has a small process growing out from it like a bud, which has given rise to the idea that the reproduction of these bodies takes place by budding. They may exhibit a row of fine dots within the capsule, and sometimes lines may be detected radiating from the nucleus to the periphery. Buchanan[2] has noted evidences which suggested to him that they reproduced themselves by sporing. Fissure- and rosette-forms, such as occur in the malarial parasite, have also been described. These bodies are found in or outside the diseased epithelial cells at the growing edge of the cancer, and are situated as a rule in the protoplasm of the cell, but may occur in the nucleus or in leucocytes.

Nature of the "Cancer-Body."—At first it was generally believed that these bodies were "parasitic protozoa"—a view which was advocated by Soudakewitch and Metchnikoff.[3] Russell,[4] and lately Sanfelice[5] and Roncali[6] have asserted, on the other hand, that they are vegetable parasites of the nature of blastomycetes, and Plimmer seems to regard this view as the more probable. Sanfelice was able to isolate blastomycetes from certain fruit-juices which were pathogenic in animals, causing the formation of tumours of the nature of adeno-carcinomata, from which the yeast could be recovered. Bra[7] has noted excrescences on certain trees in which he found the same "bodies" as occur in human cancer, and believes that cancer may be inoculated on trees and produce such excrescences.

[1] *The Practitioner*, 1899, LXII., p. 453.
[2] *Brit. Med. Journ.*, April 7, 1900 (Lettsomian Lecture by Sir William Banks).
[3] *Ann. de l'Instit. Pasteur*, 1892, VI., p. 158.
[4] *Brit. Med. Journ.*, December, 1890, II., 1297.
[5] *Zeitschr. f. Hygiene*, 1898, XXIX., p. 463.
[6] *Centralbl. f. Bakt. und Parasit.*, 1897, XXI., p. 318.
[7] *Compt. rend. de la Soc. de Biol.*, 1898.

A number of writers maintain, however, that they are epithelial degenerations. Against this view Plimmer cites the following arguments :

(*a*) They do not give the chemical reactions of any known form of degeneration.

(*b*) They are only found at the growing edge.

(*c*) They do not occur in all tumours, but only in carcinoma and sarcoma, which he regards as a connective-tissue cancer.

He found these intracellular and extracellular bodies in 1130 out of 1278 cases of cancer, taken as they came. They were present in great quantity in certain acute cases ; could be cultivated outside the body and inoculated on animals ; were pathogenic, producing endothelial tumours in which the "parasite" could be detected.

On the other hand, Pelagatti (*Virchow's Archiv*, 1897, CL., p. 247) has found structures resembling blastomycetes in carcinoma and also in rhinoscleroma, acne-keloid, scrofulodermia, and condyloma acuminatum, which he regards not as fungi, but simply as the result of an endocellular hyalin degeneration. He stained and compared sections of these pathological conditions with sections of a culture of blastomycetes imbedded in celloidin, and found that they differed considerably in their staining reactions from the cells of the fungus.

Technique in Connection with the "Cancer-Bodies."—

Examination of Fresh Tissue for the "Cancer-Bodies."—Make a film-preparation by scraping a cancerous growth and mounting the *débris* in ·75 salt-solution. With an oil-immersion lens and the iris-diaphragm almost closed, the bodies may be detected. Film-preparations may be stained in Löffler's blue or in polychrome methylene blue.

Methods of Fixing and Hardening.—

Fixing.—To demonstrate the bodies satisfactorily it is necessary to have thin sections of fresh tissue, and a more delicate fixing agent than alcohol is necessary. Plimmer recommends Hermann's solution and perchloride of mercury ; Buchanan employs Flemming's solution and bichromate of ammonia.

I. *Hermann's Solution.*—

Platinic chloride	15 parts.
Osmic acid, 2 per cent.	4 „
Glacial acetic acid	1 part.

Mix the first two ingredients and keep the mixture in the dark, and add the last at the time of using it. Place small pieces of tissue for thirty-six hours in ten times their bulk of the reagent. Wash in running water for twenty-four hours; then pass through 30, 60, and 90 per cent. alcohol, and finally absolute alcohol, twenty-four hours in each; then pass through cedar-wood oil and imbed in paraffin.

II. *Perchloride of Mercury.*—Saturate a ·75 per cent. solution of sodium chloride with corrosive sublimate. Decant when cold, and preserve in a dark-glass bottle. Add 5 per cent. glacial acetic acid at the time of using. Place the pieces of tissue in the solution for twenty-four hours; then transfer to 70 per cent. alcohol, to which may be added a few drops of a saturated solution of iodine in spirit. Increase the strength of the alcohol daily till absolute alcohol is reached. Pass through cedar-wood oil and imbed in paraffin.

The latter method, though cheaper, is not so satisfactory as the former.

The tissues may then be hardened in alcohol and imbedded either in celloidin or paraffin.

Methods of Staining the Bodies in Sections.—

After Plimmer:

I.—*Thionin Method.*—

(*a*) Stain sections from fifteen to thirty minutes in a concentrated aqueous solution of thionin.

(*b*) Dehydrate with acetone-alcohol (acetone, 1 part; absolute alcohol, 5 parts).

(*c*) Xylol, Canada balsam.

The nucleus is stained dark purple, the protoplasm bluish, and the capsule a darker purple than the nucleus.

II. *Double Staining Method.*—

A.—

(*a*) Place the sections for two hours in a 4 per cent. solution of ferric alum.

(*b*) Wash and put them in a ·5 per cent. solution of hæmatoxylin for half an hour (use Heidenhain's iron-hæmatoxylin).

(*c*) Decolorise with ferric alum, watching the process under the microscope till only the nuclei are darkly stained and the cytoplasm is colourless.

(*d*) Wash in running water.

B.—

(*e*) Stain in Ehrlich's acid fuchsin and orange G. mixture—

Saturated aqueous solution of acid fuchsin . 3 parts.
" " " " orange G. . 180 "

for three minutes, if Hermann's fixative has been used, and for one minute after perchloride of mercury.

(*f*) Clear in origanum oil.

The nucleus is stained copper-red, the protoplasm red, and the capsule deeper red.

Or—

(*e*) Stain in a 1 per cent. aqueous solution of Bordeaux red for ten minutes after Hermann's fixative, or for three minutes after fixing in perchloride of mercury.

(*f*) Clear in xylol and mount in Canada balsam.

The nucleus is stained a dark claret colour, the protoplasm lighter, and the capsule a bright red tint.

After Monsarrat.—

(*a*) Stain for half an hour in acetic carmine.

(*b*) Wash in water.

(*c*) Counter-stain for two minutes in a 1 per cent. solution of methyl violet.

(*d*) Transfer to a 25 per cent. solution of picric acid.

(*e*) Then to olive oil till no more violet colour comes off.

(*f*) Mount in Canada balsam.

Other methods are recommended, such as the Ehrlich-Biondi method, Ehrlich's acid hæmatoxylin, and an aqueous solution of carbol-fuchsin (Buchanan).

Gaylord considers that all these methods of fixing and staining are unreliable, and strongly advocates examination in the fresh state.

I.—*After Pelagatti, to distinguish them from Blastomyces.*—

(*a*) Carbol-fuchsin, five minutes.

(*b*) Wash in water.

(*c*) Polychrome methylene blue, five minutes.

(*d*) Wash in water.

(*e*) Absolute alcohol, bergamot oil, Canada balsam.

The "cancer-bodies" (Kügelchen) are stained dark red and are shiny; the surrounding tissue is stained blue.

The blastomycetes have a violet capsule and a central portion, which is either stained light violet or unstained.

II.—*After the same Author.*—

(*a*) Polychrome methylene blue, ten minutes.
(*b*) Wash in water.
(*c*) Potassium ferricyanide (2 per cent. solution), five minutes.
(*d*) Wash in water.
(*e*) Absolute alcohol, bergamot oil, Canada balsam.

The central portion of the "body" is stained dark blue, the peripheral zone lighter in colour, and the surrounding tissue light violet.

The blastomycetes are difficult to stain by this method. After prolonged staining, the capsule is stained violet, and the central part remains unstained.

III.—*After the same Author.*—

(*a*) Acid fuchsin (2 per cent. solution), ten minutes.
(*b*) Wash in water.
(*c*) Saturated aqueous solution of picric acid, five minutes.
(*d*) Saturated alcoholic solution of picric acid, three minutes.
(*e*) Absolute alcohol, bergamot oil, Canada balsam.

The "bodies" are stained purplish red, and the surrounding tissue yellow. The blastomycetes are stained citron-yellow.

IV.—*After the same Author.*—

(*a*) Stain deeply with Delafield's hæmatoxylin.
(*b*) Wash in water.
(*c*) Safranin (2 per cent. solution), ten minutes.
(*d*) Wash in water.
(*e*) Concentrated tannin solution, five minutes.
(*f*) Wash in water.
(*g*) Absolute alcohol, bergamot oil, Canada balsam.

The "bodies" are stained purplish red, the surrounding tissue brownish violet. The blastomycetes are stained with difficulty, and only the capsule assumes a brownish violet tinge.

Cultivation of the "Cancer-Bodies."—

The cultivation of these bodies outside the body has been rarely successful, but Plimmer and Monsarrat have both reported positive results.

Plimmer accomplished it in a case of a rapidly growing

cancer of the breast by using the following medium : Infusion of cancer-tissue carefully neutralised with the addition of 2 per cent. glucose and 1 per cent. tartaric acid.

Small pieces of cancerous tissue were placed in this medium in a sterile flask which was kept anaërobic. After an incubation of twenty-four hours a cloudiness was produced in the medium which increased till the sixth day, when the growth sank to the bottom, leaving the liquid clear, and no scum or pellicle formed. If this medium was solidified with agar, small whitish colonies formed in a few weeks.

Monsarrat made incisions into a fresh cancer, and scraped the edges. The scrapings were inoculated on glucose-agar. Sub-cultures on wort-agar, incubated at 37°C., grew in twenty-four hours.

Inoculation of the "Cancer-Bodies."—Intraperitoneal injections by Plimmer into guinea-pigs caused death in from thirteen to twenty days, with the formation of small nodules over the peritoneum, liver, spleen, and lungs. These were made up of endothelial cells, many of which contained the "cancer-body."

Inoculation into a scarified rabbit's cornea produced proliferation of the corneal epithelium with the "cancer-bodies" in the cells.

Monsarrat inoculated 1 c.cm. of a culture forty-eight hours old into guinea-pigs. These were killed at periods of from two to six weeks after the injection. On opening the abdomen, the omentum and peritoneal surface and liver, etc., were studded with nodules, which on section showed the "bodies" in the cells.

Gaylord [1] still more recently has inoculated a guinea-pig and a dog in the peritoneal cavity with fluid containing the parasites from a colloid cancer of the abdomen. The animals developed peritonitis, and the same organism was recovered from the abdominal fluid. Another guinea-pig was infected in the jugular vein, and died of adeno-carcinoma.

Gaylord found a similar organism in variola, and Pfeiffer has described a protozoön in connection with vaccinia.

[1] *The American Journ. of Med. Sci.*, 1901, CXXI., p. 503.

CHAPTER XXXIX.

HYPHOMYCETES OR MOULDS.

Erythrasma.—Due to the *Microsporon minutissimum.* The fungus produces a yellowish brown discoloration of the skin, with a clearly defined edge and a finely desquamating surface. It occurs, as a rule, in the axillary and genital regions.

It is a small hyphomyces with irregularly segmented filaments about ·7 μ in thickness. When the smaller segments become detached they resemble bacilli 5 μ to 7 μ long, and a few spores may be found. The threads may divide dichotomously. Scrapings of this surface examined in liquor potassae reveal on examination with a $\frac{1}{12}$ oil-immersion lens a dense meshwork of the fungus. The fungus stains easily with anilin dyes (Pl. XXXIV., Fig. 6).

To make permanent preparations, wash the scrapings in ether on a slide to dissolve the fat ; clear with glacial acetic acid ; then dry. Run a little alcohol over the specimen ; then stain with methylene blue, and differentiate in alcohol in the usual manner, and mount in Canada balsam.

Pityriasis versicolor.—Due to the *Microsporon furfur.* The mould produces on the skin irregular fawn, or brownish, finely desquamating macules, which tend to run together to form diffuse sheets.

Microscopically it is made up of branching mycelial threads and spores clustered like bunches of grapes. The mycelial threads are 1 μ to 3 μ thick, sinuous, and septate at regular intervals. The spores vary from 2 μ to 6 μ in diameter, and have a doubly-contoured capsule. It stains like the Microsporon minutissimum. Fructification takes place by sporophores generally situated at the end of the hyphae and containing conidia. Cultivation outside the body has, as a rule, been unsuccessful ; but recently Matzenauer[1]

[1] *Archiv f. Derm. u. Syph.*, 1901, LVI., p. 163.

claims to have cultivated it on Finger's "epidermis-agar," and, on making sub-cultures on ordinary agar, to have grown small round colonies which coalesced to form amber-coloured patches, which, when inoculated on the healthy skin, reproduced the disease (Pl. XXXV., Fig. 1).

Carates.—Caused by an *aspergillus* or a fungus intermediate between aspergillus and penicillium (van Thieghem). It is one of the names given to a group of tropical diseases in which discoloured scaly patches occur somewhat similar to those of Pityriasis versicolor.

Favus.

The fungus of favus is the *Achorion of Schönlein* (Pl. XXXV.). It produces on the skin peculiar sulphur-yellow disc-shaped crusts or "scutula," which emit a mousy odour, and have a cup-like depression in the centre, which is often pierced by a hair. These scutula may coalesce to produce an appearance like a honeycomb. On removing these crusts—which is easily done, as they have a friable cheesy consistence—the underlying epidermis is moist, smooth, depressed, and sometimes atrophic. The fungus attacks the hairs, renders them fragile, and gives them a characteristic lustreless appearance. The pressure of the scutula causes an atrophy of the hair-follicles, and baldness is apt to result. Favus affects not only the scalp and glabrous skin, but also the nails, and occasionally the mucous membranes.

It may occur at all ages, though it is perhaps commoner in children; but being difficult to eradicate, it frequently persists to adult life. It is rare in England, commoner in Scotland and Ireland, and very common in the Eastern countries of Europe. It is frequently transmitted from animals—the cat, mouse, rat, dog, and fowl being subject to it. Occasionally one child infects another.

Achorion Schönleinii.—It has a mycelium consisting of a number of narrow, flat, branching, truncated filaments. These vary in length and thickness; some of them form empty tubes, while others are divided up into cavities by transverse septa, and frequently contain spores. The spores are roundish, oval, or irregular in shape, and about 6 μ in diameter. In microscopic preparations of the fungus from crusts the mycelium generally preponderates, and the spores are mixed up with amorphous granular matter (Pl. XXXV., Fig. 2).

PLATE XXXV.

FIG. 1. MICROSPORON FURFUR FROM SCALES OF PITYRIASIS VERSICOLOR SOAKED IN POTASH SOLUTION.

a. Mycelium of branching threads; septate at irregular intervals.
b. Spores, regular in size and shape, and grouped like clusters of grapes.
c. Budding spore.

FIG. 2. ACHORION SCHÖNLEINII FROM A PIECE OF A SCUTULUM OF FAVUS SOAKED IN POTASH SOLUTION.

a. Mycelium of flat, branching, truncated filaments.
b. Filament split up by transverse septa and containing spores (sporophore).
c. Empty filament.
d. Spores, irregular in size and shape.

FIG. 3. SCUTULUM OF FAVUS. (× about 80.)

Cut in celloidin and stained.

a. Scutulum consisting of a mycelial felt, the majority of the threads of which are arranged perpendicularly.
b. Faintly stained dead hyphae at the periphery.
c. Deeply stained living hyphae.
d. Central mass of spores and *débris*.
e. Thin layer of the stratum corneum, forming a roof to the crust, and absent in the central depression.
f. Stretched-out epidermis, with a thin layer of the stratum corneum forming a floor to the crust.

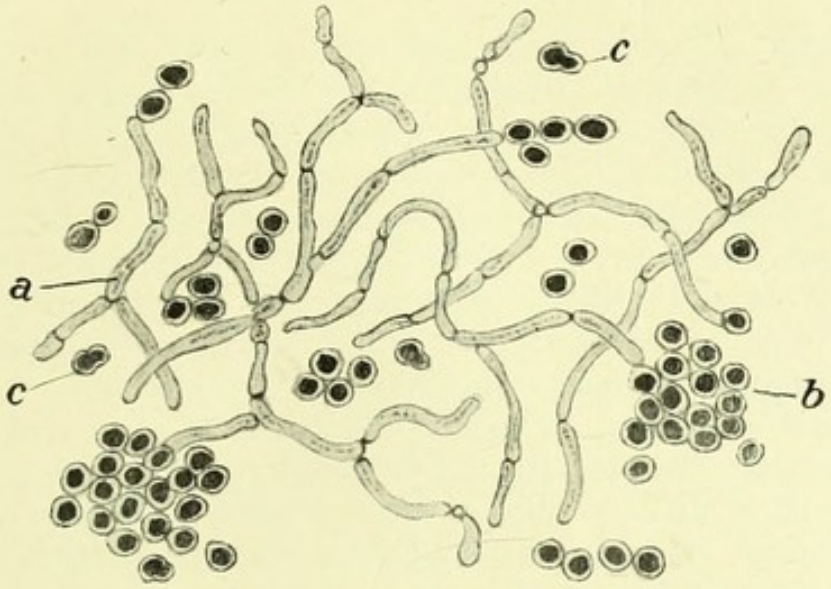

FIG. 1.

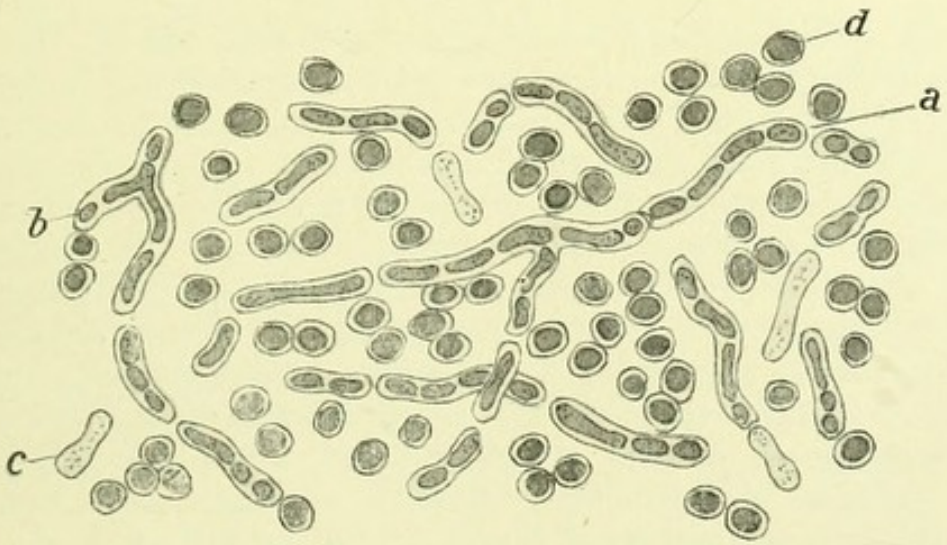

FIG. 2.

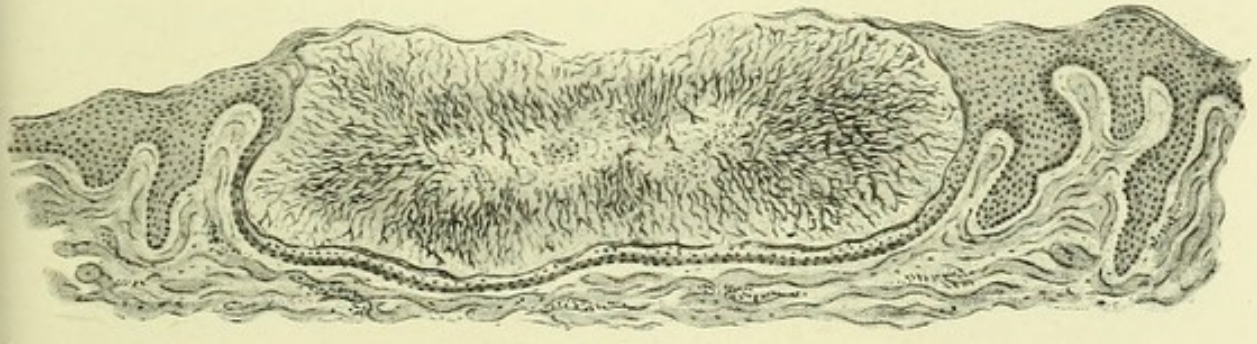

FIG. 3.

J. M. H. M., del.

(*a*) *In the Hair.*—The hair-shaft may be packed with mycelial threads 2 μ to 3 μ in breadth, jointed at intervals of 10 μ to 15 μ. These divide dichotomously at very acute angles. The threads are situated chiefly in the centre, and lie parallel to the long axis of the hair. No spores can as a rule be detected in the mycelium. Occasionally the threads divide into three or four filaments, at the ends of which rows of spores may form. This condition is known as "favic tarsus." The opaque appearance which the fungus produces in the hair is to a large extent due to air which has replaced the filaments. The mycelial threads extend down the shaft to near the root, where they usually end in a fringe. In a recently infected hair mycelial threads and spores may be found between the inner root-sheath and the hair; it then attacks the cuticle and penetrates into the hair itself (Pl. XXXVI., Fig. 2).

(*b*) *In the Epidermis: Scutula of Favus.*—The fungus is situated chiefly between the superficial and deep layers of the stratum corneum, but it may spread down into the Malpighian layer or even into the corium. The main mass of the scutulum consists of a dense mycelial felt, the filaments of which are regular and contain spores; the majority of them grow perpendicularly, and between them there is more or less granular *débris*. The mycelial mass is covered by a thin layer of the stratum corneum. Though the scutula of favus are frequently pierced by a hair, they are not invariably so, and the cupping is not necessarily due to the presence of a hair in the centre. Mibelli[1] explains the cupping as the result of the fungus, which grows from the centre of the upper surface, not being sufficiently nourished and of the active growth being greatest at the sides. In the centre of the scutulum there is a mass of spores, while at the periphery only mycelial threads occur. The growth is said by Kellogg[2] to be centripetal, and by Waelsch[3] to be centrifugal. Beneath the scutulum the prickle-cell layer generally proliferates, and an infiltration of plasma-cells associated with a rarefaction of the fibrous elements occurs in the underlying corium. Through the continuous pressure of the scutulum on the corium and the penetration of the fungus into it, an atrophy is very liable to follow the healing of the lesions (Pl. XXXV., Fig. 3).

[1] *La Riforma Med.*, April, 1891.
[2] *Monats. f. prakt. Derm.*, 1895, XXI., p. 413.
[3] *Archiv f. Derm. u. Syph.*, 1895, XXXI., p. 49.

Occasionally the presence of the fungus in the epidermis only causes scaliness or vesiculation (*herpetic favus*). When this occurs there is an inflammatory hyperæmia and infiltration of the corium, and œdema, vesiculation and parakeratosis of the epidermis. In such cases crusts may form ; but according to Unna these differ from true scutula in having numerous epidermal cells, *débris*, and leucocytes mixed up with the mycelium.

(*c*) *In the Nail.*—*See* p. 321.

Fructification of the Achorion Schönleinii.—In hanging-drop preparations Sabouraud [1] distinguished the following varieties of fructification :

1. Reproduction by endoconidia.
2. „ „ sprouting.
3. „ „ unsegmented spindles.

In impression-preparations from a culture on glucose-agar I found that the aërial fructification consisted of rods with lateral buds, occasional endoconidia and terminal non-septate capsules (Pl. XXXVIII., Fig. 3).

The Plurality of the Parasite of Favus.—Quincke was the first to suggest that there were several varieties of fungi which caused favus. Neebe and Unna [2] isolated nine forms of *Achorion* in the favus of man and animals. These were distinguished by their mode of growth on culture-media, as well as by their microscopical appearances, and were named respectively *Achorion euthythrix*, *A. atacton*, *A. radians*, *A. dikroon*, *A. akromegalicum*, *A. demergens*, *A. cysticum*, *A. moniliforme*, *A. tarsiferon*. Bodin [3] also maintains the plurality of the fungus of favus which attacks man. Biro and Sabouraud, on the other hand, maintain that there is only one parasite of favus in man—namely the *A. Schönleinii*, and that apparent variations are artificially produced by differences in the culture-media employed, and in the temperature at which they are grown, and by like considerations.

Intermediate Stages between Favus and Ringworm.—Bodin [4] has described cases in which lesions on the skin, similar to those produced by the trichophyta of ringworm, have been

[1] *La Pratique Dermatologique*, 1900, I., p. 827.
[2] *Monats. f. prakt. Derm.*, 1893, XVI., p. 17.
[3] *Les Champignons parasites de l'Homme*, Paris, 1902, p. 64.
[4] *Soc. de Biol.*, July 4, 1896.

caused by a parasite of the nature of an achorion. Fox, Blaxall, and Sabouraud have observed circinate lesions on the skin, and lesions like kerion on the scalp similar to those produced by the trichophyta, which, on cultivation, gave a culture like that of favus. Such cases demonstrate the fact that the line of demarcation between the fungi of ringworm and favus is not well defined.

Technique for the Staining and Cultivation of the Achorion Schönleinii.

Examination of the Hairs and Scutula for the Fungus.—The mycelium and spores of the fungus may be rapidly demonstrated by soaking the hairs and scutula in liquor potassae in the manner described in connection with ringworm (p. 369).

Staining of the Fungus in the Hairs.—The staining methods for the fungus in the hairs are also identical with those for the fungi of ringworm (p. 370). But as the fungus of favus is situated chiefly within the hair, and the cuticle is almost intact, it is a matter of great difficulty to obtain well-stained specimens. The method of preparing them is identical with that for the demonstration of the Trichophyton endothrix in the hair (p. 371).

Staining of the Fungus in Sections of Scutula.—

After Kellogg (*Monats. f. prakt. Derm.*, 1895, XXI., p. 413).—

(*a*) Soften the dry scutulum in warm water.

(*b*) Harden in alcohol and imbed in celloidin.

(*c*) Cut sections and put them for ten minutes in warm water, or damp them in a 2 to 5 per cent. solution of soda.

(*d*) Wash them in water and stain by one or other of the following methods :

I. *Method to demonstrate only the Living Hyphae and Spores.*—

(*a*) Stain the sections for ten minutes in polychrome methylene blue.

(*b*) Wash in water.

(*c*) Dry on the slide.

(*d*) Decolorise in anilin oil, with the addition of 1 per mille of hydrochloric acid.

(*e*) Anilin oil, xylol, Canada balsam.

II. *Method to demonstrate also the Dead Mycelium and Spores.*—

(*a*) Stain the sections in Unna's acid-fuchsin and tannin solution (Grübler) for twenty-four hours.

(*b*) Wash in acidulated water and dry on the slide.

(*c*) Drop on polychrome methylene blue solution, heat over the flame, then wash in acidulated water.

(*d*) Dry, and cover several times with the tannin-fuchsin solution.

(*e*) Wash in water and dry.

(*f*) Clear and differentiate in anilin oil, with the addition of 10 per cent. tannin.

(*g*) Anilin oil, xylol, Canada balsam.

The living hyphae and spores are stained by the methylene blue; the dead portions take on the red of the fuchsin solution.

III. *Another Method for the same Purpose as II.*—

(*a*) Stain the sections in anilin gentian violet solution for five minutes.

(*b*) Wash in water.

(*c*) Stain for two minutes in tannin-fuchsin solution.

(*d*) Wash in water and dry on the slide.

(*e*) Decolorise in anilin oil slightly acidulated.

(*f*) Anilin oil, xylol, Canada balsam.

The living hyphae and spores are stained violet, the dead fungus and the surrounding tissue have a rose-red tint.

Media for Cultivating the Achorion Schönleinii.—The fungus will grow on glycerin-agar or potato. It is very apt to be mixed up with other micro-organisms, and, according to Sabouraud,[1] it is even more difficult to obtain in pure culture than ringworm. He recommends a glucose-medium for favus, in which there is a larger proportion of peptone than in the French proof-agar for ringworm:

Pure anhydrous glucose	4	grms.
Granulated peptone	2	,,
Agar-agar	1·50	,,
Water	100	,,

The best temperature at which to grow favus is 30°C.; at lower temperatures the growth is much slower than that of ringworm.

[1] *La Pratique Dermatologique*, 1900, I., p. 820.

In about a week roundish white colonies appear. These are powdery, raised in the centre, and have a fine downy fringe. As they become older the centre becomes corrugated and wrinkled, and the culture may assume a brownish tinge. It liquefies gelatin media in a few days (three or four), while the trichophyta take about a fortnight to do so. The growths on solid media have a strong resemblance to scutula, except in colour.

RINGWORM.

Three different hyphomycetes are chiefly responsible for the various lesions of ringworm in man. These are the *Microsporon Audouini* and two trichophyta, known from the position of the spores with regard to the hair as the *Trichophyton endothrix* and the *Trichophyton ectothrix*. The trichophyta are occasionally named the large-spored fungi of ringworm or megalospora, in contradistinction to the small-spored ringworm fungus or microsporon. This designation is warranted, since, as a rule, the spores of the trichophyta are nearly double the size of those of the microsporon. Still, the size of the spores is a very variable characteristic, and one that is not thoroughly reliable. Sabouraud [1] considers that not only does the microsporon differ from the trichophyta in its morphology and cultures on artificial media, but also in its forms of fructification. This latter observation was based on the examination of the reproductive organs in the hanging-drop. Fox and Blaxall,[2] who maintain that it is preferable to base results on the examination of the aërial fructification, found that in impression-preparations of these various fungi the mode of reproduction was constant, and consisted of lateral spores sprouting from a central stem.

Technique for the Demonstration, Staining and Cultivation of the Fungi of Ringworm.—

Rapid Clinical Method of Demonstrating these Fungi in Hairs and in Scales.—Place the hair or scale on a clear slide and drop on to it the B.P. solution of potash (6·8 per cent.). If the hair be greasy, first remove the fat by rinsing it in ether. Place a cover-slip gently over the hair soaking in potash,

[1] *Les Trichophyties humaines*, Paris, 1894 ; and *Dermatophytes*, *La Pratique Dermatologique*, 1900, I., p. 744.

[2] *Brit. Journ. of Derm.*, 1896, VIII., pp. 241, 291, 337, 377 ; and *Trans. Path. Soc.*, London, 1897, p. 301.

and examine from time to time under a medium power of the microscope to find when it has "cleared up." At this "critical time" the fungus is better demonstrated than by any other method. This is chiefly due to the fact that the fungus possesses a different refractive index from that of the hair-cell or the epithelial squames. The process occupies from fifteen to thirty minutes, and may be hastened by gently heating the slide over the flame. If it be desired to preserve the specimen for a short time, glycerin is allowed to diffuse under the cover-glass, and the edges are afterwards sealed with paraffin. It is essential to avoid pressing down the cover-glass on the softened hair, as this will rupture the cuticle and otherwise cause an alteration in the relation of the fungus to the different parts of the hair. Prolonged soaking in weak liquor potassae does not destroy the fungus, though it causes a disintegration of the hair, and sometimes beautiful specimens of the fungi may be obtained from the *débris* produced by soaking hairs for a week or longer in the solution.

For diagnostic purposes, and, indeed, for the study of the arrangement of the fungus and its mode of attacking the hair, this simple method is all that is required. If the preparation be carefully made, and the relation of the parts not interfered with by a clumsy application of the cover-slip, at the "critical time" when the specimen has cleared, the preparations are far more perfect than those obtained by the more troublesome methods of staining. Several experts on this subject rely entirely on the potash method, and regard staining as superfluous.

Staining of the Fungi.

Cover-Glass Preparations.—The staining of impression-preparations of the fungi from cultures is similar to that employed for any micro-organism (p. 328). They stain readily by the Gram-Weigert method and by the substitution of carbol-fuchsin for the gentian violet of Gram's method.

Staining of the Fungi in the Hairs.—To make well-stained preparations of the fungi of ringworm in the hair, especially in the case of the endothrix variety, considerable practice is required; for in the latter the fungus is almost entirely within the hair-cuticle, and prolonged staining is necessary to penetrate to it. This results in a deep staining of the hair, which it is difficult to decolorise sufficiently to show the fungus in the centre.

PLATE XXXVI.

FIG. 1. HAIR INFECTED WITH SMALL-SPORED RINGWORM (MICROSPORON AUDOUINI, SEMI-DIAGRAMMATIC).

a. Small spores, forming a mosaic ensheathing the hair.
b. Mycelial threads in the hair, ending in a fringe at the bulb.
c. A few chains of small spores in the bulb.

FIG. 2. HAIR INFECTED WITH LARGE-SPORED RINGWORM (TRICHOPHYTON ECTOTHRIX, AFTER COLCOTT FOX).

a. Chains of spores, forming a sheath around the hair.
b. Mycelium ending in a fringe at the bulb.

FIG. 3. HAIR INFECTED WITH THE FUNGUS OF FAVUS (ACHORION SCHÖNLEINII, SEMI-DIAGRAMMATIC).

a. Mycelial threads within the hair, jointed at irregular intervals, and branching dichotomously at very acute angles.
b. Row of spores at the end of a filament.

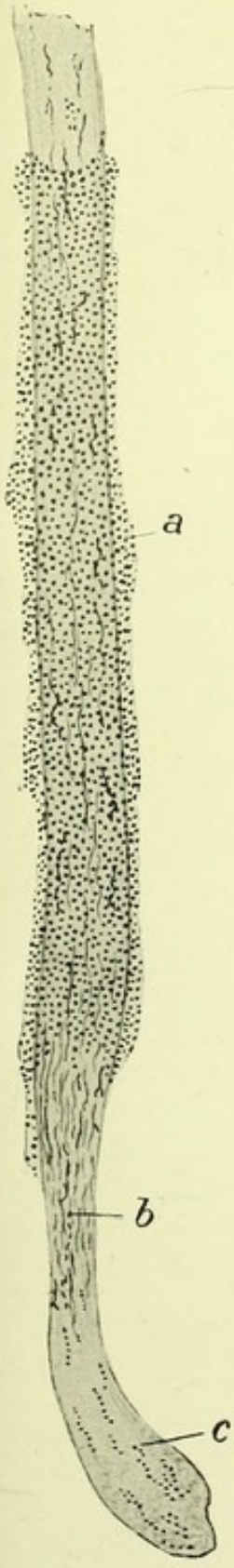

FIG. 1.

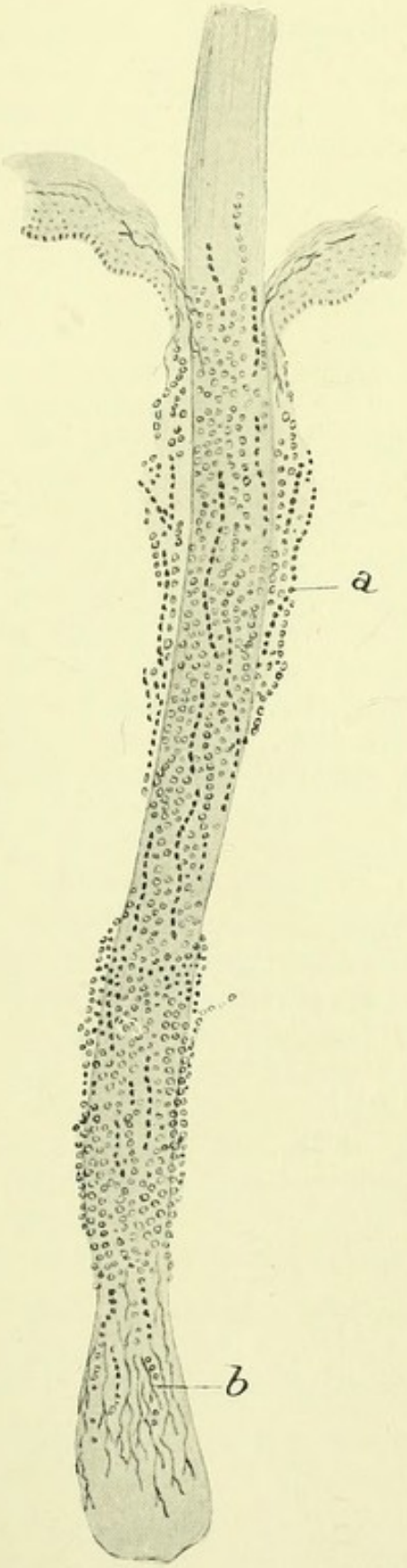

FIG. 2.
(*After* COLCOTT FOX.)

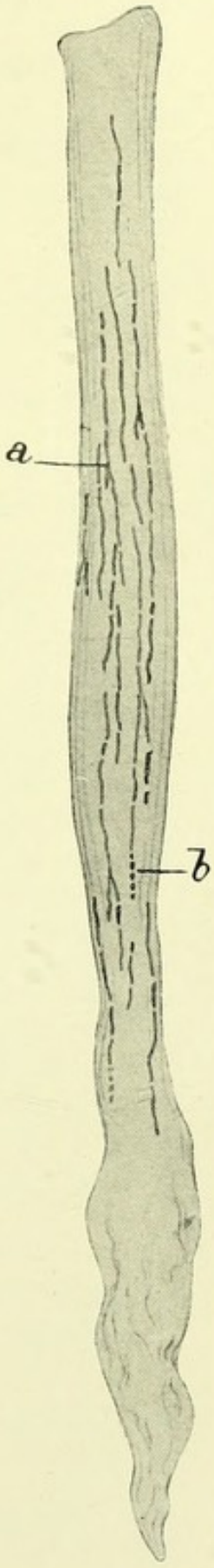

FIG. 3.

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The following method[1] *gives satisfactory results:*

(*a*) To obtain good specimens it is necessary to epilate the hair so as to bring away the bulb. This requires steady traction in the long axis of the follicle which is more or less oblique, and must not be done by a sudden jerk, or the hair will certainly break off above the bulb.

(*b*) Remove the superfluous fat from the hairs by soaking them for several minutes in ether in a watch-glass, and afterwards washing them in dilute spirit (10 per cent.).

(*c*) Transfer the hairs to a clean slide, and allow them to dry there, or dry over a flame.

(*d*) Drop on anilin gentian violet solution.

(Shake up five parts of anilin oil in a hundred of distilled water, and filter. Add to the filtrate sufficient of a saturated alcoholic solution of gentian violet to make the mixture opalescent. Prepare this freshly each time.)

As this solution rapidly evaporates, it is necessary to add fresh drops from time to time. In the case of the microsporon ten minutes is sufficient for staining; but with endothrix an hour may be necessary, and the slide should be heated now and then over the flame to soften the keratin and to increase the power of penetration of the stain.

(*e*) Decolorise for five minutes in Gram's iodine solution, poured on without washing the hairs.

(*f*) The iodine solution is then poured off the slide, and the hairs are further differentiated in anilin oil. This is the most difficult part of the process, and on it depends the success of the specimen. It should be watched from time to time under a low power. The time taken varies from a few minutes in the microsporon to several hours in the case of the endothrix. The action of the anilin oil may be greatly accelerated by the addition of a few drops of nitric acid to a watch-glass of anilin oil.

(*g*) Clear in xylol and mount in Canada balsam.

Carbol-fuchsin[2] may be substituted for gentian violet in staining, and the mycelium and spores are stained violet or red accordingly, and the hair itself remains unstained.

Adamson, previously to staining the hairs, recommends the soaking of them from ten to thirty minutes in a 5 to

[1] This method, with some slight modifications, is that which was described by Adamson in the *Brit. Journ. of Derm.* in 1895, p. 373, and by Morris in the *Practitioner* of the same year.

[2] Add a concentrated alcoholic solution of fuchsin to 100 c.c. of a 5 per cent. solution of carbolic acid till a metallic lustre appears (Lee).

10 per cent. solution of potash. A cover-slip is then placed gently over the hair, and the potash washed out by allowing a few drops of 15 per cent. alcohol to diffuse under it. The latter hardens the hair sufficiently to allow of the removal of the cover-glass. The hair is then stained.

The addition of the potash certainly facilitates the process of staining; but the *raison d'être* of the latter is chiefly to avoid the derangement of the parts, which is apt to result from the potash—and if we be satisfied that potash does no harm, why go through the elaborate process of staining except where permanent preparations are desired? Besides, the methods of staining cause a distinct shrivelling of the fungus, and are apt to interfere with the demonstration of its finer structure.

H. J. Curtis[1] recommends the counter-staining of the hairs, after they have been thoroughly decolorised by anilin oil, in a saturated alcoholic solution of eosin for one minute. This may also be readily accomplished by adding a few drops of picric acid or picro-carmine to the anilin oil used for decolorising.

Culture-Media for the Fungi of Ringworm.—The fungi of ringworm will grow on all the media in common use, such as potato, gelatin, glycerin-agar, beer-wort-agar, and bouillon. But the chief researches on the subject have been carried out with special media, in which the cultures are more luxuriant than in the ordinary media.

Special Media for Ringworm.—Sabouraud in his epoch-making researches employed a saccharin-agar-peptone medium. He observed that the addition of various sugars, such as maltose, lactose, or glucose, to the medium increased the luxuriance of the culture, and at the same time brought out in stronger contrast the peculiar characteristics in the cultures of the various fungi. He found that the addition of maltose or lactose gave a marked differentiation, while the addition of glucose greatly increased the luxuriance of the growth. The maltose medium is the one commonly employed, and is known as "French proof-agar." It consists of:

Maltose	3·8 parts.
Agar-agar	1·3 „
Peptone	0·5 part.
Water	100 parts.

The reaction of the medium is not stated.

[1] *Essentials of Pract. Bact.*, London, 1900, p. 78.

PLATE XXXVII.

HAIRS FULLY INFECTED WITH THE ENDOTHRIX VARIETY OF THE LARGE-SPORED FUNGUS OF RINGWORM.

Contents of a single hair-follicle consisting of two infected hairs and a healthy one; shows chains of large spores entirely within the cuticle of the hair.

NOTE.—I am indebted to Dr. Colcott Fox for the anomalous specimen from which this drawing was made.

PLATE XXXVII.

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The maltose of this medium was an impure substance, and the peptone was a granulated peptone obtained from a special firm in Paris. These were consistently employed by Sabouraud till, unfortunately, the firm from which the maltose was obtained became closed. Blaxall in his experiments substituted a German peptone and a pure maltose, with the result that he obtained cultures with totally different appearances; but on using the Paris peptone and maltose, the cultures were identical with those of the French observer. This fact shows the necessity of employing precisely similar media and at the same time subjecting the media to the same physical conditions, especially with regard to temperature, before attempting to compare results. The temperature at which the fungi seem to grow best is 30°C.

Blaxall strongly recommends the following medium as giving a rapid growth (three to five days) and a well-marked differentiation:

"Prepare a decoction of potatoes—half a kilogramme of powdered potato to a litre of water, steaming this well till it becomes of a light brown colour; then strain it through a fine cloth. Add to the filtrate 1·5 per cent. agar-agar and 3 per cent. of a pure maltose. The medium has a slightly acid reaction."

Method of Inoculating Hairs and Scales.—The affected portions of hairs are cut up on a sterilised slide into two or three pieces. The diseased parts can easily be recognised, as they are white and opaque, and in the case of the microsporon are surrounded by a characteristic sheath of fungus. The hair is cut up by means of a sterilised knife or by a special instrument devised by Sabouraud, which is a combination of a needle and a knife. The latter is a handled steel needle, of sufficient length to be easily pushed down to the bottom of a test-tube, with a small diamond-shaped blade at the end. By this instrument, or by an ordinary platinum needle, the pieces of the hair are generally inoculated directly on to the medium. The latter is inimical to the growth of the micro-organisms, which, as a rule, are present about the hair; but in the case of kerions or agglomerated ringworms of animal origin, various sarcinae and bacilli may be present which flourish on maltose-agar, and these require to be got rid of before inoculation. This can generally be done by rinsing the hairs thoroughly in distilled water; but where that fails, absolute alcohol should be employed. Soaking

the hairs for as long as twelve hours in absolute alcohol will not inhibit the growth of the fungus, and it destroys the contaminating micro-organisms. After sterilising the needle, the point should be moistened in the medium to cause the pieces of the hair to adhere to it, and three pieces should be planted at regular intervals on the media in a sloped test-tube. Where the morphology is to be studied or permanent preparations are desired, sub-cultures should be made either in Petri dishes, Erlenmeyer's conical flasks, or in some form of flat flask. The sub-cultures should be made, if possible, from young growths, and the flask should contain a sufficient depth of medium (about a quarter of an inch) to enable the fungus to grow luxuriantly.

When two or more fungi happen to be growing together in a tube they may be separated in the sub-cultures by Blaxall's method. After removing the plug and heating the mouth of the tube over the flame, invert the tube over a plate and tap the end of it, by which means spores will be separated off and sown singly in the medium on the plate.

When the cultures have reached a sufficient size, further growth may be stopped by inserting a piece of cotton-wool, impregnated with a few drops of formalin, into the mouth of the flask or dish, and then sealing it with paraffin. Scales and crusts are inoculated in exactly the same way as hairs, but it is advisable to rinse them in alcohol before inoculation.

Preparations for the Study of the Fructification of the Fungi.—

(*a*) *Impression-Preparations* are best for the study of the aërial fructification. They are made by gently pressing a clean cover-slip on the top of a plate-culture ; the aërial hyphae adhere to the slip, and may be fixed there by the flame, and stained.

(*b*) *Hanging-drop* cultures in bouillon and maltose show the anaërobic modes of reproduction.

(*c*) *Sections of Cultures* pressed between two cover-slips also show, on microscopical examination, the anaërobic fructifications. The film of the agar-culture may be melted in hot water, the cover-slips separated, and the fungus adhering to each slip fixed by the flame and stained.

PLATE XXXVIII.

FIG. 1. AËRIAL FRUCTIFICATION OF RINGWORM.

From an impression preparation of a culture of trichophyton ectothrix on maltose-agar, sixteen days old.

Shows aërial hyphae, with terminal and lateral buds.

Similar preparations were obtained from cultures of microsporon and trichophyton endothrix.

FIG. 2. SUBMERGED FRUCTIFICATION FROM A SCRAPING OF A CULTURE OF TRICHOPHYTON ECTOTHRIX, EXAMINED IN POTASH SOLUTION.

Fructification by endoconidia.

FIG. 3. FRUCTIFICATION OF THE ACHORION SCHÖNLEINII OF FAVUS.

From an impression preparation of a culture of favus on glucose-agar fourteen days old. It shows aërial fructification, consisting of rods with lateral bulbs, terminal non-septate capsules, and occasional endoconidia.

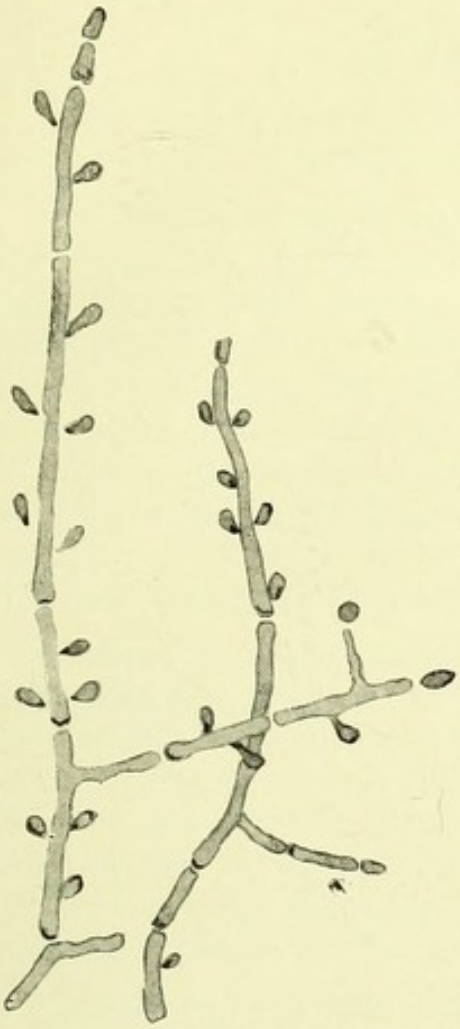

FIG. 2.

FIG. 1.

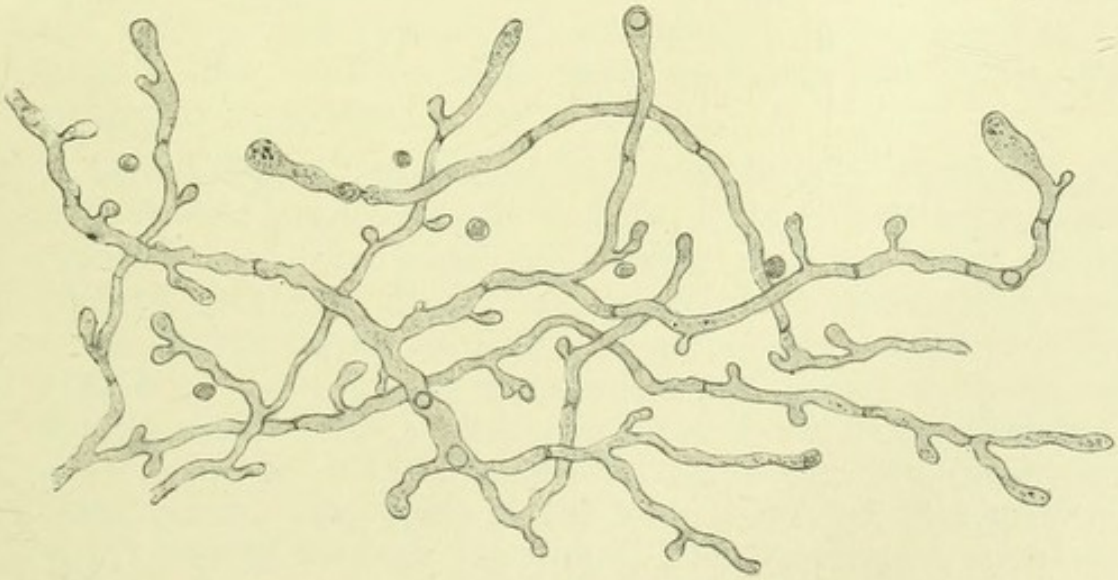

FIG. 3.

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MICROSPORON AUDOUINI.

This variety of ringworm fungus usually affects the scalp, but occasionally spreads on to the glabrous skin.

(*a*) *On the Scalp* it produces variously sized circumscribed scaly plaques, which are round or oval in shape, and run together to form polycyclical areas. Those scaly patches are covered with broken-off hairs or "stumps," which project 4 or 5 mm. above the surface of the skin, and are enveloped by a white opaque sheath of fungus.

(*b*) *On the Glabrous Skin* it forms red scaly patches, which have either an indefinite margin or a distinctly redder circinate border. In babies, in which the lanugo hairs are present, circinate lesions of the latter description occur on the scalp.

Occurrence.—It occurs chiefly in early childhood, and does not affect the scalp after puberty, though it may occur at a later age on the glabrous skin. Fox and Blaxall have reported an exceptional case in which it affected the scalp of an adult. It is the commonest form of ringworm in this country, constituting about 90 per cent. of all the cases; it forms only 60 per cent. of the cases in Paris, is unusual in Germany, and very rare in the Eastern countries of Europe.

Origin.—As a rule the infection comes from the human subject; but it has recently been shown that horses (Bodin,[1] Fox, Bunch,[2]), cats (Fox), and dogs (Bodin) may be subject to it and communicate it to man. In the latter circumstance a kerion or suppurating ringworm is apt to occur. Kerions not infrequently appear in association with the small-spored fungus, due most probably to a secondary inoculation with pyogenic organisms.

Microscopical Appearances of a Hair fully Infected by the Microsporon Audouini.—If a fully infected hair be carefully epilated it will be found to be ensheathed in a white opaque coating, extending down from about 3 mm. above the opening of the follicle to the hair-bulb, where it ends in a fringe. This sheath is made up of numerous small round or polygonal spores, which form a close mosaic, and the fringe consists of rows of spores. Within the hair, branching mycelial threads occur, which run chiefly in the long axis, and also terminate at the level of the bulb in a fringe. The mycelium is segmented at long intervals, and branches irregularly. The hair-cuticle

[1] *Les Champignons parasites de l'Homme*, Paris, 1902, p. 140.
[2] *Brit. Med. Journ.*, 1901, I., p. 323.

is more or less destroyed, and the sheath of spores is within or replaces it. Sabouraud asserted that the spores which form the mosaic are ectospores, situated at the ends of mycelial filaments. He believed that the central threads gave off lateral branches, which ended at the surface in the spores. This view is not generally accepted (Pl. XXXVI., Fig. 1).

Mode of Invasion of the Hair.—There has been considerable discrepancy of opinion as to whether the microsporon fungus attacked the hair primarily or whether it became deposited first in the epidermis of the scalp and attacked the hair secondarily. The latter view is the one borne out by the researches of Colcott Fox and Blaxall, who noted the following method of invasion "in many hundreds of specimens." They found that the branching mycelium was present first in the epidermis about the mouths of the follicles, and that it gradually spread down into the follicle encircling the hair. In the lower third of the follicle above the bulb the cuticle became frayed, and allowed the mycelium to make its way beneath it. Leslie Roberts[1] has described a keratolytic ferment in connection with the ringworm fungus, and it may be due to the action of this that the cuticle gives way. The mycelium then spreads upwards beneath the cuticle, stripping it off, and then for a short distance downwards to form the fringe. Immediately beneath the cuticle it breaks up into short segments, which are arranged in rows or groups, and, being large and swollen, are known as *giant-spores*. The latter divide into smaller spores, which coalesce to form the mosaic. A few of the threads enter and constitute the central mycelium, and these form the internal fringe.

Histo-Pathology of the Skin when affected with the Fungi.—The invasion of the fungus in the stratum corneum is accompanied by dilatation of the blood-vessels and a hyperplasia of all the cellular elements both of the epidermis and the cutis. This hyperplasia is at first purely inflammatory in nature, but later it may assume the characters of a granuloma, and plasma-cells and multinuclear cells may be found. The interepithelial lymphatics may be greatly dilated, œdema may occur in the cells, and imperfect cornification or parakeratosis, causing scaliness, and sometimes actual vesiculation, may result.

Cultivation of the Microsporon Audouini—

(*a*) *On French Proof-Agar.*—The microsporon fungus grows

[1] *Brit. Med. Journ.*, 1894, II., p. 685.

PLATE XXXIX.

Cultures of Ringworm.

Fig. 1. Culture of Microsporon Audouini on French Proof Agar, Six Weeks Old.

Shows a small central boss, surrounded by a circular depression, and delicate radiating hyphae.

Fig. 2. Culture of Microsporon Audouini on French Proof Agar, Six Weeks Old.

Shows central boss, well-marked furrows, and delicate hyphae at the periphery.

Fig. 3. Culture of Trichophyton Endothrix on French Proof Agar, Six Weeks Old.

Shows the peculiar crateriform centre, radiating furrows, and coarse hyphae at the margin.

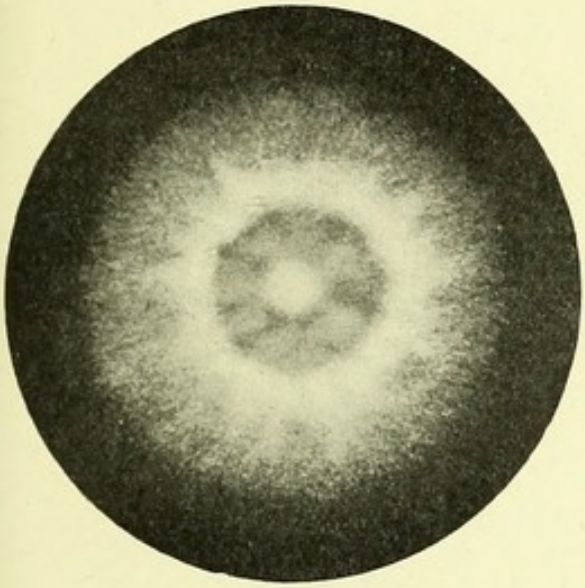
Fig. 4. Culture of Trichophyton Ectothrix on French Proof Agar.

Shows white central boss and coarse hyphae, forming tapering processes radiating from the centre. This culture was made from a child, the source of infection being a horse, the culture from which is shown in Fig. 5.

Fig. 5. Culture of Trichophyton Ectothrix on French Proof Agar, from a Horse.

Shows central mass and coarse radiating processes, which give the culture a stellate appearance.

Note.—For the excellent photographs reproduced in Figs 1, 2, and 3 I am deeply indebted to the kindness of Dr. T. Colcott Fox, and for those reproduced in Figs. 4 and 5 to Dr. J. Lemare Bunch.



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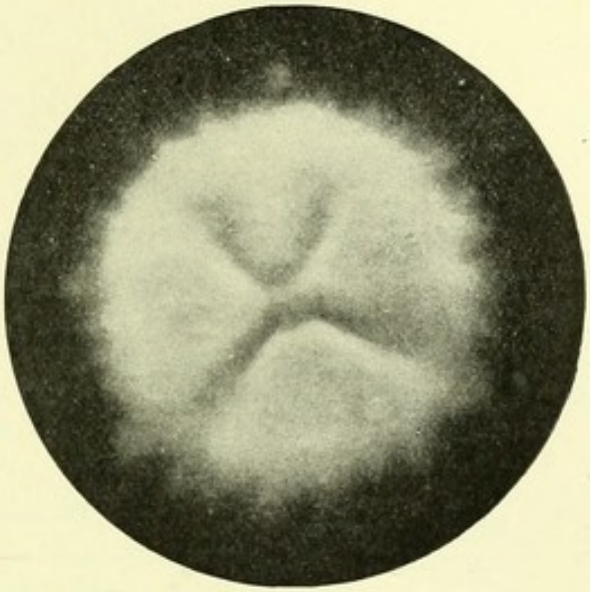

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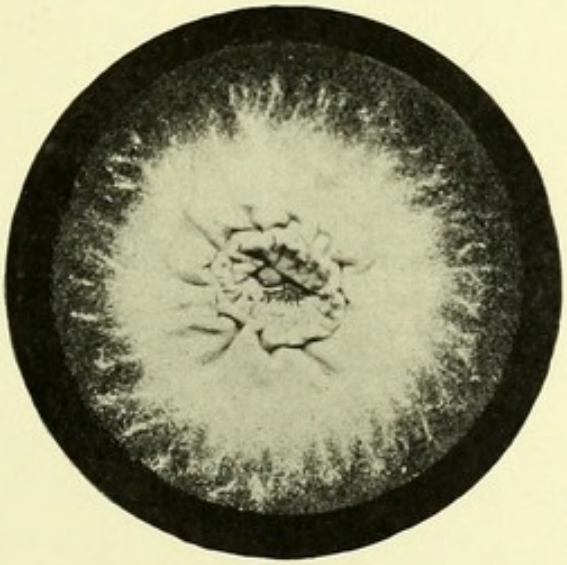

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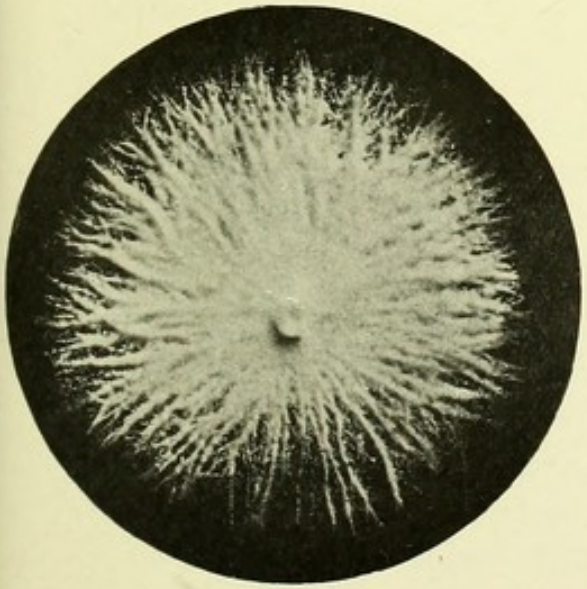


FIG. 4.

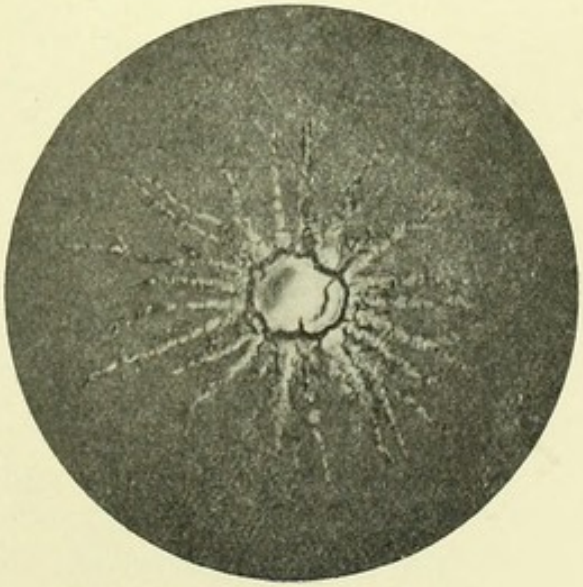


FIG. 5.

slowly. In about a week the growth becomes evident in a circular "satiny" plaque beneath the surface. The "satiny aspect" (Blaxall) is obtained in transmitted light. The margin is defined or shows a fringe of hyphae. Aërial hyphae develop in a few days and extend above the surface. As the colony increases in size, the centre becomes an opaque tuft, and the surface is broken up by concentric rings of a greyish colour. The margin presents a fine downy fringe. It takes six weeks or a couple of months for these characteristics to fully develop (Pl. XXXIX., Fig. 1).

Sabouraud showed that several variations occurred in the cultures produced by inoculating this fungus on proof-agar, and Fox and Blaxall distinguished four such variants, using the same medium for their cultivation. They found that these four invariably "bred true." In six weeks' growth the following four forms were distinguished:

1. Commonest form: Central white knob, surrounded by a whitish grey cushion, and faint concentric markings. Transparent culture.

2. Small central knob in a clear space, surrounded by a network of very delicate hyphae, which radiate to the periphery. Transparent culture.

3. White central plaque with or without a knob, with a sharply circumscribed or fleecy edge. May show geometrical markings. Opaque culture.

4. Small central knob, from which radiate golden furrows. The whole is covered with white down. Opaque culture.

(*b*) *On Potato* the microsporon grows slowly. In about ten days brown discolorations appear, which Sabouraud likened to streaks of dried blood. These become surmounted by aërial tufts of white hyphae.

Reproduction of the Microsporon.—Fox and Blaxall, by means of impression-preparations, demonstrated that the aërial fructification of the microsporon and the trichophyta was constant and that it consisted of a central rod bearing, terminally and laterally, small spores attached by a short pellicle. In cultures they found, in addition, chlamydo-spores and sprouts like those of Botrydia; but these they did not regard as true fructifications, but simply as types which might occur in submerged hyphae (Pl. XXXVIII., Fig. 1).

Sabouraud in hanging-drop preparations distinguished the following three forms of fructification:

1. Reproduction by endoconidia. Swellings appear in the

mycelial threads. The threads break and the swellings take the form of spores.

2. Reproduction by sprouts from the mycelia.

3. Reproduction by multilocular spindles or chlamydospores.

These different forms are to a great extent determined by the different media employed, and by the fungus being grown under different physical conditions with regard to temperature and the presence or absence of air.

Trichophyton Endothrix.

This fungus attacks both the scalp and the glabrous skin.

(*a*) On the *glabrous skin* it generally produces circinate rosy lesions with a distinct border.

(*b*) On the *scalp* two types of this fungus have been described which produce dissimilar lesions ; but recently this distinction has been given up by several careful observers.

1. In the first, known as the *fragile variety*, irregular patches form on the scalp, which are distinguished from those of microsporon by the absence of stumps ; these are replaced by black dots like comedones, due to the breaking off of the hairs at the mouths of the follicles. This variety has been named "bald ringworm" or "black-dot ringworm."

2. In the second variety, which is the more common of the two, short stumps occur, which are shorter than those of the microsporon and have no sheath of fungus. This is known as the *resistant variety* of endothrix. It causes a more or less rounded patch, which is slightly, if at all, scaly, and numerous smaller secondary patches over the scalp, many of which are about the size of finger-nails.

It is extremely probable that the two varieties do not depend on different types of fungus so much as on the degree of infection of the hairs, the type of hair, the condition of the scalp, and possibly the state of virulence of the fungus.

Colcott Fox has observed several cases in which the endothrix fungus attacked the beard, and has reported instances in which it has been associated with kerion of the scalp.

Occurrence and Origin.—

Endothrix may occur at any age. It forms a comparatively small proportion of the scalp-ringworms of this country,

but is in excess of those caused by the T. ectothrix. In Paris it is responsible for about 40 per cent. of the ringworms of the scalp.

It is generally stated to be exclusively of human origin, but Bunch has reported a case in which the source of infection was traced to a cat, and has succeeded, although with difficulty, in inoculating it in a guinea-pig and a rabbit.

Microscopical Appearances of a Hair infected by the Trichophyton Endothrix.—It is difficult to epilate the hairs affected by endothrix, as they are either so short that it is difficult to seize hold of them, or they break when any attempt is made to pull them out. Often the only way to obtain specimens is to express the follicles between the thumb-nail, as in pressing out comedones.

An examination of the hair shows that the cuticle is almost intact and that the hair is filled with mycelial threads and rows of spores like a necklace. Both the rows of spores and the threads are arranged in the long axis of the hair, and extend down as far as the bulb, where they form a fringe, the threads tending to divide dichotomously. The rows of spores are formed by the segmentation of the mycelial threads. The individual spores are considerably larger than those of microsporon, are frequently quadrilateral in shape, and are doubly-contoured (Pl. XXXVII.).

Mode of Invasion of the Hair.—The mycelial threads, broken up into spores, are at first seen within the follicle, encircling the hair. These threads erode the cuticle, beginning just above the bulb (Fox) where they enter the hair. Within it they divide dichotomously, and gradually proliferate till the hair becomes packed with them. The chains outside the cuticle disappear in the fully affected hairs.

Cultivation of T. Endothrix.—

(*a*) *On French Proof-Agar.*—The following is Blaxall's description of the growth: "The growth begins, about the sixth or seventh day, as a little star with divergent rays, more widely separated than those in the microspora. The early opacity of the central part of the growth also serves to distinguish this variety from that of the more transparent microspora. In ten days or a fortnight the culture becomes powdery. When sub-cultures are made, a heap is gradually thrown up in the centre, covered with powder, and spreading from the heap are beautifully ramified submerged hyphae,

lightly dusted over with powdery spores. In about a month's time the heap becomes depressed in the centre, as it were invaginated, leaving a central crateriform cavity. During the process of invagination the surface of the culture cracks, leaving little groups of whitish spores against the dull brown exterior. This gives a curious speckled appearance."

(*b*) *On Potato.*—White or yellowish powdery stars develop, which run together to form a raised surface with a flat top, covered with short white down, rarely crateriform.

Several slightly differing species of cultures of this fungus have been described.

The Mode of Fructification.—Sabouraud has described the following types of fructification in both the trichophytons:

1. Reproduction by a chain of endogenous spores (usual mode).
2. Reproduction by sprouts and clusters of spores.
3. Reproduction by chlamydospores.

Fox and Blaxall regard it as having the same aërial fructification as microsporon (Pl. XXXVIII.).

Trichophyton Ectothrix.

There are several varieties of this fungus. These attack the scalp, beard, glabrous skin, and nails. In the three former situations the lesions which they produce are associated with more or less suppuration.

(*a*) *On the Scalp.*—The Trichophyton ectothrix causes red, raised, boggy patches. These are œdematous, give a feeling of fluctuation, and have been frequently incised with the idea that they were abscesses; but, instead of pus, only a few drops of a sero-purulent fluid oozes out.

Short stumps are found dotted over the patch, which have a sheath, like the stumps in microsporon. They are easily epilated, as they are generally loose in the follicles.

(*b*) *On the Beard-Region* the fungus produces the condition known as *tinea barbae or sycosis barbae.* Here the affected patch is red and raised, and the surface is irregular and lumpy. On these lumps, stumps of hairs are present, situated in follicles, in which suppuration is present. It is a condition of folliculitis. It was this affection of the beard which probably originated the title of sycosis (σῦκον, a fig), from the superficial resemblance of the raised mass, covered with small yellow suppurating

foci, to an everted, fresh, ripe fig, with the seeds dotted over the reddish pink centre.

(*c*) *On the Glabrous Skin* very dissimilar lesions result from it, such as circinate patches with raised vesicular edges, or lumpy raised areas of the so-called conglomerate folliculitis.

(*d*) *On the Nail* (*see* p. 321).—

The chief peculiarity of the lesions caused by this fungus is the association of suppuration. This is generally stated to be the result of inoculation with pyogenic micro-organisms at the same time as the trichophyton or subsequently. Gilchrist believes that the trichophyton itself possesses pyogenic properties. He sterilised the skin of the upper arm with 1 in 500 perchloride of mercury, scarified the surface, and inoculated from a culture of the fungus. He covered the site of inoculation with sterile cotton-wool and sealed it with adhesive plaster. Pustulation occurred under this, but only pure cultures of the trichophyton were obtained.

Occurrence and Origin.—It may occur at any age. It is much rarer on the scalp than the endothrix fungus; but if we include all the regions which the fungus may infect, its frequency is about the same as that of the other trichophyton. It is of animal origin, and such animals as the horse, dog, calf, cat, and mouse are subject to it, and readily infect man.

Microscopical Appearances.—On epilating a hair, it is found that a dense sheath of fungus comes away with it, which extends down as far as the bulb. On examination, this sheath consists of a mosaic of spores, which are larger than those of the microsporon, are not so regularly arranged, and here and there show a tendency to a chain-formation. The fungus is chiefly situated outside the cuticle, but in some cases the latter becomes eroded, and chains of spores appear in greater or less numbers within the hair. For this reason Sabouraud has distinguished two varieties, according as the fungus has penetrated within the cuticle or not. These varieties he named Trichophyton ectothrix and Trichophyton endo-ectothrix. The mycelium and chains of spores run parallel with the long axis of the hair.

The spores vary in shape and size. They are frequently rectilinear in shape, and longer than they are broad. They vary from 4 μ to 12 μ in their long axis. Sepia-coloured spores have also been described. The mycelial threads from the glabrous skin vary in thickness and branch dichotomously.

The method of invasion of the hair is similar to that of the microsporon. The fungus passes down into the follicle and enters below the cuticle immediately above the bulb (Fox and Blaxall), but the circumpilar sheath does not disappear as it does when true endothrix invades the hair, but persists as the most noticeable characteristic of the infection.

Cultivation of T. Ectothrix.—The cultures of the Trichophyton ectothrix vary considerably in detail, but they have certain constant characteristics which serve to distinguish them from those of the other varieties.

(*a*) *On French Proof-Agar.*—They grow more rapidly than the other two fungi. Blaxall states that they may commence to grow on the third day as a white tuft, soon surrounded by a white powder, or by white hyphae covered with a white powder. The earliest appearance is a little star with widely divergent rays, and a central opaque mass. The stellate appearance is very characteristic of the cultures, many of which are white or cream-coloured and powdery, like fine snow. Some of them are more dense, and have a depressed, corrugated centre, and an absence of rays.

(*b*) *On Potato*, dry white powdery colonies form. These are discrete, and have a tendency to curl over. Bodin has described a trichophyton from a horse in which faviform cultures were produced, and Bunch has reported similar cultures in another case in which the infection came from a canary. Bodin found that his cultures presented a brownish tinge. Sabouraud, Fox, and Blaxall have also noted violet and purple tinges in the cultures of the ectothrix fungus. The cause of the coloration is disputed. It has been suggested that it is due to the symbiosis of a pigment-producing bacillus which has become ingested by the mycelium of the trichophyton. Fox and Blaxall regard it as an intrinsic quality of a special variety of trichophyton.

Tinea Imbricata or Tokelau Ringworm.

This type of ringworm, described by Patrick Manson, and an excellent description of the clinical appearances of which is given by Crocker, occurs in the Malayan Peninsula, the Fiji Islands, New Guinea, and other districts in the Tropics. It affects the glabrous skin, and is characterised clinically by a more or less circular scaly patch made up of wavy

PLATE XL.

FIG. 1. BUDDING YEAST FROM A CAVITY IN A BREAKING-DOWN CARCINOMA OF THE SKIN.

The yeast filled the broken-down cavities of the carcinoma. The specimen was in spirit when it was sent, so no cultivation was obtained, nor was there absolute proof that the fungus had been there during life, but it strongly suggested this, since it occurred in several cavities in which there was no apparent connection with the surface. It was regarded as an accidental contamination.

The carcinoma was alveolar in character, and resembled the acini of the sweat-apparatus in its arrangement.

I am indebted to Mr. George Pernet for the tissue from which the specimen was cut.

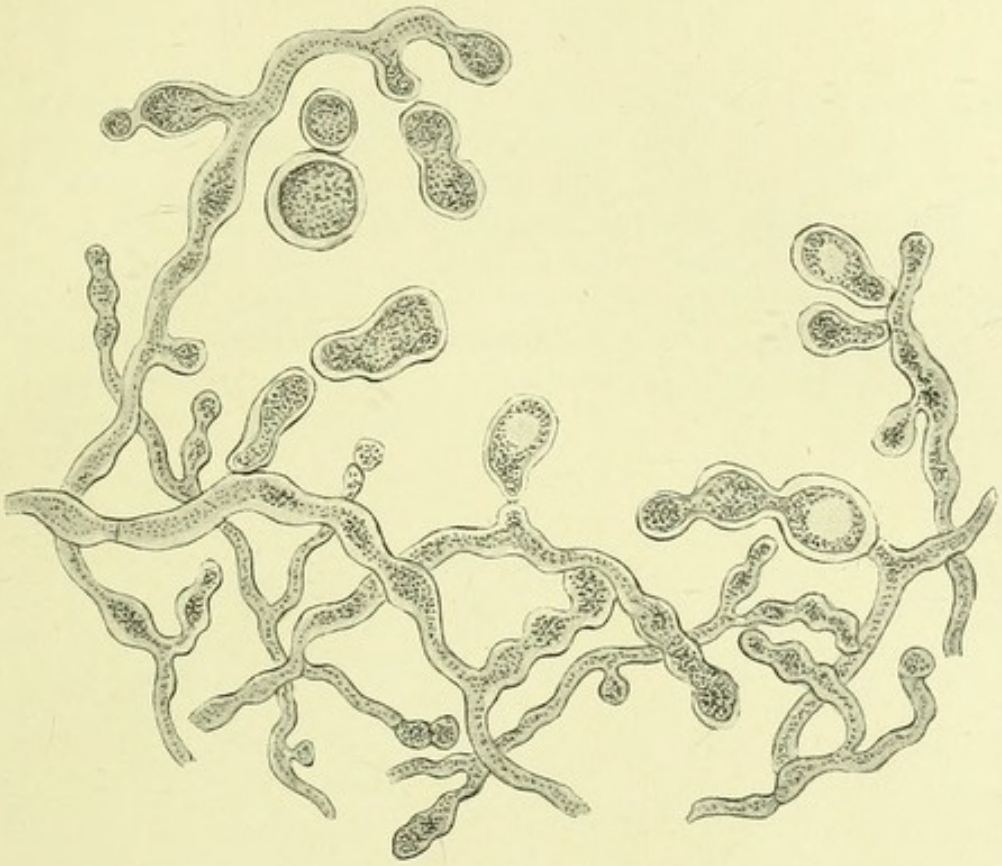
An account of this case by Allworthy and Pernet will be found in the *Brit. Journ. of Derm.*, Vol. XII., 1900, p. 350.

FIG. 2. FUNGI OF BLASTOMYCETIC DERMATITIS AND DERMATITIS COCCIDIOIDES (SEMI-DIAGRAMMATIC). (× about 800).

a. Organism with central granular portion.
b. Budding cell (typical of the organism of blastomycetic dermatitis).
c. Cell dividing by segmentation (typical of the organism of blastomycetic dermatitis).
d. Short jointed mycelial thread with budding. This appearance was found in a section of "Dermatitis coccidioides."
e. Giant-cell formation around organisms (Dermatitis coccidioides).
f. Infiltration of plasma-cells and leucocytes.

In blastomycetic dermatitis the reproduction of the fungus in the tissue takes place by budding. According to the recent paper by Drs. D. W. Montgomery, Ryfkogel, and Howard Morrow in the *Journal of Cutaneous Diseases*, January 1903, in the allied condition which they have named "Dermatitis coccidioides" the organism reproduces itself in the tissues by endocellular sporulation, and they do not regard it as a blastomyces.

NOTE.—For a piece of tissue and a culture from a case of "Dermatitis coccidioides" I am greatly indebted to Dr. Howard Morrow, of San Francisco, and for tissue from a case of blastomycetic dermatitis to Drs. Nevins Hyde and Ricketts of Chicago, through the kindness of Dr. Galloway.



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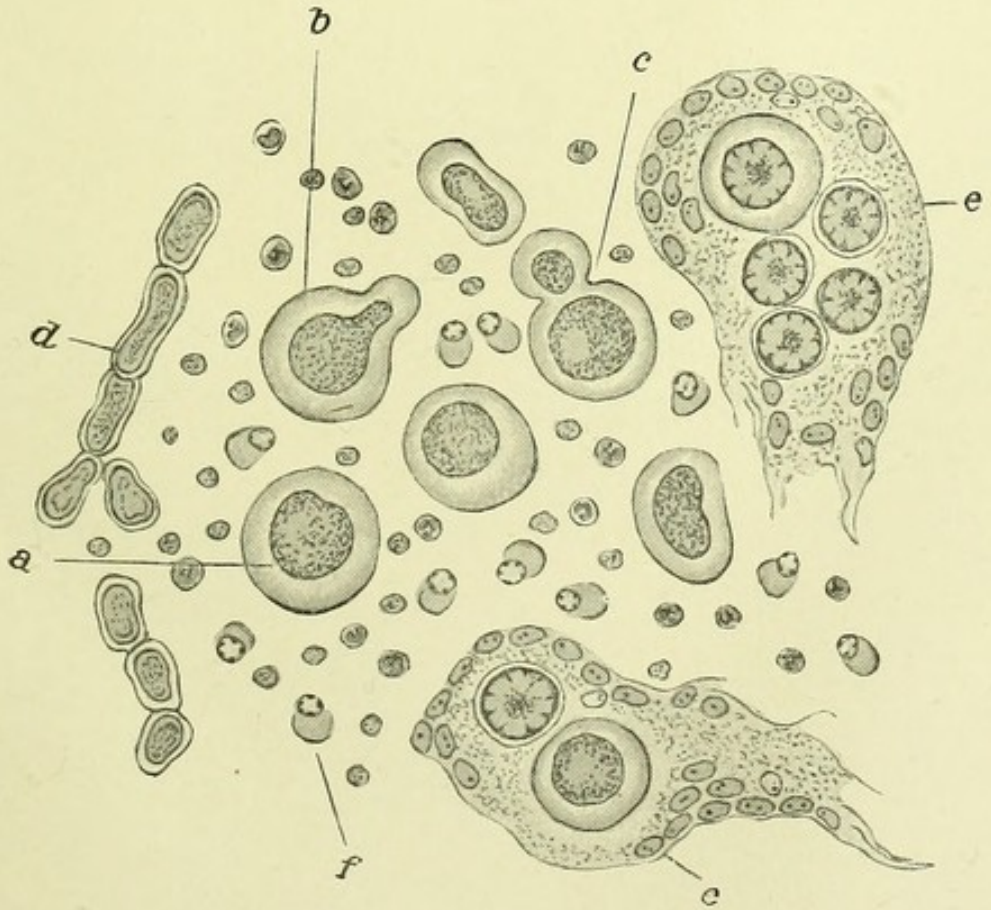

FIG. 2.

J. M. H. M., del.

concentric rings of scales. These patches coalesce, and an appearance not unlike watered silk is produced. The disease disappears spontaneously, leaving deeply coloured ringed patches. It has been compared to "figured ichthyosis." It is caused by a special fungus known as the "*Tinea imbricata*," which is made up of long, straight, or slightly curved mycelial threads which branch dichotomously, and numerous large, oval, or rectilinear spores. It fructifies like aspergillus (Tribondeau).

CHAPTER XL.

ANIMAL PARASITES.

IT will be necessary to refer to only a few of these parasites. Roughly, they may be divided into three groups—namely, those (1) which are parasitic exclusively in man, such as scabies; (2) those which are parasitic in animals and only occasional in man, such as the various ticks, etc.; and (3) accidental parasites, such as the harvest-bug, which only accidentally reaches the human skin, and injures it from an "instinct of self-preservation."

The parasites nourish themselves either from the blood (pediculi) or from the juices of the epidermis (Acarus scabiei). It is in the process of obtaining nourishment, on the one hand, and of self-protection, on the other, that the various lesions of the skin associated with the presence of the parasites are produced.

The animal parasites which find a habitat in the skin may be thus classified:

I. *Acarida*
1. Sarcoptes scabiei.
2. Ixodidae . . . Ticks.
3. Demodex folliculorum.
4. Leptus autumnalis.

II. *Insecta*
1. Hemiptera
(*a*) Cimex lectularis (bed-bug).
(*b*) Pediculi.
2. Diptera
(*a*) Pulex irritans.
(*b*) Pulex penetrans.

III. *Vermes*
1. Filaria sanguinis hominis.
2. Filaria medinensis.

Pediculi.—Three varieties of lice infest the human body, which, from the regions they attack, are named respectively :

(*a*) Pediculi capitis.
(*b*) „ vestimentorum or corporis.
(*c*) „ pubis.

These differ in shape and size. Pediculi are most commonly found in the hairy regions of the body ; they frequently have their habitat in the folds of woollen garments, and attack the body secondarily. They deposit their eggs or nits not only on the hairs of the scalp, but also on those of the axillae, and pubes, and on the lanugo hairs (Jamieson). They produce their pathological action on the skin by piercing it with their probosces, sucking up the blood of their host and injecting the toxic secretion of their salivary glands. In this way they cause punctate lesions, surrounded by an inflammatory halo and associated with more or less pruritus or urticaria. Secondary inoculations of pyogenic cocci cause the multiform appearance of the eruption due to pediculi. This occurs readily in the scalp, so that the presence of pediculi in that situation is generally associated with pustular lesions and crusts about the occipital region, and more or less post-cervical adenitis. Occasionally in weakly children ecthyma and even subcutaneous abscesses may be caused.

The lesions caused by the Pediculus pubis are associated with excessive pruritus, and not infrequently with more or less discoloration of the skin in the neighbourhood in the form of purplish or greenish *tâches*. These discoloured patches are believed to be due to the deposition of a greenish pigment by the pediculus in the skin. This pigment is formed by the pediculus from the hæmoglobin of the blood, and deposited in the fat-cells of the thorax and abdomen of the insect (Ehrmann, Oppenheim[1]). Reddish deposits have also been noted about the pubic hairs, which are generally considered to be the fæcal excrement of the pediculus.

Demodex folliculorum.—This acarus is about ·3 mm. long. It occurs in the sebaceous follicles of the face. In man it rarely produces any pathological effect, but in the lower animals, such as the dog and pig, it may give rise to a severe dermatitis. In several instances it has been known to produce pigmented patches in the human skin.

[1] *Archiv f. Derm. u. Syph.*, 1901, LVII., p. 173.

In a case described by Dubreuilh[1] rough yellowish brown patches occurred in a woman on the face and other situations, and in them numbers of acari were found.

Kraus[2] has found that they can be beautifully demonstrated by staining them with Ziehl-Neelsen's method, in which case they dye an intense red colour, while the surrounding *débris* is stained blue. The method adopted by Kraus was to express the contents of a sebaceous follicle on to a slide, and then to fix and stain the film.

Acarus Scabiei.—The female acarus measures ·35 mm. in length and ·23 mm. in breadth; the male acarus measures ·25 mm. in length and ·15 mm. in breadth. The male is situated on the surface of the skin or beneath crusts. The female, after impregnation, burrows superficially into the stratum corneum.

The presence of these parasites causes an intense pruritus (which is most severe when the patient is warm in bed) and a multiform eruption, complicated through secondary inoculation with pyogenic micro-organisms. The characteristic lesions produced on the skin are the *burrows*. These vary from a few millimetres to several centimetres in length, and appear as beaded ridges on the skin. They slope down from the surface to the basal layer of the stratum corneum, and occasionally bend up to the middle of that layer; they rarely penetrate the Malpighian layer. The opening is covered by a vesicle, pustule, or crust. The channel or "gallery" of the burrow shows numerous acarian eggs and fæces deposited in it. It terminates in a blunt dilated end, in which lies the female acarus, and this is evident on the surface of the skin as a bright shiny speck or papule. The presence of the acari is associated with irritation, which results in the dilatation of the interepithelial lymphatics and frequently in vesiculation. Unna believes this to be the result of a simple chemotactic action caused by the acarus, complicated by the presence of cocci setting up an eczematous process in addition.

Chronic cases have been described in which a desquamation of large thick scales occurred, due to a persistent catarrh of the skin. From its occurrence in Norway this type of scabies has been named *Scabies Norwegica*.

[1] *Journ. de Méd. de Bordeaux*, January 17, 1901.
[2] *Archiv f. Derm. u. Syph.*, 1901, LVIII., p. 351.

Pulex irritans.—The female flea is larger than the male, and it measures about 5 mm. by 2 mm. They cause punctate lesions, which are produced by the proboscis, and are frequently situated in the centre of an urticarial wheal.

Leptus autumnalis causes lesions similar to those produced by the *Pulex irritans*, and they originate in the same manner.

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