LECTURE XI.

MARCH 27, 1858.

PIGMENTARY ELEMENTS IN THE BLOOD. NERVES.

Melanæmia—Its relation to melanotic tumours and colorations of the spleen.
Red blood-corpuscles—Origin—Melanic forms—Chlorosis—Paralysis of the respiratory substance—Toxicæmia.
The nervous system—Its pretended unity.
Nerve-fibres—Peripheral nerves: their fasciculi, primitive fibres, and perineurium—Axis-cylinder (electrical substance)—Medullary substance (Myeline)—Non-medullated and medullated fibres—Transition from the one kind to the other: hypertrophy of the optic nerve—Different breadth of the fibres—Their terminations—Pacinian and tactile bodies.

Gentlemen,—I have still some observations to make to you in reference to the changes of the blood, more for the sake of completeness than because I am able to offer to you in doing so any decisive points of view.

In the first place I wish to mention one other condition which has recently been a great deal talked about, and might, when occasion offered, present increased interest to you, the so-called *melanæmia*. This is a condition most nearly connected with leukæmia, inasmuch we have in it to deal with elements, which, like the colourless corpuscles in leukæmia, make their way from definite organs into the blood and circulate with it. The number of recorded observations concerning this matter is already tolerably large, indeed I might almost say, larger than perhaps is necessary, for it seems indeed that here and there mistakes have slipped in, which should, I think, be again removed from the history of the affection. But unquestionably there is a state in which coloured elements are met with in the blood that do not belong to it. Isolated observations in support of this fact have already for a considerable length of time* been upon record, and indeed first occur in the history of melanotic tumours, concerning which it has frequently been declared that in their neighbourhood minute black particles are met with in the vessels, and the opinion put forward that from this source the melanotic dyscrasia arose. But this is not quite the condition which is meant when melanæmia is now-a-days spoken of. In the last ten years not a single observation has been made known which in any way adds to our knowledge concerning the passage of the particles of melanotic tumours into the blood.

The first observation concerning that class of diseases which in a narrower sense of the word is designated melanæmia, was made by Heinrich Meckel in the case of a lunatic a short time after I had published my description of leukæmia. Meckel found that here too the spleen was enlarged in a very considerable degree and pervaded by black pigment, and he therefore ascribed the change in the blood to an absorption of coloured particles from the spleen. The next observation I made myself (and that too in a class of cases which afterwards proved very fruitful) in the case of an ague-patient, who had long been afflicted with a considerable enlargement of the spleen; for I found in the blood of his heart cells containing pigment. Meckel had only observed free granules and

* Dr. Stiebel, sen., of Frankfort-on-the-Maine, calls my attention to the fact that he had already in a review of Schönlein's Clinical Lectures (in Häser's 'Archiv'), mentioned the occurrence of pigment-cells in the blood.

Note to the Second Edition.

flakes (Schollen) containing pigment. The cells which I discovered in many respects bore a resemblance to colourless blood-corpuscles; they were spherical, but frequently also rather oblong, nucleated cells, within which a greater or less number of large black granules were to be seen. In this case also the occurrence of a large black spleen was again verified. Since that time attention has been continually more and more drawn to these conditions by Meckel himself and by a number of other observers in Germany, and last of all by Frerichs, and in Italy by Tigri. Tigri has not scrupled to designate the disease *milza nera*, from the blackness of the spleen in it, whilst according to the view of Meckel which has been expanded by Frerichs, it is rather one of the more severe forms of intermittent fever which is to be explained in this way.

Fig. 76.

It has been attempted to explain the serious import of these affections by supposing that the elements, which find their way into the blood, accumulate at certain points in the more minute capillary districts, and there produce stagnation and destruction. This was especially held to be the case in the capillaries of the brain, in which they were said to attach themselves after the manner of emboli to the points of division, and so occasion sometimes capillary apoplexies, sometimes the comatose and apoplectic forms of severe intermittent fever. Frerichs has added a new and important kind of obstruction, namely, that of the minute hepatic vessels, which is said ultimately to give rise to atrophy of the parenchyma of the liver.

Fig. 76. Melanæmia. Blood from the right heart (Cf. 'Archiv f. pathol. Anatomie und Physiologie,' vol. ii., fig. 8, p. 594). Colourless cells of various shapes filled with black, and in part angular, pigment-granules. 300 diameters.

If all this be the case, there would seem to exist an extremely important series of conditions directly dependent upon the dyscrasia. Unfortunately I can myself say but little concerning the matter, inasmuch as I have not since my first case again been in a position to observe anything similar. I cannot therefore form a decided opinion with regard to the value of the relations which have been laid down with respect to the connection of the secondary changes with the contamination of the blood. I only wish to remark that all the facts with which we are acquainted concerning these conditions, in dicate that the contamination of the blood has its rise in a definite organ, and that this organ, as in the case of the colourless blood-corpuscles, is generally the spleen.

In the course of my description of the blood I have hitherto scarcely made any mention of the changes which take place in the *red corpuscles*, not by any means because I regarded them as unimportant constituents of that fluid, but because as yet remarkably little is known concerning their changes. The whole history of the red blood-corpuscles is still invested with a mysterious obscurity, inasmuch as no positive information has even at the present time been obtained with regard to the origin of these elements. We only know this much with certainty, as I have already (p. 190) had occasion to remark, that a part of the original corpuscular elements of the blood proceed just as directly from the embryonic formative cells of the ovum, as all the other tissues which build themselves up out of them. We know, moreover, that in the first months of the existence even of the human embryo, divisions take place in the cells, whereby an increase in the number of them present in the blood itself is produced. But after this time all is obscure, and this obscurity indeed corresponds pretty exactly with the period at which the corpuscles in the blood of man and the mammalia cease to exhibit nuclei. We can only say that we are acquainted with no fact whatever which speaks in favour of a further independent development, or of a cell-division, in the blood, but that everything points to the probability of a supply from without. The only hypothesis which has in more recent times been advanced with regard to the independent development of the blood-corpuscles in the blood itself, is that of G. Zimmermann,* who assumed that there were little vesicles present in the blood, which gradually grew by intussusception whilst circulating with it, and ultimately constituted the real blood-corpuscles. Now little corpuscles certainly do occur in the blood (Fig. 52, *h*), only, when they are more accurately examined, a peculiarity reveals itself which is unknown in young embryonic forms, namely that they oppose an extraordinary degree of resistance to the most different agencies. In their ordinary state they are of a beautiful dark red, the colour being very intense and frequently nearly black; if they are treated with water or acids which dissolve the ordinary red corpuscles with ease, it is observed that the little bodies require a very much longer time before they disappear. Upon adding a large quantity of water to a drop of blood, they will be seen to remain for a considerable time after the other corpuscles have disappeared. This peculiarity accords best with what occurs in the changes which take place in the blood, when it is

* Zimmermann has recently ('Archiv f. path. Anat. und Phys.,' vol. xviii., pp. 221–242) given us a more explicit statement of his views, and from it we gather that he considers the blood-corpuscles to originate in small, colourless vesicles which are introduced from the chyle into the blood and may be seen in it when its fluidity has been preserved by means of salts. But probably these vesicles are only artificial products, similar to those described nearly ten years ago by Harting ('Nederl. Lancet,' 1851, 3d ser., 1st Jaarg., p. 224).—*From a MS. Note by the Author.*

extravasated or remains for a long time stagnant within the vessels. Such changes undoubtedly lead to a destruction of the corpuscles, so that in the case of the circulating blood also the conclusion may with great probability be drawn, that the bodies in question are not young forms, engaged in development, but on the contrary old ones in process of decay. I agree therefore essentially with Karl Heinrich Schultz's view, who has described these bodies under the name of melanic (melanöse) blood-corpuscles, and regards them as the precursors of the *moulting* of the blood (Blutmauserung)—preparing for the really excrementitious transformations.

There are certain conditions in which the number of these corpuscles becomes extremely large. In very healthy individuals very few of them are found, only in the blood of the vena portæ Schultz believes he has always observed a considerable number. It is certain, however, that there are diseased conditions in which their number becomes so large, that a greater or smaller quantity of them is met with in nearly every drop of blood. These conditions cannot however as yet be classed in definite categories, because but little attention has been excited with regard to them. They are found in slight forms of intermittent fever, in cyanosis after cardiac disease, in typhoid-fever patients, in the fever accompanying ichorous infection after operations, and in the course of epidemic disorders, still always in such diseases as are accompanied by a rapid exhaustion of the mass of blood and give rise to cachectic and anæmic states. This is one of the processes in which clinical observation also might lead to the conclusion that an abundant destruction was going on in the constituents of the blood within the vessels.

In addition to these changes we have precise knowledge concerning another class distinguished by quantitative changes in the number of the corpuscles. These conditions, of which Chlorosis is the principal representative, offer a certain resemblance to those which are accompanied by an increase in the number of the colourless blood-corpuscles, to leukæmia in a narrower sense of the word and the merely leucocytotic states. Chlorosis is distinguished from leukæmia by the circumstance that the entire number of the corpuscles is smaller. Whilst in leukæmia colourless corpuscles in some sort take the place of the red ones and a real diminution in the number of the cellular elements in the blood is not produced, in chlorosis the elements of both kinds become less numerous, without the occurrence of any definite disturbance in the numerical relation existing between the coloured and colourless corpuscles. This points to a generally diminished formation, and, if we may conclude (as I certainly think one can at the present moment scarcely help doing), that the red corpuscles also are brought to the blood from the spleen and lymphatic glands, all this would indicate that in chlorosis a diminished formation takes place in the blood-glands. Leukæmia is of course much more easily explained, inasmuch as in it we find representatives of the whole mass of cellular elements and can imagine that a part of them, instead of being transformed into red corpuscles, are pursuing their development as colourless ones. In the history of chlorosis, on the contrary, much obscurity still prevails, since we cannot positively demonstrate the existence of a primary affection of the blood-glands. Anatomical observations indicate that the foundations of the chlorotic ailment are very early laid; for the aorta and the larger arteries are usually, and the heart and sexual organs frequently, found imperfectly developed, facts which lead us to infer that the disposition is either congenital or formed in early youth.

A third series of conditions may here too be mentioned, which, however, do not affect the form of the blood-corpuscles, that, namely, in which the internal constitution of these elements has undergone changes, without the production of any definite morphological effect. Here we have essentially to deal with functional disturbances which are probably connected with more subtle changes in the composition of the blood, changes in the proper *respiratory substance* (respiratorische Substanz). For just as in muscles we find the substance of the primitive fasciculus, the compact mass of syntonine, to be the contractile substance, so in the contents of the red corpuscles do we recognize the presence of the really active, respiratory substance. This under certain circumstances undergoes changes which render it incapable of continuing its functions, a kind of paralysis, if you will. That something of the kind has occurred we see from the fact that the corpuscles are no longer capable of absorbing oxygen, as may be directly proved by experiment. That molecular changes in the composition of the blood are here really at work, we find satisfactory evidence in the action of poisonous substances which, even in extremely minute quantity, so change the hæmatine that it is thrown into a kind of paralysis. To these substances belong a part of the volatile compounds of hydrogen, for example, arseniuretted and cyanuretted hydrogen, and further, according to Hoppe's investigations, carbonic oxide, of all of which comparatively very small quantities are sufficient to diminish the respiratory power of the corpuscles. Analogous conditions have already long since been observed by many in the course of typhoid fevers, in which the capability of taking up oxygen decreases in proportion as the disease assumes a severe and acute character. Microscopically, however, with the exception of a few melanic corpuscles, scarcely anything is to be seen; chemical experiment and the coarse perception of the naked eye in this instance alone discover the occurrence of peculiar changes. It may therefore be said that in this quarter really the most has yet to be done. We have rather presumptive evidence than facts.

If now we briefly sum up what I have laid before you concerning the blood, we see, either that certain substances find their way into it, which exercise an injurious influence upon its cellular elements and render them incapable of performing their functions; or that from a definite point, either from sources external to the body, or from some organ, matters are conveyed into it, which thence exercise an injurious influence upon other organs; or finally that its constituents are not replaced and regenerated in a regular manner. Nowhere in this whole series do we find any one condition, indicating that definite changes once set on foot in the blood itself can be *permanently* maintained, in other words that a permanent dyscrasia is possible, unless new agencies derived from a definite source are continually brought to bear upon the blood. This is the reason why I began by calling your attention to this point of view, which I conceive to be of extreme importance in practice also, namely, that in all forms of dyscrasiæ the chief point is to search for their local origin.

Let us now proceed to the consideration of another subject which comes next in historical importance, namely the *structure and arrangement of the nervous system.*

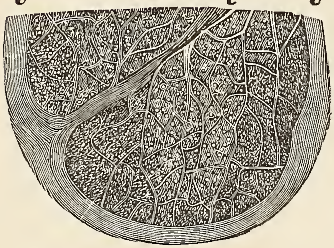
The great mass of the nervous system consists of *fibrous constituents.* It is to them that nearly all the finer physiological discoveries, which the last fifteen years have brought with them, have reference, whilst the remaining portion of the nervous system, in quantity much smaller, namely, the *grey*, or *ganglionic*, substance, has hitherto opposed difficulties even to histological investigation which are still far from being overcome, so that the experimental examination of this substance has scarcely been able to be taken in hand. It is indeed often maintained that a great deal is now known about the nervous system, but our knowledge is for the most part confined to the white substance, the fibrous portion, whilst we are unfortunately obliged to confess that, both in an anatomical, but more especially in a physiological point of view, we are still involved in the greatest uncertainties with regard to the grey substance, which, as far as its functions are concerned, manifestly holds a much higher position.

As soon as we consider the question of the influence exercised by the nervous system in the different processes of life, anatomically, a single glance suffices to show, that the point of view which neuro-pathologists have been accustomed to set out with, is a very erroneous one. For they fancied they saw in the nervous system an unusually simple whole, from the unity of which resulted the unity of the body in general, of the whole organism. But even though one has nothing but very rough anatomical ideas concerning the nerves, still one ought not to shut one's eyes to the fact that this unity is in a very sorry plight, and that even the scalpel demonstrates the nervous system to be an apparatus composed of an extremely large number of parts of relatively equal value without any single discoverable central point. The more accurately we make our histological investigations, the more do the elements multiply, and the ultimate composition of the nervous system proves to be disposed upon a plan analogous to that which has been followed in all the other parts of the body. An infinite quantity of cellular elements manifest themselves side by side, more or less autonomous, and in a great measure independent of one another.

If in the first instance we exclude the ganglionic substance and confine ourselves simply to the fibrous matter, we have on the one hand the real (peripheral) *nerves* in the narrower sense of the word, and on the other the large accumulations of *white medullary substance*, of which the greater part of the cerebrum, cerebellum, and the columns of the spinal marrow is composed. The fibres of these different parts are indeed on the whole similarly constructed, but disclose in their intimate structure such numerous, and in part, such considerable differences, that there are spots, with regard to which even at this very moment we cannot say with certainty whether the elements we have before us are really nerves, or belong to an altogether different kind of fibres. The greatest certainty has been acquired with regard to the structure of the ordinary peripheral nerves; in them the following can generally be distinguished with tolerable facility.

All the nerves which can be followed with the naked eye contain a certain number of subdivisions, or fasciculi, which afterwards separate in the form of branches or twigs. On tracing out these individual twigs which keep continually dividing, we find that the nerve under nearly all circumstances retains a fascicular arrangement until nearly its ultimate divisions, so that every fasciculus in its turn comprises a greater or less number of so-called primitive fibres. The term, primitive fibre, which is here employed, was originally selected, because a nerve-fasciculus was regarded as analogous to the primitive fasciculus of a muscle. This notion afterwards became almost obsolete, and Robin was the first who in more recent times again directed attention to the substance which holds the fasciculus together and which he called *perineurium*. It consists of very dense connective tissue, which upon the addition of acetic acid, it seen to contain small nuclei, and is different from the looser connective tissue which in its turn holds the fasciculi together and constitutes the so-called *neurilemma.*

Fig. 77.

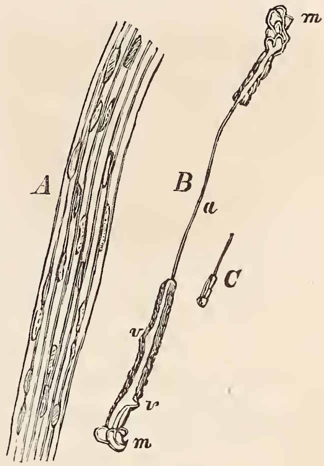


When we use the term nerve-fibre alone in its histological sense, we always mean the primitive fibres, and not the fasciculi which to the naked eye look like fibres. These ultimate fibres in their turn possess, one and all, a special external membrane, which, when it has been entirely freed from its contents—a matter certainly very difficult to accomplish, but sometimes occurring spontaneously in pathological conditions, as for example in certain states of atrophy—displays nuclei upon its walls (Fig. 5, *c*). Within these membranous tubes lie the proper *nerve-contents*, which in ordinary nerves may again be divided into constituents of two descriptions. These can scarcely be distinguished apart in a nerve which is quite fresh ; but in a short time after it has perished or been cut out, or after the action of any medium upon it, they at once separate very distinctly from one another, one of the constituents undergoing a rapid change which has generally been termed coagulation, and by means of which it is marked off from the other constituent (Fig. 78). When this has taken place there is distinctly seen in the interior of the nerve-fibre, the so-called axis-cylin-

Fig. 77. Transverse section through one of the trunks of the brachial plexus. *l*, *l*. Neurilemma, from which one thicker partition *l'* and finer prolongations, indicated by light-coloured lines, run through the nerve and divide it into small fasciculi. These exhibit the dark, punctated, transverse sections of the primitive fibres, and between them is seen the perineurium. 80 diameters.

der (the primitive band of Remak), a very fine, delicate, pale structure ; and round about it a tolerably firm, dark mass, here and there running together, the *nerve-medulla* or *medullary sheath* [white substance of Schwann] ; this fills up the space between the axis-cylinder and the external membrane. But the nerve-tube is generally so tightly filled with its contents that, when viewed in the ordinary way, scarcely anything is seen of the separate constituents, the axis cylinder being always with difficulty visible within the medullary substance. Hence the fact may be accounted for, that its very existence was disputed for years and the view proclaimed by many, that it was also an appearance due to coagulation, produced by a separation of the originally homogeneous contents into an internal and external mass. This view is however unquestionably incorrect: every mode of examination at last discloses this primitive band ; even in transverse sections of nerves the axis-cylinder is very distinctly seen in the interior, with the medulla round about it.

Fig. 78.



It is the so-called nerve-medulla which gives the nerve-fibres in general their white appearance ; wherever the nerves contain this constituent, they look white ;

Fig. 78. Grey and white nerve-fibres. *A.* A grey, gelatinous nerve-fasciculus from the root of the mesentery, after the addition of acetic acid. *B.* A broad white primitive fibre from the crural nerve : *a* the axis-cylinder laid bare, *v*, *v* a varicose state of the fibre with its medullary sheath ; at the end at *m*, *m* the medullary matter (myeline) protruding in convoluted forms. *C.* A fine, white primitive fibre from the brain, with its axis-cylinder protruding. 300 diameters.

wherever it is wanting, they appear translucent and grey. There are therefore nerves which are akin in colour to ganglionic matter, are comparatively transparent and possess a more clear and gelatinous appearance than the others; and they have thence been called *grey* or *gelatinous nerves* (Fig. 78, *A*). Between the grey and white nerve-substance therefore there does not exist the difference that the one is ganglionic and the other fibrous, but only this, that the one contains medulla and the other does not. In general the absence of medulla in a nerve stamps it as one of a lower and more imperfect kind, whilst the presence of this substance announces a more abundant nutrition and a higher development in the part.

Not long ago I made an observation in which a direct illustration of the practical importance of these two conditions was displayed in a very unexpected manner, the usually translucent grey nerve substance having been transformed into an opaque and white matter, namely in the retina. I found namely entirely by accident one day, in the eyes of a man in whom I was looking for changes of quite another kind—round about the papilla of the optic nerve, where the uniformly translucent retina is ordinarily seen—a number of whitish,

Fig. 79.

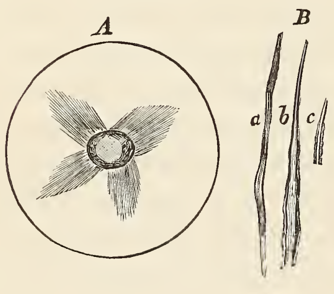


Fig. 79. Medullary hypertrophy of the optic nerve within the eye (Cf. 'Archiv f. pathologische Anatomie und Physiologie,' vol. x., p. 190). *A*. The posterior half of the globe of the eye, seen from before; from the papilla of the optic nerve proceed in four directions radiating striæ of white fibres. *B*. Fibres from this optic nerve in the retina, magnified 300 times: *a*, a pale, ordinary, slightly varicose fibre, *b*, one with a gradually thickening medullary sheath, *c*, a similar one with its axis-cylinder protruding.

radiating striæ like those which one sometimes meets with upon a small scale in dogs, and pretty constantly in rabbits in different directions. The microscopical examination showed that, like as in these animals, medullated fibres had developed themselves in the retina, and that its fibrous layer had become thicker and opaque in consequence of the assumption of medullary substance. On examining the individual fibres I found, on tracing them from the fore and middle parts of the retina backwards towards the papilla, that they gradually increased in breadth, and at the same time displayed, at first in an almost imperceptible, but afterwards in a very striking manner, an investing layer of medulla. This is a kind of transformation, therefore, which essentially impairs the functions of the retina, for this delicate membrane becomes thereby more and more impervious to light, inasmuch as the white substance does not suffer the rays of light to pass through.

The same change occurs in nerves during their development. A young nerve is a delicate, tubular structure, provided with nuclei at certain intervals and containing a pale grey substance. The medulla does not appear until afterwards, and then the nerve becomes broader and the axis-cylinder becomes distinctly defined. It may be said therefore that the medullary sheath is not an absolutely necessary constituent of a nerve, but is added to it only when it has arrived at a certain stage in its development.

Hence it follows that this substance, which was formerly regarded as the essential constituent of a nerve, according to present views plays a subordinate part. Those only who do not even now admit the existence of the axis-cylinder, regard the white substance of course not only as the greatly predominating constituent, but also as the really active element of the nerve-contents.

Now it is very remarkable that this same substance is one which most extensively prevails in the animal body. I had, curiously enough, in the first instance in the examination of lungs come across forms which presented very similar qualities to those which we observe in the medulla of the nerves. Although this was very surprising, yet I did not really think there was an actual correspondence, until I was gradually led by a series of further observations which accumulated in the course of several years, to examine a number of tissues chemically. The result showed, that there scarcely exists a tissue rich in cells in which this substance does not occur in large quantity; still it is only in the nerve-fibre that we observe the peculiarity, that the substance separates as such, whilst in all other cellular parts it is contained in a finely divided state in the interior of the cells, and is only set free when the contents undergo a chemical change, or are subjected to the action of chemical reagents. From blood-cells, from pus-corpuscles, from the epithelial cells of the most various glandular parts, from the interior of the spleen and similar glands unprovided with excretory ducts, this substance can in every case be obtained by extraction. It is the same substance which forms the principal constituent of the yellow mass of yolk in the hen's egg, whence its taste and peculiarities, especially its peculiar tenacity and viscidity which are employed for the higher technical purposes of the kitchen, are familiar to every one. It is this substance, for which I have proposed the name of *medul-*

Fig. 80.

Fig. 80. Drops of medullary matter (myeline—according to Gobley, lecithine). *A*. Differently shaped drops from the medullary sheath of cerebral nerves, after they have become swollen up with water. *B*. Drops from decomposing epithelium from the gall-bladder in their natural fluid. 300 diameters.

lary matter (Markstoff), or *myeline*, that in extremely large quantity fills up the interval between the axis-cylinder and the sheath in primitive nerve-fibres.

If the nutrition of a nerve suffer disturbance, this substance diminishes in quantity and indeed may under certain circumstances totally disappear, so that a white nerve may be again reduced to the condition of a grey or gelatinous one. This constitutes *grey atrophy*, or *gelatinous degeneration*, in which the nerve-fibre in itself continues to exist, and only the peculiar accumulation of medullary matter has been affected. Herein you may seek for an explanation of the circumstance, that in many cases where, in accordance with the results of anatomical investigation, it was formerly thought one might expect to find a part completely incapable of fulfilling its functions, proof has been afforded by means of clinical observation, aided by electricity, that the nerve is still capable of performing its functions, although in a less degree than normal. Hence too it is manifest that the medulla cannot be the constituent in which lie vested the functions of the nerve as such. To the same conclusion physical investigations also have generally led, and at the present time therefore the axis-cylinder is pretty generally looked upon as the really essential constituent of the nerve, which is also present in pale nerves, whilst in white ones it can only be distinctly isolated by the separation of the investing medullary sheath. The axis-cylinder would therefore seem to be the real *electrical substance* of natural philosophers, and we may certainly admit the hypothesis which has been advanced, that the medullary sheath rather serves as an isolating mass, which confines the electricity within the nerve itself, and allows its discharge to take place only at the non-medullated extremities of the fibres.

The peculiar nature of the medullary matter most fre quently displays itself in this way, that when a nerve is torn across or cut (Fig. 78, *m*, *m*), the medulla usually protrudes from it, presenting, especially after it has been acted upon by water, a peculiar striated appearance (Fig. 80, *A*). It takes up water namely, which is a proof that it is not a neutral fatty substance in the ordinary sense of the term, but can at most, on account of its great power of swelling up, be compared to certain saponaceous compounds. The longer the action of the water lasts, the longer are the masses which protrude from the nerve. They have a peculiar, ribbon-like appearance, keep continually acquiring new streaks and layers, and give rise to the most singular shapes. Frequently also fragments become detached and swim about, forming peculiar, stratified bodies, which in recent times have been confounded with corpora amylacea, but are distinguished from them in the most positive manner by their chemical reactions.

Fig. 81.

With regard to the histological varieties of nerves amongst themselves, investigation shows that in different parts more or less highly developed forms greatly predominate. On the one hand, namely, the nerves are essentially distinguished by the breadth of their primitive fibres, on the other hand, by the presence of medulla. We have very broad, middle-sized and small white fibres, and in like manner broad and fine grey fibres. A very considerable size is generally speaking but seldom attained by the grey ones, because the size of a nerve depends more upon the greater or less quantity of medulla it contains than upon the volume of the axis-cylinder, but still variations present themselves

Fig. 81. Broad and narrow nerve-fibres from the crural nerve with the medullary substance irregularly swollen up. 300 diameters.

everywhere, so that some nerves are coarser and others finer.

Generally, we may say, that the primitive fibres usually become finer in the terminal portions of nerves, and that the ultimate ramifications of these latter are wont to contain comparatively the finest fibres ; still this is not an absolute rule. In the optic nerve we commonly find from the very moment of its entrance into the eye only very narrow, pale fibres (Fig. 79, *a*), whilst the tactile nerves of the skin present quite up to their terminations comparatively broad and dark bordered fibres (Fig. 83). It has not yet been found possible to arrive at any certain opinion with regard to the import of the different kinds of fibres from their breadth and the proportion of medulla they contain. For a time it was believed that a distinction of this sort could be established between them, namely, that the broad fibres were to be regarded as derived from the real cerebro-spinal parts, the fine ones as parts of the sympathetic ; but this is not found to be borne out by facts, and all that can be said is, that the ordinary peripheral nerves certainly are abundantly provided with broad fibres, whilst the sympathetic nerves contain a comparatively larger portion of fine ones. In many places, as for example in the abdomen, grey, broad fibres predominate (Fig. 78, *A*), with regard to the nervous nature of which doubts are still entertained by some. For the present, therefore, no definite conclusions can be drawn as to any difference in the functions of a nerve from its mere structure, although it can scarcely be doubted that such differences must exist, and that a broad fibre must exhibit other properties, even if only quantitatively different, than a fine one, a medullated fibre others than a non-medullated one. However concerning all this nothing is at present known with certainty ; and since it has been demonstrated by more delicate physical investigations that the nerves, which had been previously assumed only to conduct in the one or the other direction, possess the power of conduction in both directions, I should not, I think, be justified in here advancing any hypotheses with regard to their centripetal or centrifugal conduction.

The great difference, gentlemen, which is to be remarked in regard to the functions of individual nerves, cannot as yet be referred so much to any difference of structure in them, as to the peculiarity of the structures with which the nerve is connected. Thus on the one hand the special function of the central organ from which the nerve proceeds, and on the other, the special nature of its distal termination, afford a clue to its own specific functions.

With reference to the terminations which the nerves present at their peripheral extremities, histology has, I should say, in the course of the last few years celebrated its most brilliant triumphs. Previously it was, as you well know, a matter of dispute whether the nerves ended in loops or in plexuses, or whether their terminations were free, and the one or the other opinion was held with equal exclusiveness. Now, we have examples of most of these modes of termination, but the fewest of that form which was for a time regarded as the regular one, namely the termination in loops.

The most manifest form of termination, though the one whose functions are, singularly enough, even now the least known, is that in the so-called *Pacinian* or *Vaterian** *bodies*—organs, concerning the import of which we are still unable to make any statement. They are found in man comparatively most marked in the adipose tissue of the ends of the fingers, but also in tolerably large

* Vater was professor at Wittenberg, and died in 1751.

numbers at the root of the mesentery; most distinctly and readily, however, in the mesentery of the cat, in which they extend a considerable distance up, whilst in the human body they are situated only at the root of the mesentery, where the duodenum comes in contact with the pancreas in the neighborhood of the solar plexus. Moreover they present great variations in different individuals. Some have very few, others a great number, of them, and it is very possible that certain individual peculiarities result therefrom. Thus I have, for example, on several occasions found a great number of these bodies in lunatics, though I do not wish at present to lay any great stress upon this discovery.

Fig. 82.

A Pacinian body, as seen with the naked eye, is of a whitish colour, usually oval and somewhat pointed at one end, from a line to a line and a half (1—1½‴) long, and firmly attached to a nerve in such a way that a single primitive fibre passes into each body. It presents a comparatively large number of elliptical and concentrical layers, which at the upper end are in pretty close contact, but at the other are separated by a wider interval, and enclose in their interior an oblong space generally some-

Fig. 82. Vaterian or Pacinian body from the subcutaneous adipose tissue of the end of a finger. *S.* The peduncle, consisting of a dark-bordered, medullated primitive nerve-fibre *n*, and the thick perineurium *p*, *p* provided with longitudinal nuclei. *C.* The body itself with the concentric layers of the perineurium which is swollen out into a bulbous shape—and the central cavity, within which the pale axis-cylinder is seen running along and terminating in a free extremity. 150 diameters.

what more pointed towards the upper end. Within these layers nuclei can be distinctly seen disposed in regular order, and on following the layers towards the stem of the nerve, they are there observed finally to pass into the perineurium which is in this part very thick. They may therefore be regarded as gigantic developments of the perineurium, which however only enclose a single nerve-fibre. Now on tracing the nerve-fibre itself we observe that its medullated portion usually extends only up to the beginning of the body, when the medulla disappears and the axis-cylinder is seen continuing its course alone. It then runs on through the central cavity, and terminates at no great distance from the upper end generally simply, yet often in a little bulbous swelling* and in the mesentery very frequently in a spiral coil. In rare cases it happens that the nerve divides and several branches pass into the body. But in every case we seem to have before us a mode of termination. What these bodies signify, what office they perform, whether they have anything to do with the function of sensation, or whether their province is to develop any one of the properties of the nervous centres, we are as yet entirely ignorant.

A certain degree of resemblance to these structures is exhibited by the *tactile bodies* which have been recently so much the subject of discussion. When the skin and more especially the sensitive part of it is microscopically examined, two sorts of papillæ, as was first discovered by Meissner and Rud. Wagner, are distinguished, the one narrower, the other broader, though certainly intermediate forms are met with (Fig. 83). In the narrow ones we constantly find a simple, in broader ones of the same class a branching, vascular loop, but no nerve. This

* Quite recently Jacubowitsch has, as he thinks, discovered a ganglion cell in this part.—*MS. Note of Author.*

point is so far of importance, that we have, by means of these observations, been made acquainted with a new nerveless structure. In the other kind of papillæ we very frequently find no vessels at all, but on the other hand nerves, and those peculiar structures which have been designated tactile bodies.

A tactile body manifests itself as an oblong-oval structure, tolerably distinctly marked off from the remainder of the papilla, and has, with some degree of boldness indeed, been compared by Wagner to a fir-cone. It is generally rounded off at the upper and lower end, and does not exhibit a longitudinal striation, as the Pacinian bodies do, but on the contrary transverse nuclei. Now a nerve runs up to every one of these bodies, and from every one of them a nerve returns, or more correctly, we usually see two nervous filaments, generally pretty

Fig. 83.

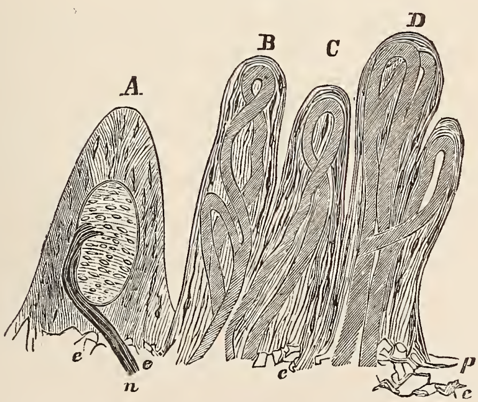


Fig. 83. Nervous and vascular papillæ from the skin of the end of a finger, after the separation of the epidermis and rete Malpighii. *A*. Nervous papilla with a tactile body, up to which ascend two primitive nerve-fibres *n*; at the base of the papilla fine elastic networks *e*, from which fine fibres radiate, between and on which connective-tissue-corpuscles are to be seen. *B*, *C*, *D*. Vascular papillæ, with, at *C*, simple, at *B* and *D*, branching vascular loops, and in addition fine elastic fibres and connective-tissue-corpuscles; *p*. the papillary body running its horizontal course, at *c* fine stellate cells belonging to the cutis proper. 300 diameters.

close to one another, which can be readily traced up to the side or base of the body. After this point their course is very doubtful, and in different cases the conditions vary so much that we have not yet succeeded in making out with certainty the relation of the nerves to these bodies. In many cases, namely, the nerve is very distinctly seen to ascend and also to entwine itself around the body. Sometimes it seems as if the body really lay in a nervous loop, and thus the possibility of a more concentrated action on the part of external agencies upon the surface of the nerve was provided for. At other times again it looks as if the nerve came to a termination much sooner, and buried itself in the body. Some have assumed, with Meissner, that the body itself belongs to the nerve which resolves itself into it. This I do not hold to be correct, and the only point which seems to me to be doubtful is, whether the nerve ends in the body or forms a loop around it.

Apart from anatomical and physiological considerations, this example is of great value in the interpretation of pathological phenomena, because we here find two complete contrasts in parts which in themselves are quite analogous; for, on the one hand, we have nerveless but vascular, on the other, non-vascular, papillæ, yet provided with nerves. The peculiar relations which the layers of the rete mucosum and epidermis bear to the two kinds of papillæ, do not appear to present any essential differences. They are nourished just as perfectly over the one sort as over the other, and seem to be just as little provided with nerves over the one as over the other.

These are facts which indicate a certain independence in individual parts and furnish distinct evidence that parts of considerable size and even richly provided with nerves can subsist, maintain their existence and perform their functions without vessels, and that on the other hand parts which relatively contain numerous vessels, can absolutely dispense with nerves without incurring any disturbance in the state of their nutrition.

LECTURE XII.

MARCH 31, 1858.

THE NERVOUS SYSTEM.

Peripheral terminations of the nerves—Nerves of special sense—The skin and the distinction of vessel-, nerve-, and cell-territories in it—Olfactory mucous membrane—Retina—Division of nerve-fibres—The electrical organ of fishes—Muscles—Further consideration of nerve-territories—Norvous plexuses with ganglioniform enlargements—Intestines—Errors of the neuro-pathologists.

The great nervous centres—Grey substance—Ganglion- [nerve-] cells containing pigment—Varieties of ganglion-cells; sympathetic cells in the spinal marrow and brain, motor and sensitive cells. Multipolar (polyclonous) ganglion-cells—Different nature of the processes of ganglion-cells.

I RETURN, gentlemen, to-day once more to the skin. The difference which exists between the individual papillæ of the skin seems to me so important theoretically, that I think I must claim your special attention to it. In the greater number of the papillæ we see, as I mentioned to you the last time, a single or, when the papilla is very large, a branched, vascular loop. The majority of these vascular papillæ have no nerves; others again which contain tactile bodies, no vessels. If we imagine the vessels and tactile bodies removed, there remains only a very small quantity of substance in the papilla, but within it there still are morphological elements, and it is easy to convince oneself that connective tissue with its corpuscles (which latter after injection are very easily distinguished from the vessels), is in immediate contact with the cells of the rete mucosum (Fig. 83). The case is especially favourable when, in consequence of any disease, as for example small-pox, a slight tumefaction of the whole thickness of the skin in the parts affected has taken place, and the corpuscles are a little larger than they normally are. In ordinary papillæ it is somewhat more difficult to discover these elements, still upon closer examination they may be seen everywhere, even by the side of the tactile bodies.

Thus, even in the finest of these prolongations of the cutis, it is not an amorphous mass which is found, bearing a constant relation to the vessels and nerves ; on the contrary this mass of connective tissue always manifests itself as the one thing invariably present in the structure, as the real fundamental constituent of the different (vascular and nervous) papillæ, and the individual papillæ do not acquire a different character until in the one case vessel, in the other nerves, are added to this fundamental substance.

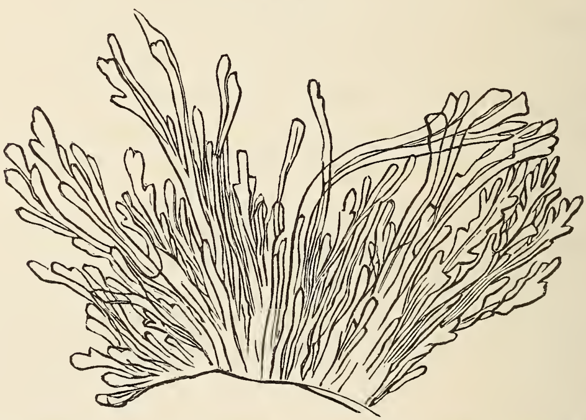
We certainly know little concerning the special relations which the vascular papillæ bear to the functions of the skin, still it can scarcely be doubted that an important relation must exist, and that as soon as we are better able to separate the different offices of the skin, greater importance will be attached to the vascular papillæ also. This much however we can even now say, that it is incorrect to imagine that a special nervous branch exists in every anatomical division of the skin : just as physiological experiments* show that considerable sensitive districts exist in the skin, so also more minute histological investigation teaches us that there is a relatively scanty termination of nerves upon the surface. If therefore we think fit to divide the skin into definite territories, those

* The allusion is to Weber's experiments with compasses.—*Trans.*

appertaining to the nerves will, as a matter of course, be larger than those belonging to the vessels. But every vessel territory (papilla) also which is marked out by a single capillary loop is divided into a series of smaller (cell-) territories, all of which certainly lie along the banks of the same vessel, but still have an independent existence, each of them being provided with a special cellular element.

In this manner it is very easy to explain how within a papilla a single (cell-) territory may become diseased. Suppose, for example, that such a territory swells up, increases in size, and continually keeps shooting farther and farther upwards, then arborescent ramifications may

FIG. 84.



arise (accuminate [spitzes] condyloma*) without the whole papilla's being affected in a like manner. The

Fig. 84. The fundamental substance (connective tissue) of an acuminate condyloma of the penis with freely budding and branching papillæ, after the epidermis and the rete mucosum have been completely detached. 12 diameters.

* The Germans speak of condylomata *lata* and *acuminata*. The condyloma *latum* is *invariably* of syphilitic origin, and is identical with the *plaque muqueuse* of the French, who *never* use the term *condylome* in *this* sense. Condyloma *acuminatum*, on the contrary (by the French termed simply *condylome*), is *not* syphilitic in its nature, but frequently occurs in gonorrhœa, though it is also met with *independently* of this disease.—*From a MS. Note by the Author.*

vessel does not shoot up until later and forces its way into the branches when they have already attained a certain size. It is not the vessel which pushes out the parts by its development, but the first signs of development always show themselves in the connective tissue of the papilla. The study of the conditions of the skin therefore affords special interest to those who wish to devote themselves to the critical examination of the doctrines held concerning general pathology. And first with regard to the neuro-pathological views, it is quite inconceivable how a nerve which lies in the middle of a whole group of nerveless parts, can contrive to force a single papilla from among this group, with which it has not the slightest connection, into a state of pathological activity in which the remaining papillæ of the same nerve-territory take no share. Just as difficult is it, in the diseases of non-vascular papillæ, to find an explanation which shall accord with the views of a humoro-pathologist. Even when in a vascular papilla the different cell-territories attain different states, these would not admit of a ready explanation, if we were to regard the whole process of nutrition in a papilla as directly dependent upon the general condition of the vessel which supplies it.

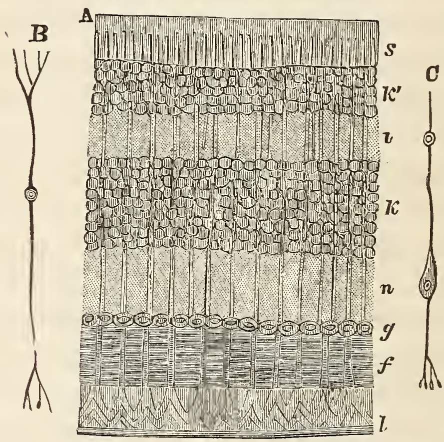
Similar considerations might be entered upon with regard to all points of the body. Still we have in the skin a particularly favourable example for demonstrating how very incorrect it is to regard all vessels as subject to a particular nervous influence. There are a number of vessels which are entirely removed from the influence of all nerves, and, if we still confine our attention to the skin, the influence which a nerve is in a condition to exercise, is limited to this, that the afferent artery, which supplies a whole series of papillæ in common (Fig. 44) may by its means be brought into an altered condition, so that a contraction or dilatation, and in correspondence with these states a diminished or increased supply of blood to a considerable district, takes place.

If now we return from this digression to our real subject, you will recollect that I had described to you my ignorance concerning the real mode of termination which the nerves have in the tactile bodies. Whether the nerve ultimately forms a loop, or in any manner directly terminates in the internal substance of the body, is not, I think, as yet absolutely decided.

If now we consider other instances of the terminations of nerves, nowhere does any probability manifest itself that they really do form loops. In every case in which more certain knowledge has been acquired, the probability has on the contrary always become greater, that the nerves either terminate in a large plexus or recticular expansion ; or that they end in special apparatuses, concerning which it is still doubtful whether they are peculiar processes of a particular shape, into which the nerves shoot out at their extremities, or whether they constitute peculiar parts, non-nervous in their nature, to which the nerves attach themselves. This latter mode of termination is, it would appear, characteristic of most of the *higher organs of sense*, but in no single instance, in consequence of the extreme difficulty which the investigation of these parts presents, have any views been proposed which have met with universal assent. Notwithstanding the numerous investigations into the structure of the retina and cochlea, the mucous membrane of the nose and mouth, that have been made in the course of the last few years, it must be confessed that the ultimate points of histological detail have not as yet been altogether satisfactorily settled. In nearly all cases there remain two possible ways in which the nerves may terminate. According to some their terminations are connected with special structures which, according to the language hitherto employed, cannot be regarded as being of a nervous nature, but are peculiar appendages of the nerves, though they are certainly stated by other observers to be directly connected with nerve-fibres, as for example in the nasal mucous membrane. This namely is regularly clothed with cylindrical epithelium, which is plentifully provided with cilia and forms several layers, lying one above the other, so that there are several rows of cells covering one another. In these, according to several recent observers, cells are met with, which terminate in a somewhat long filament, and do not, like other epithelial cells, end upon the surface, but run in an inward direction, so as to become directly continuous with the ends of the nerves. According to others, particularly Max. Schultze, on the contrary, and this view seems to be the more correct one, peculiar filiform ends of nerves force their way out between the epithelium. The objects of smell would therefore according to both views really come directly in contact with the structures forming the terminations of the nerves. Similar epithelium-like structures have recently been described as occurring also in the mucous membrane of the tongue, seated upon peculiar papillæ, which appear to possess a pre-eminently nervous character.

These structures moreover might lay claim to a certain resemblance with the ultimate terminations which we find in the case of the optic nerve in the retina, and in that of the auditory nerve especially in the cochlea—terminations, which may in the latter case, as far as their external shape is concerned, be compared to long-tailed epithelial cells, whilst those in the retina constitute structures of peculiar delicacy. In the *retina* namely the optic nerve, after its entrance into the interior of the globe of the eye, spreads out in such a way, that its fibrous elements run along on the anterior side of the retina, that side, namely, which is turned towards the vitreous body (Fig. 85, *f*) ; posteriorly, there follows a stratum of varying thickness, which belongs to the retina indeed, but in no wise proceeds from the direct expansion of the optic nerve. In this layer we see, where it borders upon the layer of pigment-cells of the choroid coat, and in immediate contact with these cells, a peculiar stratum which has been subjected to a strange destiny, inasmuch as it was for a considerable time transplanted to the anterior

FIG. 85.



side of the retina—the famous *bacillar layer* (layer of rods—Stäbchenschicht [membrana Jacobi]) (Fig. 85, *s*). This layer, which belongs to the most easily injured parts of the eye, and for this reason in many instances escaped the notice of earlier observers, consists, when viewed in profile, of a very large quantity of closely

Fig. 85. *A*. Vertical section through the whole thickness of the retina, after it had been hardened in chromic acid. *l*. Membrana limitans, with the ascending, supporting fibres. *f*. Fibrous layer of the optic nerve. *g*. Layer of ganglion-cells. *n*. Grey, finely granular layer, with the radiating fibres passing through it. *k*. Internal (anterior) granular layer. *i*. Intermediate, or intergranular, layer. *k'*. External (posterior) granular layer. *s*. Layer of rods and cones. 300 diameters. *B*, *C* (after H. Müller). Isolated radiating fibres.

packed little rods, arranged in a radiated form, and between which at certain intervals appear broader, conical bodies. When the retina is viewed from behind, *i. e.*, from the choroid coat, we see regularly arranged between these cones fine points which correspond to the ends of the little rods.

Now that which intervenes between this bacillar layer and the proper expansion of the optic nerve, is likewise a very complex affair, in which a series of layers following one another in regular succession can be distinguished. Immediately in front of the bacillar layer comes a comparatively thick stratum, which appears to be nearly entirely made up of coarse granules, the so-called external granular layer (Fig. 85, *k'*). Then comes a thinner layer which generally presents a tolerably amorphous appearance, the inter-granular layer (Fig. 85, *i*). Then we again have coarsish granules (the internal granular layer); these bodies in both layers having much the appearance of nuclei (Fig. 85, *k*). Next follows a second layer of a more uniform, finely granular or finely striated appearance, and of a more greyish hue (Fig. 85, *n*), and then only the tolerably thick stratum of the optic nerve, which in its turn is bounded by a membrane, the membrana limitans (Fig. 85, *l*), which is in close apposition to the vitreous body. Within this last layer we see, besides the fibres of the optic nerve, and situated behind them, a number of largish cells, which have the appearance of nerve-cells (Fig. 85, *g*).

This extremely complex structure in a membrane which at first sight is so simple and so delicate, readily accounts for its being extremely difficult to ascertain with certainty all the relations of its individual parts. It was one of the most important advances towards the knowledge of these relations which was made by the discovery of Heinrich Müller, that namely from behind, from the bacillar layer into the most anterior layers, a series of rows of fine fibres could be traced (*radiating fibres*, also called Müllerian fibres), which both receive the granules, and support the cones and rods (Fig. 85, *B*, *C*). This very complicated apparatus is placed as nearly as possible perpendicularly to the course of the fibres of the optic nerve. The greatest difficulty which exists with regard to the anatomical connection of the parts, is to determine whether the radiating fibres, either by bending directly round, or by a lateral anastomosis, become continuous with the optic or ganglionic fibres, and are thus themselves nervous, or whether only an intimate apposition takes place, and so the nerves bear no other relation to the radiating fibres than those of proximity. A tactile body may also, you know, be either regarded as a body formed by a swelling of the nerve itself, or as a special structure up to which the nerve only proceeds or into which it enters. This question (of the connections of the radiating fibres) has not yet been definitively settled. At one time the probability became rather stronger that direct communications existed, at another that nothing more than a mere apposition took place. It can, however, even now no longer be doubted, that this apparatus is essential to the perception of light, and that the optic nerve might exist with all its parts without in any way possessing the power of receiving impressions of light, if it were not connected with this apparatus. It is well known that just that point in the background of the eye, where there are only optic fibres and no such apparatus, is the only one which does not receive impressions of light (the blind spot). In order therefore that the light may be rendered at all capable of acting upon the optic nerve, it unquestionably requires to be collected by means of this apparatus of fibres, and it is therefore an extremely interesting question for delicate physical researches, whether the nerve itself receives at its extreme ends the vibrations of the waves of light, or whether another part exists, the oscillations of which act upon the optic nerve and produce a peculiar excitation in it. At all events there do ascend from the membrana limitans slightly curved fibres (Fig. 85, *l*), probably connective tissue with its corpuscles, which afford a kind of stay or support to the whole apparatus (supporting fibres [Stützfasern]), and are not, I should suppose, freely connected with the rest of it.

We have, gentlemen, by the consideration of these relations brought out the fact, that the specific energy of individual nerves does not so much depend upon the peculiarity of the internal structure of their fibres as such, but that a great deal must be attributed to the special terminal arrangement, with which the nerve is connected, either directly or by contact, and from which the different nerves of sense derive their peculiar powers. If for example we examine a transverse section of the optic nerve external to the eye, it offers no peculiarities as compared with other nerves, which could at all account for this particular nerve's being better able to conduct light than other nerves, whilst on the other hand the peculiar manner in which its extreme ends are distributed sufficiently explains the unusually great sensitiveness of the retina to light.

With regard to the terminations of nerves, there is still one mode to be mentioned; the *plexiform distribution.* This

Fig. 86.

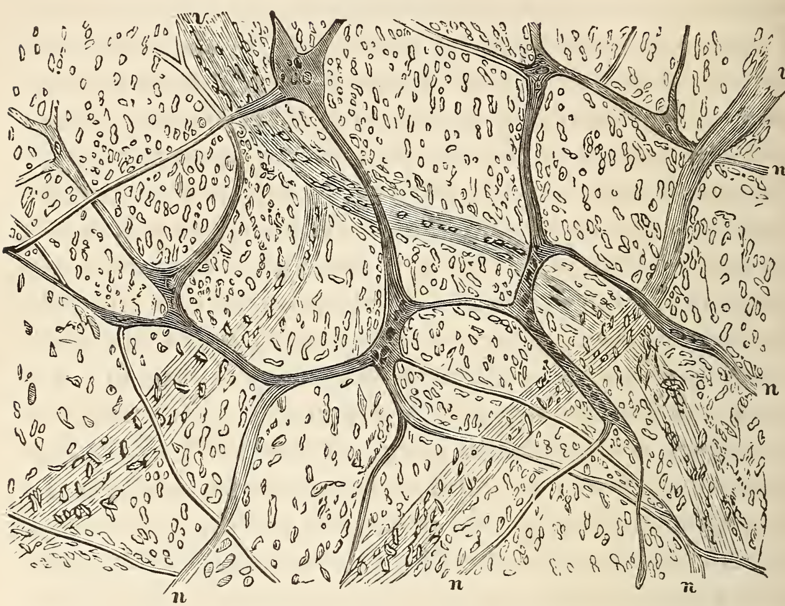
Fig. 86. Division of a primitive nerve-fibre at *t*, where we find a constriction; *b′*, *b″* branches. *a*. Another fibre, crossing the former one. 300 diameters.

is a point to which more recent researches have been principally directed by Rudolph Wagner, inasmuch as this inquirer instituted investigations into the distribution of the nerves in the electrical organ of fishes, and in so doing gave the chief impulse to the doctrine of the *ramification of nerve-fibres.* Up to that time nerves had been regarded as continuous, single tubes, which remained single throughout the whole of their course from a nervous centre to their termination. At present we know that nerves are distributed like vessels. Now seeing that nerve-fibres directly divide, usually dichotomously, and their branches again divide and subdivide, extremely abundant ramifications may in this way in time arise, the import of which is extremely different, according as the nerve is motor or sensitive, and either collects impressions *from*, or diffuses motor impulses *to*, a considerable extent of surface. A truly marvellous instance has lately come to our knowledge in the electrical nerve of the electrical silurus (malapterurus), which has become so celebrated by the interesting experiments of Dubois-Reymond. Here Bilharz has shown that the nerve which supplies the electrical organ is in the first instance only a single microscopical primitive fibre, which keeps continually dividing until it finally resolves itself into an enormously great number of ramifications which spread themselves out upon the electrical organ. Here therefore the nervous influence must all at once diffuse itself from one point over the whole extent of the electrical plates.

In man we are still in want of distinct evidence with regard to this question, because the immense distances, over which individual nerves extend, render it almost impossible to follow any single given primitive fibres from their central origin to their extreme peripheral termination. But it is not at all improbable that in man too analogous arrangements exist in some organs, although perhaps not such striking ones. If we compare the size of the nervous trunks in certain parts with the total number of operations which are effected in an organ, for example, in a gland, it can scarcely appear doubtful that at least analogous arrangements exist there also. This mode of distribution offers peculiar interest in this respect, that many parts which are separated by intervals of space are thereby connected with one another. The electrical organ is composed of a number of plates, but not every plate is supplied with nerves proceeding from the centre and intended only for it. The silurus does not set one or other of its plates in motion, but is obliged to set the whole of them in motion ; it is quite unable to divide the action. It can increase or diminish the intensity, but must always call the whole into operation. If in like manner we consider the arrangements which prevail in certain muscles, we find there is no evidence to justify us in assuming that every portion of a muscle receives special, independent nerve-fibres. On the contrary, a special division of nervous action in muscles only exists to a very limited extent, as we know from our experience in our own bodies. The neuro-pathological doctrines would lead us to infer that *the will*, *or the soul*, *or the brain* is able by means of special fibres to act upon every single part, but in reality this is by no means the case, for the nervous centres have mostly only one single path by which they can communicate with a certain number of similar elementary apparatuses.

Now with regard to *nervous plexuses*, we are at the present time acquainted with most extensive arrangements of the kind in man, in the submucous tissue of the intestines, where the relations have recently been more closely investigated, in the first instance by Meissner and afterwards by Billroth. The submucous layer of the intestines is therefore, as Willis long ago declared it to be, a

Fig. 87.



nervous tunic. On following up the afferent nerves, they are seen, after having divided, at last to break up into real networks ; these in new-born infants present at certain points very large nodules, from which the nerve-fibres spread out into interlacements, so that a certain resemblance is thereby produced to a network of capillaries.

To what extent such arrangements prevail in the body generally has not yet been determined ; for these facts also are almost entirely new, and have only recently attracted the attention of observers, but probably the

Fig. 87. Nervous plexus from the submucous tissue of the intestinal canal of a child, from a preparation of Herr Billroth's. *n*, *n*, *n*. Nerves which unite to form a network, and exhibit at their points of junction glanglioniform swellings abounding in nuclei. *v*, *v*. Vessels, and in the intervals nuclei belonging to the connective tissue. Magnified 180 diameters.

number of these nervous membranes will eventually be augmented. In order, however, to avoid any misunderstanding, I must at once add that these plexiform expansions are by no means simple, but that the large nodules I have mentioned have the appearance of ganglions, so that we have here in some sort new nervous centres presenting themselves, and affording the possibility of a reinforcement of, or obstruction to, the original impulses. For the functions of the part this arrangement is manifestly of great importance, for we should not well be able to explain the peristaltic movements of the intestinal canal, if some contrivance did not exist by which stimuli, that in the first instance were conveyed only to one spot in the canal, could be transferred from network to network and from part to part. The modes of distribution of nerves, with which we were till recently acquainted, were not sufficient to afford anything approaching an explanation of the nature of peristaltic action, whilst these investigations of Meissner's have at once furnished us with a most suitable groundwork for an interpretation of it. So much concerning the general forms which are, as far as we know at present, assumed by the peripheral terminations of the nerves.

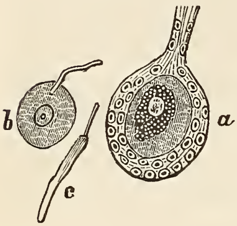
On the whole, these results correspond but little with the opinions which were formerly entertained, and with the hypotheses still advanced by the neuro-pathologists. The views of a neuro-pathologist of pure water amount, as is well known, to this, that a nervous centre is able, by means of nerve-fibres, to produce particular effects upon all, even the smallest, particles of the territory under its sway. If a mass of cancer or pus is to spring up in any little spot in the body, or merely a simple disturbance of nutrition to ensue, the neuro-pathologist requires a special arrangement, by means of which the nervous centre is enabled to have its influence conveyed into even the most minute districts of the periphery, and some route along which the messengers can travel who have been appointed to bear the order to the remotest points of the organism. Actual experience teaches us nothing of the kind. At those very spots where we know such an extremely complicated arrangement of the terminal apparatuses to exist, as I have described to you in the organs of sense, the nerves have no connection with the nutrition of the parts, and especially no demonstrable influence upon the elementary structures. In nearly all other places, either whole surfaces, or parts of organs are supplied with nerves in a uniform manner, or from these surfaces and parts of organs collective impressions are conveyed to the centres. In many parts concerning which we can certainly demonstrate that nervous influence is exercised upon them, as for example in middle-sized and small vessels, we do not yet at all know to what extent their individual constituents receive special nerve-fibres. So bad are the anatomical foundations of the neuro-pathological doctrines.

There still remains for us, gentlemen, now that we have discussed the terminal arrangements of the peripheral nerves, to consider the important series of nervous centres, or in a more restricted sense of the term, *ganglionic apparatuses*. As I lately remarked to you, we find these predominating in those parts of the nervous centres in which there is grey matter. Still the mere grey hue of a part is not decisive proof of its ganglionic nature; and in particular we must not suppose that the ganglion-cells are at all essentially concerned in the production of the grey colour, seeing that we find grey matter in many places where ganglion-cells do not exist. Thus, the most external layer of the cortex of the cerebrum does not contain any well-marked ganglion-cells, although it looks grey ; but we find there a translucent connective substance, pervaded by a large number of delicate vessels, and assuming, in proportion as these are more or less full, at one time more a reddish grey, at another more a whitish grey hue. On the other hand it frequently happens that, where there are ganglion-cells, the substance really does not look grey, but has a positive colour varying between brownish yellow and blackish brown. Thus we find spots in the brain, which have long been known by the names of substantia nigra, fusca, etc., in which the black or brown colour, which we perceive with the naked eye, is dependent upon the ganglion-cells, which form really coloured points.

This coloration appears only in the course of years. The older an individual becomes, the more conspicuously do the colours show themselves ; still under certain circumstances pathological processes also seem to accelerate their manifestation. Thus in the ganglia of the sympathetic it is a striking phenomenon, that certain morbid processes, for example, typhoid fever, appear to exercise a powerful influence in producing an early deposit of pigment. Since the pigment however constitutes a relatively foreign mass in the internal economy of the ganglion-cells, and is not, as far as we know, subservient to their proper functions, but has all the characters of an inert accidental deposit, it may really be quite possible that these conditions should be regarded as a kind of premature senescence in the ganglia. In these cases we discern in the ganglion-cells (Fig. 88, *a*) in addition to the very distinct, large nucleus with its large, bright nucleolus, the contents properly so-called, which consist of a finely granular substance, and at a certain spot enclose the pigment which is generally deposited excentrically, but sometimes around the nucleus. Under certain circumstances this deposit increases to such an extent that a great part of the cell is filled up with it. The more abundant it is, the darker does the whole spot appear to the naked eye.

Formerly it was imagined that the majority of ganglion-cells were merely round bodies, but the conviction has been gradually gaining strength, that this form is an artificial one, and that the real state of the case is rather, that processes strike out from the cell in various directions, and ultimately become continuous with nerves or other ganglion-cells. These processes are in the first instance pale, and even where their transition into ordinary, darkly-contoured nerve-fibres can be traced, they are observed (but generally not until a certain distance from the ganglion-cell) to become thicker and gradually to provide themselves with a medullary sheath. This circumstance which was formerly unknown explains how it was, that during so long a period so much obscurity prevailed with regard to these conditions. In the first part of their course, therefore, the processes of the glanglion-cells, especially in the brain and spinal marrow, are not nerves in the ordinary meaning of the word, but pale fibres which frequently bear scarcely any resemblance to the non-medullated fibres I have already described to you, and have rather the appearance of pale axis-cylinders (Fig. 88, *a*, *b*).

Fig. 88.



It was long believed that essential differences existed between the ganglion-cells according as they belonged to one or other of the three principal divisions of the

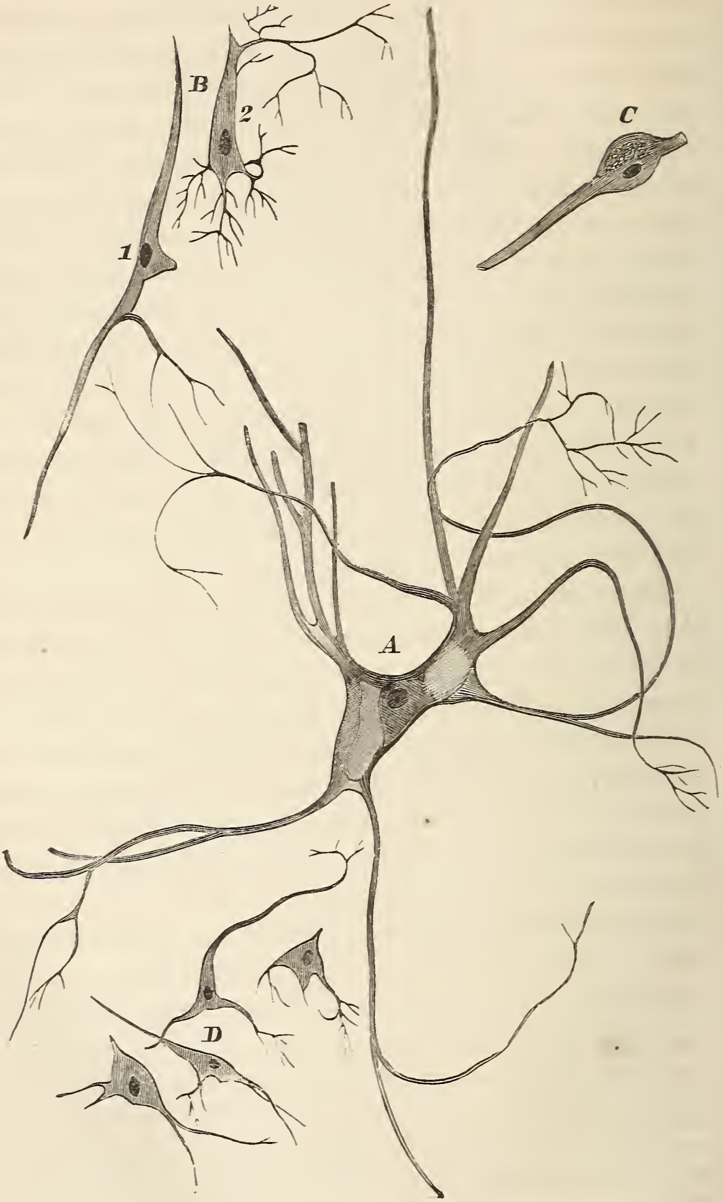
Fig. 88. Elements from the Gasserian ganglion. *a*. Ganglion-cell with nucleated sheath, which is prolonged around the efferent nerve-process; in the interior, the large, clear nucleus with its nucleolus, and round about it an accumulation of pigment. *b*. Isolated ganglion-cell with a pale process proceeding up to it. *c*. Delicate nerve-fibre with pale axis-cylinder. 300 diameters.

nervous system, and therefore especially between the cells of the sympathetic and those of the brain and spinal marrow. But in this point also the contrary has proved to be the case, especially since Jacubowitsch has brought to our knowledge the new fact, of the correctness of which I have fully convinced myself, namely, that structures which are perfectly analogous to the ordinary ganglion-cells of the sympathetic, also occur in the middle of the spinal marrow and several parts which are considered to belong to the brain. It may therefore be said, that cells belonging to the sympathetic nerve, concerning which it has already long been known that a great part of its fibres have their origin in the spinal marrow, are really also met with in the spinal marrow, and that in this respect also the cord does not form a simple and necessary contrast to the main trunk of the sympathetic.

If we examine the *spinal marrow*, which affords the clearest representation of the plan of a true nervous centre in the narrowest meaning of the word, a little more closely, we everywhere find in its grey substance (the horns), and indeed in nearly every transverse section, different kinds of ganglion-cells. Jacubowitsch has, and I believe him to be in the main correct, distinguished three different forms, of which he calls the one motor, the second sensitive, and the third sympathetic. These lie generally in separate groups.

I shall revert to this subject when I come to speak more at length concerning the spinal marrow; here I only wish to speak about the different forms of ganglion-cells. The so-called unipolar forms, are, in proportion as the examinations are conducted with more care, continually becoming more and more rare. In the great nervous centres most of the cells possess at least two processes, and very many are multipolar or, more accurately,

FIG. 89.



many-branched (*polyclonous*).* A multipolar cell is a body with a large nucleus, granular contents and, if it be particularly large, a spot of pigment, and is provided with processes running in different directions. These processes often divide into twigs and thus commences the condition of which I have already spoken (p. 290), that whole masses of filaments or fibres proceed from one point—a condition which indicates, that, in the first instance indeed according to circumstances, one path or another can be made use of, but that, when once a path has been chosen leading in the direction of the periphery, the impulse must be propagated in a relatively equable manner throughout the whole series of ramifications. These multipolar forms (Fig. 89, *A*) are mostly comparatively large, and lie accumulated in those parts which are subservient to the motor functions! and they therefore may be briefly designated motor cells.

Those forms which correspond to the sensitive spots (Fig. 89, *B*) are usually smaller and do not present such an extraordinary luxuriance of ramification as the larger ones. A large portion of them possess only three, or perhaps, four branches. Those which Jacubowitsch has called sympathetic are, on the other hand again, larger, but have still fewer branches and are distinguished by a greater roundness of shape. These are differences which are certainly not so decided, as to enable us already at once to determine in every single case from the appearance of a ganglion-cell to which category it belongs; but still, if we consider the individual groups, they are so

Fig. 89. Ganglion-cells from the great nervous centres; *A*, *B*, *C* from the spinal cord, from preparations belonging to Herr Gerlach, *D* from the cortex of the cerebrum. *A*. Large, many-rayed cell (multipolar, polyclonous) from the anterior horns (motor cell). *B*. Smaller cells with three large processes, from the posterior horns (sensitive cells). *C*. Two-rayed (bipolar, diclonous), more rounded cell, from the neighbourhood of the posterior commissure (sympathetic cell). 300 diameters.

* κλῶν, ωνὸς, a shoot, twig.—Tr.

striking, as to incite the observer to reflection upon the different qualities of these groups.

In the course of time probably further distinctions, perhaps even in the internal economy of these cells, will be detected, but at present nothing more can be stated concerning them. This is a very great and lamentable void in our knowledge, and a void which we now particularly feel, because this is just the place where we should have to discuss the pacific action of these different elements. But it must not be overlooked that these conditions are among the most difficult which are ever submitted to anatomical investigation, and that one's endeavors to produce specimens of a character to convince one's own eyes alone, nearly always fail, because it is scarcely possible to succeed in effecting a real isolation of the cells with all their processes and connections, and because, on account of the extraordinary fragility of these bodies, one is nearly always compelled to trace them out in hardened sections. When sections are made of structures which to a great extent are composed of fibres and in which these run in a longitudinal, a transverse, or an oblique direction, so that an interlacement is always presented to the view, it depends of course entirely upon a happy chance whether in a section the course of a single fibre can be followed up over a large space with a certain degree of distinctness. This difficulty can certainly be lessened by making the sections in all possible directions and thus increasing the probability of at last stumbling upon the direction followed by the divisions of a branch, but even then the obstacles still remain so great that one can hardly expect, ever to be able to take in at one view the whole of the ramifications and connections of a cell belonging to the great nervous centres, that is provided with at all a large number of branches.

In this respect also the *electrical organ* of fishes has become a particularly interesting subject for investigation, inasmuch as the one fibre which supplies the organ has been traced back by Bilharz to a single central ganglion-cell, which is so large that it can be dissected out with the naked eye. This ganglion-cell has also delicate offsets in other directions, but it has not hitherto been possible to determine their ultimate relations any more than we are able to obtain a definite notion of the minute anatomy of the human brain, and especially to discover, to what extent connections take place there between the different cells. By the investigations which have been instituted into the structure of the spinal cord, it has been shown to be extremely probable, that all the processes of the individual ganglion-cells do not become continuous with nerve-fibres, but that a part of them run to other ganglion-cells and thus establish a communication between the cells. Moreover at certain points, especially in several parts of the surface of the *brain*, still finer processes are found, which proceed from ganglion-cells and are connected with peculiar, quite characteristic apparatuses (bacillar layer of the cerebellum and cerebrum), which offer the greatest resemblance to those in the retina, those extremely delicate, vibratory arrangements of the radiating fibres.

The processes of the ganglion cells might therefore, I think, be divided into three categories ; genuine nerve-processes, ganglion-processes, and those of which the import is entirely unknown and which, it would seem, are connected with peculiar and altogether specific apparatuses, concerning which it is for the present uncertain, whether they are to be regarded as the terminations of the nerves, or only as structures placed in apposition to them.

LECTURE XIII.

APRIL 3, 1858.

SPINAL CORD AND BRAIN.

The spinal cord—White and grey matter—Central canal—Groups of ganglion-cells—White columns and commissures.
The medulla oblongata and the brain—Its granular and bacillar layer.
The spinal cord of the petromyzon and its non-medullated fibres.
The intermediate substance (interstitial tissue)—Ependyma ventriculorum—Neuroglia—Corpora amylacea.

The last time, gentlemen, I laid before you the results of the most recent observations concerning the nature and distribution of the ganglion-cells in the great nervous centres; allow me now to dwell a moment upon that organ which serves as a type in the development of the vertebratæ, and is at the same time the one whose structure we can best take in at one view, namely, the *spinal cord.*

The spinal cord presents, as is well known, and can with ease be seen by the naked eye in any transverse section, in different parts of its course, a different amount of white matter, though nearly everywhere the white matter predominates over the grey. This appears in transverse sections in the form of the well-known horns, which are distinctly marked off from the pure white of the rest of the mass by their sometimes pale grey, sometimes reddish grey colour. Wherever then the substance appears white to the naked eye, it is essentially composed of real, medullated nerve-fibres, in which only here and there a few ganglion-cells are imbedded ; and indeed a large proportion of these fibres are of considerable breadth, so that the quantity of medullary matter is at certain points extremely large.

The grey matter of the horns is the real seat of the ganglion-cells, but here too the grey colour is by no means to be entirely ascribed to the accumulation of ganglion-cells ; on the contrary, they never, as you will afterwards see, form more than a small portion of this matter, and the grey hue is chiefly due to there generally being in these parts no separation of that opaque, strongly refractive substance (myeline, medullary matter) which fills the white nerves.

It is in the centre of the grey substance that, as Stilling, especially, has shown, the *central canal* (canalis spinalis) actually exists, which had previously been so commonly supposed to be present, and had also frequently been described as of constant occurrence, but of which nevertheless no one had ever previously been able to furnish a regular demonstration. In the case of the old observers, as for example Portal, their investigations were in every instance confined to a few pathological specimens, from which they derived all the information they possessed upon the subject, and from which they inferred in a somewhat arbitrary manner that the presence of a canal was the rule.

This central canal is so minute that extremely successful sections are required in order that it may clearly be perceived by the naked eye. Usually nothing more than a rounded grey spot can be detected, which is distinguished from the surrounding parts by its somewhat greater density. It is by microscopical examination alone that we can detect in this spot the transverse section of the canal in the shape of a minute hole (Fig. 90, *c*, *c*), which, like nearly all the free surfaces of the body, is invested with a layer of epithelium. It has now taken up its stand as a really regular, constant and persistent canal. It is continued throughout the whole extent of the spinal marrow from the filum terminale, where it cannot at all times be very distinctly demonstrated, up to the fourth ventricle, where the orifice by which it opens into the so-called sinus rhomboidalis* is situated in the gelatinous substance of the calamus scriptorius. Here it may

Fig. 90.

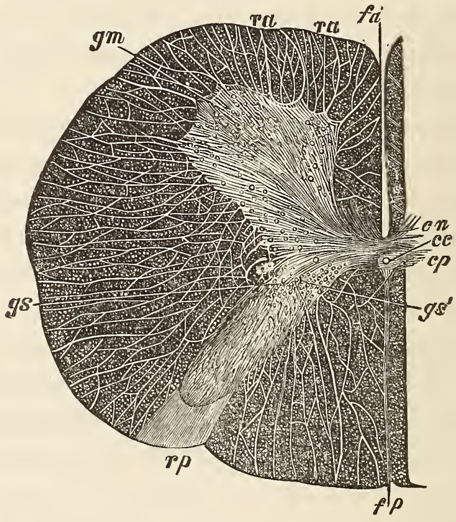


Fig. 90. The half of a transverse section from the cervical part of the spinal marrow. *fa*. Anterior fissure; *fp*, posterior fissure. *cc*. Central canal with the central thread of ependyma. *ca*. Anterior commissure with nerve-fibres crossing one another; *cp*, posterior commissure. *ra*. Anterior roots; *rp*, posterior ones. *gm*. Accumulation of motor cells in the anterior horns; *gs*, sensitive cells of the posterior horns; *gs'*, sympathetic cells. The black, dotted mass represents a transverse section of the white substance of the cord (the nerve-fibres belonging to the anterior, lateral and posterior columns) and its lobular divisions. 12 diameters.

* A name given to the floor of the fourth ventricle.

in the first instance be traced as a direct continuation from the floor of the fourth ventricle into a minute funnel-shaped fissure or line.

As for the *ganglion-cells*, they are generally found in the largest number in the anterior and lateral parts of the anterior horns. It is at this spot that we chiefly meet with the large many-rayed corpuscles which we considered the last time—corpuscles, which have in great part been traced into efferent nerves of the anterior root, and therefore give origin to motor nerves.

An analogous, but less distinctly grouped accumulation is found in the direction of the posterior horns, but there the cells are rather the small, many-rayed ones, such as those I lately described to you; they are connected with the fibres which run into the posterior root, and are therefore probably subservient to the functions of sensation. Besides, there is generally a third, sometimes more closely aggregated, at others more scattered, group of cells to be seen, which in their whole conformation remind us of the familiar cell-forms we meet with in the ganglia (Figs. 89, *C*; 90, *gs'*). Their special position in the spinal marrow is certainly not so clearly defined as that of the other parts; perhaps they should be regarded as the origin of the sympathetic roots which run from the spinal marrow to the main trunk of the sympathetic, but this is as yet by no means clearly made out.

In the white substance of the anterior, lateral and posterior columns are found the medullated nerve-fibres, which in general follow an ascending or descending course, so that in transverse sections of the spinal marrow we scarcely gain sight of anything else than transverse sections of the nerve-fibres. Under the microscope therefore we generally see dark points, every one of which corresponds to a nerve-fibre. The whole mass of fibres constituting the columns of the spinal cord is, from within outwardly, split up into a series of groups or segments chiefly following a radiating arrangement, or in some sort into wedge-shapes lobules, in consequence of a sometimes smaller, sometimes larger quantity of connective tissue with vessels pushing its way in between the separate divisions, which are of a fascicular nature like those of the peripheral nerves. This connective tissue is directly connected with the more abundant mass of it present in the grey matter. Now with regard to the nerve-fibres themselves, it is probable that a certain number of them proceed throughout the whole length of the spinal marrow, but it ought certainly not to be assumed that they are all derived from the brain ; a probably considerable portion no doubt have their origin in the ganglion-cells of the spinal marrow itself, and then bend round into the anterior or posterior columns. Besides, the conviction has more and more gained ground, that, both between the two halves of the spinal marrow and between the separate groups of ganglion-cells, direct communications, *commissures*, exist—fibres passing across from one cell to another and from one side to the other, some so as to cross with those of the opposite side (anterior commissure), and some so as to run in a straight and parallel direction (posterior commissure).

With the help of these anatomical observations a notion, though indeed as yet a very unsatisfactory one, can be formed of the routes along which the different processes are carried on within the nervous centres. *Every special function possesses its special elementary, cellular organs ; every mode of conduction finds paths distinctly traced out for it.* In general too, well-defined peculiarities in the structure of the individual nervous centres correspond to the differences of function, and particularly the posterior horns become gradually more and more strongly developed as we ascend ; and in proportion as this development proceeds, we see the medulla oblongata, the cerebellum and cerebrum, coming into view, whilst the motor parts withdraw more and more into the background and ultimately almost entirely disappear. All nervous centres, the lowest as well as the most highly developed, are disposed upon an analogous plan ; the only thing which, at least as yet, can be regarded as an especially characteristic peculiarity of the encephalon, is the circumstance, to which I called your attention in the last lecture, namely, that in the cerebrum and cerebellum processes from ganglion-cells are connected with particularly complicated apparatuses, which most resemble

Fig. 91.

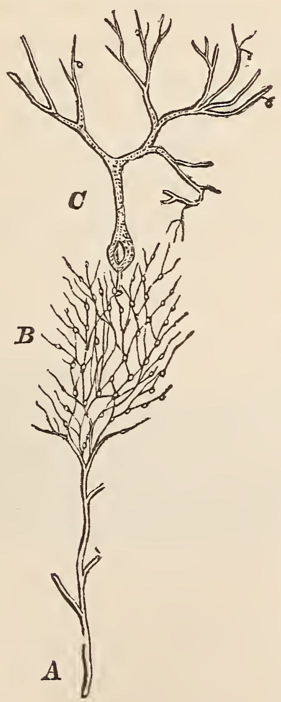


Fig. 91. Diagrammatic representation of the disposition of the nerves in the cortex of the cerebellum, after Gerlach ('Mikroscopische Studien,' plate I., fig. 3). *A*. White matter. *B*, *C*, grey matter, *B*, granular layer, *C*, cellular layer.

the granular and bacillar layers of the retina (Fig. 91) which I have brought before your notice. For here too we find branched, almost arborescent filaments, which bear upon them minute granules, often in several rows, and attach themselves to the ganglion-cells in a manner essentially differing from, and much more delicate than that observed in the case of the proper nerve-processes. This kind of ganglion-cells may very likely stand in some close connection with the psychical functions, but at present we have no accurate information upon the subject, and it will, I expect, still be a long time before anything positive can be made out about it, seeing that parts which are much more accessible to investigation, like the retina, present the very greatest difficulties to those who seek to discover the functions of the individual segments.

The conformation which we have found to exist in the spinal marrow of man is essentially the same throughout the whole series of vertebrate animals, only that in man it is generally more complicated, and exhibits a greater abundance both of nerve-fibres and ganglionic matter. I

Fig. 92.

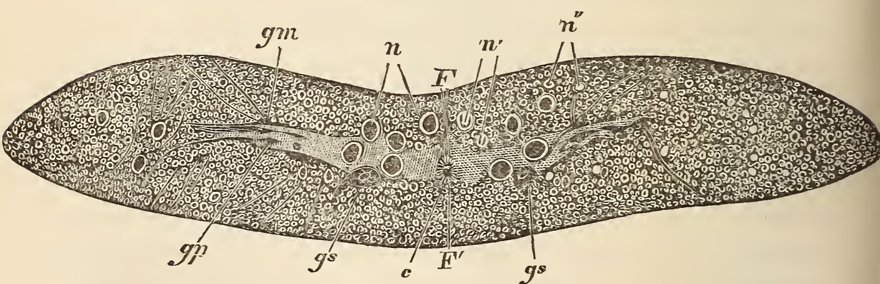
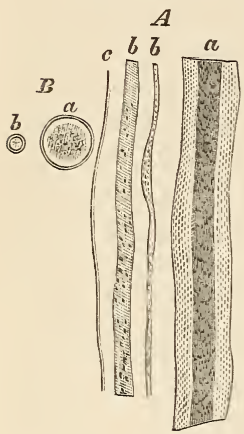


Fig. 92. Transverse section through the spinal marrow of Petromyzon fluviatilis. *F.* Anterior fissure, *F′*, posterior fissure, *c*, central canal with epithelium, *gm*, large many-rayed ganglion-cells with processes in the direction of the anterior roots, *gp*, smaller, many-rayed cells with processes running to the posterior roots, *gs*, large, roundish cells in the neighbourhood of the posterior commissure (sympathetic cells). *n*, *n*. Transverse sections of the large, pale nerve-fibres (Müllerian fibres), *n′*, gaps out of which the large nerves have gallen; *n″*. gaps belonging to smaller fibres. Besides, the cut ends of numerous finer and coarser fibres.

have brought you for comparison a section from the spinal marrow of one of the lowest of the vertebratæ, namely the lamprey (petromyzon). In this animal the spinal marrow forms a very small, flat band which has somewhat of a depression on the surface, and at first sight looks like a real ligament. On making a transverse section of it, it is found to contain the same parts that we see in man, but all only in a rudimentary form. What in ourselves we call grey matter, is also found there on both sides in the shape of a flattened oblong lobe which contains a few scattered ganglion-cells, but only very few, so that perhaps only four or five are met with on each side of the transverse section. In the centre a central canal can likewise be detected, and that too lined with an epithelial layer similar to that which occurs in man. Below and in front of it generally lie a number of largish, round cavities, which correspond to unusually large, non-medullated nerve-fibres (Fig. 93, *a*), which were first seen by Joh. Müller. Farther outwards lie a few other thick fibres, but greatly exceeding these in number a large quantity of very fine fibres which give the transverse section a very diversified, regularly dotted appearance. Among the ganglion-cells three different kinds can here also be distinguished. Towards the outside of the grey matter lie many-rayed cells, larger anteriorly, smaller and more simple posteriorly. More internally and posteriorly on the other hand we find larger, more rounded, seemingly diclonous (bipolar) cells, comparable to the sympathetic forms. These cells communicate across the middle-line by means of real fibres, and besides we find processes which run out from the spinal marrow forwards and backwards and form the anterior and posterior roots. This is the simplest plan we have, displaying these relations ; it is the general type of the anatomical structure of these parts.

A circumstance worthy of particular observation here is that in the petromyzon, in the whole substance of the spinal marrow, no medullary matter exists in an isolated form, as is the case in man; we only find simple, pale fibres, which Stannius has without hesitation pronounced to be naked axis-cylinders. But without taking into account the fact that some of them have an enormous diameter, we find upon more accurate examination, as in the case of the gelatinous grey fibres in man, a membrane very clearly seen in transverse sections, especially after it has been coloured with carmine—and in the centre a finely granular matter, so that they seem rather to correspond to entire nerve-fibres.

Fig. 93.



Hitherto, gentlemen, in considering the nervous system, I have only spoken of the really nervous parts of it. But if we would study the nervous system in its real relations in the body, it is extremely important to have a knowledge of that substance also which lies *between the proper nervous parts*, holds them together and gives the whole its form in a greater or less degree.

It is by no means very long ago since the existence of such interstitial masses of tissue was really only conceded in the case of peripheral nerves, and since the neurilemma was only traced back as far as the membranes of the spinal cord and brain, such an enveloping tissue being at most allowed to exist within the ganglia and in the sympathetic. In the nervous centres properly so called, and

Fig. 93. Pale fibres from the spinal marrow of Petromyzon fluviatilis. *A.* Broad, narrow, and extremely fine fibres. *B.* Transverse sections of broad fibres with a distinct membrane and granular centre. 300 diameters.

especially in the brain, this interstitial matter of ours was regarded as essentially nervous, for a substance of the kind appeared a natural desideratum, as long as a direct transferrence of impulses from fibre to fibre was admitted to take place, as long therefore as the necessity for a real continuity of conduction within the nerves themselves was not recognized. Thus in the brain a finely granular substance was spoken of as existing, which insinuated itself between the fibres, and though it certainly did not establish a complete connection between them, inasmuch as it occasioned a certain difficulty in the transferrence of impulses, yet nevertheless seemed to render a certain amount of conduction possible, so that when the impulse reached a certain degree of intensity, a direct transferrence from fibre to fibre could take place. This substance is however unquestionably not of a nervous nature, and if inquiry be made as to the relation which exists between it and the familiar groups of physiological tissues, it is impossible to doubt but that the substance in question is a kind of connective tissue; and therefore an equivalent of that tissue with which we became acquainted in the shape of perineurium (p. 265). But the appearance of this substance is certainly very different from that of what we call perineurium or neurilemma. These are comparatively firm, and often indeed hard and tough tissues, whilst the substance in question is extremely soft and fragile, so that it is only with very great difficulty that we can succeed in making out its structure.

I first had my attention directed to its peculiarities in investigations which I many years ago (1846) instituted into the nature of the so-called *lining membrane of the cerebral ventricles* (Ependyma). At that time the view was generally held, which had been put forward first by Purkinje and Valentin, and afterwards especially by Henle, that a real lining membrane did not exist in the ventricles of the brain, but only an epithelial covering, the epithelial cells directly resting upon the surface of the horizontally disposed nerve-fibres. This epithelial layer was what Purkinje called ependyma ventriculorum.* This assumption, it is true, was never shared in by pathologists. Pathological observation held on its course pretty unconcernedly by the side of these histological assertions. However, it appeared desirable that some understanding should be come to on the subject, since in a merely epithelial ependyma an inflammation would scarcely take place, like that which is wont to be attributed to serous membranes. The result of my investigations was, that there certainly does exist a layer beneath the epithelium of the ventricles, which in many parts has quite the character of connective tissue, but in other places possesses great softness, so that it is extremely difficult to give a description of its appearance. Every, even the slightest, traction of the part alters its appearance, and a substance now granular, now striated, now reticulated, now of any other form, is seen.

At first I thought I had succeeded in showing that a tissue analogous to connective tissue did actually exist in this part, and that the presence of a membrane could be demonstrated. But, the more I occupied myself with the examination of it, the more did I become convinced that a real boundary between this membrane and the deeper layers of tissue did not exist, and that a membrane could only be spoken of improperly, inasmuch as the notion of a membrane involves the supposition that it is more or less different from the parts beneath it, and constitutes a separable object. Now in the present

* This term has had its signification extended by the Author, who takes it to include the whole of the layer (connective tissue as well as epithelium), which rests upon the nerve-fibres and is interposed between them and the cavity of the ventricles.—*From a MS. Note by the Author.*

instance a separation of a rough kind may certainly not unfrequently be effected, but a more delicate kind of separation is altogether impossible. When the surface of any section of the ventricular wall is examined with a tolerably high power, the first thing noticed on the surface is an epithelium, sometimes in a better, sometimes in a worse state of preservation (Fig. 94, *E*). In the most favourable cases we find cylindrical epithelium with cilia, extending throughout the whole extent of the cavity of the spinal marrow (central canal) and of that of the brain (ventricles). Beneath this layer follows a sometimes more, sometimes less pure layer of a structure resembling connective tissue, which at first sight certainly appears to be separated by a sharp outline from

Fig. 94.

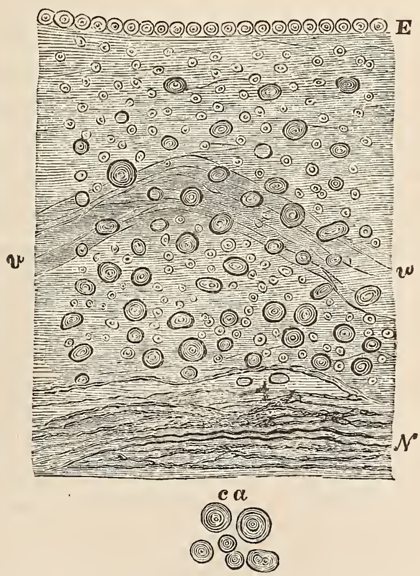


Fig. 94. Ependyma ventriculorum and neuro-glia from the floor of the fourth cerebral ventricle. *E*, Epithelium, *N*, nerve-fibres. Between them the free portion of the neuro-glia with numerous connective-tissue-corpuscles and nuclei, at *v* a vessel. In addition, numerous corpora amylacea, which are moreover represented separately at *ca*. 300 diameters.

the deeper parts, for even with the naked eye, and especially after the addition of acetic acid, an external grey and translucent layer is very distinctly seen, whilst the deeper layer looks white. This white appearance is due to the presence of medullated nerve-fibres which first occur singly, then continually become more numerous and closely aggregated, and as a rule run parallel to the surface. Thus it may certainly appear as if a particular membrane existed here, which could be separated from the uppermost nerve-fibres. But now, if we compare the substance which advances to the surface with that which lies between the nerve-fibres, no essential difference presents itself; on the contrary, it turns out that the superficial layer is nothing more than an extension upwards, beyond the nervous elements, of a portion of the interstitial tissue which is everywhere present between them, but in this layer alone is seen in all its purity. The connection therefore is a continuous one.

You see from this description that it was a very idle dispute, when it was discussed for years, whether the membrane which clothed the ventricles was a continuation of the arachnoid or pia mater, or was a special membrane. There is, strictly speaking, no membrane at all present, but it is the surface of the brain itself which directly meets the eye. In the case of articular cartilage also we must call it idle to dispute what kind of membrane invests the cartilage, since the cartilage itself advances right up to the free surface of the joint. Neither is there any prolongation from the arachnoid or the pia mater to the surface of the ventricle; the last processes which these membranes send inwardly are the choroid plexuses and the tela chorioides [velum interpositum]. Beyond these there is no serous covering found investing the internal surface of the ventricles of the brain. For this reason the conditions of the cerebral cavities cannot be exactly compared with those of ordinary serous sacs. In the tela chorioides or the plexuses, a series of phenomena may certainly manifest themselves, which are parallel to the diseases of other serous parts, but this can never take place in the same manner on the ventricular surface of the brain.

This peculiarity of the membrane, namely, that it becomes continuous with the interstitial matter, the real cement, which binds the nervous elements together, and that in all its properties it constitutes a tissue different from the other forms of connective tissue, has induced me to give it a new name, that of *neuro-glia** (nerve-cement). The view that the substance in question belongs to the class of connective tissues has recently been admitted on nearly all sides, but with regard to the extent to which any isolated structures that occur in it are to be considered as belonging to this substance, opinions are still divided. Even when I instituted my first special investigations into the structure of the ependyma of the brain and spinal cord, it turned out that certain stellate cells which are met with in the middle of the spinal marrow (in the wall of the central canal, the existence of which was afterwards more accurately demonstrated, namely, in what I called the *central thread of ependyma*), and which up to that time had been regarded as nerve-cells, unquestionably belonged to the neuro-glia. Afterwards, and especially by the Dorpat school with Bidder at its head, a series of investigations were published, in which a great number of cells in the spinal marrow were set down as belonging to this connective tissue. Bidder himself was ultimately led to regard all the cells which are found in the posterior half of the spinal marrow, and therefore those sympathetic and sensitive cells also which you have just seen, as connective-tissue-corpuscles. On

* γλία, glue.—*Tr.*

the other hand, Jacubowitsch has utterly denied the occurrence of the cellular elements of connective tissue in any part of the brain or spinal cord, and has asserted that the interstitial tissue, which by him too, indeed, is regarded as connective tissue, is an altogether amorphous, finely granular or reticulated matter, which nowhere contains a single corpuscular element. Between these extremes, I think, we are perfectly justified by experience in steering a middle course. There can, according to my firm conviction, be no doubt but that the larger cells which pervade the posterior horns of the spinal marrow are nerve-cells ; but, on the other hand, it must be maintained with equal positiveness, that, where neuroglia is met with, it also contains a certain number of cellular elements. Immediately beneath the surface of the cerebral ventricles we commonly meet with spindle-shaped cells lying parallel to it, just like those which are found in other kinds of connective tissue ; these become larger under certain circumstances, and, in oblique sections, often display themselves in the form of stellate cells (Fig. 94).

A substance altogether similar in structure to that, with which we have already become familiar in connective tissue—especially as far as its cells are concerned—is also found between the nerve-fibres of the cerebrum ; only the cells are so soft and fragile, that generally nothing but nuclei can be perceived, scattered at certain intervals throughout the mass. On making a careful search, however, even in fresh (not artificially hardened) specimens, soft cellular bodies of a roundish or lenticular form can

Fig. 95.

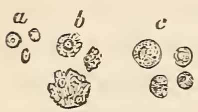


Fig. 95. Elements of the neuro-glia from the white substance of the cerebral hemispheres of a human subject. *a.* Free nuclei with nucleoli, *b*, nuclei with the granular remnants of the cellular parenchyma broken up in making the preparation, *c*, perfect cells. 300 diameters.

be detected, which possess finely granular contents and large granulated nuclei with nucleoli, and lie, certainly in no very great number, between the nervous elements. At certain spots it has indeed been hitherto impossible to draw a well-defined boundary-line between the two tissues, and especially so at the surface of the cerebellum and cerebrum, between the granules which I have already (p. 307) described to you as connected with large ganglion-cells, and the nuclei of the connective tissue. Wherever the parts are seen severed from their connections, it is not easy to make the distinction, and a positive decision is only possible as long as the parts are viewed in their natural position.

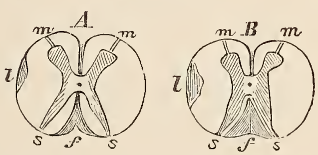
Now it is certainly of considerable importance to know that in all nervous parts, in addition to the real nervous elements, a second tissue exists, which is allied to the large group of formations, which pervade the whole body, and with which we have in the previous lectures become acquainted under the name of connective tissues. In considering the pathological or physiological conditions of the brain or spinal marrow, the first point is always to determine how far the tissue which is affected, attacked or irritated, is nervous in its nature, or merely an interstitial substance. We thus obtain at the very outset the important criterion for the interpretation of morbid processes, that the affections of the brain and spinal marrow may sometimes be rather interstitial, at others rather parenchymatous, and experience shows us that this very interstitial tissue of the brain and spinal marrow is one of the most frequent seats of morbid change, as for example, of fatty degeneration.

Within the neuro-glia run the vessels, which are therefore nearly everywhere separated from the nervous substance by a slender intervening layer, and are not in immediate contact with it. The neuro-glia extends in the peculiarly soft form, which it presents in the great nervous centres and particularly in the brain, only to those parts which must be regarded as direct prolongations of the cerebral substance, namely to the higher nerves of sense. The olfactory and auditory nerves also contain interstitial substance of the same character, whilst in all the rest, and even in the optic nerve itself, an increasing mass of a tougher tissue displays itself, which assumes quite the character of perineurium.

Perineurium and neuro-glia are therefore equivalent parts, the only difference being that the one is of a soft, medullary, fragile nature, whilst the other is akin to the well-known fibrous tissues. The neurilemma stands in the same relation to the perineurium that the membranes of the brain and spinal cord do to the neuro-glia.

Wherever neuro-glia exists, a very singular peculiarity presents itself which it has as yet been impossible to explain either chemically or physically, namely, that in every such case those peculiar bodies may be met with, which even in their structure remind one of granules of vegetable starch, whilst in their chemical reactions they altogether correspond to them—the much discussed *corpora amylacea* (Fig. 94, *ca*). They are found to the greatest extent and in the greatest numbers in the ependyma of the ventricles and spinal canal, and are the more abundant the greater the thickness of the ependyma. In many places but very few of them are found, whilst in others again their numbers increase so greatly, that the whole thickness of the ependyma is filled with them to such a degree, that it looks as if a pavement were before one. They display themselves, however, strangely enough, in pathological conditions also, frequently in great numbers, when, in consequence of some disturbing cause, the quantity of neuro-glia becomes increased in proportion to that of nervous substance, as for example after atrophic processes. In tabes dorsalis, as one used to say, or the atrophy of single columns of the cord, as we now usually interpret the old expression, we find, in proportion as the atrophy progresses, and the nerves in certain directions perish—cuneiform segments, in which the substance up to that time white becomes from without inwards grey and translucent—there being apparently a production of grey matter. This degeneration is most frequent in the posterior columns, generally in the immediate vicinity of the posterior fissure, and here it may go on, and generally does go on, in such a manner that the wedge penetrates deeper and deeper and at the same time increases in width. In these parts

Fig. 96.



then the whole substance of the medullated fibres gradually disappears, and distinct nerves are no longer discoverable—the whole spot generally consisting of neuro-glia with an enormous accumulation of corpora amylacea.

Nowhere in the body has there as yet been found anything completely analogous to structures of this sort, excepting, as I have said, in those parts which appear to be direct protrusions of the cerebral substance, namely in the higher organs of sense, in the case of which originally a certain quantity of central nervous matter entered into the sensorial capsules (Sinneskapseln) of the embryo. In the cochlea too, and the retina, bodies occur, which

Fig. 96. Section of the spinal marrow in partial (lobular), grey or gelatinous atrophy (degeneration). *f.* Posterior longitudinal fissure, *s*, *s* posterior, *m*, *m* anterior nerve-roots, communicating with the grey substance of the horns. In *A* a slighter, in *B* a more marked degree of atrophy, which is shown in the posterior columns around the central fissure *f*, and in the lateral columns at *l*. Natural size.

are allied to the corpora amylacea, although the chemical tests have as yet only proved successful in the case of those found in the internal ear.

When these bodies are isolated, they exhibit in every respect such a complete analogy to vegetable starch that, long before I succeeded in discovering the analogy in chemical reaction, Purkinje had already introduced the term corpora amylacea on account of the morphological resemblance. You are no doubt aware, that the chemical correspondence has in many quarters been doubted; the late Heinrich Meckel especially had great doubts upon the subject, and supposed them to have a greater affinity to cholesterine. In more recent times, however, the matter has been investigated even by professed botanists, and every one who has bestowed close attention upon it, has as yet acquired the same conviction which I published as my own. Nägeli pronounces these bodies to be really and truly starch.

Morphologically, they present themselves either as perfectly circular bodies with regular, concentric layers, or their centre is a little on one side; or we find twin bodies; or again the bodies are more homogeneous, pale, with a dim lustre, like fatty substances. When they are cautiously treated with a dilute solution of iodine, they assume a pale bluish, or greyish blue colour, though a great deal certainly depends upon the proper degree of concentration of the test. If afterwards we very cautiously add sulphuric acid, we obtain, when the proper effect is produced, a beautiful blue, which is best shown by allowing the reagent to act very slowly. When sulphuric acid acts violently upon them, a violet tint, which speedily becomes brownish red or blackish, is obtained, presenting a most decided contrast to the neighbouring parts, which become yellow or at most yellowish brown.

LECTURE XIV.

APRIL 7, 1858.

ACTIVITY AND IRRITABILITY OF CELLULAR ELEMENTS. DIFFERENT FORMS OF IRRITATION.

Life of individual parts—The unity of the neurists—Consciousness—Activity of individual parts—Excitability (irritability) as a general criterion of life—Meaning of irritation—Partial death—Necrosis.

Function, nutrition, and formation, as general forms of vital activity—Difference of irritability according to the different forms of activity.

Functional irritability—Nerves, muscles, ciliated epithelium, glands—Fatigue and functional restitution—Stimuli—Their specific relations—Muscular irritability.

Nutritive irritability—Maintenance and destruction of elements—Inflammation—Cloudy swelling—Kidney (morbus Brightii) and cartilage—Neuro-pathological doctrines—Skin, cornea—The humoro-pathological doctrines—Parenchymatous exudation, and parenchymatous inflammation.

Formative irritation—Multiplication of nucleoli and nuclei by division—Multinuclear cells; medullary cells and myeloid tumours—Comparison between formative muscular irritation and muscular growth—Multiplication (new formation) of cells by division—The humoro- and neuro-pathological doctrines.

Inflammatory irritation as a compound phenomenon—Neuro-paralytical inflammation (Vagus, Trigeminus).

I HAVE given you, gentlemen, a somewhat lengthy sketch of the histological arrangements of the body, in order to make the inference plain to you, which in my opinion must be the starting point of all future considerations that are instituted concerning life and vital activity—that, namely, in all parts of the body a splitting up into a number of small centres takes place, and that nowhere, as far as our experience extends, does a single central point susceptible of anatomical demonstration exist, from which the operations of the body are carried on in a perceptible manner. And even if we appeal to the experience which every one daily stores up around him, we shall find that this is the only view which concedes life to the individual parts of an organism, or allows it to the plant—the only view which enables us to institute a comparison both between the collective life of the developed animal and the individual life of its smallest parts; and also between the life of a plant as a whole and the life of the individual parts of a plant.

The opposite view which at this very moment is manifesting itself with a certain degree of energy—that namely, which beholds in the nervous system the real central point of life—is met by this extremely great difficulty, that, in the very same apparatus, in which it places its unity, it again finds the same splitting up into an infinite number of separate centres, which is presented by the rest of the body; and that in no part of the whole nervous system it can show the real central point, from which, as from a seat of government, mandates are issued to all quarters.

It may seem very convenient to say that the nervous system constitutes the real unity of the body, inasmuch as there is certainly no other system which enjoys such a complete dissemination throughout the most various peripheral and internal organs. But even this wide dissemination and the numerous connections which exist between the individual parts of the nervous system, are by no means calculated to show it to be the centre of all organic actions. We have found in the nervous system definite little cellular elements which serve as centres of motion, but we do not find any single ganglion-cell in which alone all movement in the end originates. The most various individual motory apparatuses are connected with the most various individual motory ganglion-cells. Sensations are certainly collected in definite ganglion-cells, still among them too we do not find any single cell which can in any way be designated the centre of all sensation, but we again meet with a great number of very minute centres.

All the operations which have their source in the nervous system, and there certainly are a very great number of them, do not allow us to recognise a unity anywhere else than in our own consciousness; an anatomical or physiological unity has at least as yet been nowhere demonstrable. If we really were to set down the nervous system with its numerous separate centres as the central point of all organic actions, even then the thing actually sought for, a real unity, would not have been obtained. If a clear idea is formed of the difficulties which stand in the way of such a unity, it can scarcely be doubted, but that we are continually led astray by the spiritual phenomena displayed in our own persons, in the interpretation of organic processes. Feeling ourselves to be something simple and indivisible, we always start with the presumption that everything else must be regulated by this indivisible principle. But if we trace the development of any given plant from its first germ up to the highest point in its evolution, we meet with a series of processes altogether analogous, without our being able to entertain the supposition for a moment, that such a unity exists in it, as we are led by our consciousness to suppose exists in us. Nobody has been able to detect a nervous system in plants; in no case has it been discovered that the whole of the fully developed plant was governed from a single point. All the vegetable physiology of the present day is based upon the investigation of the activity of cells, and if violent opposition is still made to the introduction of the same principle also into the animal economy, there is, I think, no other difficulty in the way but the one, that æsthetical and moral scruples cannot be overcome.

It cannot of course here be our business either to refute these scruples or to point out how they might be reconciled with the views I advocate. I have only to show in how great a degree the pathological processes which especially interest us, in all cases conduct us back to the same cellular principle, and how much they are in every case opposed to that notion of a single controlling principle, which is sought to be established by the neuro-pathologists. This opinion of mine has after all really nothing new or uncommon in it. If for thousands of years the life of the individual parts of the body has been talked about, if the position is admitted, that in diseased conditions the death of individual parts, necrosis or gangrene in them may take place, whilst the whole still continues to exist—the inference is, that something of our way of thinking had long been expressed in the views held by the world in general: only people had not formed very clear notions upon the subject. If we speak of the life of the individual parts of a body, we must also know in what way life manifests itself, and whereby it is essentially characterized. This characteristic we find in *activity*, an activity indeed, in which there is displayed by every single part, whilst it contributes its contingent, according to its peculiarities, to the general activity of the body—something identical with the life of the other parts; for else we should be in no way justified in regarding life as something in every case similar, and derivable from some common origin.

This vital activity is, as far at least as we are able to judge, nowhere, in no part whatever, carried on by means of any cause allotted to it from the very beginning, and entirely confined to it, but we everywhere see that a certain *excitation* is necessary for its production. Every vital action presupposes an excitation, or if you like an *irritation.* The *irritability* of a part, therefore appears to us the criterion, by which we can judge whether it is alive or not. Whether, for example, a nerve be alive or dead, we cannot immediately determine by an anatomical examination of it, conducted either microscopically or macroscopically. In the outward appearance, in the more obvious structural arrangements, which we are able to decipher by the aid of our auxiliaries, we rarely find sufficient to enable us to come to a decision upon a point such as this. Whether a muscle is alive or dead, we are but little able to judge, inasmuch as we find its structure still preserved in parts which perished years ago. I found in a fœtus, which, in a case of extra-uterine pregnancy, had lain thirty years in the body of its mother, the structure of the muscles as intact as if it had just been born at its full time. Czermak examined parts of mummies, and found in them a number of tissues which were in a state of such perfect preservation, that the conclusion might very well have been come to, that the parts had been taken from a living body. Our notion of the death, decease, or necrosis of a part, is based upon nothing more or less than this, that whilst its form is preserved, and indeed in spite of it, we can no longer detect any irritability in it. This has been most clearly shown quite recently in the course of some investigations into the more hidden properties of nerves. Now that, by the investigations of Dubois-Reymond, activity has been shown to exist in nerves even when in a so-called state of repose, and that it has been discovered, that in a nerve, even when seemingly at rest, electrical processes are continually going on, and that it constantly produces an effect upon the magnetic needle—now we are able, by means of this physical experiment, with certainty to judge when a nerve is dead, for, as soon as death has stepped in, those qualities cease, which are inseparably connected with the life of the nerve.

This peculiarity which we find in some parts exhibited in such a marked degree and so evidently demonstrable, becomes less and less apparent, the more lowly the organization of the part, and our criteria are least to be depended upon in the case of the class of connective tissues; for we are, indeed, really frequently much puzzled to decide whether a part composed of one of them is still alive or has already perished.

If now we proceed with our analysis of what is to be included in the notion of excitability, we at once discover, that the different actions which can be provoked by the influence of any external agency, are essentially of three kinds; and I consider it of great importance that you should pay particular attention to this point, as it will greatly assist you in the classification of pathological conditions, and because it is not wont to be set forth with particular distinctness.

When, namely, a given action is called into play, we have to deal with a manifestation either of the *function*, the *nutrition*, or the *formation* of a part. It certainly cannot be denied that at certain points the boundaries between these different processes disappear, and that between the nutritive and formative processes and also between the functional and nutritive ones, there are transitional stages; still, when they are typically performed, there is a very marked difference between them; and the internal changes which the individual excited part undergoes, according as it only performs its functions, or is subjected to a special nutrition, or becomes the seat of special formative processes, exhibit considerable differences. The result of an excitation, or if you will, an irritation, may, according to circumstances, be either a merely functional process; or the effect may be that a more or less increased nutrition of the part is induced without there necessarily being any excitation of its functions; or a formative process may set in, giving rise to a greater or less number of new elements. These differences manifest themselves with greater or less distinctness in proportion as the individual tissues of the body are more or less capable of responding to the one or other kind of excitation. When, namely, we speak of the functions of parts—in the case of a considerable number of tissues the real functions shrink into a very small compass; we are on the whole able to say but very little concerning the real functions, in the higher sense of the word, of nearly all the connective tissues, and of the great majority of epithelial cells. We are no doubt able to say what their use under particular circumstances is, still they always rather appear to be relatively inert masses, which scarcely perform any real functions in the ordinary meaning of the word, but rather serve as supports to the body, or as coverings to the different surfaces, or, in other localities, according to circumstances, act as media of union, intervention, or separation.

The case is different, on the other hand, with those parts, which, owing to the peculiar nature of their internal arrangement, are liable to a more rapid change, such as the nerves, muscles, and muscular organs, glands and a few other structures, as, for example, among the epithelia, ciliated epithelium. In all these tissues, which are subservient to important functions, we find that these functions are chiefly due to very delicate changes of arrangement, or if you wish it expressed in more precise terms, to minute changes of place, in the minute particles of the internal matter, the cell-contents. In these cases therefore it is not so much the real cell in its pure form which decides the question, as the specific matters with which it is provided internally; the chief agent is not so much the membrane or the nucleus of the cell, as the contents. It is these which, when exposed to certain influences, become comparatively rapidly changed, without our being always able morphologically to detect any trace of a change in the arrangement of the contained particles. The utmost that we can observe in the shape of a palpable result is a real locomotion of small, visible particles, but we cannot push our analysis to such an extent, as to enable us to form any opinion as to the internal cause, in virtue of which this locomotion is effected by the ultimate particles which compose the cell-contents. When an excitation takes place in a nerve, we now know that a change in its electrical state is connected with it, a change which, from all that is known to us concerning electrical excitation in other bodies, must of necessity be referred to a change in the position which the individual molecules assume to one another. If we conceive the axis-cylinder to be made up of electrical molecules, we can easily imagine that every two of these molecules take up an altered position with regard to one another at the moment the stimulus is applied. Of these processes we see nothing. The axis-cylinder looks just as usual. If we watch a muscle during its contraction, we remark, it is true, that the intervals which separate the individual so-called discs (p. 82) become shorter; and as we now know that the substance of the mus-

Fig. 97.

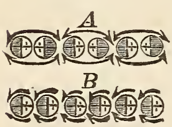


Fig. 97. Ideal diagram of the condition of the molecules of a nerve when it is at rest (in a peripolar state, *A*), or in an electrotonic (dipolar) state, *B*. From Ludwig, 'Physiolog.,' I, p. 103.

cle consists of a series of minute fibrils, which in their turn contain little granules at certain intervals corresponding to these discs, we conclude therefrom with some degree of assurance that really local changes take place in the minutest elements, though they cannot be further referred to any visible or directly recognizable cause. We cannot perceive any definite chemical change, or any alteration in the state of nutrition of the parts; we only see a displacement, a dislocation of the particles, which, however, probably depends upon some slight chemical change in the molecules composing them.

In the case of ciliated epithelium you see how the fine cilia, which are seated upon the surface of the cells, move in a certain direction, and in this direction exercise a locomotory effect upon the little particles which come near to them. If we isolate the individual cells, we see that every one of them has at its upper end a border of a certain thickness, from which little hair-shaped prolongations run out. These all move in such a way that a cilium which, whilst quiet, stands quite upright, bends forwards and then throws itself backwards. But we are unable to perceive any changes within the individual cilia, by means of which the movement is effected.

Just the same is the case with gland-cells, concerning which we cannot entertain the least doubt that they produce a definite locomotory effect. For since Ludwig has shown in his researches on the salivary glands, that the pressure of the outward current of saliva is greater than that of the inward stream of blood, the only conclusion that is left us is, that the gland-cells exercise a definite motor influence upon the fluid; and that the secretion is driven out with a definite force, which is not due to the pressure of the blood, or any special muscular action, but to the specific energy of the cells as such. Still we are just as little able to discern in a gland cell, whilst performing its functions, that its constituent particles are engaged in any peculiar material process, as we were in the case of the nerves, or ciliated epithelium.

These facts derive great support from the circumstance that we are able to perceive, that the functional activity of individual parts does experience a certain amount of impairment, if it is continued for too long a time. In all parts certain states of *fatigue* manifest themselves, states, during which the part is no longer able to originate the same amount of movement, that up to that time could be perceived in it. But, in order that they may again become competent to perform their functions, these parts by no means always require a new supply of nutriment, a fresh absorption of nutritive material ; rest alone is sufficient to enable them to resume their activity in a short space of time. A nerve, which has been cut out of the body, and used for experiment, after a certain lapse of time becomes incapable of discharging its functions ; but if it be allowed to repose under favourable circumstances, which prevent it from drying up, it gradually regains its powers. This *restitution of functional power* (functional restitution), which takes place without any proper nutritive action, and in all probability depends upon the circumstance, that the molecules which had quitted their usual position gradually revert to it—we can produce in different parts by means of certain stimuli. According to the views of the neuro-pathologists these stimuli would only act upon the nerves, and through the medium of the nerves upon the other parts ; but with reference to this very point we have some facts which cannot well be explained in any other way than by the assumption, that an influence is really exercised upon the parts themselves.

If we take a single ciliated cell, and, after entirely isolating it from the body, allow it to swim about, and wait until a state of complete repose has declared itself, we can again call forth the peculiar movements of its cilia by adding a small quantity of potash or soda to the fluid, a quantity not large enough to produce corrosive effects upon the cell, but sufficient, upon penetration into it, to induce a certain change in its contents. A peculiarly interesting fact, however, is that the number of substances which will act, as stimuli, upon ciliated epithelium, is limited to these two. This explains how it happened that Purkinje and Valentin (who, it is well known, first made experiments, and those upon a very extensive scale, upon ciliary movement), although they experimented with a very large number of substances, at last, after they had tried all sorts of things—mechanical, chemical and electrical stimuli—came to the conclusion that there was no stimulus whatever, which could provoke the ciliary movement. I had the good fortune incidentally to stumble upon the peculiar fact, that potash and soda are such stimuli. Here we certainly cannot call in any nervous influence to our aid, and such influence appears to be the less admissible for the reason that, in accordance with the well-known experiments, the ciliary movement is maintained in the dead body at a time when other parts have already begun to putrefy. The ciliated epithelium of the frontal sinuses and the trachea is found in human corpses in a state of perfect excitability thirty-six to forty-eight hours after death, when every trace of irritability has long vanished from the remainder of the body.

Much the same is the case with all other excitable parts. We see nearly everywhere that certain excitants act more readily than others, and that many are totally incapable of producing any particular effect. Nearly everywhere do we find *specific relations* or *affinities* to exist. If we cast our eyes upon the glands, it is a well-known fact that there are specific substances, by which we are enabled to act upon one gland, and not upon another ; to rouse the specific energy of one gland, whilst all the rest remain unaffected. In the case of glands it is certainly much more difficult to exclude the influence of the nerves, than in that of ciliated epithelium, still certain experiments are recorded, in which, after the section of all the nerves, say of the liver (G. Harting), it was found possible, by means of the injection of irritating substances into the blood (these being such as experience had shown to bear some intimate relation to the organ), to provoke an increased secretion in the organ.

The discussion of this subject has, as you no doubt are well aware, recently chiefly become centred in the question of the irritability of muscle, a question which has proved so difficult for the very reason that the possession of irritability was restricted by Haller with great exclusiveness to muscle. Haller with the greatest obstinacy combated the opinion that any other part was irritable ; and curiously enough he even contested the irritability of parts, which, as the minuter investigations of later observers have shown, contain muscular elements, as for example, the middle coat of the vessels. Indeed, he made use of tolerably energetic expressions when repudiating the excitability of the vessels, which even then was maintained by others. I have already informed you that there are large tracts in the vascular system (for example, in the umbilical vessels of the fœtus, where they are particularly well marked) in which enormous accumulations of muscular fibres are found, but not a trace of any nerves. Here irritability exists in a high degree ; we can produce contractions of the muscles mechanically, chemically and electrically. Just the same is the case with many other, small vessels, which by no means exhibit nerve-fibres in all their parts. In them too we can at every single point where muscles exist, at once provoke contraction.

The solution of this question has recently, as is well known, been particularly promoted by the fact that, by the employment of certain poisons, especially the woorara poison, observers have succeeded in paralyzing the nerves right down to their extreme terminations, or at least as far as these were accessible to the experiment; and this in such a manner, that the objection cannot well be raised, that the excitability of the extreme terminations of the nerves contained in the muscle is preserved. The paralysis produced by the woorara poison is completely confined to the nerves, whilst the muscles just as completely retain their irritability. Whilst the most violent electrical currents were made to act upon the nerve in vain, without the production of the least movement, the slightest mechanical, chemical or electrical stimuli are sufficient to throw the muscle experimented upon into a state of excitation.

I have mentioned these facts to you, in order that I might not be thought to treat the different divisions of my subject too unequally. The question of function, however, interests us less here. Nevertheless, you will be able to gather from what I have communicated to you, that now-a-days it can no longer be said with any show of reason that the nerves alone are irritable parts, but that we are irresistibly led to consider functional irritability, at least, as a property belonging to whole series of organs.

Far less known, gentlemen, is that clearly demonstrable series of processes in which *nutritive irritability* manifests itself—that power possessed by individual parts of taking up, when excited by definite stimuli, more or less matter and transforming it. This constitutes at the same time the first step in the most important processes which we have to follow into the domain of pathologico-anatomical facts.

A part, which nourishes itself, can in doing so either limit itself to a mere maintenance of its existence, or it may, as is especially seen in pathological cases, take up into itself a larger quantity of nutritive material than is wont to happen in the ordinary course of things. If we investigate these processes of absorption more closely, we always find that, as I have already had occasion to remark to you, the number of histological elements remains the same before and after the occurrence of the excitation; and we thus distinguish simple hypertrophies from the hyperplastic conditions, to which, in their external effects, they often bear so great a resemblance (p. 94, Fig. 27, *B*). It is, however, of extreme importance for the attainment of correct pathological notions, that we should know that a part, which in virtue of some inherent power, takes up a large quantity of material, need not on that account necessarily fall into a permanent condition of enlargement, but that on the contrary, under these very circumstances there often arises subsequently in its internal economy a disturbance which imperils the persistence of the part and becomes the proximate cause of its destruction. There are, as we know from experience, certain limits to the enlargement of every tissue, within which it is able to maintain a regular existence; if these limits be exceeded, and especially, if suddenly, we always see that obstacles spring up impeding the further life of the part, and that when the process runs a particularly acute course, a weakening of the part sets in, proceeding to a complete destruction of it.

Processes of this kind form a part of that domain which in ordinary life is assigned to inflammation. A number of inflammatory processes on their first appearance really exhibit nothing more than an increased assumption of material into the interior of the cells, entirely resembling what we find in simple hypertrophy. If, for example, we consider the history of Bright's disease in its ordinary course, we constantly find, that the very first thing which can be detected in a kidney affected with this disease, consists in this, that in the interior of the uriniferous tubules whilst still quite intact, the individual epithelial cells which are, as is well known, even in their normal state tolerably large, become still larger. These epithelial cells which fill up the tubules are not only large, but at the same time also present a very cloudy appearance, inasmuch as a larger quantity of material than usual has everywhere been taken up into the cells. The entire uriniferous tubule is thereby rendered broader, and appears even to the naked eye as a convoluted, whitish, opaque body. If we isolate the individual cells, which is somewhat difficult, as the cohesion of the particles composing them has usually begun to suffer, we find in them a granular mass apparently containing nothing else than the granules which are normally present in the interior of the cells, but which accumulate in greater numbers the greater the energy with which the process is carried on, so that even the nucleus gradually grows indistinct. This is the condition of *cloudy swelling* (trübe Schwellung), as it is met with in many irritated parts, as an expression

Fig. 98.

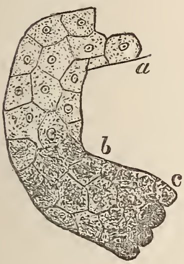


Fig. 98. Convoluted urinary tubule from the cortex of the kidney in morbus Brightii. *a*. Tolerably normal epithelium, *b*, state of cloudy swelling, *c*, commencing fatty metamorphosis and disintegration. At *b* and *c* increased breadth of the tubule. 300 diameters.

of the irritation which attends many forms of what is called inflammation. From these processes backwards to the phenomena of simple hypertrophy we find no recognizable boundaries at all. We cannot at once say, when we meet with a part enlarged in this way, and containing a greater amount of matter than usual, whether it will retain its life or perish ; and therefore it is extremely difficult in very many cases, when nothing at all is known concerning the process through which such a change has been produced, to distinguish simple hypertrophy from those forms of inflammatory processes which are essentially accompanied by an increased absorption of nutritive material.

In these processes too it is scarcely possible to refuse the individual elements, when incited by a stimulus directly applied to them, the power of taking up an increased quantity of material ; at least it is opposed to all the results of experience, to assume that such an increased absorption must be due to a special innervation. If we select a part which, in accordance with all observation, is entirely destitute of nerves, as for example, the surface of an articular cartilage, we can, as was shown many years ago by the beautiful experiments of Redfern, produce altogether similar effects by means of direct stimuli. In precisely the same way, there are not unfrequently observed, in chronic diseases of cartilage, nodular elevations of the surface ; and upon examining such spots microscopically we find the same thing that I showed you in a former lecture in a costal cartilage (p. 48, Fig. 9), namely, that the cells which at other times are very delicate, small, lenticular bodies, increase in size, swell up into large, round corpuscles, and in proportion as they take up more matter, enlarge in all directions, so that at last the whole spot forms a little protuberance above the surface. Now in articular cartilage no nerves at all are found; the terminal ramifications of those nearest to it are at best situated in the medulla of the bone immediately adjoining, and that, perhaps, is separated from the irritated spot of the surface by an intact, intervening layer of cartilaginous tissue one or two lines in thickness. Now it would indeed be contrary to all experience to conceive that a nerve could from the medulla of the bone exercise a special action upon the cells of the surface of the cartilage, which were the seat of irritation, without a simultaneous affection of the cells lying between the nerve and the irritated spot. If we draw a thread through a cartilage, so that merely a traumatic irritation is produced, we see that all the cells which lie close to the thread become enlarged through an increased absorption of material. The irritation produced by the thread extends only to a certain distance into the cartilage, whilst the more remote cells remain altogether unaffected. Such observations cannot be explained otherwise than by assuming that the stimulus really acts upon the parts to which it is applied; it is impossible to conclude that it is conducted to the nerve by any channel perhaps more in accordance with the neuro-pathological doctrine, and then only by reflex action conveyed back again to the parts.

There certainly are but few tissues in the body which are so completely destitute of nerves as cartilage, but even when we observe what happens in the parts most abundantly supplied with nerves, we find in every case, that the extent of the irritation, or to speak more accurately, the extent of the irritated area, by no means corresponds to the size of any particular nerve-territory, but that in a tissue in other respects normal the size of the affected area essentially corresponds to that of the local irritation. If we make the experiment with the thread, upon the *skin*, a whole series of nerve-territories are intersected by it. Still the whole of the territories belonging to the nerves which lie along the thread, are not thrown into the same morbid condition, but the nutritive irritation is limited to the immediate vicinity of the thread. No surgeon expects in operations of the kind, that all the nerve-territories traversed by the thread, will become diseased in their whole extent. Great complaints would have to be raised against nature, if every ligature, every seton were to exercise an irritating influence, beyond the limits of the parts with which it is in immediate contact, upon the whole extent of the nerve-districts which it passes through. Thus we see in a tissue in which what takes place in such a case can be very clearly traced, namely in the *cornea*, that in parts of it to which no vessels extend, there are certainly still nerves which possess a reticular arrangement, and leave larger and smaller districts of tissue between them altogether devoid of nerves. Now if we apply any stimulus directly to the cornea, as for example, a red hot needle, or lunar caustic, the district which is thereby set in morbid action by no means corresponds to the distribution of any nerve. It once happened to me with a rabbit that the cautery lighted precisely upon a nervous filament, but the morbid action remained confined to the immediate vicinity of this spot, and by no means spread over the whole district appertaining to the nerve.

It is therefore utterly impossible, even if observations, like those on cartilage which I have laid before you, are not allowed to have any weight, not to admit that the phenomena of irritation in parts supplied with nerves are in no respect different from those which occur in nerveless parts, and that the immediate effects essentially depend upon the enlargement and tumefaction of the surrounding elements, so that when there are many of them, a visible swelling of the whole part is the result. This is what you observe when a ligature is anywhere drawn through the skin. If on the following day the immediate vicinity of the thread be examined, an active enlargement of the cellular elements is found, quite irrespective of the distribution of vessels and nerves in the part.

There is, as you see, an essential difference between what I here lay down and the opinions which have generally been advanced with regard to the proximate causes of these swellings. According to the old maxim: ubi stimulus, ibi affluxus, it was generally conceived that the first thing which took place was an increased afflux of blood (which was itself referred by the neuro-pathologists to the excitation of sensitive nerves), and then that the immediate consequence of the increased afflux was an increased excretion of fluid from the blood, constituting the exudation which filled the part.

In the first timid attempts which I made to alter this conception, I employed the expression *parenchymatous** *exudation*, retaining the term exudation, out of deference to prevailing opinion. I had, namely, convinced myself that in many places where a swelling had occurred, there was absolutely nothing else to be seen than tissue. In a tissue which consisted of cells, I could, after the swelling (exudation) had taken place, still see nothing

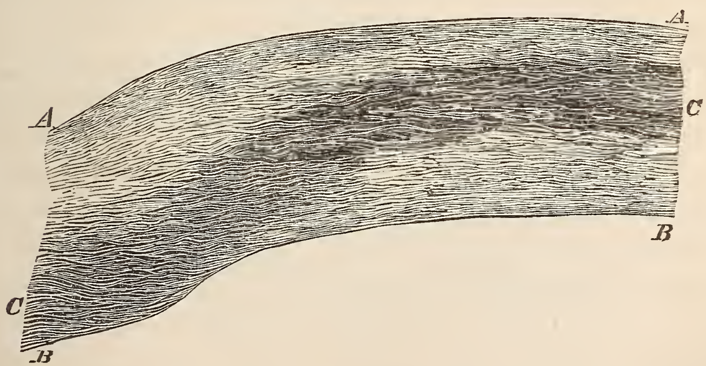
* The term Parenchyma was first employed by Erasistratus of Alexandria to designate the mass of tissue *which lies between the vessels of a part*, and in his opinion formed a kind of affusion from them. Thus Galen says (Isagoge s. Introductio, cap. xi.): "Cerebrum ex nullo principali vase compositum esse videtur Erasistrato, eoque nutrimenti parenchyma, *i. e.*, affusio, ipsi esse videtur." In the same way the word is used by Vesalius (De humani corp. fabricâ, lib. V., cap. 7) and by Thom. Bartholin (Anatome, lib. I., cap. 14), for the proper substance of the liver, lying external to, or between, the vessels. It therefore essentially denotes the tissue of which an organ is constituted. In a narrower sense those constituents of an organ which are peculiar to it, and give it its specific character, may be distinguished as its *proper parenchyma*, in contra-distinction to its merely interstitial tissue. In my book the term has been used in both of these senses.—*From a MS. Note by the Author*

but cells; in tissues composed of cells and intercellular substance, nothing but cells and intercellular substance; the individual elements indeed were larger, fuller and filled with a quantity of matter with which they ought not to have been filled, but there was no exudation in the manner in which it had been imagined to exist, namely free, or in the interstices of the tissue. All the matter was contained in the elements of the tissues themselves. This was what I intended to express by the term, parenchymatous exudation, and hence the name, parenchymatous inflammation, is derived—a name which was, indeed, used in former times, but in quite another sense from that I meant—and which is now more generally employed than is perhaps desirable. It is, however, at all events important that you should draw a distinct line of demarcation between this form of irritation as a general standard and the other forms (especially the formative one), inasmuch as in it only the constituent elements of a tissue already existing in the body take up a larger quantity of material, and besides these enlarged elements nothing else is present.

I will immediately send round a preparation to you, in which you will see a very characteristic example of such an inflammation. It is almost the most striking example which for a long time has come before me. It is a specimen from a case of so-called Keratitis, from one of Herr von Graefe's patients, in whom, after violent, diffuse phlegmonous inflammation of the extremities, an extremely rapid inflammatory opacity of the cornea took place. When the cornea was put into my hands, it seemed to me as if it were opaque and swollen in its whole thickness. The vessels of the borders were very full of blood. But when I made a section through the part, it at once became evident, even with a low power, that the opacity extended by no means uniformly throughout the whole cornea, but was limited to a definite portion of the tissue. This portion is so characteristic in reference to the different explanations possible, that the case, I think, presents especial interest theoretically.

It turned out namely that the opacity began in the immediate proximity of the posterior surface and at the circumference of the cornea, close to the membrane of Descemet [posterior elastic lamina of Bowman] at the point where the iris is attached. Thence the opacity, assuming almost the shape of a flight of steps, mounted up into the cornea till within a certain distance of the external surface. Then it proceeded at the same level, till it descended upon the other side again in a similar manner. Thus an opaque bow was formed throughout the whole substance of the cornea, without reaching the external (anterior) surface and without encroaching upon the central parts of the posterior surface. If we

Fig. 99.



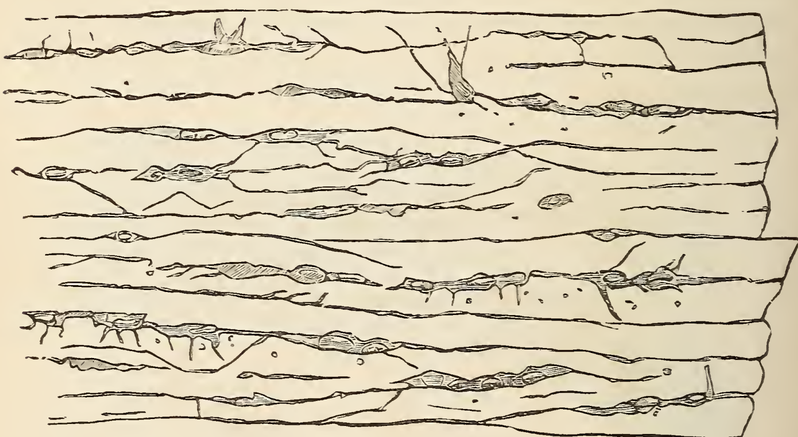
imagine the nutrition of the cornea to proceed from the aqueous humour, the opacity did not assume the form

Fig. 99. Parenchymatous keratitis. *A*, *A*, Anterior (external), *B*, *B*, posterior (internal) side of the cornea. *C*, *C*. The clouded zone with enlarged cornea-corpuscles. 18 diameters.

that might have been looked for, for then we should rather have expected that the hindermost layer would be the first to undergo the change. If any influence from without had been here in operation, the opacity must have been seated in the most anterior layers ; if again the opacity were one which essentially proceeded from the vessels, we might, inasmuch as they chiefly lie along the border and nearer to the anterior surface, have expected to find the principal disease there. Finally, if the changes had their origin in the nerves, we should have found the opacity spread in the form of a network on the surface—and not a bow of this kind.

The substance of the cornea consists, you know, according to general opinion, of lamellæ (plates) which run in a more or less parallel direction through the

Fig. 100.

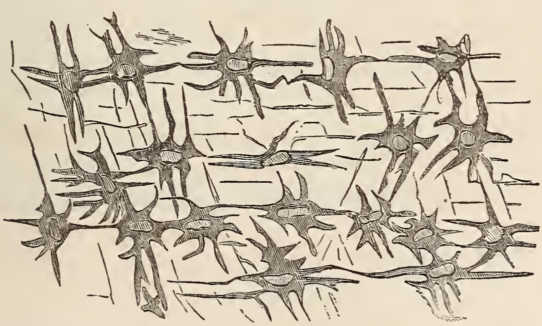


cornea. Now if this opinion be the correct one, we should have to deal with a process which, whilst advanc-

Fig. 100. Perpendicular section of the cornea of the ox, for the purpose of showing the form and anastomoses of its cells (corpuscles). Here and there are seen the cut ends of some of the processes of the cells, looking like fibres or points. 500 diameters. From His, 'Würzb. Verhandl.,' IV., plate IV., fig. I.

ing from lamella to lamella, each time moved a little farther on. Only the cornea is not composed of perfect lamellæ, but of layers, which certainly are on the whole placed one against the other in a lamellar form, but yet are connected with one another ; they do not lie any how, more or less firmly or loosely upon one another, but there exist direct connections between them. It is therefore rather a large coherent mass, which is interrupted in certain directions by cellular elements, just as is the case in the very different tissues which we have already specially considered. A vertical section discloses spindle-shaped cells which anastomose with one another, but at the same time also possess lateral processes ; and in consequence of their being regularly imbedded in the basis substance, this lamellar, foliated or plate-like arrangement of the whole tissue is produced. When viewed upon the surface, in horizontal section, they show themselves in the form of many-rayed, stellate but very flat cells, which may be compared to bone-corpuscles.

Fig. 101.

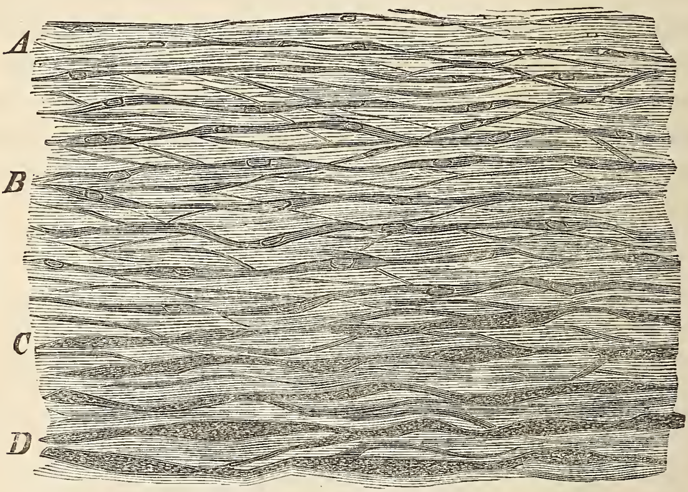


If now in this case of ours we follow the process with a higher power, we discover, what may easily be shown

Fig. 101. Horizontal section of the cornea, parallel to the surface and showing the stellate, flat corpuscles, with their anastomosing processes. From His, loc. cit., fig. II.

to be the case in every form of keratitis, that the change is essentially seated in the corpuscles or cells of the cornea, and that in proportion as we approach the clouded spot either from without or within, the little narrow cells continually become larger and more cloudy. At last we find them presenting almost the appearance of sacculated canals or tubes. Whilst this enlargement of the elements, this acute hypertrophy, if you will, is going on, the contents of the cells are at the same time becoming more cloudy, and it is this cloudiness of the contents which in its turn occasions the opacity of the whole coat, for the proper basis-substance appears to be altogether unaffected.

Fig. 102.



This cloudiness of the contents is in part occasioned by particles which are of a fatty nature, so that the process seems to have begun to assume the character of a degenerative disease. I should have had no hesitation in believing that a destruction of the cornea had here

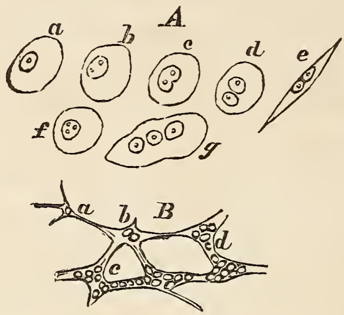
Fig. 102. Parenchymatous keratitis (cf. Fig. 99), seen with a higher power. At *A* the cornea-corpuscles in a nearly normal condition, at *B* enlarged, at *C* and *D* still more enlarged, and at the same time clouded. 350 diameters.

really set in, but Herr v. Graefe assures me that, from what he has seen, such conditions may, when the disease runs a favourable course, terminate in resolution. And there is really nothing at all in the matter at variance with this possibility; for, since the cells still exist and the only thing required is that their changed contents be got rid of, a complete restitution may no doubt take place.

Now just this doctrine of a *simply nutritive restitutional power* is of very great importance practically. In such a case as this, where nothing has taken place excepting that the cells, without ceasing to display their activity, have accumulated in their cavities a larger quantity of material than usual, everything is prepared for the process which we call reabsorption; the cells can transform a certain quantity of the material and convert it into soluble substances, and the material in this form may disappear in the very same way in which it came. The structure in the main remains the same all the while nothing foreign has thrust itself in between the parts the tissue presents throughout its original constituents.

From the phenomena of this nutritive irritation direct transitions to incipient *formative changes* are often seen. If namely, we follow up the higher degrees of irritation which take place in a part, we find that the cellular elements, shortly after they have experienced the nutritive enlargement, exhibit further changes which begin in the interior of the nuclei, generally in such a manner that the nucleoli become unusually large, in many cases somewhat oblong, and sometimes staff-shaped. Then as the next stage we usually see that the nucleoli become constricted in the middle, and assume the form of a finger-biscuit (Bisquit), and a little later two nucleoli are found. This division of the nucleoli is an indication of the impending division of the nucleus itself, and the next stage is, that about such a divided nucleolus the finger-biscuit-like constriction, and afterwards the real division, of the nu-

FIG. 103.



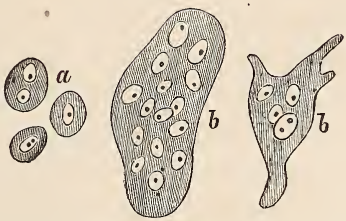
cleus takes place, as we have already seen in colourless blood- and pus-corpuscles (Figs. 11, *A*, *b*; 56, 63). Here we manifestly have to deal with something essentially different from what we had before. In the simple hypertrophy consequent upon nutritive irritation, the nucleus may remain quite intact; here, on the other hand, we frequently see that the contents display a relatively slight amount of change, the utmost being that the cells become larger, whence we infer that a quantity of new material has been taken up into them.

In many cases the changes are limited to this series of transformations, of which the division of the nucleus must be regarded as the conclusion. This may be repeated, so that three, four or more nuclei arise (Fig. 15, *b*, *c*, *d*). Thus it comes to pass that we sometimes find cells—not merely in pathological conditions, but also not unfrequently where the development is altogether normal—which contain twenty to thirty nuclei or more. Recently in the marrow of bones, especially in young children, cells have been observed, where the entire structure is

Fig. 103. Cells from a melanotic tumour of the parotid gland extirpated in 1851 by Herr Textor. *A*. Free cells with division of the nucleoli and nuclei. *B*. Network of connective tissue-corpuscles with division of their nuclei. 300 diameters.

full of nuclei, which often attain the size of the whole original cell. Such formations occur in many tumours in

Fig. 104.



such large quantities, that in England a particular species is thereby distinguished, and on the proposal of Paget a myeloid tumour (medullary swelling) has been received into the classification. This formation is not, however, confined to the medulla of the bones, but occasionally occurs in nearly all situations.

Muscle, upon irritation, exhibits precisely similar forms. Whilst transversely striated muscles are generally provided with nuclei at certain intervals, though in no great abundance, we find, on examining a muscle in the neighbourhood of an irritated part, as for example, a wound, a corroded or ulcerated surface, that a multiplication of the nuclei is going on in it; we see nuclei with two nucleoli; then come constricted, and then divided, nuclei (Comp. Figs. 23, *b*, *c*; 24, *B*, *C*), and so it goes on, until we find in different places whole groups of nuclei lying side by side, in which the divisions have taken place to a large extent, or else whole rows of them, one behind the other. In the most marked cases of this sort the number of nuclei increases to such a degree, that at first sight we can scarcely believe we are looking at muscles; and that fragments of the primitive fasciculi offer the greatest

Fig. 104. Cells from the marrow of bones. *a*. Small cells with single and divided nuclei. *b*, *b*. Large, many-nucleated cells. 350 diameters. From Kölliker, 'Mikr. Anat.,' I., p. 364, fig. 113.

resemblance to those *plaques à plusieurs noyaux* which Robin has described in the marrow of bones. This is something quite peculiar which looks extremely like the commencement of a real new-formation, only that new-formations in the ordinary sense of the word are not limited to single cell-constituents. Besides we must bear in mind this very important fact, that exactly the same limitation takes place in the earliest embryonic development of muscle, in the course of the first growth of the primitive muscular fasciculi. For this is the manner in which muscle originally grows. If a growing muscle be watched, the same division of the nuclei is witnessed, and after groups and rows of nuclei have arisen in it, they are, in the course of growth, gradually thrust farther and farther asunder by the continual increase of the intermediate sarcous substance. Now although a growth in length has not as yet been demonstrated with certainty in a pathologically irritated muscle—I say demonstrated, because there really is a probability that something of the kind may yet be proved to be the case—we must still hold the perfect analogy of morbid irritative processes with the natural ones of growth to be a well-ascertained fact. For the formative act of real growth begins with a multiplication

FIG. 105.

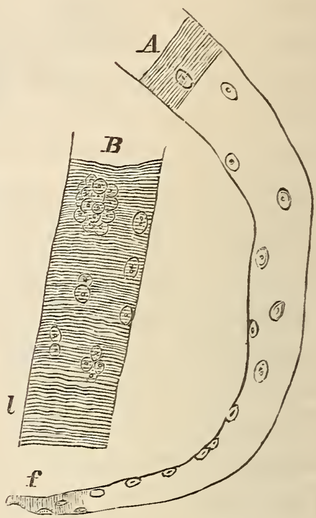
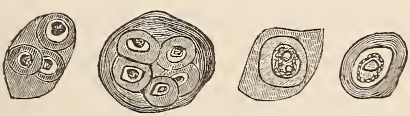


Fig. 105. Division of nuclei in primitive muscular fasciculi from the immediate neighbourhood of a cancerous tumour in the thigh. At *A* a primitive fasciculus, the transverse striation of which is not represented all the way down, with its natural, spindle-shaped extremity *f*, and incipient multiplication of the nuclei. *B*. Strongly marked proliferation of nuclei. 300 diameters.

of the centres, inasmuch as the nuclei must, as was long since shown by John Goodsir, be regarded as the central organs of the cells.

If now, gentlemen, we advance a step further in these processes, we come to the *new formation of the cells themselves.* After the multiplication of the nuclei has taken place, the cell may certainly, as we have seen, continue to subsist as a coherent structure ; still the rule is, that even after the first division of the nuclei, the cells themselves undergo division, and that after some time two cells are found lying closely side by side, separated by a more or less straight partition, and each provided with a nucleus of its own (Fig. 6, *b*, *b*). This is the natural, regular manner in which the real multiplication of cellular elements takes place. Then, the two cells may separate, if the tissue is one which possesses intercellular substance (Fig. 6, *c*, *d*) ; or may remain lying close to one another, in the case of a tissue simply composed of cells (Fig. 27, *C*). This series of processes, which in their subsequent course lead to a continually proceeding division of the

Fig. 106.



cells, and to the production of large groups of cells from single ones (Figs. 9, 22), occurs in the adult body just as unquestionably as the result of a direct irritation of the tissues, as the class we spoke of before. If, for example, we follow up a little farther the case which we before considered, of the production of a simple mechanical irritation by drawing a thread through the parts, we usu-

Fig. 106. Cells from the central substance of an intervertebral cartilage of an adult. Intra-capsular multiplication of cells. 300 diameters.

ally observe that the swelling is not simply limited to the enlargement of the existing cells, but that they divide and multiply. Round about a thread, which we draw through the skin, a number of young cells generally show themselves as early as the second day. The same change may be brought about by the application of a chemical stimulus. If, for example, caustics be applied to the surface of a part, the first thing that happens is that the cells swell up and then, when the process follows a regular course, divide, and begin to proliferate more or less abundantly. Here too we have still to deal with actions which do not exhibit the slightest difference in the real mode of their accomplishment, whether the part be provided with nerves, or destitute of them, whether it contain vessels or not.

Accordingly, we cannot say that any part of these processes appears to be necessarily dependent upon nervous or vascular influence, but, on the contrary, we are in all these cases referred to the parts themselves. The relation of the vessels is not by any means to be explained in the way in which it is ordinarily done; the absorption of matter into the interior of the cells is unquestionably an act of the cells themselves, for we are as yet acquainted with no method enabling us to produce this kind of proliferation in the body, by any mode of experimentation, through the medium of an agency primarily affecting either the nerves or the vessels. The circulation may be heightened in the parts as far as it is possible to heighten it, without the production of such an increased nutrition of the parts as to give rise to any swelling or multiplication of the elements themselves. Those very experiments too upon the section of the sympathetic nerve which I have already mentioned, have, as is well known, proved (I myself have very frequently performed this experiment and watched its effects with this especial object) that an increased afflux of blood may last for weeks—an afflux of blood accompanied by a marked elevation of temperature and corresponding redness, as great, both of them, as we ever meet with in inflammations—without the production of the least enlargement in the cells of the part, or the excitation of any process of proliferation in them. Irritation of the nerves may be combined therewith. But when the tissues themselves are not irritated, when the irritation is not made to act upon the parts themselves, either by the direct application of the irritating matters, or by their introduction into the blood, the occurrence of these changes cannot be relied upon. This is a most important argument, from which I draw the conclusion that these active processes have their foundation in the special action of the elementary parts, an action which does not depend upon an increased afflux of blood or any excitation of the nerves, but which is certainly promoted by them, though it can also continue entirely independent of them, and manifests itself with just as great distinctness in a paralyzed and nerveless part.

In support of these positions I will only add that more recent observations have gradually done away with the whole class of the so-called *neuro-paralytical inflammations*. The two nerves with which we are almost exclusively concerned in the discussion of inflammatory phenomena, are the pneumogastric and the fifth pair, after the section of which, in one case, pneumonia, in the other, those celebrated changes in the eyeball have been observed to declare themselves. These observations have now been explained in this way, that inflammations certainly may come on after such sections, but that the real interpretation to be put upon them is, that they *manifest themselves in spite of the section.** With regard to the pneumogastric it was, as is well known, long since shown by Traube that the paralysis of the rima glottidis, whereby the entrance of the buccal fluids into the air-passages is facilitated, is the principal source of the inflammation ; besides, the more accurate interpretation of the pathological specimens has determined, that a great part of what had been called pneumonia, was really nothing more than atelectasis with hyperæmia of the lungs ; actual pneumonia may with certainty be avoided, if the possibility of the penetration of foreign bodies into the bronchi is cut off. The same has been ascertained to be the case with the inflammations coming on after the section of the fifth pair, and indeed by means of a very simple experiment. After a number of attempts of the most varied kind had been made for the purpose of removing the different disturbing influences affecting the eye that was deprived of its sensibility, a very simple method was at last discovered in Utrecht for providing the eye with a substitute for its sensitive apparatus ; for Snellen sewed before the eyes of animals, in which he had cut the fifth pair, their still sensitive ears. From that time the animals had no more attacks of inflammation, inasmuch as on the one hand a direct protection was afforded to the eye, and on the other the animals were preserved by the presence of a sensitive covering from all traumatic influences. As soon as sensation was re-established, not in the eye itself, but only before the eye, what was really nothing more than a traumatic inflammation was got rid of.†

* For if, as the neuro-pathologists assume, irritation produces inflammation through the medium of the nerves, then, when the nerves are cut, all inflammation ought to be impossible.

† In the text the influence of the section of nerves is perhaps not described with

We can therefore now say, there is no form of disturbance of this kind known which can be traced to the abolition of the action of a nerve. A part may be paralyzed without becoming inflamed ; it may be anæsthetic without becoming exposed to this danger. There is always required in addition some special irritation, either of a mechanical or chemical nature, and proceeding either from without or from the blood, in order to produce the peculiar liability.

In this manner therefore we have, as you see, a series of connecting links between facts eminently pathological and the most common processes of physiological life facts of which the special import can, however, only be understood and defined, when the distinctions are made to which I called your attention at the commencement of the lecture, that is, when the different kinds of irritation are separated according to their functional, nutritive

sufficient minuteness. According to the author's views, of which a more detailed account may be found in his Handbuch der spec. Pathologie und Ther. Erlangen, 1854 (Vol. I., pp. 31, 50, 80, 276, 314, 319), the section and paralysis of nerves certainly exercise some influence upon the nutrition of the tissues, although perhaps only an indirect one. The states arising from such causes he has classed together under the name of Neurotic Atrophy. Parts which have in this way suffered derangement in their nutrition, and as a consequence have become weakened, are less capable of controlling the disorders by which they are attacked, and accordingly simple irritation in them readily becomes aggravated into inflammation (asthenic inflammation). But in these cases the inflammation is always the consequence of some special irritation, never the direct result of the section of the nerves. Still, as in the case of the fifth pair and the pneumogastric, such section may be the cause of irritants' (foreign bodies and other agents) more readily acting upon the anæsthetic or paralyzed parts. Cl. Bernard has recently declared that the section or irritation of nerves in weakened parts produces effects which cannot be elicited in healthy ones. We have therefore here to deal with a very complicated state of things. The change in the nerve is generally succeeded by a disturbance in the function or circulation of the part, or in both, and when the part is already weakened (*i. e.*, altered in its nutrition) this disturbance may prove a source of irritation to it, and thus the effects be produced which Bernard ascribes to other causes. In quite a similar manner we see that, even when the nervous supply is in its normal state, purely mechanical disturbances in the circulation act upon weakened parts as morbid irritants.—*From a MS. Note by the Author.*

or formative nature. If they are jumbled together, as they have been by the neurists, and especially, if the formative and nutritive processes are not kept apart, then it is impossible to arrive at any simple explanation of the phenomena.

Those states of irritation which we witness in the course of the severer forms of disease—the really *inflammatory kinds of irritation*—never in any case admit of a simple explanation. In inflammation we find side by side all the forms of irritation of which I have given you an analysis. Indeed, we very frequently see, that when the organ itself is made up of different parts, one part of the tissue undergoes functional or nutritive, another formative changes. If we consider what happens in a muscle, a chemical or traumatic stimulus will perhaps in the first instance produce a functional irritation of the primitive fasciculi ; the muscle contracts, but then nutritive disturbances declare themselves. On the other hand in the interstitial connective tissue, which binds the individual fasciculi of the muscle together, real new-formations are readily produced, commonly pus. Here we have to deal with a formative irritation, whilst the inflamed primitive fasciculus commonly produces no pus, any more than it does new muscular substance ; on the contrary we most frequently see, when the irritation has attained a certain height, degenerative processes set in. In this manner the three forms of irritation may be distinguished in one part. Of course there may be in addition also an irritation of the nerves, but this has, at least if we do not take function into account, no connection of cause and effect with the processes going on in the tissue proper, but is nothing more than a collateral effect of the original disturbance. This must, in my opinion, be regarded as the most important result derived from the facts of Special Histology, and it is all the more certain because it can be tested both by experiment and by physiological and pathological experience.

Soon, I will show you how in the study of inflammatory processes a clearer apprehension of their nature may hereby be obtained.

LECTURE XV.

APRIL 10, 1858.

PASSIVE PROCESSES. FATTY DEGENERATION.

Passive processes in their two chief tendencies to degeneration; Necrobiosis (softening and disintegration) and induration.

Fatty degeneration—Histological history of fat in the animal body; fat as a component of the tissues, as a transitory infiltration, and as a necrobiotic matter.

Adipose tissue—Polysarcia—Fatty tumours—Interstitial formation of fat—Fatty degeneration of muscles.

Fatty infiltration—Intestines; structure and functions of the villi—Reabsorption and retention of the chyle—Liver; intermediate interchange of matter by means of the biliary ducts. Fatty liver.

Fatty metamorphosis—Glands; secretion of sebaceous matter and milk (colostrum)—Granule-cells and granule-globules—Inflammatory globules—Arteries; fatty usure and atheroma in them—Fatty débris.

We have, gentlemen, hitherto nearly always spoken of the *actions* of cells and the processes which manifest themselves in them, when, in consequence of any external influence, they give signs of their vitality. There take place in the body, however, also a tolerably large number of *passive processes*, in which, as far at least as can be demonstrated, there is no particular activity displayed by the cells. Allow me therefore, before we proceed farther in the description of the active processes, to speak a little more in detail concerning these passive processes. For the history of the affections of cells, as they are exhibited to us in our patients, is generally composed of processes, which belong, some of them, rather to the active class, and some of them, rather to the passive one ; and the obvious results are in many cases apparently so similar in both classes, that the ultimate changes which we meet with, after the continuance of the process for a certain time, may very nearly be the same. Here particularly it was for a time, very difficult to define the boundaries, and a great part of the confusion which marked early microscopical efforts, was occasioned by the extraordinary difficulty there was in separating active and passive disturbances.

Passive disturbances I call those changes in cellular elements, whereby they at once either merely lose a portion of their activity, or are so completely destroyed, that a loss of substance, a diminution in the sum total of the constituents of the body is produced. Both series of passive processes, taken together, viz., those which are in the first instance marked by an essential diminution of power, and those which terminate in a complete destruction of the parts, constitute the chief part of the domain of what is called *degeneration*, although—a point that we must hereafter consider more closely—a great part of what must be called degeneration must be transferred to the series of active processes.

It makes of course an extremely great difference whether a vital element continues to subsist as such, or whether it entirely and completely perishes : whether at the conclusion of the process, it still exists, even though in a condition of much diminished functional power, or whether it is altogether destroyed. And here we have the important practical distinction, that in the one series of processes there is a possibility of a repair of the cells, whilst in the other direct repair is impossible, and a regeneration can only take place by means of a substitution of new cells from the neighbourhood. For when a cell has perished, it is of course impossible for any further development to originate in it.

This latter category, where the cells are destroyed during the course of the process, I proposed a few years ago to designate by a term which has been employed to express disease generally by K. H. Schultz, viz., *Necrobiosis.** For we have, namely, always here to deal with a gradual decay and death, a dissolution, we might almost say, a necrosis. But the idea of necrosis really does not offer any analogy to these processes, inasmnch as in necrosis we conceive the mortified part to be preserved more or less in its external form. Here on the contrary the part vanishes, so that we can no longer perceive it in its previous form. We have no necrosed fragment at the end of the process, no mortification of the ordinary kind, but a mass in which absolutely nothing of the previously existing tissues is preserved. The necrobiotic processes, which must be completely separated from necrosis, are in general attended by *softening* as their ultimate result. This commences with a friability of the parts ; they lose their coherence, at last really liquefy, and more or less moveable, pulpy or fluid products take their place. We might therefore without more ado name this whole series of necrobiotic processes softenings, if a number of them did not run their course, without the malacia's ever becoming apparent to the naked eye. As soon, namely, as a process of this sort sets in in a compound organ, as for example, a muscle, a palpable myo-malacia is certainly produced when all the muscular elements at a given point are at once affected ; but it happens far more frequently that, in the course of a muscle, only a comparatively small number of primitive fasciculi are affected,

* Necrobiosis is *death* brought on by (altered) *life*—a spontaneous wearing out of living parts—the destruction and annihilation consequent upon life—natural as opposed to violent death (mortification.)—*From a MS. Note by the Author.*

whilst the others remain almost intact. Then indeed a softening really does occur, but such a minute one, that it is altogether imperceptible to the naked eye and can only be demonstrated microscopically. In this case we generally make use of the expression, atrophy of muscle, although the process which has attacked the individual primitive fasciculi, does not in any way differ in its nature from the processes which we at other times term softening of muscle.

This is the reason, why the term softening, which must be reserved for coarse pathological anatomy, cannot simply be applied to histological processes, and why it is better to say necrobiosis, when we have to do with these more delicate processes. The common feature of all the varieties of the necrobiotic process is, you know, that the affected part at the close of the process is destroyed, nay annihilated.

A second class of passive processes is formed by the *simply degenerative forms*, in which, at the conclusion of the process, the affected part is in some condition or other less fitting it for action, and has generally become more rigid. This group might therefore be termed *hardenings* (*indurations*) and thus a group be formed distinguishable even externally from the necrobiotic processes. Only the term induration also would easily be misunderstood, inasmuch as in this class likewise many conditions occur, in which the hardness of the organ on the whole at least does not become more considerable, but only isolated, very minute parts undergo change, so that no very striking effects are apparent to the sense of touch.

Allow me now to hold up to you as types a few of the processes belonging to this class, which are of the greatest importance in a directly practical point of view.

Among the necrobiotic processes the one which is unquestionably the most widely spread and the most important in the course of all cellular disturbances, is *fatty metamorphosis*, or as it has also long been wont to be called, *fatty degeneration.* This process is attended by a continually increasing accumulation of fat in different organs. Even the old notion of fatty degeneration involved the idea of a continually increasing change of such a nature that pure fat at last took the place of whole parts of organs. It has turned out, however, that this old notion, which is even now retained by many in the language of pathology, includes a great number of completely different processes, and that errors would inevitably be committed if it were sought to interpret the whole group from a pathogenical point of view, in a simple manner.

The history of fat in its relation to the tissues may, generally speaking, be considered under three aspects. We find namely one class of tissues in the body, which serve as physiological reservoirs for fat, and in which the fat is contained as a kind of necessary appurtenance, without however their own permanency being in any way endangered by its presence. On the contrary, we are actually accustomed to estimate the well-being of an individual by the amount of fat contained in certain tissues, and to regard the degree of fulness presented by the individual fat-cells as a criterion of the successful progress of the interchange of matter generally. This forms therefore a complete contrast to the necrobiotic processes, in which the part, in consequence of the accumulation of fat, really altogether ceases to exist.

A second series of tissues do not constitute regular reservoirs for fat, on the contrary fat is found in them only at certain times and transitorily, for after a short time it again disappears from them, without their being on that account left in an altered state. This is the case in the ordinary absorption of fat from the intestinal canal. When we drink milk, we expect in accordance with old experience that it will gradually pass from the intestines into the lacteals, and thence be conveyed into the blood ; we know that the passage of digested matters from the intestines into the lacteals takes place through the epithelium and the villi, and that some hours after a meal the epithelium and the villi are full of fat. Now, with respect to such a fat-containing villus or epithelial cell, we take for granted that in the natural course of events it will at last yield up its fat, and after some time again become perfectly free from it. This is fatty infiltration of a purely transitory character.

Finally, we have a third series of processes, namely, those which lead to necrobiosis and which have of late frequently been regarded as peculiarly pathological ones. But, as it has been shown to be the case in all other conditions that pathological processes are not specific ones, but, on the contrary, that others analogous to them exist in normal life, so also the conviction has been acquired that this necrobiotic development of fat is an entirely regular and typical process in certain parts of the body, nay that it is even met with in very obvious forms in physiological life. The most important types of this process we find on the one hand in the secretion of milk, the sebaceous matter of the skin, the cerumen of the ears, etc., and on the other in the formation of the corpus luteum in the ovaries. In all these parts a development of fat takes place precisely in the same manner that we meet with it in the nocrobiotic fatty metamorphosis occurring from morbid causes, and in what we call sebaceous matter, milk or colostrum we have formations analogous to the pathological masses of fat which constitute fatty softening. If in any person milk is manufactured in the brain instead of in the mammary gland, this constitutes one form of cerebral softening; the product may morphologically exactly correspond with what in the mammary gland would have been quite normal. The great difference, however, is this, that, whilst in the mammary gland the cells which perish are replaced by a succession of new cells, the disintegration of elements in an organ which is not arranged so as to furnish such a succession, leads to a permanent loss of substance. The same process which in one organ yields the happiest, nay the sweetest, results, brings along with it in another, painful lesions.

If then you picture to yourselves these three different physiological types, we have in the first case an accumulation of fat in the cells in such a way, that at the close of the process every single cell is entirely full of it. This yields us the type of the so-called *adipose cellular tissue*, or simply, *adipose tissue*, as it occurs in such large masses especially in the subcutaneous tissue, where it on the one hand gives rise to beauty, particularly in the female figure, and on the other to the pathological conditions of obesity or polysarcia. Fat-cells always possess a membrane and fatty contents, but the fat so completely fills up the interior, and the membrane is so extremely thin, delicate and tense, that usually nothing else is seen than

Fig. 107.

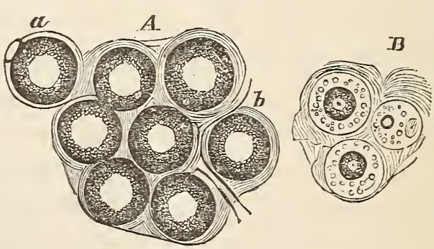


Fig. 107. Adipose cellular tissue from the panniculus [adiposus.] *A*. Ordinary subcutaneous tissue, with fat-cells, some interstitial tissue, and at *b* vascular loops; *a*, an isolated fat-cell with membrane, nucleus and nucleolus. *B*. Atrophic fat in phthisis. 300 diameters.

the drop of fat, and thus it was, until very recently, still a matter of discussion whether the fat-cells really were cells. It is in reality very difficult to come to a distinct decision upon the subject, but supporting testimony of a very beautiful character is supplied in the course of natural processes. When a person becomes thinner, the fat gradually disappears, the membrane loses somewhat of its tension, is no longer so thin and delicate, and thus becomes more clearly manifest, being sometimes distinctly separated from the drop of fat, and even provided with a recognizable nucleus (Fig. 107, *A*, *a*). We have here therefore a real, complete cell with nucleus and membrane, though the contents have been almost entirely supplanted by the fat it has taken up. This so-called adipose cellular tissue is a form of connective tissue (p. 76), and when it undergoes retrogressive metamorphosis, it is clearly seen to be reduced to connective or mucous tissue, for between the cells a small quantity of intercellular substance again becomes apparent (Fig. 107, *A*, *b*, *B*).

This species of adipose tissue it is, gentlemen, which under certain circumstances not only gives rise to polysarcia and obesity, from continually increasing quantities of connective tissue becoming involved in this accumulation of fat, but is also the foundation of all anomalous fatty structures, for example, of lipomata. The different forms of these structures, and particularly real fatty tumours, are distinguished from one another only by the greater or less quantity of interstitial connective tissue, which the tumour contains, and upon which their greater or less consistence depends. It is the same form of accumulation of fat which we see appear in morbid conditions in a series of cases which, in compliance with old tradition, are still called fatty degeneration; and it is indeed particularly the *fatty degeneration of muscles* which in many instances presents nothing else than a more or less advanced development of adipose cellular tissue between the primitive muscular fasciculi. It is a similar process to that which we meet with in the fattening of animals, and which is often exhibited in simply fattened muscles in the human body. Fat-cells insinuate themselves between the primitive muscular fasciculi, and lie of course in stripes in the direction of the muscular fibres, which may remain unchanged. The development in this case has its origin in the interstitial tissue of the muscle. At the commencement of the development, and when it proceeds with very great regularity, it may happen, that single rows of fat-cells lying one behind the other alternate with the rows of muscular elements. In this case, where the primitive fasciculi are forced asunder, and the circulation in the muscle is generally disturbed in consequence of the abundant development of fat, so that the flesh becomes pale—it looks to the naked eye as if there no longer existed any muscular tissue whatever. If, for example, in an inferior extremity, which in consequence of an anchylosis of the knee has remained unexercised, the gastrocnemii are examined, we find nothing but a yellowish mass exhibiting scarcely any striæ and without any appearance of flesh, but upon a more minute examination it is discovered, that the primitive muscular fasciculi still pass, essentially unaltered, through the fat. In this case the fat forms an impediment to the use of the muscle, but the primitive fasciculi still exist and are to a certain

Fig. 108.

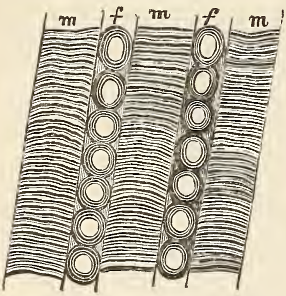


Fig. 108. Interstitial growth of fat in muscle (fattening). *ff.* Rows of interstitial fat-cells; *m, m, m,* primitive muscular fasciculi. 300 diameters.

extent capable of action. This process therefore is essentially different from necrobiosis, where the muscular fibres as such completely perish. Here we have a purely interstitial formation of adipose tissue, ordinary connective tissue becoming converted into adipose tissue, and the term, fatty degeneration, which is so very liable to be misunderstood, should be avoided.

This form occurs pretty frequently, especially in the heart, and may, when it attains a great extent, produce considerable derangement in the motor power of the muscular substance of this organ, but in pathological importance it stands far below real fatty metamorphosis, although this again in its outwardly visible results much resembles it. The hearts described by the old anatomists as fatty were in a great measure only hearts infiltrated with fat; on the other hand, what is meant at the present day when genuine fatty degeneration (metamorphosis) of the heart is spoken of, is not this obesity of the heart, this interlarding of its fibres with fat-cells, but rather a real transformation of its substance, going on in the interior of the fibres (Fig. 23). In the latter case the fat lies *in*, in the former *between* the primitive fasciculi.

The second series of processes consists in the transitory accumulation of fat in certain organs, as we meet with it in a typical form in digestion. When a fatty substance has been eaten, and has passed into the state of emulsion, we find that, when it has reached the upper end of the jejunum, and to some extent even in the duodenum, the villi of the mucous membrane become whitish, clouded and thick, and more minute examination shows, that they are filled with extremely minute granules, much more minute than can be produced by any artificial emulsion. These granules, which are found even in the chyme, come in the first instance into contact with the cylindrical epithelium with which every single intestinal villus is invested. On the surface of every epithelial cell we find, as was first discovered by Kölliker, a peculiar border which, when the cell is seen in profile, exhibits minute and fine striæ; when viewed from above, and seen upon the surface, the cell appears hexagonal and, as it were, dotted over with a number of minute points (Comp. the epithelium of the gall-bladder, Fig. 14, and also Fig. 109, *A*). Kölliker has put forward the conjecture, that these fine striæ and dots correspond to minute pore-canals, and that the absorption of the fat is effected by its minute particles being taken up through these minute pores upon the surface of the epithelial cells. But the object is one which is accessible only to the highest powers of our optical instruments, and it has therefore hitherto been impossible to obtain perfectly clear notions as to whether the striæ really correspond to fine canals. or

Fig. 109.

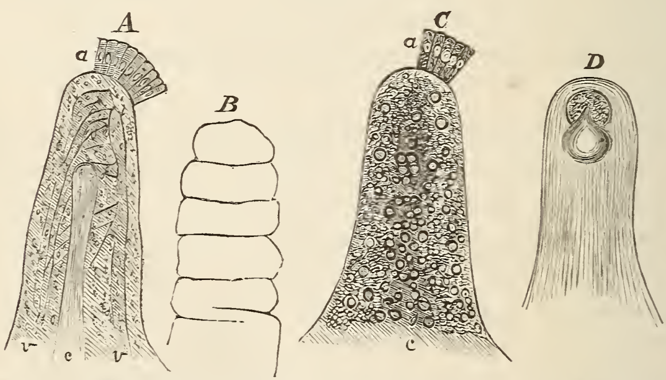


Fig. 109. Intestinal villi, showing the absorption of fat. *A*. Normal human intestinal villus from the jejunum; at *a* the cylindrical epithelium in part still investing it with the delicate border and nuclei; *c*, the central lacteal vessel; *v*, *v*, blood-vessels; in the rest of the parenchyma the nuclei of the connective and muscular tissue. *B*. Villus in a state of contraction, from a dog. *C*. Human intestinal villus during the absorption of chyle, *D*, in a case of retention of chyle; at the apex a large fat-drop, emerging from a crystalline envelope. 280 diameters.

whether, as Brücke supposes, the truth is rather that the whole of this upper border is composed of little rods or pillars resembling cilia. I must confess that my own investigations also have rather disposed me to adopt this latter opinion, especially as comparative histology shows us real ciliated epithelium to be the equivalent structure in the same parts. At all events this much is certain, that, a short time after digestion has taken place, the fat no longer lies only outside, but is found also inside, the cells, and first at their outer end; then it gradually advances farther and farther inwards in the cells, and indeed so distinctly in rows, that it might easily give rise to the impression, that fine canals ran throughout the whole length of the cells themselves (Fig. 109, *C*, *a*). But this too is a question which will not, I think, with our present optical instruments, be so very speedily settled. At any rate, the plain fact remains, that the fat passes through the cells, and this indeed in such a way, that at first only their outer end is filled with it, then a time comes when they are quite full of fat, then a little later the outer part again becomes entirely free from it, whilst the inner still contains a little, until at last all the fat entirely vanishes from the cells. In this manner its gradual progress may be followed from hour to hour. After the fat has advanced as far as the inner extremity of the cells, it begins to pass into the so-called parenchyma of the villus (Fig. 109, *C*). Whether the epithelial cells have an orifice below, and whether, as has been quite recently maintained by Heidenhain junior, they are connected with extremely minute canals formed by the connective-tissue-corpuscles, is not quite decided, though it is very probable. It is extremely difficult to come to any definite conclusions with regard to these extremely minute arrangements of the substance of tissues. In the interior of the villi we generally find the network of blood-vessels a little below the surface (Fig. 109, *A*, *v*, *v*), whilst in its axis there is a tolerably wide canalicular cavity with a blunt extremity, the commencement of the lacteal vessel, as far as it can at present be determined with certainty (Fig. 109, *A*, *c*). At the periphery of the villi Brücke has discovered a layer of muscular fibres, which is of great importance in digestion, inasmuch as by its help an approximation of the apex of the villus to its base, a shortening is effected, as may very readily be seen. Upon cutting off villi from the intestine of an animal just killed, they may be seen under the microscope to contract, become wrinkled, thicker and shorter (Fig. 109, *B*); thereby a pressure from without inwards is manifestly produced, which promotes the onward movement of the juices. So far the matter is tolerably clear, only what sort of a structure the rest of the parenchyma has, it is extremely difficult to see. Upon the outer side of the muscular layer, smallish nuclei are seen, which, as I pointed out many years ago, are now and then pretty distinctly enclosed in fine, cellular elements. But whether these parenchymatous cells anastomose with one another so as to form a special network, I am unable to say. During the process of absorption it looks as if the fat which keeps penetrating farther and farther into the interior of the villi, filled up the whole parenchyma.* At last it reaches the central lacteal, and there the regular current of chyle begins.

The whole process therefore presupposes an emulsive condition of the fat, which penetrates through the parts

* I have quite recently convinced myself by the examination of transverse sections of villi, filled with chyle, in man, that the fat does not lie scattered in the parenchyma, but forms deposits in the interior of special minute cavities (cells?).—*Note to the Second Edition.*

everywhere in a state of extremely minute division; in the regular course of events the particles are so extremely minute, that if the chyle is examined when fresh and still warm, scarcely a trace of the solid particles can be detected in it. But every disturbance which occurs in the process of absorption, and impedes the onward movement of the fatty particles, causes them to run together; larger granules separate in the tissues, drops appear which continually increase in volume, until at length they attain quite a large size. These are found even in the epithelial cells or within the tissue of the villi, and indeed it sometimes happens that the ends of the lacteals grow wider, and swell out into a bulbous form from the great accumulations of fat, so as to be recognized even by the naked eye. Nowhere have they been so frequently witnessed in a striking form, as in cholera, and a good description of these appearances as occurring in this disease was published as far back as 1837 by Böhn. They indicate nothing more than an obstruction to the current of lymph in consequence of the disturbances in the respiration and circulation (Fig. 109, *D*). Since attacks of cholera are well known to occur with preponderating frequency during digestion and are attended by greatly impeded respiration, which makes itself felt throughout the whole venous system, they must of course also react upon the stream of chyle. Thus the enormous accumulation (retention) of fat in the villi is explained. This is therefore, if you will, a pathological condition, but it only depends upon a transitory obstruction, and we have every reason to suppose that, when the current again becomes free, these large drops of fat are gradually removed. But here we set foot upon other domains, where the boundaries of pathology can only be traced with great difficulty, and this is particularly the case with the liver.

It has been known from of old that the *liver* is the organ, which is by far the most liable to fall into a state of fatty degeneration, and the knowledge of this state has long been derived from popular experiment. The history of the pâtés de foie gras proves this in the most agreeable manner, although M. Lereboullet of Strasburg maintains that the fatty livers of geese are physiological ones, essentially different from the pathological ones which are not eaten, but only observed. However, I must confess that I have hitherto been unable to discover the difference between physiological and pathological fatty livers; on the contrary, I believe that it is only by admitting the identity of the two that correct notions with regard to the pathological fatty liver can be obtained. We are namely acquainted with a fact which was likewise first observed by Kölliker, that in sucking animals, a few hours after digestion has taken place, a kind of fatty liver is a constant physiological occurrence. When of the same litter of animals some are made to fast, while others are allowed to suck, those which have sucked have a fatty liver a few hours afterwards, whilst the others have not. The fatty liver appears quite pale, though certainly not so white as a goose's liver. This observation led me to examine the question of the relation of the fat to the liver a little more minutely, and I certainly think we may positively conclude that there does exist a close connection between the physiological and pathological forms.

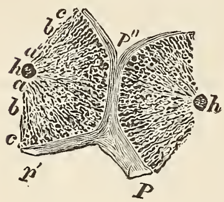
I found, namely, that a short time after the hepatic cells display this repletion with fat, a similar condition is found in the course of the biliary ducts, and that both in them and in the gall-bladder the epithelium presents the same appearances which we have witnessed in the intestinal epithelium during the absorption of fat. You only require therefore to invert the picture we just now considered

(Fig. 109) ; instead of a villus, invested externally with epithelial cells, imagine a canal clothed on the inside with epithelium. The delicate cylindrical epithelium in the gall-bladder has the same striated border as that in the intestine (Fig. 14), and the fat is seen in the same way to penetrate into it from without, to pursue its course downwards and after a time to pass into the wall of the gall-bladder. The same may be said of the biliary *passages* (duct. biliferi, hepat., cystic., choledoch.), which are also provided with cylindrical epithelium of a similar structure. I have watched the same process also in young sucking animals after digestion, and there it is easy to convince oneself that the fat, which for a time is contained in the hepatic cells, is manifestly excreted from them into the biliary ducts, but that in the course of these ducts the fat is reabsorbed and thus a second time returns into the circulation.

Such an *intermediate interchange of matter* as this, where the fat passes from the intestine into the blood, from the blood into the liver, from the liver into the bile, and thence again into the lymphatics, or into the capillaries which conduct the blood back to the hepatic veins and to the heart, presupposes of course, just as absorption in the intestines does, that the conveyance back again must take place under favourable circumstances ; if any disturbing cause arises, a retention will of course ensue, and the place of the fine granules will gradually be occupied by large drops. But this is the mode of proceeding as it can really be traced in the fatty liver.

Upon studying a fatty liver, it is generally seen that the fat is first deposited in that zone of the acini which is immediately contiguous to the capillaries into which the branches of the portal vein break up (Fig, 110. *c*, *c*). When sections of the organ are carefully examined with the naked eye, it looks in many parts as if one had an oak-leaf with its ribs and indentations before one ; the ramifications of the branches of the portal vein correspond to the ribs, the fatty zone to the substance of the leaf. The more abundant the infiltration, the broader does the fatty zone become, and there are cases in which the fat fills the whole of the acini up the central (intralobular) hepatic vein (Fig. 110, *h*) and every single cell is crammed full of fat. In rare cases it certainly happens, that we find just the reverse, and that the fat lies around the central vein ; these are cases which are probably to be explained by supposing that the fat is already in process of excretion and only the last cells still retain a little of it. Only we must take care not to confound with this condition a kind of fatty, necrobiotic atrophy which occurs particularly in chronic cyanosis.*

Fig. 110.



If now we consider the process in detail, we find that the manner in which the hepatic cells fill themselves, entirely corresponds to that, in which an epithelial cell in the intestine becomes filled with fat. At first we find fat-granules widely scattered, and indeed very small. They become more numerous, more closely aggregated, and after a time larger ; at the same time the cells be-

Fig. 110. The adjoining halves of two hepatic acini. *p*. A branch of the portal vein with braches *p' p''*, corresponding to the interlobular veins. *h*, *h*. Transverse sections of the intralobular, or hepatic, vein. *a*. The pigment zone, *b* the amyloid zone, *c* the fat zone. 20 diameters.

* Cyanosis (chronic) is here used to express the general venous congestion which is consequent upon chronic affections of the lungs and heart. "Since (as the Author says in a MS. note) it has become known that cyanosis, even when produced by congenital malformation of the heart, does not arise from a commingling of arterial and venous blood, but from an obstruction to the venous circulation, it has seemed reasonable to designate every more general hyperæmia, due to such obstruction, by the same term." "Acute cyanosis," he adds, "occurs in acute affections of the lungs, as for example, in pertussis."—Tr.

come larger, swell up, and larger and smaller drops of fat are found in them (Fig. 27, *B*, *b*), until, when filled to the utmost, they present the same appearance as those of adipose tissue; scarcely any membrane, and scarcely ever a nucleus is seen, nevertheless they both still continue to exist. This is the condition which is called fatty liver, in the proper sense of the word.

In it too we have what we found to be the case in adipose tissue—a *persistence of the cells.* There is no such thing as a fatty liver in which the cells have ceased to exist; these constituents of the organs always exist, only they are almost entirely filled with drops of fat instead of with their ordinary contents. It can scarcely be doubted but that even in this condition they still contain a certain amount of matter capable of performing its functions. For in many animals, as for example the cod-fish from which liver-oil is obtained, the functions of the organ are still performed, however large the quantity of oil contained in the cells. In man too, even in the most advanced stage of fatty liver, we still find bile in the gall-bladder. So far therefore these conditions can in no respect be compared to the necrobiotic conditions, which are found in the course of fatty degeneration in so many other parts, and in which the elements perish. In fatty degeneration, in the ordinary sense of the word, we find, in the later stages of the affection, somewhere or other, friable, softened places, where the fat is contained in free drops—in some sort fatty abscesses. It is therefore a fact of extreme importance, and one which I consider to afford very decided indications for the correct appreciation of this form [fatty liver], that in it there is always a persistence of the histological constituents, and that, however much these constituents may become filled with foreign substances, they still continue to exist as cells. Hence it follows, that a fatty condition of the liver may be removed, that it is curable, without any particular regenerative processes being required for the cure. The only requisite is, that the causes of the retention be removed, and the hepatic cells be freed from fat. It is true we have no positive information respecting either the one or the other of these points. We are not acquainted with the states which lead to the retention of the fat, nor with the conditions under which it can again be expelled. However, now that we have got so far, it will probably also be possible to make out the remaining facts. For it is conceivable, for example, that simply the elasticity of the histological elements is of importance ; that when the cell walls become relaxed, they may readily admit a quantity of matter, and tolerate its presence in them, whilst, if they are very elastic, a removal, an expression of their contents, may be more likely to ensue. The state of the circulation also is certainly of importance, and the frequent occurrence of fatty liver in chronic affections of the lungs and heart is certainly in no small degree to be ascribed to the increased pressure to which the venous blood is subjected.

What I was particularly anxious, gentlemen, to render evident to you, was the great difference which this kind of fatty degeneration presents from that which we have previously considered. Whilst there we saw arise between the proper specific constituents of the organ—fat-cells which belonged to the connective tissue, here it is the specific gland cells themselves which are the seat of the fat. On the other hand, you must take into consideration the great difference from the necrobiotic processes of fatty degeneration, in which the cells as such disappear.

We have now, gentlemen, to consider this third series of fatty conditions a little more closely, those, I mean, which are attended by a destruction of the elements, and of which we have set up the secretion of milk and sebaceous matter as the true types. That these two secretions are analogous to one another, is simply explained by the circumstance that the mammary gland is really nothing more than an enormously developed and peculiarly formed accumulation of cutaneous (sebaceous) glands. In their development both classes are perfectly analogous. Both are produced, by means of a progressive proliferation, from the internal layers of the epidermis (p. 68, Fig. 18, *A*). To the same category also belong the ceruminous glands of the ear, and the large glands of the axilla. In all these cases the fat, which constitutes the chief constituent of milk, at least as far as its external appearance is concerned, and which furnishes the sebaceous secretion, originates in the interior of epithelial cells which gradually perish and set the fat free, whilst scarcely a trace of the cells is preserved. The sebaceous glands are generally seated on the sides of the hair-follicles at some depth below the surface; we there find a series of minute lobules, into which a prolongation of the rete mucosum is uninterruptedly continued. The cells of this become more numerous and larger, so as to fill the gland-sacs with a nearly solid matter. Then the fat begins to be

Fig. 111.

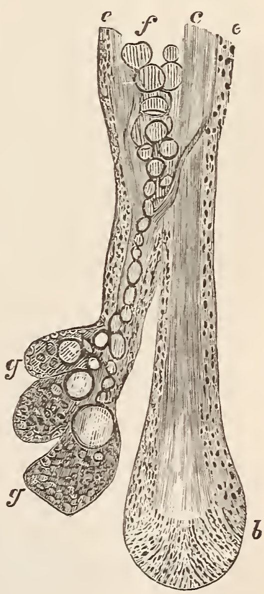


Fig. 111. Hair-follicle with sebaceous glands from the skin. *c*. The hair, *b* its bulb, *e*, *e*, the layers of cells dipping down from the epidermis into the hair-follicle. *g g*. Sebaceous glands in the act of secreting sebaceous matter; at *f*, the secretion mounting up by the side of the hair and accumulating. 280 diameters.

secreted into their interior, at first in small particles, which soon become larger, and after a short time the individual cells can no longer be distinctly perceived, but only conglomerations of large drops, which rise up out of the gland into the hair-follicle. If we unravel the gland so as to form a flat surface, its layers of cells would have the appearance of epidermis, only that the oldest cells do not become horny, but are destroyed by fatty metamorphosis. The secretion is a purely epithelial one, like the seminal secretion.

This process furnishes us at the same time with an accurate representation of the *formation of milk*. You need only imagine the ducts much lengthened, and the terminal acini greatly developed; the process remains essentially the same: the cells multiply abundantly; the multiplied cells undergo fatty degeneration, and ultimately there remains scarcely any material traces of these cells excepting the drops of fat. The closest resemblance to the manner in which the secretion of sebaceous matter ordinarily takes place, is presented by the earliest period of lactation when the so-called *colostrum* is yielded. A colostrum-corpuscle (Fig. 112, *C*) is the still coherent globule which results from the fatty degeneration of an epithelial cell. The formation of colos-

Fig. 112.

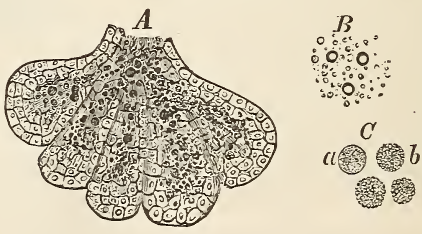


Fig. 112. Mammary gland during lactation, and milk. *A*. Lobule of the mammary gland, with milk issuing out of it. *B*. Milk globules. *C*. Colostrum, *a*, a distinct fat-granule cell, *b*, the same with evanescent nucleus. 280 diameters.

trum and sebaceous matter differs in this respect only, that the fat-granules remain smaller in the former case, and that whilst large drops very soon show themselves in sebaceous matter, in colostrum the last cells which are observed, usually contain only minute fat-granules, very densely aggregated, whereby the whole cell acquires a somewhat brownish appearance, although the fat has no actual colour. This is the granular corpuscle (corps granuleux) of Donné.

For the discovery of this gradual transformation of cellular bodies into fat-granule masses we are indebted to Reinhardt. Still he shrank from extending this important discovery of the formation of colostrum to the history of milk in general, for the reason, that, during the later periods of lactation properly so-called, granulated bodies are no longer met with. It is, however, unquestionable, that between the earlier formation of colostrum-corpuscles and the later one of milk, there is no other difference than this, that in the formation of colostrum the process goes on more slowly, and that the cells maintain their cohesion longer, whilst in the secretion of milk the process is acute and the cells more speedily perish. Perfectly developed colostrum contains an extremely large number of granulated corpuscles, milk nothing more than a number of comparatively large and small drops of fat, mixed up together, the so-called *milk-corpuscles* (Fig. 112, *B*), which are nothing more than drops of fat, and like the majority of the drops of fat that occur in the animal body are surrounded by a delicate, albuminous membrane, called by Ascherson the *haptogenic** membrane (haptogenmembran). But the individual drops (milk-corpuscles) correspond to the drops which we find in the secretion of

* *I. e.*, produced by contact.—Transl.

sebaceous matter ; they are produced by the coalescence of the minute granules which appear in the secretion of colostrum.

Now that we have seen these types of physiological transformation, gentlemen, the description of the pathological changes no longer offers any difficulty. With the exception of very few structures, as for example, red blood-corpuscles and the nerve-fibres in the great nervous centres, nearly all other cellular parts may under certain circumstances undergo a similar metamorphosis, which displays itself in a precisely similar manner, that is, isolated, extremely minute globules of fat appear in the cell-contents, become more abundant, and gradually fill up the cell-cavity, without, however, running together into such large drops, as is the case in fatty infiltration and in the adipose-tissue formations. Usually, the development of the fat-granules first declares itself at some distance from the nucleus ; very seldom does it begin at the nucleus. This is the cell which has long been called the *granule-cell.* Then comes a stage, in which the nucleus and membrane are indeed still to be seen, but the fat-granules lie as close to one another as in colostrum corpuscles ; only at the spot where the nucleus lay, there is still a little gap (Fig. 66, *b*). From this stage there is but a short step to the complete destruction of the cell. For a cell never remains for any length of time in the state of a granule-cell, but as soon as it has once entered into this stage, the nucleus generally disappears at once, and ultimately the membrane also, probably by a species of solution. Then we have the simple *granule-globule*, or as it was formerly called, *inflammatory globule* [exudation-corpuscle], which Gluge first described under this name (Fig. 66, *e*).

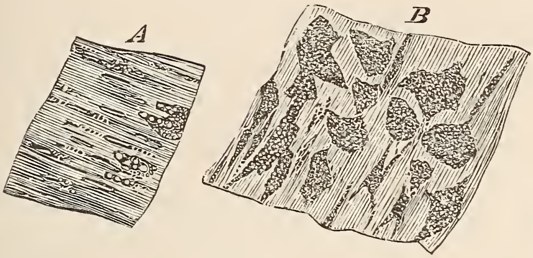
Gluge in this made one of those mistakes which not unfrequently marked the early periods of microscopy. He saw, when examining a kidney, bodies of this sort in the interior of a canal, which he took for a blood-vessel; this happening at a time when the doctrine of stasis was most in vogue, he imagined he had before him a vessel with stagnating contents which were disintegrating, and generating inflammatory globules. Unfortunately the blood-vessel was a uriniferous tubule; what he took to be parts of disintegrating blood-corpuscles, was fat; and what he called inflammatory globules, fatty degenerated renal epithelium. One might easily have spared oneself this error in the history of stasis, but at that time there were few people who knew what was the appearance of uriniferous tubules and how they might be distinguished from vessels, and thus some time elapsed before this theory of inflammation was put down.

At present we call the body a granule-globule and regard it as the first distinct proof of degeneration, when the cell no longer retains its existence as a cell, but merely its former shape remains, after the parts which really constitute a cell, namely the membrane and the nucleus, have completely passed away. After this, in accordance with external circumstances, either a complete destruction of the parts ensues, or they may still persist, coherent. If, namely, we have to deal with very soft parts, in which much fluid or juice has been present all along, the granules fall asunder. The medium which bound them together and enabled them to retain the globular form, namely, a remnant of the old cell-contents, is gradually dissolved. The globule breaks up into a crumbling mass, which is often still somewhat coherent in places, but from which one drop of fat after another is detached, so that the correspondence with milk is very beautifully displayed.

This is the manner in which the disintegration of nearly all parts takes place, which essentially consist of cells and naturally contain a good deal of fluid, as for example pus among familiar pathological products (p. 216, Fig. 66). If, on the contrary, the parts are in themselves somewhat more rigid, so that movement in and displacement of, the fatty mass takes place with less facility, the fat remains in the form of the previous cell. Of this we meet with an example in the fatty degeneration of the walls of arteries.

In the aorta, the carotids and the cerebral arteries, changes of the inner coat are often seen with the naked eye of such a nature, that small, whitish spots of a rounded or angular form, occasionally running one into the other, project somewhat above the surface. If an incision is made at these spots, it is found that they are quite superficial, that they lie in the innermost layer of the internal coat and must not be confounded with the really atheromatous condition. If such a spot be cut out, it is found that a fatty degeneration of the connective-tissue-corpuscles of the innermost coat has taken place ; and since they are branched cells, we do not here have granule-cells in their ordinary rounded form, but often very long, fine bodies, which here and there swell up into the form of a spindle or star, and in which the fat-granules lie heaped up like strings of pearls, whilst between there still remains intermediate substance quite intact. It is the cellular elements of the connective tissue which in these cases undergo the change in their totality. Afterwards the intermediate substance also softens, the cellular fat-granule masses fall asunder, and the current of blood carries away the particles of fat with it. In this way a number of uneven places are produced upon the surface of the vessel, which swell up as long as the process continues, afterwards become worn away (usurirt), and acquire a slightly velvety appearance, without there being any ulceration

FIG. 113.



in the proper sense of the word. This is a particular form of *fatty usure* which occurs in many parts, as for example in articular cartilages, and even on the surface of mucous membranes, for example, that of the stomach (Fox). But at no time does the matter accumulate in such abundance as is the case in abcesses which have undergone fatty degeneration. If, on the other hand, a similar process commences beneath the surface, as in the atheromatous process, the fatty degeneration then proceeds from below upwards, and the surface is not reached until the last. By softening, the so-called *atheromatous deposit* (Heerd*) is produced, which contains a softened mass resembling the contents of atheromata [sebaceous,† or epidermic, cysts] of the skin, in which

Fig. 113. Fatty degeneration of cerebral arteries. *A*. Fatty metamorphosis of the muscular cells of the circular-fibre coat. *B*. Formation of fat-granule cells in the connective-tissue-corpuscles of the internal coat. 300 diameters.

* Heerd (hearth) in the sense in which it is here employed, has no precise equivalent in English, although it exactly corresponds to the French *foyer*. "It denotes," says the Author, "the spot, where the fire of the disease burns, but expresses at the same time that this spot is a limited one." I have therefore translated it by various words, such as deposit, dépôt, seat (of the disease), collection, patch (atheromatous), focus, &c.—TRANSL.

† These cysts are wrongly called sebaceous, inasmuch as they are essentially *epidermic*, and are generally derived, not from the sebaceous glands, but from the hair-follicles. The atheromatous matter is in these cases chiefly composed of degenerated and disintegrated epithelium.—*From a MS. Note by the Author.*

the mixture of sebaceous matter and epidermis produces a pultaceous mass. What we find in the arteries is a mixture of fatty débris with softened intermediate substance; and, since the fatty mass is shut off, a kind of enclosed deposit results—as it were an abscess. It is only after the softening has proceeded to some extent that the surface gives way, and matters issue from the cavity into the vessel, whilst others proceed from the blood into the cavity.

In this manner *destruction*, *demolition*, *ulceration* is produced, and ultimately the *atheromatous ulcer*, a species of ulcer very nearly allied to the ordinary forms of ulceration, but indebted for its origin to fatty metamorphosis alone. It is a product of the [atheromatous] deposit, but it no longer contains any formed elementary parts. Cholestearine indeed may still be set free, but we have really and truly to deal with a destructive and ultimately ulcerative process. It is only in those parts, in which, as in the mammary and sebaceous glands, there is a succession of new cells, that the process of fatty metamorphosis can continue for any length of time without leading to such an annihilating result. But, even in these instances, the different cells affected ultimately perish and break up, as in the really fatty degeneration.

LECTURE XVI.

APRIL 14, 1858.

A MORE PRECISE ACCOUNT OF FATTY METAMORPHOSIS.

Fatty degeneration of muscles—Fatty metamorphosis of the substance of the heart—Formation of fat in the muscles in distortions.

Corpus luteum of the ovary—Fatty metamorphosis of pulmonary epithelium—Yellow softening of the brain—Arcus senilis.

Optical properties of fattily degenerated tissues—Renal epithelium in Bright's disease—Successive stages (cloudy swelling, fatty metamorphosis, fatty detritus [débris], atrophy)—Inflammatory globules—Similarity of the result in inflammatory and non-inflammatory changes.

Atheromatous process in arteries—Its relation to ossification—Inflammatory character of the process; its analogy with endocarditis—Formation of the atheromatous deposit—Appearance of cholestearine—Arterio-sclerosis—Endoarteritis—Calcification and ossification of arteries.

Mixed, activo-passive processes.

To-day, gentlemen, I have sent round a few specimens of fatty degenerations, in part to serve as a supplement to what you saw at the last lecture.

One or two of these preparations are intended to display the fatty degeneration of the substance of the heart. You will observe that, even with the naked eye, certain changes can be recognized in the heart, namely, a discoloration of its whole substance (which no longer presents the red hue of muscle, but wears a pale yellow tint), and besides peculiar spots on the papillary muscles. If you examine these more closely, you will perceive, in the direction of the primitive fasciculi, short, yellowish streaks which communicate so as almost to present a plexiform arrangement, and pervade the substance of the papillary muscles, whilst they offer a striking contrast to the reddish colour of proper muscular substance. This is the perfect form of genuine fatty metamosphoris of the real muscular substance of the heart, which differs most essentially from obesity of the heart, in which this organ becomes extremely fat and adipose tissue here and there so infiltrates its walls, that scarcely any muscle is to be perceived. Between the two conditions there always remains the notable difference, that in the former case whole portions of active substance are interrupted by parts which are manifestly no longer capable of action.

FIG. 114.

I have besides brought you another specimen of muscle we obtained yesterday at the suggestion of our confrère Berend. A body, namely, with posterior (angular) and lateral curvature (Kypho-Skoliose) was brought for post-mortem examination, and, when we examined the muscles at the point of curvature, we found the longissimus dorsi at the spot where it passed over the projection, converted into quite a flat, thin, pale yellowish mass. At one point the muscle has, with the exception of a membranous layer, entirely disappeared, its red hue has altogether vanished; towards the lower part the muscle also presents an abnormal appearance, but there it is composed of alternate longitudinal red and yellow streaks. This is the form exhibited by most fattily degenerated muscles which we find in distortions of the

* Fig. 114. Fatty degeneration of the muscular substance of the heart in its different stages. 300 diameters.

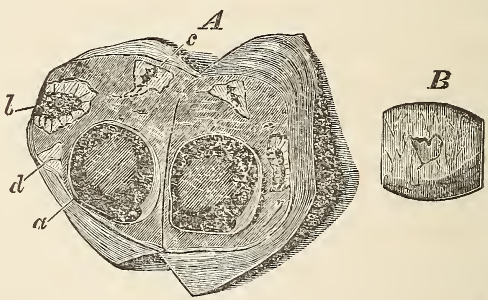
limbs, as for example, in the different kinds of club-foot. In these it generally turns out, that, in the parts corresponding to the yellow streaks, there is not only a real transformation of the muscular substance, but that an interstitial development of adipose tissue has also nearly constantly taken place there, so that it lies in rows between the primitive muscular fasciculi, and thereby produces a striation which looks yellowish to the naked eye, and is due to an arrangement very similar to that which gives rise to the red striation of genuine muscular tissue.* This is precisely how matters stood in the case I spoke of recently (p. 364, Fig. 108), where we found a row of fat-cells between every two primitive fasciculi ; the yellow that you saw there, was not altered muscle, but a mass of fat which had grown in between the muscular fibres. But in addition to such interstitial adipose tissue there is in the case now before us a parenchymatous degeneration in the same muscle ; the substance of the muscle is also really in a state of fatty degeneration. The degenerated fibres are, however, only to be seen with the naked eye in the lower parts of the muscle, whilst the portion which lay in immediate contact with the greatest projection of the thorax and had been subjected to the greatest tension, to the naked eye presents no trace of muscular tissue. Under the microscope, however, we even there find isolated muscular fibres lying close to one another and still distinctly transversely striated, and others plentifully filled with fat. You see, therefore, that these are two different conditions ; the one form, where the muscle is interrupted in the course of its primitive fasciculi by degenerated places, and where

* For, as each row of fat-cells lies between two primitive fasciculi (Fig. 108), the fat (like the substance of the fasciculi, the cyntonine) has a layer of sarcolemma upon each side of it, so that, if the syntonine atrophies, the fat *appears* to have taken its place and to lie *within* the primitive fasciculi, and many well-known authors have taken this to be the case.—*From a MS. Note by the Author.*

therefore the same primitive fasciculus, is, as it pursues its course, now in a state of degeneration, now preserved in all its integrity ; the other form in which the disease sweeps along the primitive fasciculus, and this undergoes the change in its whole extent at once, and where therefore normal and degenerated fasciculi lie side by side, and may alternate with one another.

Here is another specimen from a young female (who died shortly after menstruation in consequence of a burn) in which you will find a very beautiful corpus luteum in the ovary. I lay it before you because you will be able to see, from it, how obviously fatty metamorphosis may display itself to the unaided eye. The incision into the ovary has been made perpendicularly to the surface, at a point where a little prominence and slight rent upon the surface mark the place at which the ovule has emerged (Fig. 115, *B*). From the point in the tunica albuginea where the follicle has burst, the very broad, yellowish

Fig. 115.



white layer (Fig. 115, *A*, *b*), from which the body derives its name, is seen running around a red mass. It is this

Fig. 115. Formation of corpora lutea in the human ovary. *A*. Section of an ovary : *a*, a follicle recently burst and filled with coagulated blood (extravasation, thrombus), and around it the thin yellow layer ; *b*, a follicle, which had burst at an earlier period, already corrugated, and provided with a diminished thrombus and thickened wall ; *c*, *d* a still more advanced stage of retrogressive metamorphosis. *B*. External surface of the ovary, with the fresh rent caused by the bursting of the follicle, from the cavity of which the thrombus is seen peeping out. Natural size.

layer which, in a puerperal corpus luteum, is of very great breadth and has a rather reddish yellow tint; in a menstrual corpus luteum it is narrower, and very distinctly separated on the inner side from the freshly extravasated contents which have filled up the follicle emptied by the extrusion of the ovule. This internal red mass consists entirely of thrombus, or blood-clot. The external layer essentially consists of fattily degenerated cells, and the yellow colour which it bears is occasioned by the refraction produced by the numerous minute particles of fat. This is not a real colour, but a phenomenon of interference.

A similar change you see in a lung which we took today out of the body of a man who, after caries of the internal ear, had a thrombosis of the transverse sinus with gangrenous metamorphosis, and, in consequence, gangrene of the lung. The cells we have here to deal with were not taken, however, from the actual seat of the gangrene itself, but from a condensed spot in the neighbourhood, where a very abundant accumulation of masses of proliferating epithelium (catarrhal pneumonia) had taken place. In this case you can see the difference between fat-granule-cells (Fig. 66), and other forms of granule-cells, very prettily shown. For in these masses of epithelium which have filled up the alveoli of the lung, you find extremely numerous pigment-cells, such as in cases like this are brought up in great quantity in the sputa, which are indebted to them for the well-known smoky grey spots (Fig. 11, *b*). At first sight it is difficult to make a distinction between fat-granule-, and pigment-cells, inasmuch as in both cases apparently the same image is offered to our view. In the one case the cells appear as brownish yellow corpuscles, although their individual particles have no positive colour; in the other, on the contrary, they contain unquestionable, grey, brown, or black, pigment. The diagnosis of ordinary granule-cells, by which fat-granule-cells are always meant, is, however, very important, because in other parts also, as for example, in the brain, we find both sorts of granule-cells, those containing fat and those containing pigment, side by side ; and even when the affection is limited to very small spots in this organ, it is very important* for the interpretation of the objects found to know whether they belong to the one or the other class. For in the brain also the accumulation of a number of minute particles of fat may on the whole, through the multiplication of the refracting points, occasion an intense yellow colour. The different proportion of fat and the degree of its division produce a greater number of varieties of colour which at last manifest themselves very distinctly to the naked eye, so that the more minute and the more closely aggregated the fatty particles are, the more marked is the production of a pure yellow or brownish-yellow hue even to the naked eye. What we call yellow softening of the brain is also really nothing more than a form of fatty degeneration, where the yellow appearance of the affected spot is owing to the accumulation of finely granular fat. As soon as this is removed, the colour also disappears, although the fat thus extracted is by no means of so deep a hue as the spot whence it was derived. The refraction of light between the extremely minute particles is the chief cause of this phenomenon of colour.

It is self-evident that at every point, where the fatty degeneration attains a high pitch, great opacity will always present itself. A transparent part becomes opaque when it undergoes fatty degeneration ; this we see, for example, in the cornea, the fatty clouding of which may become so marked in arcus senilis, that an en-

* For the pigment would point to apoplexy, the fat to softening

tirely opaque zone is thereby produced. Even in places, where the parts were originally not transparent, but only translucent, a complete opacity may be seen to declare itself in proportion as the process of fatty degeneration progresses.

Consider, for example, a kidney in the stage of fatty degeneration. I show you here a preparation which does not present the ordinary granular atrophy of Bright's disease, but a more chronic and smooth form. The convoluted uriniferous tubules of the cortex are very much enlarged, and the whole of its epithelium is in a state of fatty degeneration, so that within the tubules there is really nothing else to be seen than a densely crowded mass of fat-granules. If however microscopical sections are very carefully prepared, the fat-granules are in the first instance still seen collected in isolated groups (as granule-cells or granule-globules, Fig. 98); but upon slight pressure the mass disperses in such a way, that the whole uriniferous tubule is uniformly filled with finely emulsive contents. Even with the naked eye you can distinctly recognize the change; and as soon as one has become accustomed to discriminate with some degree of accuracy between these less obvious conditions, there is not the slightest difficulty in discovering from the aspect of such a part the presence of a change in the renal epithelium, and that indeed of this particular kind, for there is no other form of change which could be compared to it. If you examine the surface of the kidney you will perceive that over the rather greyish, transculent ground, upon which the Stellulæ Verheynii* stand out, small opaque spots are scatterred in the most varied manner, most of them forming not real points, but usually small segments of an arc. These will always be found to be parts of

* The stellate veins.—Transl.

the convolutions of uriniferous tubules which have mounted up to the surface. These yellowish, opaque-looking convolutions correspond to fattily degenerated uriniferous tubules, or to speak more accurately, to uriniferous tubules filled with fattily degenerated epithelium. If a section be compared with the surface, the same markings are very distinctly seen to run through the whole of the cortex, from the periphery down to the upper borders of the medullary cones, and to invest the individual cones formed by the tubuli recti which are prolonged into the cortical substance—at pretty regular intervals.

If sections are made in such a case in the neighbourhood of the surface and parallel to it, we readily obtain a view embracing the fattily degenerated tubules by the side of more normal ones, and of unaffected glomeruli. With a lower power and by transmitted light, we see close to the Malpighian bodies which appear as large, light, globular structures, the convolutions of the degenerated uriniferous tubules interlacing in various ways, and the convoluted tubules distinguished by their opaque, shaded appearance from the straight ones, which are lighter and more translucent.

I will here call your attention to the circumstance, that in all fatty parts, where, by reflected light and as we usually view objects with the naked eye, we see whitish, yellowish, or brownish-yellow parts—by transmitted light, as generally employed for microscopes, and especially with the higher powers, either black, or brownish black, or at least very dark parts, surrounded by sharply-defined shadows, appear. A granule-globule which, when lying together with several others, produces a spot white and opaque to the naked eye, will, when viewed by transmitted light, display a nearly black appearance.

We have now compared a series of examples of fatty degeneration, and may henceforth confine ourselves to the consideration of genuine *fatty metamorphosis*, in which the normal structure of the part is ultimately destroyed, and the place of the histological elements is gradually occupied by a purely emulsive mass, or, more concisely, *fatty débris*. It makes no difference whether it is a pus-cell, a connective-tissue-corpuscle, a nerve- or muscular fibre, or a vessel which experiences the change ; the result is always the same ; namely, milky débris. an amorphous accumulation of fatty particles in a more or less highly albuminous fluid. But though we hold to the agreement of all cases of fatty metamorphosis in this respect, it by no means, however, follows that the importance of this change as a morbid process is in every case the same. This you may at once infer from the circumstance, that, whilst I have introduced this process to your notice in the category of purely passive disturbances, one of the very structures which we most frequently find in it, the granule-globule, has been regarded as a specific element of inflammation. For years an inflammatory globule [exudation corpuscle] was looked upon as an essential phenomenon in the process of inflammation, and in fact, the frequency with which cells in a state of fatty degeneration are found in inflamed parts, affords sufficient proof, that in the course of inflammatory processes, which it is impossible we should ever regard as simply passive processes, such transformations must take place. It is therefore very essential to find a means of distinguishing between the two classes. This offers indeed in particular cases very great difficulties, and according to my conviction the only possible method by which clear notions upon the subject can be obtained, consists in examining whether the condition of fatty degeneration is a primary or secondary one, whether it sets in as soon as the disturbance can be perceived, or whether it does not occur until some other perceptible disturbance has gone before. Secondary fatty degeneration, or that in which this peculiar transformation occurs only in the second place, generally succeeds to a first and active stage; a whole series of those processes which we do not scruple to call inflammations run their course in such a way, that a fatty metamorphosis sets in as the second or third anatomical stage of the change. Here therefore the fatty degeneration does not arise as a direct result of the irritation of the part, but where we have the opportunity of more accurately tracing the history of the changes, it nearly always turns out, that the stage of fatty degeneration has been preceded by another stage, namely that of *cloudy swelling*, in which the parts enlarge and increase in extent and density, in consequence of their absorbing a large quantity of matter into themselves. Absorbing I say advisedly, because I hold it to be untrue that the part is in any way forced by external influences to take up this matter, or that it is inundated with exudation proceeding from the vessels, for the same phenomena present themselves also in parts which have no vessels. It is only when the accumulation has attained such dimensions, that the natural constitution of the part is thereby endangered, that a fatty disintegration is set up in the interior of the elements. Thus we may designate fatty degeneration of the renal epithelium as a stage of Bright's disease (or as I say, parenchymatous nephritis), which has been preceded by a stage of hyperæmia and swelling, in which every epithelial cell accumulated a large quantity of cloudy matter in itself, without there having been originally a trace of a drop of fat observable. Thus we see that a muscle under the influence of agencies which it is universally conceded produce inflammation, as for example after wounds, and chemical corrosions, swells up, that its primitive fasciculi become broader and more clouded, and that as a second stage the same fatty degeneration commences in them, which at other times we see primarily arise.

It may therefore certainly, when quite general terms are used, be said, that there does exist an inflammatory form of fatty degeneration ; still, strictly speaking, this inflammatory form is never anything more than a later stage, a termination, which announces the commencing disintegration of the structure of the tissue, when the part is no longer in a condition to continue a separate existence, but is to such an extent abandoned to the play of the chemical forces of its constituent parts, that the next result is its really complete dissolution. Now inflammatory conditions of this kind are of very great importance, because in all parts whose essential elements become changed in this manner, no immediate restitution is possible. When inflammation takes place in a muscle and in its course the primitive muscular fasciculi fall into a state of fatty degeneration, as a rule they also perish, and we afterwards find a loss of substance in the muscle at the spot where the degeneration took place. The kidney, whose epithelium has passed into a state of fatty degeneration, nearly always shrivels up, and the result is a permanent atrophy. In exceptional cases something perhaps occurs, which reminds us of a regeneration of the epithelium, but usually a collapse of the entire structure ensues. The same thing is witnessed in the brain in yellow softening, no matter how it may have been caused. Whether there have been inflammation or not, a vacuity is formed, which is never again filled up with nervous matter. Perhaps a simple fluid may replace the wanting tissues, but as to any reproduction of a new, functionally active part, that must ever be out of the question.

Herein you must seek the explanation of the circumstance, that conditions apparently very similar, and which from a pathologico-anatomical point of view might be declared to be identical, in a clinical point of view lie widely apart, and that the same forms of changes are met with in analogous parts, without, however the whole process, to which they belong, being the same. When a muscle falls into a state of simple fatty degeneration, its primitive muscular fasciculi may have just the same appearance as if inflammation or permanent tension had acted upon it. Myocarditis generates forms of fatty degeneration in the substance of the heart altogether analogous to those due to excessive dilatation of the cardiac cavities. When one of these, for example, either through some obstruction to the current of the blood, or from insufficiency of the valves, is permanently much dilated, fatty degeneration of the muscular tissue constantly manifests itself in the part which has been most stretched. This form, morphologically speaking, completely resembles the early stages of myocarditis, and in many cases it is utterly impossible to say with certainty in what way the process may have arisen.

I have, in order to clear up to some extent these difficulties, as they are presented by an important, frequent and at the same time much misunderstood process, prepared a series of specimens exhibiting *really atheromatous conditions of the arteries*. For it is particularly in the case of these conditions that the confusion, which has prevailed with regard to the interpretation of the change, has perhaps been the greatest.

At no period in the course of this century has a complete understanding ever been come to as to what was to be understood by the expression atheromatous change in a vessel. Some have taken the term in a wider, others in a narrower sense, but still it has perhaps been taken in too wide a sense by all. When, namely, the anatomists of the last century applied the name of atheroma to a definite change in the coats of arteries, they of course had in their minds a condition similar to that of the skin, to which ever since the days of ancient Greece, the name of atheroma, grit-follicle, (Grützbalg) [sebaceous or epidermic cyst], had been assigned. It is self-evident, therefore, that the idea of atheroma presupposes a closed sack. Nobody ever called anything in the skin an atheroma that lay open and uncovered. It was therefore a curious misapprehension when people recently began to call changes in the vessels atheromata, which were not seated below the surface and shut off from the surrounding parts, but belonged to the surface. Thus it has come to pass that, instead of an enclosed deposit being, in accordance with the original meaning of the term, called atheromatous, a change has frequently been so termed which commences quite at the surface of the internal arterial coat. When the matter began to be examined more minutely, and fatty particles (Fig. 113) were found at very different points in the walls of the vessels, both when atheroma was, and was not, present—when at last the conviction was obtained, that the process of fatty degeneration was always the same and was identical with the atheromatous change, it became the custom to unite all the forms of the fatty degeneration of arteries under the designation atheroma. Gradually, people even came to speak of an atheromatous change in vessels, that only possessed a single coat, for in them too we meet with fatty processes.

At all times there have moreover been observers who regarded the ossification of vessels as a change belonging to the same category as atheroma. Haller and Crell believed that the ossification proceeded from the atheromatous matter, and that this was a juice which, like that exuding under the periosteum of bone, was capable of generating plates of bone out of itself. Afterwards it was recognized that atheromasia and ossification were two parallel processes, which, however, might be referred to a common origin. Now it would, I think, have been logical, if in the next place an understanding had been come to as to what this origin was, from which the atheromatous change and the ossification proceeded. But, instead of this, the track of fatty degeneration was pursued, and thus the atheromatous process was extended to a number of vessels, in which, on account of the thinness and the simple structure of their walls, the formation of any dépôt, which could really be compared to an atheromatous cyst of the skin, was altogether impossible.

The state of the matter here also is more or less very simply this, that two processes must be distinguished in the vessels, which are very analogous in their ultimate results; first, the *simple fatty metamorphosis*, which sets in without any discoverable preliminary stage, and in which the existing histological elements pass directly into a state of fatty degeneration and are destroyed, so that a larger or smaller proportion of the constituents of the walls of the vessel perishes; and, in the next place, a second series of changes, in which we can distinguish *a stage of irritation* preceding the fatty metamorphosis, comparable to the stage of swelling, cloudiness, and enlargement which we see in other inflamed parts. I have therefore felt no hesitation in siding with the old view in this matter, and in admitting an inflammation of the inner arterial coat to be the starting point of the so-called atheromatous degeneration; and I have moreover endeavoured to show that this kind of inflammatory affection of the arterial coat, is in point of fact exactly the same as what is universally termed endocarditis, when it occurs in the parietes of the heart. There is no other difference between the two processes than that the one more frequently runs an acute, the other a chronic, course.

By the establishment of this distinction between the different processes which occur in the arteries, the difference of the course they pursue is at once accounted for. Last time I laid an artery before you, on the inner surface of which you saw little whitish patches, which were due to simple fatty transformation. To-day you see very extensive patches in the aorta, in which the atheromatous change has taken place. But, as is wont to be the case in changes of this kind, in addition to the specific transformation attendant upon the chronic inflammatory processes going on in the deeper parts, you find on the surface also a simply fatty change, so that we have the two processes occurring together. If now we examine atheromasia a little more minutely, for example in the aorta, where the process is the most common, the first thing we see present itself at the spot where the irritation has taken place, is a swelling of larger or smaller size and not unfrequently so large as to form a really hump-like projection (Buckel) above the level of the internal surface. These projections are distinguished from the neighbouring parts by their translucent, cornea-like appearance. In their deeper parts they look more opaque. When the change has lasted for a certain time, the first further metamorphoses do not show themselves at the surface, but just where the internal comes into contact with the middle coat as has been very well described by the old writers. How often have they distinctly contended that the internal coat could be stripped off over the affected spot!

Hence arose the description of Haller, that the pultaceous, atheromatous mass lay in a close cavity, as it were a little cystic tumour between the internal and middle coat. The only mistake was, that the tumour was regarded as a distinct body separable from the coats of the vessels. It is rather the internal coat itself which without any well defined limits passes into a state of degeneration within the prominent spot. The farther this degeneration advances, the more distinctly does an enclosed collection arise out of the destruction of the deepest layers of the internal coat; and at last it may be that the swelling fluctuates, and that upon cutting into it the pultaceous matter is evacuated, like the pus, when an abscess is cut into. Now if the mass be examined which is present at

Fig. 116.

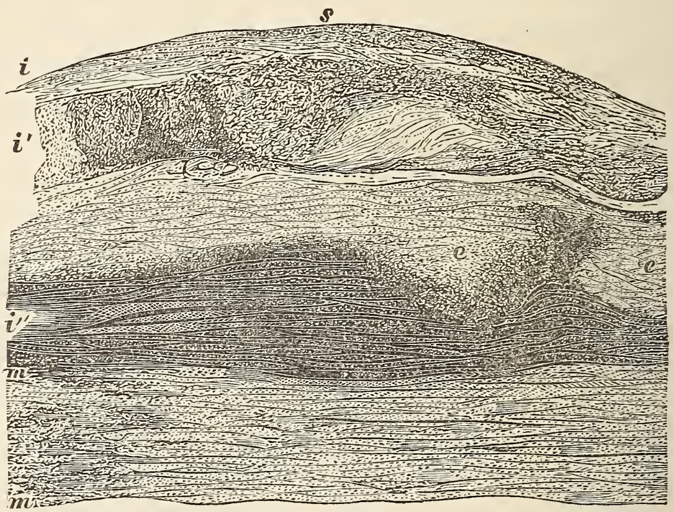


Fig. 116. Vertical section through the walls of the aorta at a sclerotic part in which atheromatous matter is already in the course of formation. *m m'*. Middle coat, *i i' i''*, internal coat. At *s* the highest point of the sclerotic part where it projects into the cavity of the vessel, *i* the innermost layer of the internal coat running over the whole dépôt, *i'* the proliferating, sclerosing layer, preparing for fatty degeneration, *i''* the layer immediately adjoining the middle coat which has already undergone fatty degeneration, and at *e*, *e*, is in process of direct softening.

the close of this process, numerous plates of cholestearine are seen, which display themselves even to the naked eye as glistening lamellæ ; large rhombic tablets, which lie together in large numbers, side by side, or covering one another, and altogether produce a glittering reflection. In addition to these plates, we find under the microscope black-looking granule-globules, in which the individual fat-granules are at first very minute. These globules are often present in very large quantity ; some of them are seen, breaking up, and falling to pieces, particles of them swimming about, as in milk. Besides these there are amorphous fragments of tissue of larger or smaller size which still cohere, and are rather due to the softening of the rest of the substance of the tissue which has not undergone fatty degeneration ; and in them heaps of granules are here and there imbedded. *It is these three constituents together, the cholestearine, the granule-cells and fat-granules, and finally the large lumps of half-softened substance, which give the atheromatous matter its pultaceous character*, and really produce a certain degree of resemblance to the contents of a pultaceous [sebaceous, epidermic] cyst (Grützbeutel) of the skin. With regard to the cholestearine, it is by no means a specific product, appertaining to this kind of fatty transforma-

Fig. 117.

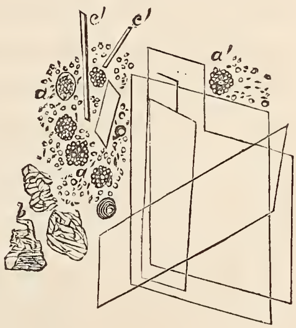


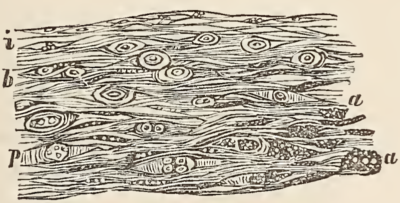
Fig. 117. The pultaceous atheromatous matter from a patch in the aorta. *a a'*. Fluid fat, the product of the fatty metamorphosis of the cells of the internal coat (*a*), which become transformed into granule-globules (*a' a'*), then disintegrate and set free large and small drops of oil (fatty débris). *b*. Amorphous, granularly-wrinkled flakes of tissue softened and swollen by imbibition. *c*, *c'*. Crystals of cholestearine; *c* large rhombic plates; *c*, *c'* fine rhombic needles. 300 diameters.

tion alone. On the contrary, we see in every case, where fatty products remain stagnant for a considerable time within a closed cavity in which but little interchange of matter can go on, that the fat sets free cholestearine. All the masses of fat which we meet with in the body contain a certain quantity of cholestearine in combination. As to whether the cholestearine which is set free had already previously existed, or whether a real new formation of it takes place in the parts, not a word can as yet be said, inasmuch as no chemical fact has, it is well known, been made out, which throws any light upon the manner in which the formation of cholestearine is effected, or upon the substances, out of which cholestearine may be formed. This much, however, we must hold fast, that cholestearine is a product set free at a late period from stagnating, and, particularly, from fatty matters.

I may take this opportunity to mention the reaction of cholestearine with iodine and sulphuric acid, which has recently become important, and is similar to that which we have already (p. 31) considered when speaking of the cellulose of plants. When, namely, iodine alone is added to cholestearine, no change is seen any more than in cellulose, under similar circumstances; but when, on the other hand, sulphuric acid is applied to the iodized mass of cholestearine, its plates become coloured and assume, particularly at first, a brilliant indigo-blue tint, which gradually passes into a yellowish brown, until the cholestearine is converted into a brownish drop. Sulphuric acid alone produces a fatty-looking substance which is neither cholestearine, nor any special combination of cholestearine and sulphuric acid, but a product of the decomposition of the former. Sulphuric acid alone also produces very beautiful phenomena of colour with cholestearine.

If now, gentlemen, we trace the development of the atheromatous condition a little further back, we come—anteriorly to the period when the pultaceous matter is found in the seat of the atheroma—across a stage, where nothing more is found than fatty degeneration in its ordinary form of granule-cells, and we distinctly convince ourselves, that the process in this stage absolutely differs in no respect from that which in the case of the heart and kidney we have just declared to constitute the stage of fatty metamorphosis. At this period, immediately before the formation of the dépôt, the state of matters, as seen with a high power, is about as follows. On making a section we see the fatty cells which are interspersed through the tissue becoming larger towards the middle and lying more closely together, but gene-

Fig. 118.



rally bearing the form of cells; but, as we proceed from within outwards they become smaller and less numerous. All these cells are filled with small, fatty granules which strongly reflect the light. Hereby is produced what looks to the eye in a section like a whitish spot. Between these fatty corpuscles runs a meshed

Fig. 118. Vertical section from a sclerotic plate in the aorta (internal coat, inner surface) in process of fatty degeneration; *i*, the innermost part of the coat with round nuclei, isolated, and in groups of several (divided). *h*. The layer of enlarging cells; networks are seen with spindle-shaped cells which enclose sections of cells resembling those of cartilage. *p*. Proliferating layer; division of the nuclei and cells. *a*, *a'*. The layer which is becoming atheromatous; *a*, the commencement of the process, *a'*, the advanced stage of fatty degeneration. 300 diameters.

basis-substance, the really fibrous stroma of the internal coat, which we plainly see continued towards the exterior into the normal internal coat. This fact, that we are able to acquire the direct conviction that the fibrous layer which lies over the dépôt, is continued into the fibrous layer of the neighbouring normal portions of the internal coat, is one of especial value in the interpretation of these processes. In this manner the view which was for a considerable time defended by Rokitansky also, that the affection consists in a deposit *upon* the internal coat, is refuted. In a vertical section it is distinctly seen that the most external layers run in a curve over the whole swelling and return into the internal coat, and the old writers were quite right when they said—speaking of a stage in which the formation of the atheromatous dépôt had already made considerable progress—that the internal coat over the whole of the dépôt could be stripped off in a piece. On the other hand, however, we can convince ourselves, that the inferior layers of the internal coat run directly into the dépôt, and that their continuity has been broken by their degeneration, so that we have not to deal either with an interjacent deposit (between the internal and middle coat), as the old writers supposed, but the whole of what we have before us is degenerated internal coat.

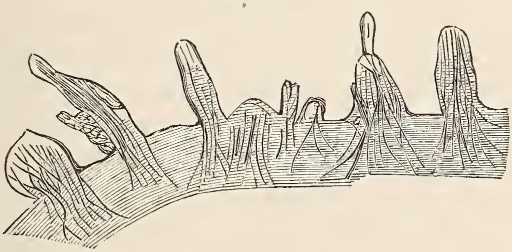
In some particularly violent cases the softening manifests itself even in the arteries not as the consequence of a really fatty process, but as a direct product of inflammation. Whilst at the circumference a fatty softening takes place, in the centre of the seat of change a yellowish cloudy appearance is seen to arise, whereupon the substance almost immediately softens and disintegrates, and a mass of coarse, crumbling fragments is found (Fig. 116, *e*, *e*) which fills the centre of the atheromatous dépôt.

In the last place, it is a question where the seat of the fatty degeneration really is. Here too again (as in the cornea) it may be imagined that the fat is deposited in spaces intervening between the lamellæ ; and even now there are still a small number of histologists who will not admit, that connective tissue contains only cells, and no empty spaces. But if a section through one of these (atheromatous) patches be examined from below upwards, it is seen that the same structure which presents itself in the fatty parts, shows itself also in the merely horny or half cartilaginous layers. Bands of fibres, in the intersections of which small lenticular cavities appear, are found there as they are also in the normal condition of the internal coat; but in the cavities and in the bands of fibres lie cellular elements (Fig. 118). The enlargement which the part undergoes in consequence of the process and which we call sclerosis, depends upon this; the cellular elements of the coat increase in size and a multiplication of their nuclei takes place, so that spaces are not unfrequently found in which whole heaps of nuclei are lying. This is the mode in which the process sets in. In many cases division occurs in the cells, and a great number of young cells are met with. These afterwards become the seat of the fatty degeneration (Fig. 118, *a*, *a′*), and then really perish. Thus we have here an active process, which really produces new tissues, but then hurries on to destruction in consequence of its own development. But one who knows that the fatty degeneration is here only a termination, and that the process is really a formative one, inasmuch as it begins with a proliferation —he can readily imagine the possibility of another termination, namely *ossification*. For here we have really to do with an ossification, and not merely, as has recently been maintained, with a mere calcification ; the plates, which pervade the inner wall of the vessel, are real plates of bone. Since they form out of the same sclerotic substance from which in other cases the fatty mass arises, and since a real tissue can only arise out of a pre-existing one, it follows of course that, when the process terminates in fatty metamorphosis, we cannot assume this to consist in a simple dissemination of fatty particles which has taken place in whatever interspaces we like to fix upon.

The essential difference which exists in a large vessel, as for example, the aorta, between this process [atheroma] and simple fatty degeneration is therefore this, that in the latter a very slight swelling arises on the surface of the internal coat, a swelling, which at once disappears if the superficial layers be removed by a horizontal section, and beneath which there still remains a portion of the coat unaltered. In the other case, on the contrary, we have in the extreme stage a dépôt which lies deep beneath the comparatively normal surface, afterwards bursts, discharges its contents and forms the *atheromatous ulcer*. This commences as a small hole in the internal coat, through which the thick, viscous contents of the atheromatous dépôt are squeezed out on to the surface in the form of a plug; gradually more and more of these contents is evacuated and carried away by the stream of blood, until at last there remains a larger or smaller ulcer which may extend as far as the middle coat, and indeed not unfrequently involves it. We have therefore always to deal with serious disease of the vessel leading to just as destructive results, as we see in the course of other violent inflammatory processes. You need only apply these observations to the history of *endocarditis*, and you will have a correct notion of all that goes on there also.

In the valves of the heart also we find simple fatty degeneration taking place both at the surface and deep beneath it. The process generally pursues its course so latently that no disturbance is perceptible during life, nor are we able, in the present state of our knowledge, to name any very obvious anatomical change as being the subsequent result of it. On the other hand, what we call endocarditis, what can be demonstrated to arise in the course of rheumatism, and may indubitably appear as a sort of equivalent to the rheumatism of the peripheral parts, begins with a swelling of the deceased spot *itself*. There is, namely, no exudation, but the cellular elements take up a greater quantity of material, and the spot becomes uneven and rugged. Then we see, when the process runs its course somewhat slowly,

Fig. 119



either that an excrescence, a condyloma arises, or that the swelling assumes a more mammillated form, and afterwards becomes the seat of a calcification which may produce real bone. If the process runs a more acute course, the result is either fatty degeneration or softening. The latter gives rise to the ulcerative forms, in which the valves crumble to pieces, drop off, and em-

Fig. 119. Condylomatous excrescences of the mitral valve; simple, granular swellings (granulations) and larger prominences (vegetations), some villous, others branched and putting forth secondary buds; in all elastic fibres running upwards. 70 diameters.

bolical deposits are produced in remote parts (Fig. 73, p. 242).*

Only in this manner, by observing, namely, the earliest stages of the changes, is it possible to form certain and practically useful opinions with regard to pathological processes. Never ought one, basing one's opinion upon the difference of the processes in a clinical point of view, to allow oneself to be induced to regard their ultimate products as necessarily different. The most violent inflammatory processes which run their course in quite a short time, may have the same terminations as those which, in other cases, are brought about more slowly.

It is not my intention to go through the series of the different passive disturbances which may possibly arise in the later stages of irritative conditions, in detail. Else we should be able to discover analogous instances in the history of nearly all degenerative atrophies. In all cases we must discriminate between the conditions in which a part becomes directly the seat of such a retrograde metamorphosis, and those in which it previously underwent an active change.

The description which I have given you of the fatty processes directly applies to the class of *calcifications.* If it be wished to discriminate between ossification and calcification, it is not sufficient to keep the ultimate result in one's eye. A part does not become true bone,

* This theory of the detachment of fragments from the valves of the heart, and of the consequent secondary occlusions (embolia) was propounded by me, with illustrations from the histories of patients and the results of post-mortem examinations (Archiv f. path. Anat. und Phys. vol. I., p. 134) as far back as 1847, or five years before Dr. Kirkes, to whom the honour of this discovery is still generally ascribed in England, published his papers on the subject. My observations concerning the detachment of the thrombi in the veins were published a year earlier than this, viz., in 1846, and I then hinted at the occurrence of the same process in the arteries, although I did not give a full account of it until 1847.—*From a MS Note by the Author.*

because it takes up lime into its intercellular substance and has stellate cells present in it; it may in spite of all this be nothing more than calcified connective tissue. When we speak of pathological ossification, we always presuppose that the mass which ossifies has been called into existence by an active process, an irritation, and not that a previously existing tissue assumes the form of bone, by absorbing calcareous salts. We have therefore calcifications and ossifications in the vessels. In ancient times everything was called ossification. Many of the more recent observers have denied that it ever does occur in vessels. Ossification does however really occur, but so does mere calcification, or, as I will briefly term it, *petrifaction*. The latter is comparatively more frequent in the peripheral arteries, so that the condition which is generally regarded as a special criterion of the atheromatous process and in which the radial artery is felt to be hard and calcareous, and the femoral or popliteal is perceived to have hard and rigid walls, is no proof at all that the process is an atheromatous one. Very frequently this induration has its seat in the middle coat. In this case the calcification really invades the muscular elements, so that the fibre-cells of the circular-fibre coat are transformed into calcareous spindle-shaped bodies. The calcareous matter may in these cases also invade the neighbouring parts, but the internal coat may possibly remain quite unaltered. This is a process therefore, which differs more from what is termed the atheromatous process than periostitis from ostitis. This species of calcification has no necessary connection whatever with an inflammation of the artery, it occurs most commonly in cases where there is a tendency to calcifications generally, and where calcareous salts are set free at other points in the economy and circulate with the juices. This much at least can with certainty be affirmed, that we are as yet acquainted with no stage in these changes, which is at all akin to inflammation.

On the contrary, we see ossification declare itself in the internal coat of vessels in precisely the same manner as when an osteophyte forms on the surface of bone amidst all the phenomena of inflammation. The osteophytes of the inner table of the skull and of the cerebral membranes follow the same course of development as the ossifying plates of the internal coat of the aorta and even of the veins. They always begin with a proliferation of the pre-existing connective tissue, whereby partial swellings are produced, in which the deposition of the calcareous salts does not take place until a late period. As soon as this real ossification exists, we cannot help regarding the process as one which has arisen out of an irritation of the parts, stimulating them to new, formative actions; so far therefore it comes under our ideas of inflammation, or at least of those processes which are extremely nearly allied to inflammation. When a process of this sort is accessible to treatment, we have always other indications for practice, than in those cases, in which our object is, by the agency of stimulating substances, to prevent the occurrence of certain passive disturbances which hinder the part from discharging its natural functions.

What I have said will suffice, I think, to make these, in my opinion, extremely important distinctions clear to you. In the next lecture I will lay before you that one among the degenerative processes which is at the present moment the least clear, namely the lardaceous or amyloid degeneration.

LECTURE XVII.

APRIL 17, 1858.

AMYLOID DEGENERATION. INFLAMMATION.

Amyloid (lardaceous or waxy) degeneration—Different nature of amyloid substances: concentric and laminated amyloid bodies (brain, prostate), and amyloid degeneration properly so-called—Its course—Commencement of the affection in the minute arteries—Waxy liver—Cartilage—Dyscrasic (constitutional) character of the disease—Intestines—Kidneys: the three forms of Bright's disease (amyloid degeneration, parenchymatous, and interstitial nephritis)—Lymphatic glands—Functional disturbances of the affected organs.

Inflammation—The four cardinal symptoms and their predominance in the different schools: the thermic and vascular theory; the neuro-pathologists, exudations—Inflammatory stimuli—Lesion of function—Exudation as a consequence of the activity of the tissues; mucus and fibrine—Inflammation as a complex irritative process—Parenchymatous and exudative (secretory) form.

I WILL to-day, gentlemen, from among the changes which must in general be rather ranked with that class of degenerations which are attended with a diminution of functional power, introduce to your notice one, which has recently acquired especial interest, namely that which has been by some called the *lardaceous* (bacony—speckig), by others the *waxy*, whilst I have given it the name of the *amyloid*, change. The term lardaceous change has again come more into use chiefly through the instrumentality of the Vienna school. You know that the term itself is of tolerably ancient date in medicine as a denomination for a firm, compact, homogeneous appearance of parts. We find it has been employed for centuries, and even in recent times tumours have been termed lardaceous. Still the term, lardaceous changes, as now used, has but very little to do with these tumours, and rather refers to things, upon which the old writers, who, I think, were better connoisseurs in bacon than our friends in Vienna, would hardly have bestowed such a name. The appearance of such organs, namely, as in accordance with Viennese ideas, are said to look like bacon, bears, according to northern notions, a much greater resemblance to wax, and I have therefore now for a long time, like the Edinburgh school, made use of the term waxy change instead. When we look at a liver or lymphatic gland which constitutes a well-marked specimen of this condition, what strikes the naked eye most, is the translucent, but at the same time, dull appearance which the cut-surfaces exhibit; the natural colour of the parts is also more or less lost, so that a material, at first more of a grey tint, but afterwards perfectly colourless, seems to fill the parts. The translucent nature of the tissue allows, however, the red of the vessels and the natural hue of the neighbouring parts to glimmer through, so that the altered spots in different organs have rather a yellowish, reddish, or brownish tinge; but this is not a colour belonging to the substance deposited.

The first facts, by the help of which we were enabled to determine more accurately the nature of this substance which had previously been taken, sometimes for a peculiar fatty matter, sometimes for albumen or fibrine, sometimes, finally, for a colloid substance, were furnished by the application of iodine to animal tissues. It will now soon be five years since I first discovered the peculiar reaction of the corpora amylacea found in the nervous centres with iodine, which I have already described to you, and since I had my attention directed to the extraordinary resemblance which these bodies present to vegetable structures—a resemblance such that they have been regarded, now rather as real starch, now rather as analogous to cellulose. The next organ I came across, although there is no close resemblance in external appearance between it and the ependyma, was the spleen and indeed a condition of it, in which its follicles were wholly converted into this translucent, waxy matter (sagoey spleen—Sagomilz). Soon afterwards H. Meckel published his well-known observations which demonstrated the occurrence of this substance in several places, but especially in the kidneys, the liver and the bowels, and we afterwards succeeded in finding it in different other parts, in the lymphatic glands, throughout the whole of the digestive tract, in the mucous membranes of the urinary passages, and finally even in the substance of the muscular organs—the heart, and the uterus—as well as in the interior of cartilages—so that at the present moment there are but few parts of the body that we do not know may undergo this peculiar change.

If we investigate the matter more closely, it seems that two allied, but not identical, substances must be distinguished. In the first place we find bodies which in their chemical properties are more analogous to real vegetable starch, and in form too bear an extraordinary resemblance to vegetable starch-granules, inasmuch as they constitute more or less round, or oval structures, formed by a succession of concentric layers. To this class belong, above all, the corpora amylacea of the nervous system (Fig. 94). Many of the laminated amyloid bodies are of very large size ; their diameter may become so considerable, that they may be very distinctly recognized with the naked eye. To this category belong, in particular, a part of the laminated bodies, that are found in the prostate of every adult man and under certain circumstances accumulate in large quantities, so as to form the so-called prostatic concretions; and also rare forms of a similar kind which have been shown by Frederich to occur in several conditions of the lungs.

These formations vary in size from very small, simple, homogeneous looking structures up to gigantic bodies, in which, when they are regularly formed, we see a succession of very numerous layers. Just as the small amyloid corpuscles of the nervous system are frequently composed of two separate ones and constitute twin structures, it very frequently happens here also, that a common envelope encloses separate centres (Fig. 120, *d*, *e*). Nay, in isolated cases this goes on to such an extent, that whole heaps of smaller bodies are held together by larger common layers. These very large

Fig. 120.

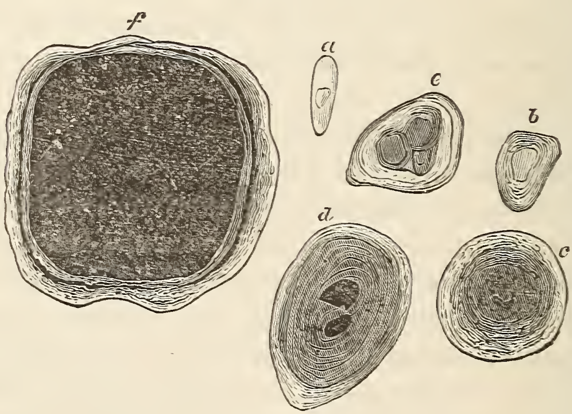


Fig. 120. Laminated prostatic amyloid bodies (concretions); *a*, oblong, pale homogeneous corpuscle, with a nucleus-like body. *b*. A larger, laminated corpuscle with pale centre. *c*. A still larger corpuscle with several layers and a coloured centre. *d*, *e*. Bodies with two and three centres, in *d* of a deeper colour. *f*. Large concretion with a dark-brown, large centre. Magnified 300 diameters.

though certainly more rare, forms may attain a diameter of two lines, so that they can easily be isolated from the tissue in which they lie, and be subjected to examination even with the naked eye. There seems to be scarcely any doubt, but that in these cases a substance is set free, which gradually adheres to the outside of pre-existing bodies all round, and that therefore we have not here to deal with the degeneration of a definite tissue, but with a kind of separation and precipitation, such as we see occur in the case of other concretions from fluids. It may, with some probability be concluded, that the prostate, through the dissolution of its elements, furnishes a fluid which, by the gradual formation of deposits, produces these particular forms.

Now the peculiarity of these structures is, that by the simple action of iodine they very frequently assume just as blue a colour as vegetable starch does. According as the substance is more or less pure, its colour changes, so that when, for example, there is much albuminous matter mixed up with it, it becomes green instead of blue ; for the nitrogenous substance is rendered yellow by iodine, and the amyloid blue, so that the whole effect produced is green. The greater the quantity of nitrogenous matter, the browner does the colour become, and not unfrequently do we find, side by side in the prostate, concretions, which, after the application of the iodine, present the most varied colours. So far these formations are distinguished from those little amylaceous corpuscles of the nervous system, which, one and all, assume a blue or bluish grey colour on the addition of iodine. It must also be remarked, that many prostatic bodies, though quite analogous in their structure, only become yellow or brown upon the addition of iodine, and consequently differ in chemical constitution.

Essentially different from this separation of starch-like matter, which lies *between* the elements, are the degenerations of the tissues themselves, in which all their constituents (parenchyma and interstitial tissue), as such, become directly filled with a substance also of an amyloid nature, and are gradually infiltrated with it just as tissues become infiltrated with lime in calcification. No two things can be more justly compared than calcification and the amyloid change (lignification). This (amyloid) substance, which produces the real degeneration of the tissue, exhibits the peculiarity, that it never becomes blue under the influence of iodine alone. At least no case is as yet known, in which the substance has yielded this colour with iodine in the parenchyma of tissues. On the contrary, a peculiar yellowish red colour is seen to arise, which it is true in many cases has a slight tinge of reddish violet, so that a certain approximation is manifested to the blue of real starchy matter. On the other hand, it displays pretty regularly a real, either perfectly blue, or violet colour, when the application of iodine is followed by the very cautious addition of sulphuric acid. A certain degree of practice indeed is requisite ; the exact proportion must be hit upon, inasmuch as the sulphuric acid generally destroys the substance very quickly, and either very indistinct colorations are obtained, or the colour manifests itself only for a moment, and then immediately disappears again. Thus this substance is less nearly allied to starch properly so-called and more akin to cellulose, as I have already described it (p. 31). But from cellulose again it is also distinguished by the fact of its becoming coloured upon the application of pure solution of iodine, whilst real cellulose is not at all coloured by iodine alone. Cellulose behaves precisely like cholestearine which remains colourless when treated with iodine, but on the other hand assumes a blue, or under certain circumstances a red, or orange colour upon the addition of iodine and sulphuric acid (p. 400).

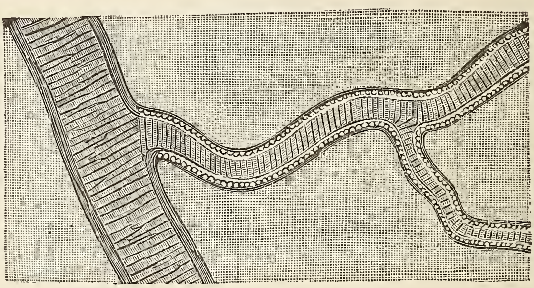
Owing to this multiplicity of reactions it is really still very difficult to say with certainty to what class the substance belongs. Meckel has followed up the idea with great care, that we have to deal with a kind of fat which is more or less identical with cholestearine ; but we are as yet unacquainted with any kind of fat which combines in itself the three qualities of becoming coloured upon the addition of iodine alone, of remaining colourless upon the addition of sulphuric acid alone, and of assuming a blue colour when acted upon by iodine and sulphuric acid. Besides the substance itself does not in any way behave like a fatty matter ; it does not possess the solubility which characterizes fat ; and in particular no substance can be obtained from these parts by extraction with alcohol and ether, which possesses the peculiarities of the original one. According to all this there is rather a correspondence with vegetable forms, and the view may still be maintained, that we have here to deal with a process comparable to that which we see set in during the development of a plant, when the simple cell becomes invested with capsular layers, and gradually grows woody.*

* The analyses of amyloid spleens recently made by Kekule and Carl Schmidt have yielded such a large proportion of Nitrogen, that both these chemists have come to the conclusion that the amyloid substance is of an albuminous nature. We know, however, from experience, that the results furnished by these analyses of whole organs are very little to be depended upon, so little indeed, that no chemist was ever able to infer from any analyses he had made of the liver, that it was rich in Glycogen. Only when we have discovered the means of isolating the amyloid substance, shall we be able to come to any definite conclusion with regard to its nature.

To Schmidt's analyses of the corpora amylacea of the brain we cannot attach the slightest importance, because his statements concerning them were founded upon an error. He says, namely, he selected for his analyses a choroid plexus (from a human brain) rich in corpora amylacea. But corpora amylacea are never found in

These changes can be best followed in those structures which must on the whole be regarded as the most frequent and the earliest seat of this change, namely the *smallest arteries.* These first undergo the transformation, and only after the constitution of their walls has become changed, is the infiltration wont to extend to the surrounding parenchyma, until at last the whole district of tissue to which the artery leads has experienced the change. If in an amyloid spleen we trace one of these small arteries, whilst it breaks up into so-called penicillus, we see how its wall, in itself already a thick one, becomes thicker in proportion as the change advances, and how at the same time the calibre of the vessel becomes con-

FIG. 121.



siderably diminished. This accounts for the circumstance, that all organs which experience the amyloid change in a considerable degree, look extremely pale ; an

FIG. 121. Amyloid degeneration of a small artery from the submucous tissue of the intestine, with its trunk still intact. 300 diameters.

large numbers in these plexuses—indeed it seems to me doubtful whether they are ever *formed* there. The concentric corpuscles which Schmidt examined were therefore probably those sabulous bodies (Sandkörper—acervulus cerebri, brain-sand) which are nearly always present in the choroid plexuses and so greatly resemble the corpora amylacea in structure, that they were actually taken by Remac to be such. Schmidt, thinking he had the same substance before him in the spleen, published his two analyses with the idea that he was thereby furnishing a doubly strong proof of the albuminous nature of this animal amyloid substance.—*From a MS. Note by the Author.*

ischæmia of the parts is produced by the obstruction which the narrowed vessels oppose to the influx of blood. If now we examine in which of the histological elements of the vessels the substance is first found, it seems to be pretty constantly seated in the little muscles of the circular-fibre coat. First of all the place of every fibre-cell is occupied by a compact, homogeneous body, in which the centre of the nucleus at first still appears as a hole, but gradually every trace of a cellular structure is lost, so that at last a kind of spindle-shaped flake (Scholle) remains, in which neither membrane, nucleus nor contents can be distinguished. In the calcification of small arteries exactly the same process takes place ; the individual fibre-cells of the middle coat take up calcareous salts, at first in a granular, afterwards in a homogeneous form, until they are at last transformed into homogeneous-looking calcareous bodies, of a spindle-shaped form, which coalesce and produce plates of a considerable size. In like manner the amyloid substance pervades whole tracts of tissue, and the walls of the artery are transformed into a mass at last nearly completely homogeneous, compact, shining with reflected light and colourless, which not only does not possess the hardness of calcified parts, but on the contrary exhibits a high degree of friability.

Now when a change of this nature has advanced to a certain height, an analogous change takes place also in the parenchyma of the organs. This can nowhere be so distinctly traced as in the *liver*. Here it sometimes happens, that we meet with stages, where nothing else in the whole organ is altered, excepting the minute branches of the hepatic artery. On making fine sections through the liver, carefully washing them and applying iodine, we sometimes see, even with the naked eye, the small iodine-red lines and points which correspond to the cut branches of the hepatic artery. In a later stage, however, it is essentially the hepatic cells which are affected by the change; and indeed, what is again very characteristic, just those hepatic cells, between which lie the capillary ramifications of the hepatic artery. If namely we picture to ourselves a single acinus of the liver, we can, in accordance with the pathological changes which may often be recognized even with the naked eye, distinguish three different zones within each acinus (Fig. 110). The most external part, which lies next to the branches of the portal vein, is the chief seat of fatty infiltration; the intermediate part, which receives the capillary terminations of the hepatic artery, belongs to the amyloid degeneration, and the central part of the acinus around the vena hepatica is the most common seat of pigmentary infiltration. Even with the naked eye the pale colourless, translucent and resistant zone of the waxy or amyloid change is sometimes recognized between the most external yellowish white, and the most internal yellowish, or greyish brown, layer.

If a single hepatic cell be watched, its previous granular contents, which give every hepatic cell a slightly cloudy appearance, are seen gradually to become homogeneous; the nucleus and cell-wall gradually disappear, and at last a stage sets in in which nothing more can be perceived than an absolutely homogeneous, slightly shining body, if you will, a simple flake (Scholle). In this manner the whole of the hepatic cells in the zone I have described are sometimes converted into amyloid flakes, and if the process attains a very high pitch, the change at last even oversteps this zone, and it may happen, that nearly the whole substance of the acinus is transformed into an amyloid mass. Thus out of the hepatic cells there is at last produced in these cases a kind of corpora amylacea, only they are not laminated like those we have already spoken of, but form uniform, homogeneous bodies, in which no internal division, no indication of the peculiar course of their formation can be recognized.

If we take all these facts together, it appears pretty probable, that we have here to deal with a gradual infiltration of the parts with a substance which has been conveyed to them from without. This is a view which derives essential support from the fact, that nearly always when this change declares itself, a considerable number of organs are affected, and that the process is not confined to a single spot, but that many places in the body are simultaneously affected. Hereby the whole process really acquires an essentially dyscrasic appearance. The only place, where, until now at least, an entirely independent development of this change has been observed by me, and where it may therefore with some degree of probability be assumed that the formation is autochthonous and not imported from without, is *permanent cartilage.* The cartilages, particularly in people somewhat advanced in life, assume in various places—as for example, the sterno-clavicular articulations, the symphyses of the pelvis, and the intervertebral cartilages—a peculiarly pale-yellowish hue, and then we may be tolerably certain, that if we try the iodine test with them, we shall obtain the peculiar coloration. These colours are not seen so much in the cartilage-cells as in the intercellular substance, and as cases of the sort do not occur simultaneously with amyloid degeneration of large internal organs, but quite independently, in individuals, who in the rest of their body manifest nothing of the kind—it seems that we really have here to deal with a direct transformation, and not with any importation from without.

But in vain have I hitherto endeavoured to detect any definite change in the blood, from which the inference might be drawn, that this was really the source of the deposits. There exists as yet but one single observation, that points to the presence of analogous bodies in the blood, and this is so strange an one, that we can scarcely attempt to ground an explanation of the process upon it. A physician of Toronto in Canada had namely, in compliance with the wish of a patient suffering from epilepsy, examined his blood and discovered in it peculiar, pale bodies. When then he read of my observations with regard to the coloration of the corpora amylacea of the brain by iodine, his patient recurred to his mind, and, I think after the lapse of five years, he again took blood from him, and again found the bodies, which are really said to have exhibited the reaction. In opposition to this observation, it is strange that nobody else has ever seen anything of the kind, and as an extremely persistent dyscrasia must here have been in operation, we should scarcely be justified in drawing conclusions from this observation, with regard to the cases we are considering, where the disease attains its height in a much shorter time, and we have in the blood at least been able to detect nothing of the kind. Moreover great doubts must be entertained with respect to the accuracy of the observation. Starch-granules may very easily find their way into different microscopical objects, so that (with all due respect for the observer) as long as matter turns upon a solitary observation, it must be admitted to be possible that there was perhaps an error.* I am as yet much more inclined to admit, that the blood in this disease under-

* Dr. Carter of Edinburgh, and after him, M. Luys of Paris, fell into a similar error, when they imagined they were in a condition to prove that an excretion of starch took place through the skin. M. Rouget (Journal de Physiologie par Brown-Séquard, Tom. ii., p. 85) has shown that this starch is derived from external sources, from articles of food, and that its presence upon the skin therefore is merely accidental.—*From a MS. Note by the Author.*

goes a chemical alteration in its fluid constituents, than that it contains the pathological substances in a material form.

At all events it is unquestionable, that the amyloid change even now holds a very high place among pathological processes. The inevitable result of the affection is, that the parts which are the seat of it, become totally incapable of discharging their special functions; that, for example, gland cells which are changed in this manner, are no longer in a condition to perform their special glandular functions, and that vessels can no longer subserve the nutrition of the tissues, or the secretion of the fluids, the duties they had been in the habit of performing.

These considerations afford a ready explanation of the circumstance that clinical disturbances so regularly concur with these anatomical ones. We find, on the one hand, well-marked conditions of cachexia, and on the other, with extreme frequency, dropsy with the whole complex group of changes, which are usually included in the idea we form of Bright's disease. In nearly every instance, in which the amyloid affection reaches an advanced stage, the patients are in a state of great marasmus. There are cases where the whole extent of the digestive tract from the buccal cavity to the anus does not contain a single minute artery, which is not affected with this disease, and wherein every part of the œsophagus, stomach, small and large intestines, the small arteries of its mucous membrane are found changed in this way.

Now this state of things is very apt to escape observation, because this kind of metamorphosis, which exercises such a decided influence upon the functions of the intestines (causing deficiency of absorption, and tendency to diarrhœa), produces scarcely any effect perceptible to the naked eye. The intestines are pale and have a grey, translucent, sometimes slightly wax-like appearance ; but this, however, is so little characteristic, that no inference can with certainty be drawn from it with regard to the internal changes, and the only possibility of determining the point, when one has no microscope at hand, consists in the direct application of the test. One need only brush a little iodine upon the surface, and a number of densely aggregated, yellowish- or brownish-red spots are soon seen to start up, whilst the interjacent mucous membrane merely looks yellow. These red points are the villi of the intestine, and if one of them be placed under the microscope, the walls of the small arteries and even of the capillaries, which ramify in them, and sometimes also the parenchyma, are seen to be coloured iodine-red.

The most important disturbances of this kind with which we are as yet acquainted, are those which arise in the kidney. A large proportion of the cases of Bright's disease, especially of the chronic ones, are assignable to this change, and must therefore be separated from many other similar forms as constituting a special, altogether peculiar affection. Kidneys affected in this way were called in Vienna, at a time when the chemical reaction was not yet known, lardaceous kidneys (Specknieren). I must however again remark that it is impossible to distinguish immediately with the naked eye, whether this particular change has taken place or not, and that a part of the so-called lardaceous kidneys exhibit nothing more than a kind of induration. Not until iodine has been employed can a diagnosis be readily made. If a solution of iodine be applied to a quite anæmic cortex, a number of red points usually first appear which correspond to the glomeruli, and sometines fine streaks also, which are the afferent arteries ; and next to this, when the disease is very severe, red parallel lines are also seen within the medullary cones, lying very close to one another. These are all arteries. The affection of the arteries becomes sometimes so severe, that, after the application of the test, a clear view of the whole course of the vessels is obtained, as if one had a very complete artificial injection before one. But in these very kidneys an injection is hardly practicable. Even the finer materials which we employ as injections, are much too coarse to be able to pass through the narrowed vessels. Upon examining one of these glomeruli microscopically, we see that from the point, where the afferent artery breaks up, the loops are no longer the fine, delicate tubes that they formerly were; on the contrary they appear compact and nearly solid. Now as these are just the parts which manifestly constitute the real points at which the secretion of the fluid portion of the urine is effected, we can easily conceive that in such cases disturbances in the secretion of urine must arise. Unfortunately we have as yet no completely satisfactory analyses, but it seems that many cases of albuminuria, which are attended with a considerable diminution in the secretion of urea, are connected with these very conditions, and that the excretion becomes more and more scanty in proportion as the disease increases in intensity.* These cases are very frequently complicated

* This is what we might expect to take place, wherever we suppose the urea to be secreted. If it is secreted by the epithelium, the epithelium must take it up out of the blood which circulates in the intertubular capillaries. But if the glomeruli only allow a small quantity of blood to pass through them, a small quantity only finds its way into these capillaries, and so but little urea can be taken up and excreted. In those cases in which there is an abundant flow of *watery* urine, the water is chiefly derived from the vessels of the medullary substance, in consequence of the increased (collateral) pressure upon them. Thus the amyloid degeneration of the Malpighian bodies and their afferent arteries has much less influence upon the excretion of water, than upon that of urea. The peculiar views first put forward by the Author concerning the circulation in the medullary substance of the kidney, and the common origin (from the same branches of the renal artery) of the arteriæ rectæ of the medullary cones (pyramids), and of the

with anasarca and with dropsy of the different cavities, and may exhibit in the completest manner all the symptoms of Bright's disease. They differ however essentially from the simply inflammatory form of Bright's disease, which I designate *parenchymatous nephritis*, in this respect, that in the latter the disease has not so much its seat in the glomeruli or the arteries, as in the epithelium of the kidney, and that the change is often for a long time confined to the epithelium, whilst the glomeruli themselves may in such cases still appear unchanged when there is scarcely any epithelium remaining in the substance of the cortex. From these forms a third again must be distinguished, where the *interstitial tissue* is predominantly affected, where thickenings take place around the capsules and uriniferous tubules, constrictions and contractions are effected, and thereby mechanical obstructions to the current of the blood are produced, which must naturally be attended by secretory changes.

It is very important that you should discriminate between these different varieties which exist in what is apparently a single disease, because you will hence see how it is that the facts which have been ascertained concerning the one class cannot forthwith be applied to the other classes, and that neither the same physiological inferences nor the same therapeutical maxims are equally applicable in every one of these several conditions. At the same time, however, it must not be overlooked that these three different forms by no means always appear

afferent arteries of the cortex, whereby, in the case of a diminished flow of blood through the latter set of vessels, an increased circulation takes place through the former—will be found in his Archiv. f. path. Anat. und Phys. vol. xii., p. 310, and investigations confirmatory of them have recently been published by Dr. Beale (Arch. of Med., 1859, No. IV., p. 300. According to those (*e. g.*, Bowman) who make all the arterial blood pass through the glomeruli, no such collateral relationship could exist between the cortex and medulla.—*From a MS. Note by the Author.*

unmixed, but that on the contrary frequently two, and sometimes all three, of them exist simultaneously in the same kidney.

Amongst the other preparations which I place before you I have, especially on account of its distinctness, chosen the amyloid disease of the *lymphatic glands.* In these the state of things is much the same as in the spleen. We see on the one hand the small arteries, on the other the essential substance of the glands (*i. e.*, the mass of minute cells which fill the follicles), undergoing the change. You will remember from a previous occasion (p. 208, Fig. 61), that there are follicles lying beneath the proper capsule of the gland, and that these follicles are made up of a

Fig. 122.

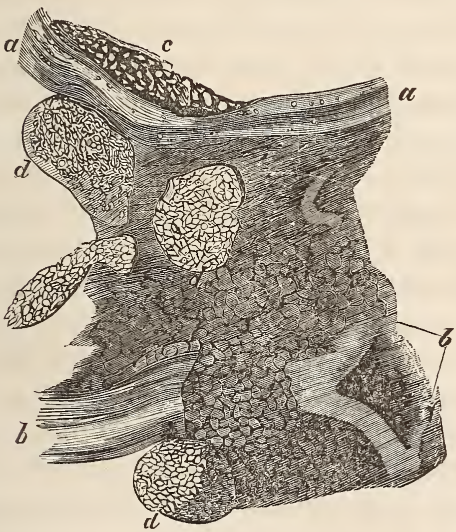


Fig. 123.

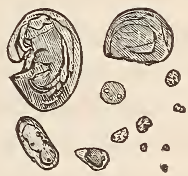


Fig. 122. Amyloid degeneration of a lymphatic gland, from a drawing made by Dr. Fripp of Bristol. *a*, *b*, *b*. Vessels with greatly thickened, shining, infiltrated walls. *c*. A layer of fat-cells at the circumference of the gland. *d*, *d*. Follicles with their delicate reticulum and corpora amylacea. 200 diameters. Compare Würzburger Verhandlungen, Vol. VII, Plate III.

Fig. 123. Isolated corpora amylacea of different sizes, some of them ruptured, from the gland represented in Fig. 122. 350 diameters.

delicate network, in which the small cells of the gland are heaped up, cells, which seem to have a double duty to perform, inasmuch as they discharge their own special functions as gland-cells, and at the same time, as we suppose, serve as the starting-points for the development of blood-corpuscles. The arteries run first in the interstices of the follicles, and there break up into capillaries which form a web round the follicles, and sometimes even penetrate into their interior. Now the amyloid disease consists on the one hand in a thickening and narrowing of these arteries, so that they convey less blood, and on the other hand in the conversion of the small cells contained in the individual meshes of the follicles into corpora amylacea, so that afterwards instead of a number of cells in every mesh of the follicle, a single large corpus amylaceum is met with. Thereby the gland acquires even to the naked eye the appearance as if it were sprinkled all over with little spots of wax, and when examined microscopically, it looks as if the contents of the follicles were a pavement of closely set stones.

Concerning the importance of these changes, empirically not much can be affirmed ; but, if the contents of the follicles are the essential components of a lymphatic gland, and if from them proceeds the development of the new constituents of the blood, we must, I think, conclude, that this disease of the lymphatic glands and the spleen (in which the follicles are likewise generally affected), must exercise a directly injurious influence upon the formation of the blood ; and that the effects therefore produced by the disease are not remote ones, but that the formation of the blood immediately suffers an alteration, so that anæmic conditions must ensue. To the stream of lymph also an obstruction may arise, and in this way again deficiency of absorption, tendency to dropsy, etc., be produced.

If we apply iodine to sections of such glands as these, all the diseased parts become coloured red, whilst every part that retains its normal structure merely becomes yellow. The capsule, which consists of connective tissue, the fibrous trabeculæ between the follicles, the delicate intrafollicular network which separates the different corpora amylacea, and lastly those follicles which contain normal cells, remain yellow. All the other parts assume the iodine-red hue. If we add sulphuric acid, these parts become of a dark reddish brown, or violet red—or if one hits the mark, pure blue; but if there are still nitrogenous particles present, the colour becomes green or brownish red.

Now, gentlemen, that we have established the classification of morbid disturbances generally according to the difference of action in the tissues, I think of treating more in detail of the process, which the practical physician, according to the ordinary mode of speaking, most frequently meets with, namely *inflammation.*

Our notions of inflammation have undergone an essential change in consequence of the observations, of which you have now heard a certain part. Whilst until quite recently it was the custom to look upon inflammation as a real entity, as a process everywhere identical *in its essence*, after I made my investigations no alternative remained, but to divest the notion of inflammation of all that was ontological in it, and no longer to look upon the process as one differing in its essence from other pathological processes, but only to regard it as one differing *in its form and course.*

In the descriptions given of inflammation by the old writers—as preserved to us in the dogmatical writings of Galen—among the four cardinal symptoms (calor, rubor, tumor, dolor) heat is, as is well known, the most promi nent, for it is the symptom from which the process has acquired its name. Afterwards, in proportion as the question of animal heat in general, and of heat in pathological conditions in particular, withdrew into the background, great importance was attached to the redness, and thus it happened that even in the last century, at the time when mechanical theories were in vogue, when especially Boerhaave considered inflammation to consist in an obstruction of the vessels, and in the stasis of the blood consequent upon it, the notion of inflammation was more or less grounded upon supposed conditions of the vessels. After the facts of pathological anatomy had extended their compass, hyperæmia was, especially in France, declared to be the necessary and regular starting point of inflammation. The exclusiveness, with which this view has been maintained even up to our own times, was in a great measure an after-effect of Broussais' views which became the prevailing ones in consequence of the development of the pathologico-anatomical school. Hyperæmia gradually superseded all the other essential symptoms.

A change in the doctrine on a grand scale has really only been attempted by the Vienna school, for they too, like the French school, grounding their system of pathology upon pathological anatomy, have put the products of inflammation in the place of the symptoms of inflammation. What, basing their opinion upon their own experience, they especially had in view, and sought to establish as the essence of inflammation, was the product, which, in accordance with traditional notions, was designated as one which had necessarily proceeded from the vessels—as an exudation. In the old classification of symptoms, the swelling, corresponded pretty nearly with the exudation of the Vienna school, and it might therefore be said that, as previously, first the heat, and then the redness, had held the first place, so now the swelling occupied the foremost rank. It is only in the more speculative views of the neuro-pathologists that the pain is, as is well known, regarded as the essential and original change in the act of inflammation.

There can be no doubt, but that of these different positions the anatomical doctrine of the Vienna school would be the most correct, if it could be demonstrated, that, as the language of most of the physicians of the present day would lead us to believe, an exudation really does take place, in every case of inflammation; that the swelling is essentially occasioned by this exudation; and especially, that this exudation ought to be regarded as a constant and typical one, and the quantity of fibrine contained in it as a criterion of its inflammatory nature.

I have already, in the previous lectures, endeavoured to show you, in what a considerably restricted sense the term exudation must be employed, and how essentially the activity of the elements of the tissues themselves is concerned in the appearance of matters, which we certainly must regard as derived from the vessels and deposited in the parts affected. A good deal is, as we have seen, not so much exudation, as, if I may so express myself, an educt from the vessels in consequence of the activity of the histological elements themselves.

Irritation must, I believe, be taken as the starting-point in the consideration of inflammation, and it is because Broussais and Andral regarded the matter in this light, that I consider the views advanced by them to be the most correct. We cannot imagine inflammation to take place without an irritating stimulus (irritament),* and the

* The term *irritament* (Reiz, which, however, sometimes means *irritant*, stimulus) is intended to express the change (mechanical or chemical, palpable (anatomical) or molecular) which takes place in a tissue in consequence of the action of an *irritant*—a change, therefore, which is of a *purely passive* nature (lesion), and which

first question is, what conception we are to form of such a stimulus.

We have already seen that the irritation may in general be traced to one of three different sources, according as it is a functional, nutritive or formative irritation which has taken place. Now there can be no doubt, but that functional stimuli (irritaments) do not play an essential part in inflammation, and for the simple reason, that—a point upon which all the more recent schools at least are agreed—to the four characteristic symptoms *lesion of function* (functio læsa) must be added.

If there be a disturbance of function in inflammation, this presupposes that the inflammatory stimulus (irritament) must be of such a nature as to cause changes in the composition of the part which render it less capable of performing its functions. Nobody would expect a muscle which is inflamed, to perform its functions normally; every one supposes that the contractile substance of the muscle has thereby experienced certain changes. Nobody would expect an inflamed gland-cell could secrete normally, but we should look upon the disturbance of secretion as a necessary consequence of the inflammation. Nobody could expect an inflamed ganglion-cell or nerve to discharge its functions, or normally to respond to stimuli. The conclusion, therefore,

(subsequently) provokes changes in the neighbouring parts not *directly* altered by the irritant—the consequence of which is their *action* or *reaction*. This condition, which is an *active* one, based upon the physiological powers of the parts, represents *irritation* in the proper sense of the word, and as the starting-point in every form of inflammation. See Archiv f. path. Anat. und Phys. vol. xiv., p. i. (Reizung und Reizbarkeit).

The matter will perhaps be rendered clearer by the following familiar illustration:—Suppose three people were sitting quietly on a bench, and suddenly a stone came and injured one of them, the others would be excited, not only by the sudden appearance of the stone, but also by the injury done to their companion, to whose help they would feel bound to hasten. Here the stone would be the *irritant*, the injury the *irritament*, the help an expression of the *irritation* called forth in the bystanders.—*From a MS. Note by the Author.*

that must in accordance with the commonest experience be necessarily drawn from all this is, that changes must have occurred in the composition of the cellular elements altering their natural functional power. Such changes, when they occur after the application of stimuli which are not powerful enough to destroy the parts at once, or to exhaust their functional power, are only possible when the stimuli are either nutritive or formative. And in fact this conclusion is confirmed by what occurs in inflammation. For now-a-days we find the view is already pretty generally spread, that in inflammation we have in the main to deal with a change in the act of nutrition, nutrition being here indeed regarded as embracing the formative and nutritive processes.

If therefore we speak of an inflammatory stimulus (irritament), we cannot properly intend to attach any other meaning to it, than that, in consequence of some cause or other external to the part which falls into a state of irritation, and acting upon it either directly or through the medium of the blood—the composition and constitution of this part undergo alterations which at the same time alter its relations to the neighbouring parts (whether they be blood-vessels or other structures) and enable it to attract to itself and absorb from them a larger quantity of matter than usual, and to transform it according to circumstances. Every form of inflammation with which we are acquainted, may be naturally explained in this way. With regard to every one, it may be assumed that it begins as an inflammation from the moment that this increased absorption of matters into the tissue takes place, and the further transformation of these matters commences.

This view accords to a certain extent, as you no doubt see, with that which has been maintained by the upholders of the vascular theory, according to which the exudation is regarded as an immediate consequence of the hyperæmia, and in which it is assumed that inflammation, when it has once declared itself, is characterized by the presence of a substance more or less foreign to the natural composition of the part. The only question is whether the hyperæmia really forms the actual commencement of these processes.

If inflammation were necessarily dependent upon hyperæmia, you can well imagine that it would be logically impossible to speak of inflammations in parts which do not stand in an immediate relation to vessels. We could not imagine an inflammation taking place at a certain distance from a vessel. It would be completely impossible to speak of an inflammation of the cornea (excepting as occurring at its border); of an inflammation of cartilage (excepting as occurring in the parts immediately adjoining the bone); or of an inflammation in the internal substance of a tendon. But if we compare the processes which present themselves in these parts with those which are ordinarily seen in inflamed parts, the result is unquestionably that the same inflammatory processes may occur everywhere alike, and that the changes in the vascular parts can in no essential particular be distinguished from those which take place in the non-vascular ones.

The term inflammatory (*i. e.*, according to the common definition, fibrinous) exudation, has, as you are aware, been somewhat loosely applied, inasmuch as it has been taken to include different kinds of exudation (fibrinous and non-fibrinous) furnished by different processes, upon all of which, however, the common name of inflammation has been bestowed. When, for example, inflammations of mucous membranes are spoken of, it is not generally supposed, that the mucous membrane will furnish a fibrinous exudation. We are indeed acquainted with mucous membranes, where fibrinous exudations are of pretty frequent occurrence, for example, the mucous membrane of the respiratory organs. But we know also that free (superficial) fibrinous exudations are scarcely to be met with on the mucous membrane of the digestive tract, and that they at most accompany the more serious, and especially the gangrenous and specific forms. When laryngitis is spoken of, the presence of croup is not immediately inferred. In a case of cystitis, we do not expect to find the inner surface of the bladder covered with a fibrinous layer. In the whole series of so-called gastric inflammations we find, especially at the commencement of the process, scarcely anything more than an abundant secretion of mucus. If therefore we still call these catarrhal inflammations, inflammations, if we do not wish entirely to cast them out of the class of inflammations, we must admit that there may exist a mucous as well as fibrinous exudation in inflammations, and that the inflammations with a mucous exudation form a special category, appertaining to certain organs. For, as is well known, we do not find them in all the tissues of the body, but nearly exclusively on mucous membranes.

If now you consider the fibrinous exudations a little more closely, there can be no doubt at all, but that in this point they entirely agree with the mucous ones. For we do not meet with fibrinous exudations in all parts of the body; we know of no form of exudative encephalitis, for example, which furnishes a fibrinous exudation. Just as little is there a form of hepatitis known, in which fibrinous exudations occur. There is indeed an inflammation of the investing membrane of the liver (perihepatitis), just as there is an inflammation of the membrane of the brain, in which fibrine may be set free, but nobody has ever met with fibrine in a case of genuine hepatitis. Just as little is there fibrine to be found in the ordinary inflammation of the substance of the heart (myo-carditis).

On the other hand, you must bear in mind that, starting with certain preconceived notions, observers have imagined fibrinous exudations to take place in many parts, where they are not really to be seen. If because pus has been obtained from a fibrinous exudation, it is therefore imagined that, wherever pus shows itself, a fibrinous exudation must be regarded as its source, no very great power of observation is required to convince oneself, that this is an error. Take any ulcerated surface you please, wipe off the pus, and collect what then comes out; you will either have a serous fluid or pus, but you will not see that the surface you have wiped becomes covered with a fibrinous layer. If we confine ourselves to those parts, where inflammations with real, unquestionable fibrinous exudation do occur, we have a category nearly as limited as that of the mucous inflammations. In such a category the first place is occupied by the serous membranes proper, which even upon slight inflammatory irritation generally produce fibrine; the second place is filled by certain mucous membranes, in which, in a great number of cases, fibrinous inflammations unmistakably arise, as an aggravation out of mucous ones. Ordinary croup does not generally at its very outset manifest itself in the form of fibrinous croup; at the commencement, at a time when the danger may already be very considerable, there is often nothing else found than a mucous or muco-purulent false membrane. Not until after a certain lapse of time does the fibrinous exudation set in, and then it does so in such a manner, that we can trace the transitions in the same false membrane, and see that a certain portion is manifestly mucous, another manifestly fibrine, whilst in a third part it can no longer be affirmed with certainty whether the one or the other is present. Here therefore both substances appear as substitutes for one another. Where the inflammatory irritation is more violent, we see fibrine, where slight, mucus, appear.

With regard to mucus, however, we know, that it does not exist in the blood like fibrine. Although a mucous membrane produces incredibly large masses of mucus in a short time, they are nevertheless products of the membrane itself; the membrane is not infiltrated with mucus coming from the blood, but the peculiar mucin matter, the principle of mucus, is a product of the membrane, and is conveyed to the surface by means of the fluid oozing through (transuding) from the blood. In the same manner I have also attempted, as I intimated to you on a former occasion (p. 195), to overthrow the opinion, which is wont to be entertained with regard to the origin of fibrine. Whilst until now fibrine has been regarded as a real transudation from the liquor sanguinis, as the outflowing plasma, I have proposed the explanation, that the fibrine, like the mucus, is a local product of those tissues, on and in which it is found, and that it is conveyed to the surface in the same way as the mucus of the mucous membrane. I then showed you, how we have in this way a most ready explanation of the fact, that in proportion as, in a given tissue, the production of fibrine increases, so also the amount of fibrine in the blood increases; and that the fibrinous crasis is just as much a product of the local disease, as the fibrinous exudation is a local product of the local metamorphosis of matter. Never has any one —any more than it is possible for him by a change of pressure directly to produce mucus from the blood in any place which does not itself produce mucus—been able to produce fibrine by any change in the pressure of the blood; what transudes never consists of anything but serous fluids.

I am accordingly of opinion, that, *in the sense* in which it has usually been assumed to exist, *there is no inflammatory exudation at all*, but that the exudation which we meet with, is essentially composed of the material which has been generated in the inflamed part itself through the change in its condition—and of the transuded fluid derived from the vessels. If therefore a part possesses a great number of vessels, and particularly if they are superficial, it will be able to furnish an exudation, since the fluid which transudes from the blood conveys the special products of the tissue along with it to the surface. If this is not the case, there will be no exudation, but the whole process will be limited to the occurrence in the real substance of the tissue of the special changes which have been induced by the inflammatory stimulus.

In this manner, two forms of inflammation can be separated from one another; the *purely parenchymatous inflammation*, where the process runs its course in the interior of the tissue, without our being able to detect the presence of any free fluid which has escaped from the blood; and the *secretory* (*exudative*) *inflammation* (which belongs more to the superficial organs) where an increased escape of fluid takes place from the blood and conveys the peculiar parenchymatous matters along with it to the surface of the organs. That there are two different forms is clearly shown by the fact that they occur for the most part in different organs. There are certain organs which, under all circumstances, only suffer from the parenchymatous affection, and others again which in nearly every instance exhibit a superficial exudative inflammation.

The distinction into adhesive and purulent forms, which has generally been made in accordance with the example of Hunter, has reference to a much later stage in the process ; the first point to be considered is always, how far the tissues themselves become changed and their products assume a degenerative character, or how far, through the passage of the fluids, the part is again freed from what it has generated in itself, and how far thereby the degeneration of the part is avoided. Every parenchymatous inflammation has from its outset a tendency to alter the histological and functional character of an organ. Every inflammation with free exudation in general affords a certain degree of relief to the part ; it conveys away from it a great part of the noxious matters with which it is clogged, and the part therefore appears comparatively to suffer much less than that which is the seat of a parenchymatous disease.

LECTURE XVIII.

APRIL 21, 1858.

NORMAL AND PATHOLOGICAL NEW-FORMATION.

The theory of continuous development in opposition to the blastema- and exudation-theory—Connective tissue and its equivalents as the most general germ-store of new formations—Correspondence between embryonic and pathological new formation—Cell-division as the most general starting-point of new formations.

Endogenous formation—Physalides—Brood-cavities.

Different tendencies of new-formations—Hyperplasia, direct and indirect—Heteroplasia—Pathological formative cells—Difference in their size and in the time required for their full development.

Description of the development of bone as a model-formation—Difference between formation and transformation—Fresh and growing, in opposition to macerated, bone—Nature of medullary tissue—Growth in length of tubular [long] bones; proliferation of cartilage—Formation of marrow as a transformation of tissue; red and yellow, normal and inflammatory marrow—Osseous tissue, calcified cartilage, osteoid tissue—Bone territories: caries, degenerative ostitis—Granutions in bone—Suppuration of bone—Maturation of pus—Ossification of marrow—Growth of long bones in thickness: structure and proliferation of the periosteum.

Granulations as analogous to the medulla of bones, and as the starting-point of all heteroplastic development.

Gentlemen,—I propose to-day, in illustration of *formative irritation*, to portray to you the most important features in the history of pathological new-formations, for a knowledge of these will throw light upon a series of events which present themselves both in the more complicated formation of tumours, and in the more simple inflammatory irritative processes. That I at present entirely reject the blastema doctrine in its original form, you have no doubt already gathered from the previous lectures. In its place I have put the very simple doctrine of the *continuous development of tissues out of one another*. The chief point therefore in individual cases is to determine the particular manner in which the various tissues arise, and by means of definite examples to make oneself acquainted with all the different directions which it is possible this development may follow.

My first observations, in consequence of which I began to entertain doubts with respect to the prevailing blastema and exudation doctrine—as to how far namely, new-formations could be derived from this source—date from researches of mine on *tubercle*.* I found namely that a series of tubercular deposits in different organs, especially in the lymphatic glands, the membranes of the brain and the lungs, never at any time exhibited a discernible exudation, but always, during the whole course of their development, presented organized elements, without its ever being possible to observe either in them, or before they existed, any stage in which amorphous, shapeless matter was present. As long as eight years ago I discerned that the development which takes place in the lymphatic glands upon the occurrence of the well-known scrofulous changes, begins in such a way, that the first conditions met with entirely correspond to those which in other instances are designated by the name of hypertrophy; for nuclei and cells are found in great abundance, though they afterwards break up and directly supply the material for the final accumulation of cheesy substance. The view which I derived

* See a paper on tuberculosis and its relations to inflammation, scrofulosis and typhoid fever. Verhandlungen der physikalisch-medic. Gesellschaft zu Würzburg, 1850, vol. i., p. 81.

from these investigations of mine, namely, that a tissue undergoing hypertrophy may supply a completely abnormal, diseased product, appeared to me all the more significant, because I had simultaneously detected an altogether similar series of developmental changes whilst examining an entirely different body, namely, the so-called *typhous matter* (Typhus-masse). At that time the view of the Vienna school had been universally adopted, that, in the different typhous processes, an exudation of an albuminous nature and soft, medullary character filled the parts, and that thereby swellings of a medullary appearance were produced. But whether the typhous matter be examined in the lymphatic glands of the mesentery, or round about the follicles of Peyer's patches, no exudation capable of organization is at any time met with, but always a directly continuous development from the pre-existing cellular elements of the glands, the follicles and the connective tissue, to the typhous matter.

These observations were of course as yet insufficient to justify me in setting about effecting a general change in the existing doctrine, because we see organic elements arise at numberless points, where at that time at least cellular elements were altogether unknown to exist as normal constituents, and there was therefore scarcely any other explanation possible than that new germs were formed by a kind of generatio æquivoca [spontaneous generation] out of the mass of blastema. The only places besides the glands, where such a development arising out of previously existing elements might have been inferred with some degree of probability to take place, were the surfaces of the body with their epithelial elements. Then it was, that my investigations into the nature of the connective tissues, with which I have already so much plagued you, proved entirely decisive. From the moment that I was able to maintain that there was scarcely any part of the body which did not possess cellular elements—that I could show that bone-corpuscles were real cells, and that connective tissue in different places contained, now a larger, now a smaller, number of really cellular elements—from that moment germs in abundance were supplied from which new tissues might possibly be developed. In fact, the more the number of observers increased, the more distinctly was it shown, that by far the greater number of the new-formations which arise in the body proceed from connective tissue and its equivalents. From this rule comparatively few pathological new-formations are excepted, and these belong on the one hand to the class of epithelial formations, and on the other are connected with the more highly organized tissues of a specific, animal (p. 55) nature, for example, the vessels. We may therefore, with trifling restriction, *substitute for the plastic lymph, the blastema of the earlier, the exudation of the writers, connective tissue with its equivalents as the common stock of germs* (Keimstock) *of the body*, and directly trace to it as the general source the development of new-formations.

If we take a definite internal organ, for example, the brain or the liver, it was scarcely possible, as long as people saw nothing more than nervous matter in the brain, and admitted the existence of nothing more than vessels and hepatic cells in the liver, to imagine the occurrence of a new-formation in them without the intervention of a special formative matter. For it was of course easy to convince oneself that new-formations do not in the liver usually proceed from the hepatic cells or the vessels. And that in the substance of the brain, the nerves as such do not give rise to new-formations, has been known ever since the microscope has been employed, for since that time it has been known that medullary cancers are not due to the proliferation of nervous matter, but consist of cellular elements of another kind. In fact, the body appears to us at the present day, as Reichert was the first to note, to be made up of a more or less continuous mass of connective tissue-like constituents, in which at certain points other things, such as muscles and nerves, are imbedded. Now it is in this more or less connected frame-work, that, according to my investigations, genuine new-formation goes on, and that in accordance with the same law, which regulates embryonic development.

This law of the correspondence between embryonic and pathological development was, as you know, laid down by Johannes Müller, who continued the investigations commenced by Schwann. But at that time the contents of an ovum were placed on a level with blastema; it occurred to no one that the whole process of development in the ovum took place within the limits of a cell, but it was concluded simply, that there was a certain quantity of organizable material in the ovum, which—in virtue of a peculiar power innate in it, by means of some organizing force, or as those would have it who regard the matter from a "higher" point of view, impelled by an organizing idea—transformed itself into this or that particular shape. But here too the conviction has been gradually acquired, that the matter in question is a cellular substance, and if what has been most rigidly maintained by Remak is correct, namely, that the cleavage of the yolk also is due to a visible division of cells, to the growing in of membranous partitions into the interior of the ovum, and their coalescence, we have not here to deal with a free organizing impulse taking place within the yolk, but with progressive acts of division on the part of the originally single cell. But long before this simple view of the process of the cleavage in the yolk had been arrived at, it had been very distinctly perceptible that in pathological processes a comparison between plastic exudations, or blastema, with the matters contained in the ovum, was obviously inadmissible, and that, where really formed parts were found, they had proceeded from a pre-existing part, a cell.

The mode of origin of new formations is, as it seems, a double one. We have, namely, either to do with a *simple division*, such as we discussed when treating of irritation (p. 346). We then see the whole series of

Fig. 124.

Fig. 124. Proliferation of the growing cartilage of the diaphysis of the tibia of a child. Longitudinal section. *a*. The cartilage-cells on the border of the epiphysis, some of them simple, some of them in a state of commencing proliferation. *b*. Groups of cells that have arisen from the repeated division of simple cells. *c*. Groups of cells lying near the calcifying border of the diaphysis, and considerably developed through the growth and enlargement of the individual cells; the intercellular substance growing continually more and more scanty. *d*. Section of a bloodvessel. 150 diameters.

changes from the division of the nucleolus to the final division of the cell. If an epithelial cell acquires two nuclei, divides and this process is repeated, a long series of developmental changes may, by means of a continual repetition, be produced. If the skin becomes irritated in consequence of continued friction, and the irritation is increased to a certain point, the epithelium will thicken, and if the proliferation is very energetic, it may lead to the production of tolerably large tumour-like formations. The same mode of development which is presented by layers of epithelium, we meet with also in the interior of organs. In cartilage, for example, where the individual cellular elements are inclosed in an intercellular substance, the place of each of them is at last occupied by an accumulation of numerous cells, the whole group, like the cell from which it proceeded, being shut off from its neighbors by the intercellular substance. This mode of development, therefore, is one which, though very simple in itself, may, since it originates in dissimilar parts, produce very different results.

But we have besides another class of new-formations

Fig. 125.

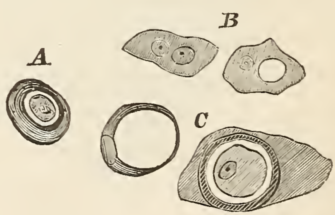


Fig. 125. Endogenous new formation; cells containing vesicles (physaliphores). *A*. From the thymus gland of a new-born infant together with epithelioid cells: in the interior of a vesicle which has a double contour (more distinctly marked in *C*) and is besides surrounded by a cell-like border, lies a perfect nucleated cell. *B*. *C*. Cancer-cells (Cf. Archiv. für pathol. Anatomie, Vol. I., Pl. II., and Vol. III. Pl. II.) *B*, one with two nuclei; *C*, one with a physalid which nearly fills the whole cell and another, where the physalid (brood-cavity) again encloses a perfect nucleated cell. 300 diameters.

in the body which are indeed much less well known, and of which the special peculiarities cannot as yet be seized with such great precision. These are processes, where we see *endogenous* changes set in in the interior of pre-existing cells. In a simple cell a vesicular cavity forms, which, contrasted with the somewhat cloudy and generally slightly granular contents of the cell, presents a very clear, bright, homogeneous appearance. In what manner cavities of this first kind, which I class together under the name of *physalides*, arise, is not yet altogether certain. The greatest probabilities are in favour of the nuclei being, in certain forms, likewise the starting-point of these formations. For, beside these cells, others are seen with two nuclei, one of which, in several of them, has become somewhat larger and brighter than usual, though still preserving the character of a nucleus. Subsequently, this vesicle becomes so large that the cell is gradually almost entirely filled with it, and its former contents with the nucleus only look like a little appendage to the vesicle. So far the process is tolerably simple. But besides these vesicles, thus growing and filling the cells, others are met with, in the interior of which elements of a cellular nature are enclosed. This is of pretty frequent occurrence in cancerous tumours, but also in normal parts, for example in the thymus gland. This form seems to indicate, that in fact by means of a process which cannot be directly traced to any division of the pre-existing cells, and indeed in peculiar vesicular cavities (which I have named *brood-cavities* (or -vesicles —Bruträume),) in the interior of cellular elements, new elements of a similar kind may be developed. However, this is at all events a condition which plays but a subordinate part in the whole history of new-formations; the regular form is the one first described. There are only a few pathological new-formations, in the history of which this endogenous development plays any distinct part, whilst in nearly all forms cell-division is met with to a great extent.

The essential points of difference between the several modes of development of cells are therefore these: in one class of formations the divisions proceed with a certain regularity, so that the ultimate products from their very beginning exhibit a complete correspondence with the parent structures, and the young structures at no time deviate in any remarkable degree from the parent-cells. Such processes are in ordinary life mostly designated as hypertrophies, but I have, in order to express the nature of the change more accurately, proposed the name of *hyperplasiæ*, inasmuch it is not an increase in the nutrition of existing parts that takes place, but a real formation of new elements (p. 94).

In another class the development proceeds in such a way, that divisions certainly also do take place, but make very rapid progress and produce cells which gradually decrease in size, and ultimately in some instances become so small, that they can scarcely be distinguished to be cells. The proliferation may cease at this point, and then the cells severally begin to grow, and to become larger; and under certain circumstances a structure may in this case again also be produced analogous to that in which the development originated. This, however, is not usually the case; generally, the young cells pursue a somewhat different course of development, and a heterologous structure begins to form.

The mode of development, which I here describe to you, may also run its course in such a way, that the cells do not at once begin to divide, but the nuclei first greatly multiply, becoming continually more numerous and at the same time smaller. We find something similar to this in pus, in which a division of the nuclei very rapidly takes place, and generally in such a way, that the originally single nuclei at once divide into a considerable number of smaller ones, which at first remain coherent. But in pus it is not certain whether the division of the nucleus is succeeded by a real division in the cell, whilst in other new-formations this is certainly the case—only the complete division, or if you will, the cleavage, of the cells is delayed for a long time, and this intermediate stage of the mere division of the nuclei continues for a disproportionately long period, and seems to occur in some sort independently.

These two plans are the ones regularly followed by all those kinds of new-formations which do not *directly* lead to hyperplasia ;* the normal condition is here in the first instance interrupted by an intermediate state, in which the tissue appears essentially changed, without one's being able straightway to determine whether a growth of a benignant or malignant nature will be developed out of it. This is a stage of seemingly absolute indifference ; from the appearance of the individual elements it cannot at all be inferred what their real destiny is ; they behave exactly like the so-called formative cells of the embryo, which also at first exactly resemble one another, no matter whether a muscular or nervous element, or anything else, is about to proceed from them. Nevertheless I regard it as very probable that delicate internal differences do really exist, which to a certain extent determine beforehand the subsequent metamorphoses—not merely potential differences in the formative cells, but really material differences, only of so

* There are processes which begin with Hyperplasia and end with Heteroplasia, and others again, which begin with Heteroplasia and end with Hyperplasia. The new formation of vessels, for example, never begin straightway with the formation of vessels, but first of all cells are formed (heteroplasia), and afterward vessels (hyperplasia) are developed out of these cells.—*From a MS. Note by the Author.*

delicate a nature, that we are not as yet able to demonstrate them.

In the development of the embryo a phenomenon has been known for years which positively indicates the existence of such differences in the formative cells, inasmuch as the different segments of the ovum run through their phases of development with different degrees of rapidity, and especially those parts which are destined to form the higher organs, run through their individual stages with much greater celerity than those whose lot it is to form the lower tissues. In the size of the cells also differences seem to exist. In a similar manner we frequently see that in pathological formations also differences occur in reference to the time occupied in their development. Whenever the development of the cells takes place with great rapidity, we may be sure it is a more or less heterologous development. An homologous, hyperplastic formation always presupposes a certain tardiness in the processes which give rise to it; the cells generally remain of a larger size, since the divisions do not usually proceed until very small forms are produced.

Though so extremely simple in nature and in theory, these modes of development are certainly extremely difficult of demonstration in individual places. The parts which apparently ought to be the most conveniently situated for the purpose of investigation, and in which Henle indeed, as long as twenty years ago, all but made the discovery of such a development, are the epithelia. Here, where a development often so abundant takes place upon the surface of a membrane, one would suppose it must be extremely easy to trace its course accurately in the individual cells. Henle, you know, endeavoured to show that mucus-corpuscles, and indeed many forms which belong to pus, were produced on the surface of mucous membranes along with the epithelium in such a way, that no real difference was to be perceived between the two classes in their earliest stages, and that the mucus-corpuscles must therefore in some sort be looked upon as epithelial cells that had gone astray, as children that had turned out ill, that had been impeded in the progress of their development by some early disturbance, but really were intended to become epithelial cells. Unfortunately the notion was then and long afterwards prevalent, that epithelium like all other tissues was normally developed out of a blastema. It was, you know, imagined that on the surface of every mucous membrane in the first instance there transuded a plastic fluid from the vessels running to the surface, and that the epithelial cells were formed out of it. Schleiden's theory was steadfastly adhered to, that nuclei first form in a fluid, and that membranes do not develop around them until afterwards. At present, however much the different surfaces presented by the skin and the mucous and serous membranes are examined, the conviction is everywhere unmistakeably acquired, that the cellular elements extend down to the very surface of the connective tissue, and that there is nowhere a spot, where free nuclei, blastema or fluid exist, but that on the contrary it is especially the deepest layers which contain the most densely crowded cells. If, at the time when Henle made his investigations, it had been known, that no blastema ever exists in these parts, and that no development de novo ever takes place there, but that the epithelial cells there present must have been developed either from old cells or from the connective tissue underneath them, he too would certainly also have come to the conclusion, that mucus- or pus-corpuscles which are not furnished by an ulcerating surface (which would of course be destitue of epithelium) must be derived by direct descent from pre-existing epithelial cells.

So nearly, even at that time, had correct views upon the subject been obtained, but the blastema theory enthralled men's minds, and we all stood under its influence. Besides, it appeared impossible to point out everywhere in the interior of the tissues the requisite antecedent structures. Not until cellular elements had been shown to exist in connective tissue did it become possible to produce a germinal tissue (Keimgewebe) which is at present everywhere, and from which in the most various organs similar growths may be developed. Now that we know that connective tissue—or tissues equivalent to it—exists in the brain, the liver, the kidneys, in muscle, cartilage, skin, etc., now there is of course no longer any difficulty in conceiving how the same pathological product may arise in all these apparently so dissimiliar structures. No specific blastema of any sort, deposited in all these parts, is at all required, but only the application of a similar stimulus to the connective tissue of the different localities.

Now with regard to the details of this doctrine, allow me in the first place to bring to your notice a concrete example of normal development, which will perhaps be the best calculated to supply you with a picture of the often so complicated processes with which we are here concerned. I choose as my example that organ, in which the process of development is in itself best known, and which at the same time on account of the peculiarity of its structure least admits of misinterpretation, namely the *bones*. They are too hard and thick for any one to talk about the presence of blastema or exudation in their proper parenchyma. The growth of the bones at the same time affords us direct standards wherewith to compare the different new-formations, which may occur in the bones in morbid conditions, for every one of these new-formations finds a certain prototype in the normal development of bone.

All the larger bones grow, as is well known, in two directions. This is most simply shown in the long bones, which gradually increase in length and thickness. The growth in length takes place from cartilage, that in thickness from periosteum. But a flat bone also is invested on the one hand with cartilaginous parts or their equivalents (sutures) and on the other with membranes which correspond to periosteum. A growth from cartilage and a growth from periosteum can therefore be distinguished in every bone. This furnishes us with a plan of the development of long bones, which is found even in the writings of Havers, and according to which the new layers of bone incapsulate the old ones, and every more recent layer is not only wider but longer than that next above it in age. Every new layer of osseous substance which is formed out of periosteum is longer (higher) than the one immediately preceding it, inasmuch as new layers of perichondrium are being continually converted into periosteum. At the same time every new layer of osseous substance which grows out of cartilage is broader (thicker) than that which went before it, inasmuch as every new layer of the (growing) cartilage which proceeds to ossification surpasses its predecessor in breadth (thickness). The growth from cartilage, however, can only take place in the direction of the extremities of the bone, inasmuch as the cartilage of its diaphysis is, at a very early period of intra-uterine life, so completely ossified,* that no cartilage remains ex-

* This complete ossification in long bones is not confined to intra-uterine life, but every new layer of cartilage which grows out of the terminal cartilage up to the age of puberty ossifies (when matters follow a normal course) throughout its whole thickness, so that no cartilage remains at the circumference of the bone.—*From a MS. Note by the Author.*

cepting at the two ends. Now a tissue once ossified ceases (save under exceptional circumstances) to grow so that any increase of thickness in the diaphysis must be wholly due to a development out of periosteum, in which growth proceeds much more slowly than in cartilage. This is the reason why the shaft of a long bone is narrower than its extremities.* Whilst in this way parts which were previously either connective tissue or cartilage, are converted into bone, the development of the medullary tissue is going on within the bone. The original bone is extremely dense, a very solid and relatively compact mass. Subsequently the substance of the bone disappears more and more, one part of it after another is dissolved, and the medullary cavity [canal] arises, the size of which is not in any way restricted to that of the original osseous rudiment, but often considerably exceeds it. Thus the development of bone, when taken as a whole, does not consist merely in the gradual apposition of a succession of fresh osseous layers derived from periosteum and cartilage, but also in the continual replacement of the innermost layers of the bone by masses of marrow.

In the interpretation of these facts the blastema theory was long appealed to as the great authority. Havers and Duhamel, who made excellent investigations into the history of bone, started with the supposition that a nutritious juice (succus nutritius) was secreted, from which the new masses arose. The development of the marrow was imagined to consist in a formation of cavities, into which first a viscous juice and then a fatty matter was secreted—cavities which were invested by the medullary membrane, and whose contents varied

* For a diagram of the growth of long bones, see Havers (Osteologia nova. Francof. 1692, Tab. I., fig. 1), and Kölliker (Handbuch d. Gewebelehre, 3d edit., Leipzig, 1859, p. 259).

with age. However, as I have already pointed out to you, there are no sacs in the areolæ of the bones, but a continuous tissue, the medullary tissue, which fills the medullary spaces [cancelli] and cavities and belongs to the class of connective tissues, although it considerably differs from ordinary connective tissue. We have therefore here to deal, as you see from this simple fact, with a substitution of tissues. As osseous tissue* is formed out of periosteum and cartilage, so marrow is formed from osseous tissue, and the development of a bone consists not merely in the formation of osseous tissue, but it presupposes that the series of transformations goes beyond the stage of bone, and that medullary tissue is then produced. Medullary tissue therefore constitutes in some sort the physiological termination of the formation of bone as an organ.

However simple this view may be, still it furnishes us with a picture of the growth and history of bone different from the traditional one. Formerly, observers nearly always contented themselves with viewing the matter much in the same light that osteologists are wont to do; they took a macerated bone, examined it when divested of all its soft parts, and built up the processes accordingly. It is, however, necessary that the relations should be traced in the moist, living healthy or diseased bone, and that one should pay attention not only to the development of bone upon the outside from the growing layers of the cartilage and periosteum, but also to that of the medulla on the inside, as the ultimate product of the development in this class of tissues, even if it be not the noblest one. The most important and really

* *Osseous tissue* (tela ossea, tissu osseux) = bone corpuscles + calcified intercellular substance. *Bone* as an *organ* = osseous tissue + medullary tissue + periosteum + vessels + nerves. *Osseous substance* is sometimes taken to mean a portion of bone considered as an organ.—*From a MS. Note by the Author.*

decisive point, through which the whole subject of bone acquires another aspect, is, I consider, this, that the bone in the formation of marrow is not simply dissolved and its place taken by some exudation or blastema, but that the dissolution of the osseous substance is a transformation of the osseous tissue, and that the dissolution results from a transformation of the intercellular substance of the bone into a soft mass of tissue which is no longer in a condition to retain the calcareous salts. If therefore you ask whence the new elements come which arise in the midst of osseous tissue, or how a cancer or collection of pus can form in the middle of the compact cortex of bone, I return you the very simple answer, that they arise in precisely the same manner, that in the course of the natural and normal development of bone the marrow arises. In no part does the osseous tissue first dissolve, then an exudation, and next a new-formation, follow, but the existing tissue is directly converted into the succeeding one. The existing osseous tissue is the matrix of the succeeding cancerous tissue, the cells of the cancer are the immediate descendants of the cells of the bone.

If now we consider the course of the formation of bone a little more in detail, we find, as we have already in part seen, that the cartilage prepares for ossification in such a way, that its cells in the first instance become larger; that divisions then take place in them, first in the nuclei and afterwards in the cells themselves; that these divisions then proceed with great rapidity, so that we obtain larger and larger groups of cells, and in a comparatively short time the place of a single cell is occupied by a relatively very large group of cells (Fig. 124). You will remember from my first lecture (p. 33), that a cartilage-cell is distinguished from most other cells by its secreting a special membranous capsule in which it is inclosed. This membranous capsule, on the division of the cells which it contains, sends in septa between them, which serve as new envelopes for the young cells, yet in such a way, that even the gigantic groups of cells, which proceed from each of the original cells, are still enclosed in the greatly enlarged parent capsule.

It is manifest, that the greater the number of cells which undergo this change, the larger the cartilage will become, and that the height to which any one of us

FIG. 126.

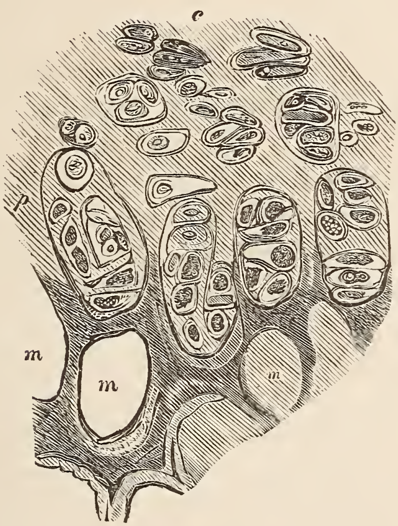


Fig. 126. Vertical section through the ossifying border of a growing astragalus. *c*. Cartilage with smallish groups of cells, *p*, the layer where the proliferation and enlargement are the most marked along the line of calcification. In the cartilage-cavities are seen, partly complete nucleated cells, partly shrivelled, angular and granular looking bodies (artificially altered cells). The dark mass advancing into the intermmediate substance represents the deposition of calcareous salts, behind which the formation of medullary spaces (*m*, *m*, *m*) and osseous trabeculæ [spicula] is here beginning with unusual rapidity. The marrow has been removed; round the cavities which lie farthest back, the trabeculæ are surrounded by a lighter border of young osseous tissue (produced from marrow.) 300 diameters.

attains, essentially depends upon the extent to which growth occurs in the individual groups of cartilage-cells. Whether we ultimately become tall or short, is, if I may say so, left entirely to the discretion of these elements. When the growth of the proliferating cartilage has reached this point, the cellular elements are very close together, so that a comparatively trifling quantity of intercellular substance lies between them (Fig. 124). The farther the development advances, the more does the appearance of the cartilage alter, and at last it looks almost like dense-celled vegetable tissue. The cells themselves however are difficult to be seen, because they are extremely sensitive ; they readily shrivel up upon the addition of the mildest fluids and then appear like angular and jagged corpuscles, almost analogous to those of bone, with which however they have at this time nothing to do.

The cells which have sprung from this excessive proliferation of the originally simple cartilage cells, constitute the parent structures from which proceeds all that afterwards arises in the longitudinal axis of the bone, and especially the osseous and medullary tissue. The cartilage-cells may be converted by a direct transformation into marrow-cells and continue as such ; or they may first be converted into osseous, and then into medullary, tissue ; or lastly they may first be converted into marrow and then into bone. So variable are the permutations of these tissues in themselves so nearly allied, and yet in their external appearance so completely distinct. When a direct transformation into marrow is the first effected, the old intercellular substance of the cartilage at the border next to the bone begins first of all to grow soft ; then some of the adjoining capsules usually also very soon experience this change, so that the cellular elements come to be more or less set free in a softer basis-substance. Simultaneously with the occurrence of this softening the chemical reaction of this tissue also becomes altered, and we always obtain the distinct reaction of mucin. At the same time divisions begin to take place, and this not in the same way as previously, when the cellular elements at once separated into two new analogous cells (hyperplasia), but rather in such a way, that a number of little nuclei arise in them (physiological heteroplasia). Subsequently, in proportion as this process of transformation reaches a higher and higher pitch, and fresh portions of the intercellular substance are continually being converted into this more homogeneous and soft matter, the cells generally divide, and we obtain a number of smaller ones, which are very minute in comparison to the large cartilage-cells, from which they proceeded, and contain either a single nucleus with a nucleolus, or sometimes also, like pus-corpuscles, several nuclei. Thus gradually arises a tissue extremely rich in cells, *the young, red, medullary tissue*, as we generally find it in the marrow of new-born infants. If the process stops here, the size of the transformed spot indicates at the same time the extent of the subsequent medullary space. Subsequently, these little cells may take up fat, and then it appears, first in small granules, but by degrees in large drops, and at last to such an extent that the cells are entirely filled with them. Thereby the original medullary tissue is transformed into adipose tissue; the fat, however, is always contained in the interior of the marrow-cells, as it is in the cells of the panniculus adiposis. But this *yellow, fatty* marrow does not occur in all bones. In the bodies of the vertebræ we almost always find the small cells. In the long bones of the adult the fatty marrow always occurs normally, but in pathological conditions it may very rapidly yield up its fat, the elements may divide and we then again have red, but inflammatory, marrow.

In this whole series of allied processes from the first development of marrow out of cartilage until the production of inflammatory marrow—the last disturbance which manifests itself in injured bones (as we see in amputations)—there at no time exists any amorphous substance, blastema or exudation; we can always trace the descent of one cell from another; every one of them has been directly developed from an earlier one, and will have as long as the proliferation continues, a direct progeny of cells.

The second series of transformations in the longitudinal axis of the cylindrical [long] bones is furnished by the osseous tissue, which may arise out of marrow and cartilage. In the one case the marrow-, in the other, the cartilage-cells, become the subsequent bone cells. This act of real ossification, the production of the osseous tissue, is extremely difficult to observe, chiefly for the reason, that what first takes place in the course of these processes, is not the production of real osseous tissue, but only the deposition of calcareous salts. Generally, namely, there first of all takes place in the immediate vicinity of the border of the bone a calcification of the cartilage, which gradually advances, first along the borders of the larger groups of cells, and then around the individual cells, always following the substance of the capsules, so that every individual cartilage-cell is surrounded by a ring of calcareous substance. But this is not yet bone, it is nothing more than calcified cartilage, for, upon dissolving the calcareous salts, the old cartilage is again brought into view—and indeed it offers no analogy to bone in any other respect excepting in the presence of calcareous salts.

Now, in order that this calcified cartilage may become

Fig. 127.

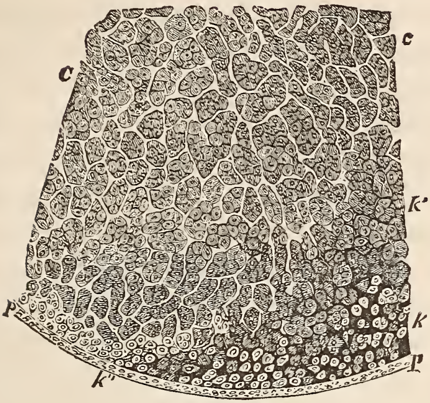


Fig. 128.

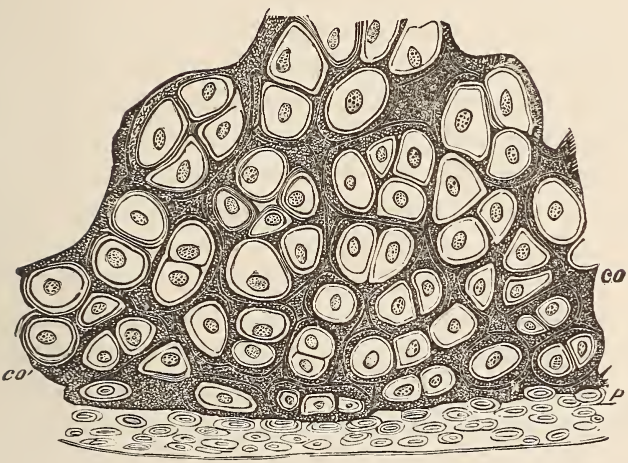


Fig. 127. Horizontal section through the growing cartilage of the diaphysis of the tibia of a seven months' fœtus. *C c.* The cartilage with groups of cells that have undergone proliferation and enlargement; *p p*, perichondrium. *k.* Calcified cartilage, in which the individual groups of cells, and cells, are enclosed in calcareous rings; at *k'* larger rings, at *k''* progress of the calcification along the perichondrium. 150 diameters.

Fig. 128. Right corner of Fig. 127, more highly magnified. *co.* Calcified cartilage *co'* commencement of calcification, *p* perichondrium. 350 diameters.

real bone, it is necessary that the cavity in which every cartilage-cell lies, be converted into the well-known, radiated, jagged bone-cavity [lacuna]. This process is so extremely difficult to obtain a sight of, because on making sections the masses of lime crumble away before the knife, and furnish débris within which it is impossible to see well what really is present. In this circumstance you must seek for an explanation of the fact, that up to the present time there are still, and probably still will be for several years, continual disputes with regard to the mode of origin of bone corpuscles. I hold that view to be correct, according to which the bone-corpuscles* in certain places directly originate out of the the cartilage-corpuscles, and indeed in this way, that in the first place the cavity of the capsule which invests the cartilage-cell, becomes narrower, manifestly because fresh capsular matter is deposited on the inside. But in proportion as this takes place, the inner border of the capsular cavity begins to assume a distinctly indented appearance† (Fig. 133, *c'*) and the space occupied by the original cell is thereby considerably diminished. In rare

* Cartilage-corpuscle = capsule + cartilage-cell; bone-corpuscle = bone-cell.—*Transl.*

† The lacunæ may be said really to have no existence in *living* bone (or osteoid tissue); they are merely the gaps (holes) in the intercellular substance in which the bone- (or osteoid-) cells lie, and are normally so entirely filled by these cells, that it is impossible to give the outlines of both in a drawing. The outline of the cell is the outline of the lacuna. Who, in drawing a deal-board, would ever think of giving a second contour to every knot, in order to represent the outline of the gap which would result from the falling out of the knot! Hence Authors have come to speak of the *nuclei* of lacunæ, whereby of course they mean the nuclei of the cells which fill the lacunæ, but which, thanks to the deeply rooted but erroneous impression left upon their minds by microscopical sections of *macerated* bone, they have failed to recognize, or have not even sought for, taking for granted they had lacunæ before them. In the preparation of sections, however, the cells frequently shrink, so that an interval is left between them and the walls of the lacunæ.

What is here said of the lacunæ of course equally applies to the canaliculi. Both represent the margins of the calcified intercellular substance, where it comes into contact with the bone-cells and their processes.—*Based upon MS. Notes by the Author.*

cases, we still succeed in finding cartilage-corpuscles, in which the capsular cavity has (without the occurrence of calcification) become diminished in consequence of the deposition of new capsular matter, so as to assume the form of a bone cavity (lacuna)—which it generally assumes only after ossification—whilst the old cellular element (the cartilage-cell with its nucleus) still remains in it. After this—still without the occurrence of any calcification—the boundary disappears which originally existed between the capsules of the cartilage-cells and the basis-substance, and we find jagged elements* (the future bone-cells) in an apparently entirely homogeneous substance—in other words, a tissue still soft, though in structure like bone (osteoid tissue, Fig. 133, *o*). Usually this process is concealed by means of the early calcification of the cartilage and only certain processes, for example, rickets, give us the opportunity of seeing the osteoid transformation take place in just the same manner in those parts of the cartilage also which are beginning to calcify.

But the old limits of the capsule still represent the real district which is under the sway of the bone-corpuscule, and, as I pointed out to you at the commencement of my lectures (p. 41) with an especial reference to this point, in pathological conditions this district comes again not only in force but also into view. Within these limits we see the bone-corpuscle accomplish its peculiar destinies. If, for example, the bone is by any cause impelled to enter

* The cartilage-cells (and the same holds good of the marrow-cells) during ossification throw out processes (become jagged) in the same way that connective-tissue corpuscles, which are also originally round, do, both physiologically and pathologically. These processes—which in the case of the cartilage-cells are generally formed after, but in that of the marrow-cells frequently before, calcification has taken place—bore their way into the intercellular substance, like the villi of the chorion do into the mucous membrane and into the vessels of the uterus, or like the pacchionian granulations (glands) of the pia mater of the brain into (and occasionally *through*) the calvarium.—*From a MS. Note by the Author.*

upon new transformations, one bone-corpuscle after another with its territory experiences the change. At the border of necrosed portions of bone, when the line of demarcation forms, we may distinctly observe, that the surface of the bone, when viewed along the edge, becomes marked with excavations, the extent of which corresponds to the original cells. Upon the surface vacuities are observable, which in some instances run together and form holes. The bone-corpuscle which formerly occupied the site of the hole has, in proportion as it under-

Fig. 129.*

Fig. 129. Line of demarcation in a piece of necrosed bone from a case of pædarthrocase; † *a*, *a*, *a* the necrosed bone with very much enlarged osseous corpuscles and canaliculi; here and there slight indications of excavations upon the surface. *b*, *b*. The vacuities, which have taken the place of the cell-districts of the bone (Cf. Fig. 134), seen at the side of the object on a different level; here and there enlarged bone-corpuscles still to be seen through a layer of basis-substance which covers them. *c*, *c*. Completely empty cavities. 300 diameters.

* The drawing was made from a somewhat thick preparation, and does not represent one level surface, but three different planes which form, as it were, terraces, one above the other. Of these *c* is distinctly in focus; *b* is on a lower (or higher) level, and is less distinctly seen; *a* is lower (or higher) still, and is therefore still more out of focus. Hence it is that the canaliculi (which besides are badly represented), are not clearly seen.—*From a MS. Note by the Author.*

† Necrosis (scrofulous) of the fingers in children.

went transformation itself, also determined the surrounding parts to enter upon the change. These are the processes, without the aid of which it is impossible to comprehend the history of caries. For the whole essence of caries consists in this : the bone breaks up into its territories, the individual corpuscles undergo new developmental changes (granulation, suppuration), and remnants* composed of the oldest basis-substance remain in the form of small, thin shreds in the midst of the soft substance. I traced this out again only to-day in a stump, in which, a fortnight after amputation, periostitis with slight suppuration and incipient peripheral caries was found to exist. When in such a case the thickened periosteum is stripped off, we see, at the moment it quits the surface and the vessels are drawn out from the cortex of the bone, not, as in normal bone, mere threads, but little plugs, thicker masses of substance ; and if they have been entirely drawn out, there remains a disproportionately large hole, much more extensive than it would be under normal circumstances. On examining one of these plugs you will find that around the vessel a certain quantity of soft tissue lies, the cellular elements of which are in a state of fatty degeneration. At the spot where the vessel has been drawn out, the surface does not appear even, as in normal bone, but rough and porous, and when placed

* In ossification (in cartilage) there is a portion of the original intercellular substance of the cartilage—that, namely, which lies between the large groups of cartilage-cells (secondary cells—Tochterzellen)—which, though it belongs to the groups as wholes, yet when these, in the course of ossification, are transformed into a number of isolated bone-cells, becomes, comparatively speaking, almost entirely independent of these cells individually (which have their own *immediate* intercellular substance to attend to, and from most of which it must be separated by a considerable interval), and therefore escapes the changes which befall them. It is this portion (well shown in Fig. 126, where it is represented by the trabeculæ separating the medullary spaces *m*), which remains behind in caries, whilst the *secondary* intercellular substance perishes. In other processes, however, which run a more chronic course (in cancer, for example), everything is destroyed.—*Based upon MS. notes by the Author.*

under the microscope, you remark those excavations, those peculiar holes, which correspond to the liquefying bone-territories. If it be asked therefore in what way bone becomes porous in the early stage of caries, it may be said that the porosity is certainly not due to the formation of exudations, seeing that for these there is no room, inasmuch as the vessels within the medullary canals (Figs. 32, 33) are in immediate contact with the osseous tissue. On the contrary, the substance of the bone in the cellular territories liquefies, vacuities form, which are at first filled with a soft substance, composed of a slightly streaky connective tissue with fattily degenerated cells. If round about a medullary canal the territory of one bone-corpuscle after another liquefies, you will after a time find the canal bounded on all sides by a lacunar structure. In the middle of it the vessel conveying the blood still remains, but the substance around about is not bone or exudation, but *degenerate tissue*. The whole process is a *degenerative ostitis*, in which the osseous tissue changes its structure, loses its chemical and morphological characters, and so becomes a soft tissue which no longer contains lime. The tissue, which fills the resulting vacuity in the bone, may vary extremely according to circumstances, consisting in one case of a fattily degenerating and disintegrating substance (the bone-corpuscles perishing), and in another of a substance rich in cells and containing numerous young cells ; this latter is formed by the division and proliferation of the bone-corpuscles, and the newly produced substance is very analogous to marrow. Under certain circumstances this substance may grow to such an extent, that—if we again borrow our illustration from the surface of the bone, where a vessel sinks in—the young medullary matter sprouts out by the side of the vessel, and appears as a little knob, filling one of the pits in the surface. This we call a *granulation*.

When we examine granulations for the purpose of comparing them with medullary tissue, we find that no two descriptions of tissue more closely correspond. The marrow of the bones of a new-born infant could at any time, both chemically and microscopically, be passed off as a granulation. Granulations are nothing more than a young, soft, mucous tissue, analogous to marrow. There is an inflammatory osteoporosis, which, as has been correctly stated, merely depends upon an increased production of medullary spaces, so that the process which is quite normal in the interior of a medullary cavity, is met with also more externally in the compact cortex. It (the osteoporosis) is distinguished from granulating peripheral caries only by its seat. If you go a step further and suppose the cells, which in osteoporosis are present in moderately large numbers, to become more and more abundant, whilst the intercellular substance constantly becomes softer and diminishes in quantity, we have *pus.* The pus is here no special product, separable from the other products of proliferation and formation ; it is certainly not identical with the pre-existing tissues, but its origin can be directly traced back to the elements of the pre-existing tissue. It is not produced by any special act, by any creation de novo, but its development proceeds from generation to generation in a perfectly regular and legitimate manner.

We have therefore before us a whole series of transformations ; the bone first produced and proceeding from cartilage may undergo a transformation into marrow, then into granulation-tissue, and finally into nearly pure pus. The transitions are here so gradual, that the pus which is in immediate contact with the granulations, constitutes, as is well known, a more mucous, stringy, and tenacious matter, which really contains mucin like the granulation-tissue, and only when we proceed farther outwards, exhibits the properties of completely developed pus. The perfect pus of the surface gradually passes, as we descend, into crude pus, the mucous, tenacious, immature pus of the deeper layers, and what we call *maturation* depends simply upon the gradual conversion of the mucous intercellular substance of the originally tenacious pus, which is allied in structure to granulations, into the albuminous intercellular substance of pure pus. The *mucus* dissolves and the creamy fluid is produced. *The maturation is therefore essentially a softening of the intercellular substance.* So direct is the connection which subsists between development, and retrograde metamorphosis, physiological and pathological conditions.

In just the same manner that the cartilage-cell may become a bone corpuscle, the marrow-cell also may become a bone-corpuscle. In the medullary spaces of bone those marrow-cells which are situated at the circumference, generally assume at a later period a more oblong form, and take a direction parallel to the internal surface of the medullary spaces, and the medullary tissue in this situation has a more fibrous appearance and has indeed been regarded as a medullary membrane, but it should not be separated from the marrow in the centre of the spaces, and only constitutes the most compact layer of the medullary tissue. Now as soon as osseous tissue is about to form, the nature of the basis-substance alters. It becomes firmer, more cartilaginous, and the individual cells appear to lie in largish cavities. Gradually they become jagged, from sending out little processes, and then nothing more is required than that calcareous salts should deposit themselves in the basis-substance—and the bone is complete. Thus here again also the osseous tissue is formed by a very direct transformation; and by the deposition of one such osteoid * layer after another

* Osteoid I call the tissue which, when it takes up calcareous salts, becomes bone,

from the medulla, a compact substance is produced, like that of the cortex, which is always characterized by the lamellar deposition of osseous tissue in the previously existing medullary spaces. The original bone is always pumice-stone-like, and porous ; its porosities become filled by the subsequent development of osseous lamellæ from the layers of the marrow, the process continuing until the vessel, which does not admit of ossification, alone remains.

Now with regard to the development of bones in *thickness*, the process is in itself much simpler, but it is also at the same time very much more difficult to see, because ossification here proceeds very rapidly, and the proliferating periosteal layer is so thin and delicate, that extremely great care is required in order to catch sight of it at all. Pathology furnishes us with an incomparably better opportunity for studying the process than physiology. For it is just the same whether the bone grows physiologically in thickness, or pathologically in consequence of periostitis ; the difference is only one of quantity and time.

When fully developed, the periosteum consists for the most part of a very dense connective tissue which contains an extremely large quantity of elastic fibres, and in which the vessels ramify, before they pass on into the cortex of the bone itself. Now when the growth of the bone in thickness commences, we see that the most internal, vascular layer (of the periosteum) increases in thickness and swells up, and then it is said an exudation has taken place, it being taken for granted, that every swelling proves the occurrence of an exudation, and that the exudation here lies between the periosteum and the bone. But if you set to work and

—in other words, soft, uncalcified, osseous tissue.—*From a MS. Note by the Author.*

analyze the substance deposited, no trace of any plastic exudation is found; the swollen spot appears on the contrary organized in its whole thickness from without inwards, and this most distinctly close to the bone, whilst towards the surface of the periosteum the structural relations can be less readily unravelled. This swelling may under certain circumstance increases to a very considerable extent. In periostitis we do not unfrequently see, you know, regular nodes formed, and one need only recall the more physiological history of callus after fracture. In either of these cases we seek in vain for an exudation. If the thickened layers are traced in the direction of that part of the periosteum which still remains unthickened, we can very distinctly see what Duhamel long ago exhibited in a very beautiful manner, but is forgotten over and over again, namely, that the layers which constitute the thickening are ultimately all of them continued into the layers of the periosteum. As little as the periosteum is unorganized, so little are the thickened layers without organization. Microscopical examination shows at the surface of the bone a slightly striated basis-substance, and in it, numerous,

Fig. 130.

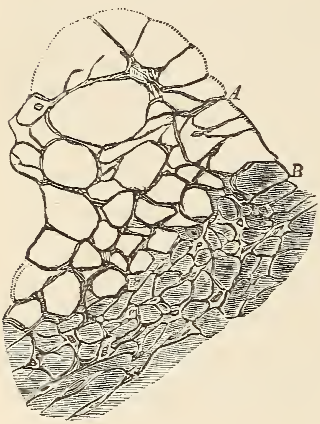


Fig. 130. Vertical section through the periosteum and periosteal surface of a parietal bone from a child. *A.* The proliferating layer of the periosteum with anastomosing networks of cells and division of nuclei. *B.* Formation of the osteoid layer by means of the sclerosis* of the intercellular substance. 300 diameters.

* Sclerosis signifies thickening with condensation.—*From a MS. Note by the Author.*

small, cellular elements ; the farther we recede from the bone, the more do divisions of cells occur, and at last we meet with the simple, very small connective-tissue-corpuscles of the periosteum. The division follows the same course as in cartilage, only that the dividing cells of the periosteum are very delicate. The greater the irritation, the greater also the proliferation, and the more considerable the swelling of the growing spot.

The cells which thus result from the proliferation of the periosteal corpuscles are converted into bone-corpuscles exactly in the way I described when speaking of the marrow. In the neighbourhood of the surface of the bone the intercellular substance grows dense and becomes almost cartilaginous, the cells throw out processes, become stellate, and at last the calcification of the intercellular substance ensues. If the irritation is very great, the corpuscles grow very considerably, and then real cartilage is produced ; the corpuscles enlarge to such an extent that they grow into large, oval or round cells, and each of these forms a capsule around itself by secretion. In this manner cartilage may arise in the periosteum also, by means of a direct transformation of its proliferating layers, but it is by no means necessary that real, true cartilage should be produced ; generally only the osteoid transformation takes place, when the intercellular substance becomes sclerotic and at once calcifies.

Thus it is, that on the surface of every growing bone, as Flourens particularly has shown, new bone is continually deposited layer after layer, and that the new layers grow round the old bone in such a way, that a ring, which is early put around the bone, after a time lies inside it, enclosed by the young layers which have formed outside around it. These are connected with the old bone by means of little columns which give the whole a pumice-stone like appearance, and here too the subsequent condensation into cortical substance is accomplished by means of the formation—within the individual cavities bounded by the little columns—of concentric layers of osseous substance out of the periosteal marrow.

These are the normal and pathological processes which we recognize in the formation of bone. From them you may gather, that we have in them to do with a series of permutations or substitutions, which lead in one case to a higher, in another, to a lower form of structure, but are however constantly connected with one another, and, according to the conditions which operate upon the parts, assume sometimes one aspect, sometimes another. It is in our power to incite individual portions of cartilage to ossify, or to transform themselves into a soft tissue. In this whole series the marrow stands alone as the type of the heterologous forms, inasmuch as it contains the smallest and least characteristic cells. The young medullary tissue presents the same structure as the young formations, with which all heterologous tissues begin, and since, as I have already hinted, it at the same time constitutes the real type of all granulations, it may be said that, *wherever new-formations are about to arise on a large scale, a substitution analogous to the type of young medullary tissue* (*granulation*) *also takes place;* and that, no matter how great the solidity possessed by the old tissue, *a kind of proliferation nevertheless always takes place, which produces the germs of the subsequent elements.*

LECTURE XIX.

APRIL 24, 1858.

PATHOLOGICAL, AND ESPECIALLY HETEROLOGOUS NEW-FORMATION.

Consideration of some forms of pathological formation of bone. Soft osteoma of the maxillæ—Rickets—Formation of callus after fracture.

Theory of substitutive new-formation in opposition to exudative—Destructive nature of new-formations—Homology and heterology (malignity)—Ulceration—Mollities ossium—Proliferation and luxuriation—Medulla of bones, and pus.

Suppuration—Its two forms: superficial, occurring in epithelium; and deep, in connective tissue—Eroding suppuration (skin, mucous membrane): pus and mucus-corpuscles in their relations to epithelium—Ulcerative suppuration—Solvent properties of pus.

Connection of destruction with pathological growth and proliferation—Correspondence of the first stage in pus, cancer, sarcoma, etc.—Possible duration of the life of pathologically new-formed elements, and of pathological new-formations considered as wholes (tumours)—Compound nature of the larger tuberous* tumours (Geschwulstknoten), and miliary character of the real foci (Heerde)—Conditions of growth and recurrence: contagiousness of new-formations and importance of the anastomoses of cells—Cellular pathology in opposition to the humoral and neuristic—General infection of the body—Parasitism and autonomy of new-formations.

Gentlemen,—I will to-day begin by laying some pathological preparations before you, for which I remained in your debt last time.

I begin with an interesting object which has lately come into my hands, and exhibits with a distinctness

* Tuberous, in contradistinction to infiltrated, tumours (infiltrations).—*From a MS. Note by the Author.*

which I have rarely had occasion to witness, the transitions from periosteal connective tissue into osteoid tissue, and this too with a peculiar modification, inasmuch as calcification has not taken place in large portions of the parts which already possess a structure of bone. The preparation comes from a tumour in the jaw of a goat, and contributes towards our knowledge of the transitions from connective tissue into osteoid tissue about the same information, that the history of rickets has supplied us with concerning the transformation of cartilage. The tumour which affected the superior and inferior maxillæ, but each separately, has such little density, that it can be cut with great facility, and only in a few places does the knife meet with greater resistance. On making thin sections, we see, even with the naked eye, that the more and less dense portions alternate with each other, so that the whole has a reticular appearance. When examined under the microscope with a low power,

Fig. 131.

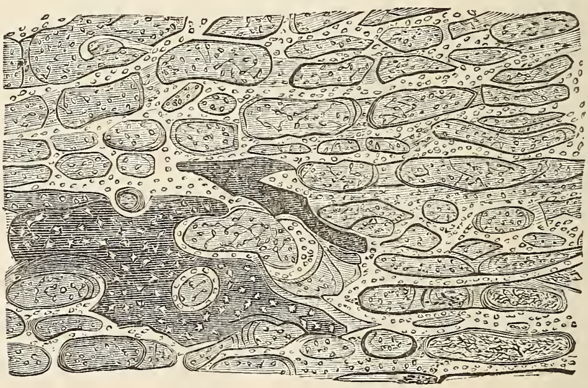


Fig. 131. Section from the soft osteoma from the jaw of a goat—showing the characters of periosteal ossification. Networks of osteoid trabeculæ with jagged cells enclose primary medullary spaces, filled with fibrous connective tissue. The dark parts represent calcified and completely developed osseous tissue. 150 diameters.

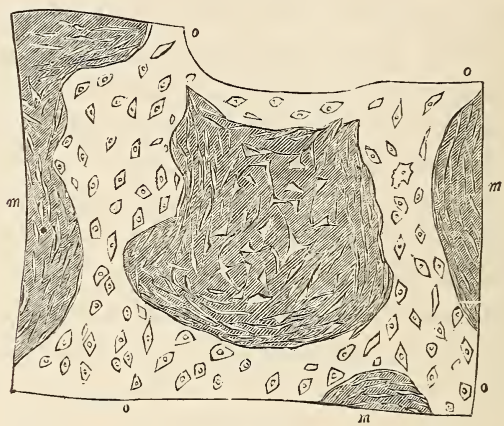
it is at once perceived that the disposition of the constituent parts is entirely that of a bone, for (primary*) medullary spaces and trabecular networks alternate with each other, just as if the observer had before him the medullary spaces and trabeculæ of a spongy bone. The substance which forms the trabecular networks, is on the whole dense, and is therefore readily distinguishable, even with a low power, from the more delicate substance which is enclosed by the trabeculæ and fills the cavities of the meshes. This latter substance presents, when more highly magnified, a finely striated fibrous appearance. The bands of fibres in part run parallel to the borders of the trabeculæ. In these latter the same structures can be seen with a high power, that are usually presented by the bone, namely jagged corpuscles, distributed with great regularity.

This structure exactly corresponds to that which we have seen in the development of bone from periosteum; it is, in short, the plan followed in the growth of bone in thickness. Wherever young periosteal deposits are examined, there is found in the meshes of the network, formed by the osteoid substance, this primary marrow containing fibres, but no cells, as is the case at a later period. This primary marrow consists of the remains of the periosteum itself (after its proliferation), which have not yet undergone the transformation. The transformation into osteoid tissue advances into the proliferating periosteum in the first instance always in such a way,

* The *primary* medullary spaces formed out of *periosteum* are subsequently all filled with compact bone, and it is by the conversion of this into true mucous medullary tissue, abounding in cells (which afterwards take up fat) that the *secondary* medullary spaces are formed. Of the primary medullary spaces formed out of *cartilage*, however, a considerable number do not pass through any such intermediate stage as that just described as occurring in periosteal ossification, but become *at once* filled with true medullary tissue and are therefore equivalent to the ordinary, *secondary* medullary spaces.—*From a MS. Note by the Author.*

that the fibrous tissue becomes condensed (sclerotic), though only partially so, the condensation beginning at the bone and proceeding outwards in certain directions; in this way there arise, at first resting like columns upon the bone, hardish cones * which are united by transverse bands, parallel to the surface of the bone, and thus con-

Fig. 132.



stitute this network. If now acetic acid be applied to these parts, we see at once that the whole fibrous mass which fills the alveoli, contains the most wonderful connective-tissue-corpuscles, which are so arranged, that next to the trabeculæ all around they lie in concentric rows, whilst in the most internal parts of the marrow they constitute stellate corpuscles which anastomose with one another, as you have already seen on many occasions. But that in some parts the trabeculæ have already become true bone, one may very beautifully convince

Fig. 132. A portion of Fig. 131, more highly magnified. *o*, *o*. The osteoid trabeculæ; *m*, *m*, *m* the primary medullary spaces with spindle-shaped and reticulating cells. 300 diameters.

* These are the little columns mentioned in p. 110 as being perpendicular to the long axis of the bone, and as intervening between the Haversian system—*Transl.*

oneself at the spots, where calcareous salts are really deposited in them. Whilst the periphery of such calcified trabeculæ (Fig. 131) offers a brilliant, almost cartilaginous appearance, in their middle an opaque, finely granular matter presents itself which pervades the intercellular substance, and towards the interior of the trabeculæ passes into a nearly homogeneous, calcareous layer, in which at intervals the osseous corpuscles may be recognized. Here we have therefore already a complete osseous network, and at the same time an exact picture of the regular growth of bone in thickness.

If, however, the spots are very carefully examined, where the borders of these trabeculæ and bands of bone come into contact with the fibrous substance of the meshes, it is seen that no perfectly defined limit exists there, but that the intercellular substance of the osteoid tissue is gradually lost in the intercellular substance of the fibrous marrow, so that here and there a few of the connective-tissue-corpuscles of the fibrous connective tissue are included in the sclerotic substance of the trabeculæ. Hence you may infer, that the formation of the real osseous substance from connective tissue is essentially effected by the gradual change of the intercellular substance, and that this loses its originally fibrous nature and becomes converted into a dense, shining, cartilaginous mass, without its ever really attaining however to the structure of cartilage. Here there is never a stage exactly corresponding to any of the known forms of cartilage, but it is out of connective tissue that we see the osteoid substance directly arise, which in cartilage also and marrow is the first to arise when they become bone. This is so far very important, that you can from all these instances acquire the conviction that people have been mistaken in speaking of the cartilage of bone (Knochenknorpel). Cartilage as such can only calcify ; when it is to become bone, a transformation of its tissue must take place, the chondrine-containing basis-substance must become converted into a gelatine-yielding intercellular substance.

I have, moreover, gentlemen, made a series of preparations from ricketty bones for you—on the one hand, because rickets above all offers an especially favourable opportunity for obtaining an insight into several processes of the normal growth of bone, which in other cases are obscured by the presence of calcareous salts—and on the other hand, because you will thus form some idea of the peculiarity of this process, as such.

Rhachitis, has, as you are aware, by more accurate investigation been shown to consist not in a process of softening in the old bone, as it had previously generally been considered to be, but in the non-solidification of the fresh layers as they form ; the old layers being consumed by the normally progressive formation of medullary cavities, and the new ones remaining soft, the bone becomes brittle. But besides this essential feature of the non-occurrence of calcification in the parts, there is displayed also a certain irregularity in growth, so that stages in the development of bone which, when the formation is normal, ought to set in late, set in at a very early period. In normal growth, the pointed processes, in which shape the calcareous salts shoot up into the cartilage, form, along the margin of calcification, such a completely straight line, that it should almost be described as mathematically regular. This condition ceases to obtain in rickets, and the more so, the greater the severity of the case ; interruptions occur in such a way, that in some places the cartilage still reaches a long way down, whilst in others the calcification has mounted up to a considerable height. These uncalcified parts sometimes become so completely separated from one another, that they remain forming specks of cartilage in the midst of the bone, and surrounded on all sides by it—and that cartilage is still found at points where the bone ought long since to have become transformed into medullary tissue. The farther the process advances, the more, however, do we also meet with isolated, scattered masses of lime in the cartilage, in many instances to such a degree, that the whole of the cartilage on section appears dotted with white points. The irregularity of the process is further shown in this, that whilst in the normal course of things the medullary spaces should begin to form only at a short distance behind the margin of calcifiation (Fig. 126), they here exceed these limits, and in many cases a series of connective cavities extends far beyond the border of calcification, which are filled with a soft, slightly fibrous tissue, and besides have vessels running up into them. Medullary spaces and vessels are therefore met with, where normally and properly not a single medullary cell, and scarcely a single vessel ought to be found.

In this manner there may at all times be found side by side in the parts, where the process has attained its height, a whole series of different histological conditions. Whilst in other cases we find at a certain definite point cartilage, at another calcification, at a third, bone, or medullary tissue, here everything lies in the greatest confusion; in one place, medullary tissue, above it osteoid tissue, or bone, by its side calcified cartilage, and below it, perhaps, cartilage still retaining its original condition. The whole of the rhachitic portion of the diaphysal cartilage—and it may extend for a considerable distance—of course acquires no real firmness, and this is one of the chief causes of the liability to distortion, which ricketty bones exhibit, not in the continuity of the diaphyses, but at the articular ends. This is in many cases extremely considerable and is the sole cause of many a deformity, as, for example, in the thorax. The curvatures in the continuity of the bones are always infractions,* those of the epiphyses are due to the proliferation of the cartilage and constitute simple inflexions ; and it is easy to conceive that parts, which are so entirely deprived of their regular development (as they are in rickets), and ought, properly, to be densely impregnated with calcareous salts, must retain great mobility.

Fig. 133.

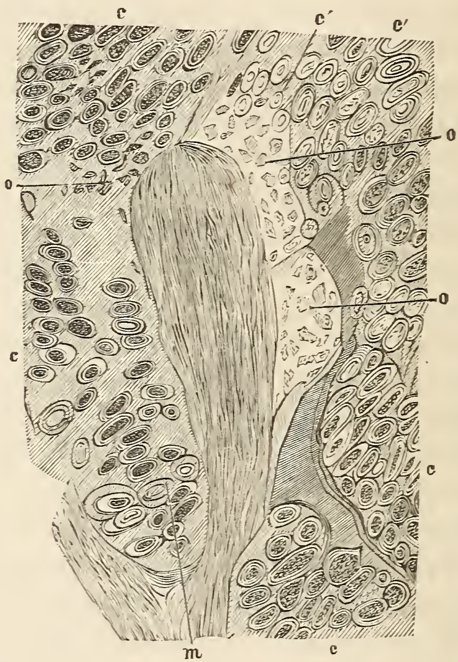


Fig. 133. Vertical section of cartilage from the diaphysis of a ricketty, growing tibia from a child two years old. A large conical process of medullary tissue, sending out a lateral band on the left side, extends from *m* up into the cartilage ; it consists of fibrous basis-substance with spindle-shaped cells. At the circumference, at *c*, *c*, *c* the cartilage in a state of proliferation with large cells and groups of cells; at *c′*, *c′* commencing thickening and internal indentation of the cartilage-capsules which at *o*, *o* coalesce and form osteoid tissue. 300 diameters.

* By infraction I understand an incomplete fracture (solution of continuity) *within* the periosteum, which remains intact.—*From a MS. Note by the Author.*

The enlargement and multiplication of the individual cells takes place in the same manner, as in the cases we have already considered ; but inasmuch as at a later period individual parts in the cartilages, that properly ought to have become bone, do not calcify, and especially a formation of medullary spaces often takes place a long way up above the border of calcification—in many of these rhachitic parts the whole history of the development of bone is clearly revealed in a connected form. Large and often very vascular conical processes of fibrous medullary tissue are seen extending upwards from the bone into the cartilage, and it may be very distinctly perceived, that these processes do not force their way into the cartilage from without, but that they owe their origin to a fibrillation of the intercellular substance of the cartilage itself. It is around them chiefly that the osteoid transformation of cartilage also can best be seen, and particularly that the gradual conversion of a cartilage-corpuscle into a bone-corpuscle can very distinctly be witnessed. Out of the cartilage-corpuscle which has a moderately thick capsular membrane, arises a structure, provided with a capsule continually increasing in thickness, within which the space for the cell constantly grows smaller, and which, when it has attained a certain degree of thickness, acquires indentations on its inner wall, like the so-called dotted canals of vegetable cells. Such is the mode in which the first rudiments of the bone-corpuscle are traced, after which a fusion of the capsule with the basis-substance very generally ensues, and with the production of anastomosing processes from the cells the formation of the bone-corpuscle is completed. At times isolated osteoid cartilage-corpuscles calcify alone without the occurrence of any fusion ; and whilst between them lies the ordinary intercellular substance of cartilage, the capsules of the osteoid corpuscles fill themselves completely with calcareous salts. In other places on the contrary the fusion of the capsules with the intercellular substance takes place very rapidly ; the new intercellular substance formed by this fusion assumes a coarsely fibrous appearance, and in the place of several groups of cartilage-cells we see a fibrous mass, containing jagged osseous (bone-), or osteoid corpuscles. There is therefore no sharply defined boundary in the tissue, but the condensed or fibrous substance, which surrounds the jagged bodies, is directly continuous with the translucent substance which holds the cartilage together. Essentially, however, it is the same structure.*

This isolated transformation of single cartilage-cells into bone corpuscles is obviously of the greatest impor-

Fig. 134.

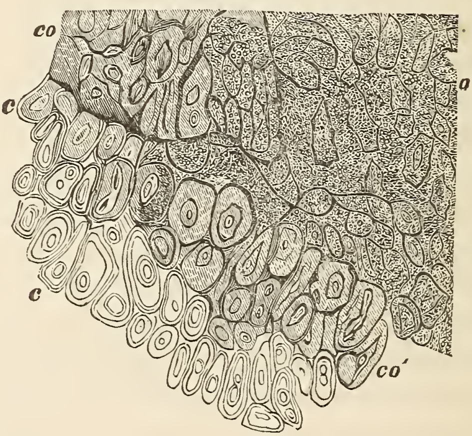


Fig. 134. Insular ossification in ricketty diaphysal cartilage. *c*, *c*. Ordinary growing (proliferating) cartilage, *c′*, increasing thickening of the capsules with formation of an indented cavity (osteoid cartilage-cells), *co′*, calcification of similar, still isolated cartilage-cells, *co*, commencing fusion of the capsules of calcified cartilage-cells, *o*, osseous substance. 300 diameters. (Cf. Archiv. f. path. Anat, Vol. XIV., Plate I.

* The following section, including the history of the formation of callus, has been transferred to this place from the next lecture, inasmuch as a better understanding of it is thus insured.

tance to the cellular theory in general. In this specimen (Fig. 134) the whole series of these processes is seen at a glance. Where the completely ossified portion, in which the bone-corpuscles are developed with perfect regularity, adjoins the cartilage, you see a zone where the conversion of cartilage-corpuscles into perfect osseous substance may be viewed within the limits of a very short space. At the point of transition a number of corpuscles are found lying close to one another like hazel-nuts—distinguished from ordinary cartilage-corpuscles by their dark contours, hard appearance, and unusually great brilliancy, and enclosing in a small, indented cavity a little cell; these little cells are the still isolated* bone-corpuscles with calcified capsules which they have retained from that earlier period in their existence when they were cartilage-cells. It is especially important that you should see these bodies thus isolated—in situ, in order that you may comprehend those other processes, in which in bone the territories† belonging to the bone-cells fall out (p. 462, Fig. 129). When an object of this kind has once been accurately examined, it is impossible that doubts can any longer arise as to whether cartilage-cells can become bone-corpuscles, and I cannot conceive how it is that even the most recent (and those very careful) observers still start the question, whether bone-corpuscles are not *in all cases* structures obtained by a circuitous route, and not directly produced from cartilage-corpuscles. It is

* Isolated, because their capsules have not yet become fused with the basis-substance.—*From a MS. Note by the Author.*

† In bone formed *directly* (i. e., without the intervention of medullary tissue) out of cartilage, the territories of the bone-cells correspond to the cartilage-capsules. But when bone is developed out of any other tissue, the limits of these territories cannot be distinguished at all during growth, and it is only when gaps arise (through disease) in the bone around the bone-cells that these limits are defined.—*From a MS. Note by the Author.*

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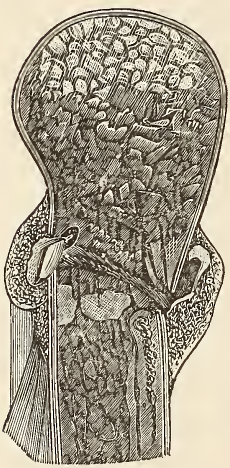
no doubt true, that in the case of the normal growth in length of bone most of the bone-corpuscles do not directly proceed from cartilage-corpuscles, but are immediately derived from marrow-cells and only mediately from cartilage-cells; but it is just as true that cartilage-cells also can be transformed straightway into bone-corpuscles. It is now a long time since I called attention to one spot in particular, where the conversion of cartilage into osteoid tissue can be very distinctly viewed, namely at the points of transition from cartilage to perichondrium in the neighbourhood of the border of calcification of growing bones. Here the boundaries between the different forms of tissue are completely obliterated, and all sorts of transitions between round (cartilaginous) and jagged (osteoid) cells are seen.

The next preparations have reference to the *pathological new formation of bone*, or, if you will, to the *physiological formation of callus.* They are derived from a very recent fracture of the ribs, around which a thick mass of callus has been deposited. In reference to this process I will add a few words, as it is one that has been much discussed and is very important in a surgical point of view.

You have seen from what I have just been describing to you, that there are several ways in which the new formation of bone is effected, and that the old supposition that either the one or the other mode must be considered as the only prevailing one, is incorrect. The pre-existence of cartilage is by no means necessary for the formation of bone; on the contrary, an osteoid substance is very frequently formed by a direct sclerosis in connective tissue, nay, ossification is thus really more easily effected than when it takes place in real cartilage. We see also by the history of the theories concerning callus, that the endeavour to show that it is always developed in the same way or out of the same substance (*e. g.* extravasated blood, periosteum, medullary tissue, exuded fluids, etc.) has proved the greatest obstacle to the true perception of the real state of things, and that all have really had right upon their side, inasmuch as new bone in fact builds itself up out of the most different materials. Unquestionably, when the case runs a very favourable course, that path is chosen in which the new formation can be most conveniently effected, and it is by far the most convenient way, when the periosteum produces a very large portion of the whole. This takes place in the following manner: the periosteum grows dense towards the edges of the fracture, and there gradually swells up, the swelling being of such a nature, that separate layers or strata can afterwards pretty clearly be distinguished in it. These continually become thicker and more numerous, in consequence of the constant proliferation of the innermost parts of the periosteum—and of the formation, by means of a multiplication of their cellular elements, of new layers, which accumulate between the bone and the relatively still normal parts of the periosteum. These layers may become cartilage, but it is not necessary, nor yet the rule. For we find that, in the greater number of favourable cases of fracture, where cartilage is produced, not the whole mass of the periosteal callus is produced from cartilage, but a greater or less portion of it is always formed out of connective tissue. The layers of cartilage generally lie next to the bone, whilst the farther we proceed outwards, the less does the formation out of cartilage, and the more a direct transformation of connective tissue, prevail.

The formation of bone is, however, by no means restricted to the limits of the periosteum—very commonly it extends beyond them in an outward direction, and often penetrates, in the form of spicula, nodules, and protuberances, to a very considerable depth into the neighbouring soft parts. It is self-evident that in these cases we have by no means to deal with any proliferation of the periosteum in any outward direction, but that an ossifiable tissue arises out of the interstitial connective tissue of the neighbouring parts. Of this it is very easy to convince oneself, because osseous spicula are found shooting up in the interstitial tissue of the neighbouring muscles. In the preparation from the fractured ribs places are still to be found in the external parts, where fat has been included in the ossification. It cannot be said therefore that the formation of callus around fractured parts is altogether a periosteal formation; in all cases where it takes place with a certain abundance, it transgresses the limits of the periosteum, and invades the connective tissue of the surrounding soft parts.

Fig. 135.



There is a second kind of callus-formation completely different to this — that namely, which takes place in the midst of the bone *from the medullary tissue.*

At the moment when the bone in a case of fracture

Fig. 135. Transverse fracture of the humerus with formation of callus, about fourteen days old. On the outside is seen the porous capsule of the callus produced from the periosteum and soft parts, the innermost layer on the right side being still cartilaginous. On the left lies detached a fragment shivered off from the cortex of the bone. The two fractured ends are connected by a (dark-red) fibrinous layer of hæmorrhagic origin; the medulla on both sides is very dark (owing to hyperæmia and extravasation), in the lower fragment several porous islands of callus are seen which have been produced by the ossification of the medulla.

is shivered, a number of little medullary spaces are naturally opened. In the neighbourhood of these, the still closed medullary spaces are seen nearly invariably, when matters follow a regular course, to become filled with callus, new lamellæ of bone attaching themselves to the internal surface of the osseus trabeculæ which bound the spaces, just as in the ordinary growth of bone in thickness, the originally pumicestone-like layers become compact by the deposition of concentric lamellæ. In this manner it happens, that after some time a larger or smaller new layer of bone is found, filling up the end of the medullary canal of each fragment, so as to occasion its occlusion. This is a kind of a new formation which has nothing in common with the former one, as far as their starting points are concerned, but has its origin in quite another tissue, and is altogether different in its palpable result, inasmuch as it produces, within the confines of its own bone, a condensation of that portion of the marrow which lies in the immediate vicinity of the fracture. Even in cases where the ends of the bones perfectly coincide, an internal formation of bone such as I have described takes place in the medullary canal of each fragment, producing its occlusion.

These two kinds are the usual and normal ones. Around the two fractured ends the swelling takes place, in the interior, the condensation. Gradually, in proportion as the extravasated blood is absorbed—the new masses of tissue which have been developed between the broken ends draw nearer to one another, and round about the fracture forms a bridge- or capsule-like communication by means of the ossification of the soft parts. There is therefore but little reason to ask whether the callus proceeds from free exuded or extravasated matter. No doubt an extravasation takes place in the first instance into the space between the fractured ends, but the extravasated blood is generally pretty completely reabsorbed, and it contributes comparatively but very little to the real formation of the subsequent uniting media.

We discussed, gentlemen, last time, the chief points in the history of new-formations. You remember that, according to our ideas, every kind of new-formation—inasmuch as it has its origin in pre-existing cellular elements and takes their place—must necessarily be connected with a change in the given part of the body. It is no longer possible to defend an hypothesis such as that which, based upon the supposed existence of plastic matters, was formerly maintained, namely, that a substance was deposited *between and upon* the existing elements of the body, which produced a new tissue out of itself and thus represented a clear accession to the body. If it is true that every new-formation proceeds from definite elements, and that usually divisions of the cells are the means by which the new-formation is produced, it becomes of course self-evident that *where a new-formation takes place, certain histological elements of the body must generally also cease to exist.* Even a cell, which simply divides and out of itself produces two new cells like itself, thereby ceases to exist, even though the whole result is only the apparent apposition of a cell. This holds good for all kinds of new-formations, both for benignant as well as for malignant ones, and it may therefore in a certain sense be said, that *every kind of new-formation is really destructive, and that it destroys something of what previously existed.* But we are, as it is well-known, accustomed to judge of destruction according to the more obvious effects produced, and when we speak of destructive formations, we do not so much mean those, in which the result of the new-formation is analogous to the old one, as some product or other deviating more or less from the original type of the part. This is the point of view to which I have already (p. 93) directed your attention when treating of the classification of pathological new-formations. By it is a reason, sensible and in correspondence with the facts, afforded for the separation of *all new-formations into homologous and heterologous ones.*

Heterologous we may call not only malignant, degenerative neoplasms, but we must also thus designate every tissue which deviates from the recognized type of the part, whilst we should call all that homologous, which, although new-formed, still reproduces the type of its parent soil. We find, for example, that the so extremely common form of uterine tumour, which has been designated fibrous or fibroid, has in every respect the same structure that the walls of the "hypertrophied" uterus have, inasmuch as it consists not only of fibrous connective tissue and vessels, but also of muscular fibre-cells. The tumour may, as it is well-known, become so large, as not only to embarrass the uterus in all its functions in an extreme degree, but also to exercise through pressure the most injurious influence upon the neighbouring parts. In spite of this, it must always be considered an homologous structure. On the other hand we cannot help employing the term heterologous formation, as soon as, by means of a process which at first seems to represent a simple multiplication of the parts, a result is obtained which is essentially different from the original condition of the spot. A catarrh for example in its simple form may be attended by a multiplication of the cellular elements on the surface of the mucous membrane, without the new cells' being essentially different from the pre-existing ones. Thus I brought along with me for you last time a vagina with very marked leucorrhœa. You saw there no doubt that the cells in leucorrhœa very closely resemble those of epithelium of the part, although they no longer entirely retain the typical form of pavement epithelium. The less, however, they approach in their development the typical forms of the epithelium of the part, the more incapable do they become of performing their functions. They are moveable upon a surface, to which they ought properly to adhere, they flow down* and produce results which are incompatible with the integrity of the parts.

In the narrower sense of the word heterologous new-formations are no doubt alone destructive. The homologous ones may accidentally bec ome veryinjurious, but still they do not possess what can properly be called a destructive (in the unscientific and traditional sense of the word), or malignant character. On the other hand every kind of heterologous formation, whenever it has not its seat in the entirely superficial parts, has a certain degree of malignity clinging to it. And even superficial affections, though entirely confined to the most external layers of epithelium, may gradually exercise a very prejudicial influence. Let us only reflect what happens when a large surface of mucous membrane continually secretes, and heterologous products are constantly engendered upon it which do not become persistent epithelium, but continually keep flowing down from the surface of the mucous membrane. In such a case, in addition to the blennorrhœa (and its consequences, anæmia, neuralgia, etc.), we find erosions.

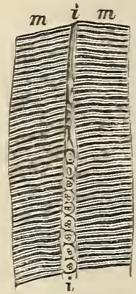
It seems to me important that I should bring before you a definite example of the mode in which destruction in its more obvious forms is effected, in order that you

* Καταρρέω (catarrh).

may see how it leads to ulceration and to the formation of cavities in the interior of parts. It does indeed appear like a contradiction to say that a process, which produces new elements, destroys, but this contradiction nevertheless is merely a seeming one. If you imagine in a part, which had previously been firm, a new-formation to arise of which the individual constituents are loose and easily moveable one upon the other, the process will of course always be attended by a very important change in the usefulness of the part. The simple conversion of bone into medullary tissue (pp. 452, 453) may become the cause of great fragility in the bones, and *osteomalacia* [mollities ossium] essentially depends upon nothing else than the conversion of compact osseous substance into medullary tissue. An excessive formation of medullary spaces gradually advances from the interior of the bone towards the surface, deprives the bone of its firmness, gives rise to a tissue in itself quite normal, but of no service in maintaining the necessary firmness of the parts, and thus in some sort inevitably leads to a loss of cohesion. Marrow is an extraordinarily soft tissue, which in those conditions, where it is red and rich in cell, or atrophied and gelatinous, becomes nearly fluid. From marrow to perfectly fluid tissues is only a short step, and the boundaries separating marrow and pus cannot in many places be assigned with any degree of certainty. Pus is in our eyes a young tissue, in which, amidst the rapid development of cells, all solid intercellular substance is gradually dissolved. A single connective-tissue cell may in an extremely short space of time produce some dozens of pus-cells, for the development of pus follows an extremely hurried course. But the result is of no service to the body, *proliferation becomes luxuriation.* Suppuration is a pure process of luxuriation, by means of which superfluous parts are produced, which do not acquire that degree of consolidation, or permanent connection with one another and with the neighbouring parts, which is necessary for the existence of the body.

If now in the next place we investigate the *history of suppuration*, we immediately discover that we must distinguish two different modes of pus-formation, according namely as the pus proceeds from tissues of the first two kinds mentioned in our classification (p. 55), i. e., *from epithelium or from connective tissue.* Whether there are also forms of suppuration proceeding from a tissue of the third class, from muscles, nerves, vessels, etc., is at least doubtful, because of course the elements of connective tissue which enter into the composition of the larger vessels, the muscles and the nerves, must be eliminated from the really muscular, nervous and vascular (capillary) elements. With this reservation we can for the present only maintain the possibility of two modes of pus-formation.

Fig. 136.



As long as the pus is formed out of epithelium, it is naturally produced without any considerable loss of substance and without ulceration. But this is in every instance the case, where pus is produced in connective tissue. The real state of the matter therefore is exactly the reverse of what it was previously imagined to be, when a solvent property was ascribed to pus. *Pus is not the dissolving, but the dissolved, i. e., the transformed, tissue.* A part becomes soft, and liquefies whilst suppurating, but it is not the pus which occasions this softening, on

Fig. 136. Interstitial purulent inflammation of muscle in a puerperal woman. *m*, *m*. Primitive muscular fibres. *i*, *i*. Development of pus-corpuscles by means of the proliferation of the corpuscles of the interstitial connective tissue. 280 diameters.

the contrary, it is the pus which is produced as the result of the proliferation of the tissue.

The development of pus we daily see upon different surfaces, both on the skin, and on mucous and serous membranes. We can observe its development most surely where stratified epithelium naturally exists. If you follow the development of pus upon the *skin*, when the process is unaccompanied by ulceration, you will constantly see that the suppuration proceeds from the rete Malpighii. It consists in a growth and development of new cells in this part of the cuticle. In proportion as these cells proliferate, a separation of the harder layers of the epidermis ensues, and they are lifted up in the form of a vesicle or pustule. The place where the suppuration chiefly occurs corresponds to the superficial layers of the rete, which are already in process of conversion into epithelium ; if the membrane of the vesicle be stripped off, these (layers) usually adhere to the epidermis and are stripped off with it. In the deeper layers we may watch how the cellular elements, which originally have only a single nuclei, divide, how the nuclei become more abundant, and single cells have their places taken by several, which in their turn again provide themselves with dividing nuclei. Here too people have generally helped themselves out of the difficulty by assuming that in the first instance an exudation was poured out, which produced the pus in itself, and this is the reason why, as you well know, most investigators into the development of pus especially selected fluids which were secreted from injured surfaces. It was very conceivable that, as long as no doubts were entertained with regard to the discontinuous formation of cells, the young cells should without more ado be looked upon as independent new-formations, and that the notion should be entertained that germs arose in the exuded fluids, and gradually becoming more numerous, supplied the pus. But the matter is on this wise, that, the longer the suppuration lasts, the more certainly is one series of cells after the other in the rete involved in the process of proliferation, and that, whilst the vesicle is rising up, the quantity of the cells which grow into its cavity is constantly becoming greater. When a variolous pustule forms, there is at first only a drop of clear fluid present, but nothing arises in it ; it only loosens the neighbouring parts of the rete Malpighii.

Precisely the same is the case with *mucous membranes.* There is not a single mucous membrane which may not under certain circumstances furnish puriform elements. But here too a certain difference always presents itself. A mucous membrane is all the more in a condition to produce pus without ulceration, the more completely the epithelium it possesses is stratified. All mucous membranes with a single layer of cylindrical epithelium (intestines),* are much less adapted for the production of pus ; that which is produced on them, even though it have quite the appearance of pus, frequently turns out upon close examination to be only epithelium. The intestinal mucous membrane, especially that of the small intestine, scarcely ever produces pus without ulceration. The mucous membrane of the uterus, and of the fallopian tubes, though it is frequently covered with a thick mass of quite a puriform appearance, almost always secretes †

* In the air passages (nose, larynx, trachea, bronchi) we commonly find several layers of cylindrical epithelium lying one above the other.—*From a MS. Note by the Author.*

† *Secrete* in this and similar places does not of course mean to separate from the *blood*, but from the *tissue itself*, whose elements (cells) are *separated* (detached) at the surface, and, when mixed with the serous effusion from the blood, removed. The detachment of the cells is effected sometimes by means of the fluid which transudes from the blood, sometimes by the continual growth of a succession of new cells beneath them, and sometimes in consequence of their own round form. In desquamation of the cuticle the second of these methods, in several forms of catarrh the

epithelial cells only, whilst on the other mucous membranes, as for example on that of the urethra, we see enormous quantities of pus secreted, as in gonorrhœa (Fig. 63) without even the slightest ulceration being present on the surface. This depends essentially upon the presence of several strata of cells, the upper forming a kind of protection to the deeper ones, of which the proliferation is thus for a time secured. The pus is at last either borne away by the production of new masses of pus beneath it, or there occurs simultaneously a transudation of fluid, which removes the pus-cells from the surface, just as in the secretion of semen the epithelial elements of the seminal tubules furnish the spermatozoa, and in addition a fluid transudes which sweeps them away. But the spermatozoa do not arise in the fluid—this is only the vehicle for their onward movement. In this manner we frequently see fluid exude on the surface of the body, without our being able to regard it as a *cyto*blastema. If a proliferation of epithelium simultaneously takes place upon the surface, the elements detached by the transuded fluid will also be found to consist of nothing but proliferating epithelium.

If now *pus-*, *mucus-* and *epithelial cells* be compared with one another, it appears that there certainly does exist a series of transitional forms, or intermediate stages, between pus-corpuscles and the ordinary epithelial structures. By the side of perfectly formed pus-corpuscles, provided with several nuclei, are very commonly found somewhat larger, round, granular cells with single nuclei, the so-called mucus-corpuscles (Fig. 11 *B*) ; a little further on we see perhaps still larger cells of a typical form and with single, large nuclei, and these we call epithelial cells. But the epithelial cells are flat, angular, or cylindrical,

third, on many serous membranes, the first, is the one pursued. Any two, or all three of them, however, may of course coincide.—*From a MS. Note by the Author.*

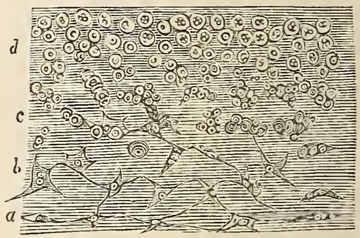
whilst mucus- and pus-corpuscles under all circumstances remain round. Even from this circumstance may be derived an explanation of the fact that, whilst the epithelial cells, which cover, and are in close apposition to, one another, acquire a certain firmness of cohesion, mucus- and pus-corpuscles which lie but loosely one against the other, and are of a spherical shape, retain a great degree of mobility and are easily displaced.

It has been said before now that mucus-corpuscles are nothing more than young epithelium ; another step and pus-corpuscles would be nothing more than young mucus-corpuscles. This is a somewhat erroneous notion. It cannot be maintained that a cell, which up to the point when it becomes a so-called mucus corpuscle has preserved its form as a spherical body, is still in a condition to assume the typical form of the epithelium, which ought to exist in the part ; and just as little can it be said that a pus-corpuscle, after it has developed itself in the regular manner, is capable of again entering upon a course of development calculated to produce a relatively permanent element of the body. The cells, in which the development of epithelial, mucus-, and pus-cells originates, are young forms, but they are not pus-corpuscles. In pus every new cell at a very early period sets about dividing its nucleus ; after a short time the division of the nucleus reaches a high pitch, without any further growth on the part of the cell. In mucus the cells are wont merely to grow, and in some instances to become very large, but they do not pass certain limits, and above all they do not assume any typical form. In epithelium, on the contrary, the elements begin even at a very early period, to assume their particular form, for " what is to become a hook, right early gets a crook." The very youngest elements however, which are found in pathological conditions, cannot be called epithelial cells, or at least they have as yet nothing typical about them, but are indifferent formative cells, which might also become mucus- or pus-corpuscles. Pus-, mucus- and epithelial cells are therefore pathologically equivalent parts which may indeed replace one another, but cannot perform each other's functions.

Even from this it follows that the distinction which it has been sought to establish between mucus- and pus-corpuscles, and for the discovery of which prizes were proposed in the last century, really could not be found out, and that the "tests" could never be otherwise than insufficient, inasmuch as the cells developed upon mucous membranes do not always possess a purely purulent, purely mucous, or purely epithelial character, but on the contrary in a great majority of cases a mixed condition exists. Nearly always, when a catarrhal process developes itself upon a large mucous surface, as, for example, in the urinary passages, quantities of puriform matter are produced, but its production is confined within certain limits, beyond which only mucus is secreted, and the secretion of mucus also at some point changes into a formation of epithelium. This mode of suppuration must of course always have for its result, that, in places where it reaches a certain height, the natural coverings of the surface do not attain their full development, or that, where they possess a certain degree of solubility, they are removed and destroyed. A pustule on the skin destroys the epidermis, and so far we may assign a degenerative character to these forms of suppuration also.

But degeneration in the usual sense of the word, only occurs when deeper parts are attacked. This more deeply seated pus-formation regularly takes place in the *connective tissue.* In it there first occurs an enlargement of the cells (connective-tissue corpuscles), the nuclei divide and for some time multiply excessively. The first stage is then very soon followed by divisions of the cells themselves. Round about the irritated parts, where before single cells lay, pairs or groups of cells are subsequently found, out of which a new-formation of an homologous kind (connective tissue) usually constructs itself. More in the interior on the contrary, where the cells were early abundantly filled with nuclei, heaps of little cells soon appear, which at first still preserve the direction and forms of the previous connective-tissue corpuscles. Somewhat later we find here roundish collections, or diffuse "infiltrations," in which the intermediate tissue is extremely scanty and continually liquefies * more and more, in proliferation of the cells extends.

Fig. 137.



If this process takes place beneath a surface which does not participate in the morbid change, the layers of epithelium are sometimes seen, still perfectly coherent, to run over the irritated and somewhat swollen part. The outermost layer of the intercellular substance is also often long preserved, whilst all the deeper parts of the connective tissue are already filled with pus-corpuscles, are "infiltrated," or "absceded" † (abscedirt). At last the

Fig. 137. Purulent granulation from the subcutaneous tissue of a rabbit, round about a ligature. *a.* Connective-tissue corpuscles. *b.* Enlargement of the corpuscles with division of the nuclei. *c.* Division of the cells (granulation). *d,* Development of the pus-corpuscles. 300 diameters.

* This liquefaction (and the same is true of the liquefaction we have described as occurring in bone, p. 465) is a purely chemical process; the collagenous (gelatine-yielding) substance is first transformed into mucus, and then, becoming converted into an albuminous fluid, liquefies.—*From a MS. Note by the Author.*

† *I.e.*. converted into an abscess.—*Transl.*

surface gives way, or without giving way is directly transformed into a soft, diffluent mass. This mode of suppuration gradually yields the so-called *granulations* which always consist of a tissue, where, in a small quantity of soft intercellular substance, more or less numerous, and, at least in the strictly proliferating stage of the granulations, round, cellular elements are imbedded. The nearer we come to the surface, the more do the cells, which in the deeper parts were mostly uni-nucleated, present divisions in their nuclei, and on the extreme confines they can no longer be distinguished from pus-corpuscles. Then a detachment of the epithelium is wont to take place, and finally it may be that the basis-substance liquefies and the individual elements are set free. If the proliferation continues abundant, the mass keeps constantly breaking up, the cells pour themselves out upon the surface, and a destruction takes place, which makes deeper and deeper inroads into the tissue, and throws up more and more of its cells upon the surface. This is an *ulcer* properly so called.

According to the common notion, which supposed the pus to be derived from some exudation or other, this kind of ulceration was not at all easy of comprehension; people always found themselves obliged to assume a special kind of transformation in the tissue in addition to the suppuration, and at last they went so far as to attribute a certain chemical solvent power to pus. But by surgical experiments the conviction has long since been acquired in the most manifold ways that pus has no solvent power. Bones have been placed in cavities full of pus and left there for weeks, and when they were afterwards weighed, they had if anything become heavier, through the absorption of fluid matters, but no softening had been produced excepting that occasioned by decomposition. How far the tissue is destroyed by real solution, chiefly depends upon whether the basis-substance which surrounds the young cells, becomes completely fluid. If it retains a certain degree of consistence, the process is confined to the production of granulations, and these may just as well proceed from a surface whose continuity is perfect, as from one where there is a breach of it. In surgery it is generally assumed that granulations form upon the walls of the breach occasioned by a loss of substance, but in every case they arise directly out of the tissue. They are found directly seated upon bone without any loss of substance in it having preceded them. They are found also in direct contact with the cutis under the intact epidermis, and with mucous membranes. Only in proportion as they become developed, do the mucous membranes lose their normal character.

Every development of the kind gives rise, as it proceeds, to separate masses (foci—Heerde) of new tissue, just in the same way indeed that growing cartilage produces, in the immediate vicinity of the margin of ossification, those large groups of cells (Fig. 124), each of which corresponds to a single pre-existing cartilage-cell. We have in fact to do with a process which finds its counterpart in the ordinary phenomena of growth. As a cartilage, when it does not calcify, as for example, in rickets, at last becomes so moveable that it can no longer perform its functions as a supporting structure, so we see everywhere that the firmness of a tissue gradually disappears through the development of granulations, and during suppuration. However different therefore these processes of destruction apparently are from the processes of growth, at a certain point nevertheless they entirely coincide. *There is a stage, when it is impossible to decide with certainty, whether we have in a part to deal with simple processes of growth, or with the development of a heteroplastic, destructive form.*

This mode of development, which I have just described to you, is not, however, in any way peculiar to pus alone, but characterizes every heteroplastic formation; the first changes which we have shown to take place are found occurring in exactly the same manner in heteroplasms of every sort up to the most extreme and malignant forms. The first development of cancer, of cancroid and of sarcoma exhibits the same stages; if the course of their development be traced sufficiently far back, we at last always come across a stage, in which, in the younger and deeper layers, indifferent cells are met with, which do not until a later period, according to the particular nature of the irritation to which they are exposed, assume the one or the other type. We may therefore, taking new-formations in general, consider the history of the greater number, and especially of those which principally consist of cells, from an entirely similar point of view. The form of ulceration which is presented by cancer in its latest stages, bears so great a resemblance to its suppurative ulceration, that the two things have long since been compared, and quite in the olden time a parallel

FIG. 138.

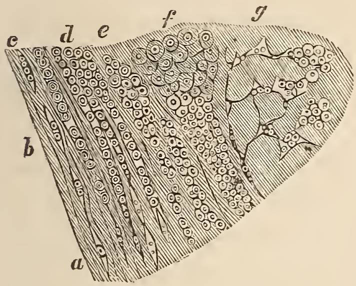


Fig. 138. Development of cancer from connective-tissue in carcinoma of the breast. *a*. Connective-tissue corpuscles, *b*, division of the nuclei, *c*, division of the cells, *d*, accumulation of the cells in rows, *e*, enlargement of the young cells and formation of the groups of cells* (foci—Zellenheerde) which fill the alveoli of cancer, *f*, further enlargement of the cells and the groups. *g*. The same developmental process seen in transverse section. 300 diameters.

* When these groups of cells fall out, the alveoli (loculi) of cancer appear, the relation of the group to the alveolus being the same as that of the bone-cell to the lacuna.—*From a MS. Note by the Author.*

was drawn between the eroding form of suppuration, or chancre, and the "suppuration" or sanious ulceration* (Verjauchung) of cancer.

But there are essential differences between the individual species of new-formations in consequence of their elements' attaining to very different degrees of development, or to express myself otherwise, in consequence of the length of time their elements are calculated to last—*the average duration of the life of the individual elements*—being extremely different. We know, that if we examine a spot a month after suppuration has taken place in it, although the pus is apparently still present, we can no longer rely upon finding unaltered pus in the collection. Pus which has lain anywhere for weeks and months is, strictly speaking, no longer pus, but disintegrated matter, débris, dissolving particles of pus, which have become altered by fatty degeneration, putrefying processes, calcareous deposits and the like. On the contrary we find that a cancerous tumour may last for months, yet still contain the whole of its elements intact. We can therefore positively affirm, that a cancer-cell is capable of existing longer than a pus-corpuscle, just as we know that the thyroid body exists longer than the thymus gland, and that certain organs, for example individual parts of the sexual organs, early perish in the course of ordinary life, whilst others retain their existence throughout the whole of life. So it is also with pathological new-formations. At a time when certain forms have long since entered upon their course of retrogressive metamorphosis, others are just begin-

* Jauche (sanies) always conveys the idea of decomposition. We call Mistjauche the fluid obtained by the maceration of manure. Verjauchung is the process during which the substances are decomposed which subsequently furnish the Jauche. The French *putrilage* is nearly equivalent to Jauche in its pathological acceptation, only the latter is rather thinner and more liquid.—*From a MS. Note by the Author*

ning to attain their full development. In the case of many new-formations, retrograde metamorphosis begins comparatively so early, nay constitutes to such a degree what is ordinarily met with, that the best investigators have looked upon its different stages as the really characteristic ones. In the case of tubercle, for example, we find that the majority of all modern observers who have made it their professed study, have taken its stage of retrograde metamorphosis for the real typical one, and that inferences have hence been drawn with regard to the nature of the whole process, which with equal right might have been drawn with regard to the different stages of the retrograde metamorphosis of pus and cancer.

We are as yet able in the case of very few elements to give in numbers with absolute certainty the average length of their life. There manifestly exist variations similar to those we meet with in normal organs. But among all pathological new-formations with fluid intercellular substance there is not a single one, which is able to preserve its existence for any length of time, not a single one, whose elements can become permanent constituents of the body, or exist as long as the individual. This may no doubt seem doubtful, because many forms of malignant tumours subsist for many years, and the individual retains them from the time of their development until his death, which may perhaps occur at a very advanced age. *But the tumour as a whole must be distinguished from its individual parts.* In a cancerous tumour which lasts for many years, the same elements do not last the whole time, but within its limits there occurs a frequently very numerous succession of fresh formations. The first development of a tumour takes place at a definite point, but its subsequent growth does not consist in the production of a constant succession of new-formations from this point, and in the occurrence there is an intus-susception (absorption) of material, by means of which the existing parts enlarge and so the whole tumour grows. On the contrary around the original focus* (Heerd), little new foci are formed, which increasing in size, group themselves around the first, and so gradually give rise to a continually progressing enlargement of the existing tuber.† If the tuber is seated on the surface, we find on section a semicircular zone of the most recently formed matter, at its periphery; if it is in the middle of an organ, the newly apposed foci form a spherical cortex around the older centre. If we examine a tumour after it has existed perhaps a year, it usually turns out that the elements first formed no longer exist in the centre. There we find the elements disintegrating, dissolved by fatty changes. If the tumour is seated on a surface, it often presents in the centre of its most prominent part a navel-shaped depression, and the portions immediately under this display a dense cicatrix which no longer bears the original character of the new-formation. These retrograde forms I have described as occurring in cancer, especially in the liver, lungs and intestines, where they are not unfrequently met with, and can readily be demonstrated.

It is always possible to convince oneself, that, *what is called a tumour*, *constitutes a conglomerate mass*, *often extraordinarily large*, *made up of a number of little miliary foci* (lobules), of which every single one must be referred to a single or a few parent elements. Inasmuch as the formations progress in this manner, no

* *Focus* here signifies the first rudiment of a tumour, produced by the proliferation of a limited group of cells. See note on Heerd, p. 381.—*From a MS. Note by the Author.*

† Tuber = tuberous tumour. See note, p. 471.

matter whether they consist of pus, tubercle or cancer, new young zones are being constantly added on to the old ones, and we may, if we intend to trace the course of development, calculate with great certainty upon always finding the young parts at the extreme circumference, the old ones always in the centre. *But the zone produced at the latest period of the disease extends to a considerable distance beyond the zone of degeneration that can be discerned by the naked eye.* If we examine any proliferating tumour of a cellular character, we often find, three to five lines beyond its apparent limits, the tissues already in a state of disease, and exhibiting the first traces of a new zone. This is the chief source of local recurrence after extirpation, for it proceeds from the zone that cannot be detected by the naked eye, beginning to grow in consequence of the increased supply of nutritive material which results from the removal of the original tumour. No new deposit from the blood takes place there, but the new-formed germs, which already lie in the neighbouring tissue, run through their further development in the same manner that it would otherwise have taken place, or perhaps even still more quickly.

This fact I regard as extremely important, because it shows us that all these formations have essentially a *contagious character.* As long as it was imagined that the mass once formed increased only by the growth of its constituents, it would of course look as if all one had to do for the purpose of getting rid of it was merely to cut off from the tumour all further supply of material. But there is manifestly a contagious matter formed in the tumour itself, and when the cells, which are in its immediate neighbourhood and are connected by anastomoses with the diseased cells, likewise enter upon the heterologous proliferation, it is impossible, I think, to come to any other conclusion in the matter, than that the degeneration of the neighbouring parts arises in precisely the same manner as that of the nearest lymphatic glands which lie in the course of the stream of lymph which proceeds from the diseased part. The more anastomoses the parts possess, the more readily do they become diseased, and *vice versâ*. In cartilage malignant affections are so rare, that it is usually assumed to be altogether insusceptible of them. Thus in a joint the cartilaginous investment alone is sometimes found intact, whilst everything else has been destroyed. Thus too we see that fibrous parts which are rich in elastic elements, are very little disposed to become diseased by contagion. On the other hand, the softer a basis-substance is and the better the conveyance can take place, the more certainly we may expect, that, when occasion offers, new foci of disease will arise in the part. I have therefore come to the conclusion—the only one I think the facts warrant—that the infection is directly transferred by the means of the morbid juices from the original seat of the disease to the anastomosing elements in the neighbourhood, *without the intervention of vessels and nerves.* The nerves are indeed often the best conductors for the propagation of contagious new-formations, only not as nerves, but as parts with soft interstitial tissue.

Here we have the importance of the anastomosing cellular elements of tissues, and the value of the cellular theory most clearly exhibited, and, when once we have become acquainted with this mode of conduction, we are afterwards able with a certain degree of probability to foresee in what direction, in parts possessing this means of conveyance, the disease will extend, and where finally the greater or less danger lies. It has hitherto been impossible to prove whether the infection of remote parts is effected by the conveyance of juices, in the same way that the infection of neighbouring parts is, and especially whether the blood takes up anything noxious from the diseased spot and conveys it to a distant place. I must confess that I am acquainted with no sufficiently convincing facts bearing upon the matter, and must still allow it to be possible that the diffusion by means of vessels may depend upon a dissemination of cells from the tumours themselves. There are, however, many facts, which speak but little in favour of the infection's taking place by means of really detached cells, for example, the circumstance that certain processes advance in a direction contrary to that of the current of lymph, so that after a cancer of the breast, disease of the liver takes place whilst the lung remains unaffected. Here it seems pretty probable that juices are taken up, which occasion a further propagation (p. 254).

Allow me still to add a few words upon a subject which can here be dispatched off hand, namely, the so-called *parasitism* of new-formations.

It is self-evident, that the view taken of parasitism by the old writers who held it to be applicable to a large proportion of new-formations, is completely borne out by facts, and that in reality every new-formation which contributes to the body no serviceable structures, must be regarded as a parasitical element in the body. Only bear in mind that the idea conveyed by parasitism does not differ from that conveyed by the autonomy of every part of the body excepting in degree, and that every single epithelial and muscular fibre-cell leads a sort of parasitical existence in relation to the rest of the body, just as much as every individual cell in a tree has in relation to the others a special existence, appertaining to itself alone, and deprives the remaining cells of certain matters. Parasitism in a narrower sense of the word, develops itself out of this idea of the independence of individual parts. As long as the requirements of the remaining parts demand the existence of a part, as long as this part is in any way useful to the other parts, so long will it not be termed a parasite ; but it becomes so from the moment that it becomes foreign or injurious to the body. The epithet, parasitical, must therefore not be restricted to a single class of tumours, but applies to all heteroplastic forms, which do not in the course of their further metamorphoses give rise to homologous products, but furnish neoplasms which in a greater or less degree are alien to the composition of the body. Every one of their elements will withdraw matters from the body which might be used for other purposes, and as it has at the very outset destroyed normal parts and even its first development presupposes the destruction of its parent structures it both plays a destructive part at the commencement of its career, and a depredatory one throughout its course.

LECTURE XX.

APRIL 27, 1858.

FORM AND NATURE OF PATHOLOGICAL NEW-FORMATIONS.

Nomenclature and classification of pathological new-formations—Consistence as a principle of division—Comparison with individual parts of the body—Histological division—Apparent heterology of tubercle, colloid, etc.

Difference of form and nature: Colloid, Epithelioma, Papillary tumour, Tubercle.

Papillary tumours: simple (condylomata, papillomata) and specific (villous cancer and cauliflower-tumour).

Tubercle: infiltration and granulation—Inflammatory origin of tubercle—Its origin from connective tissue—Miliary granules, and solitary masses—The cheesy metamorphosis.

Colloid: myxoma—Collonema—Mucous or gelatinous cancer.

Physiological types of heterologous new-formations: lymphoid nature of tubercle, hæmatoid of pus, epithelioid of cancer, cancroid, pearly and dermoid tumours, and connective-tissue-like of sarcoma—Infectiousness according to the amount of juice.

Comparison between pathological new-formations in animals and vegetables—Conclusion.

If, gentlemen, we prosecute the train of thought which we have pursued in the last lectures, it seems to me that the question which you will perhaps next ask me, is, at what point the differentiation of new-formations really begins. You will remember that, according to our views the great majority of new-formations have their origin in connective tissue or parts equivalent to connective tissue, and that the first rudiments of all new-formations are nearly of the same nature, and that in particular the division of the nuclei, their multiplication, and the final division of the cells show themselves in nearly all new-formations, in the benignant as well as in the malignant, in the hyperplastic as well as in the heteroplastic ones, in the self-same manner. Unquestionably, however, this similarity of nature is transitory; it is not long before some one characteristic feature displays itself in each individual structure, whereby we are enabled distinctly to recognize its nature.

With regard to this question of the criteria of new-formations, no agreement in opinion has indeed even at the present moment been come to, and here too therefore it is incumbent upon me now to show how I have arrived at my views, which in many respects so widely differ from those generally held, and for what reasons I have deemed myself obliged to quit the beaten track.

The names which have been bestowed upon individual new-formations, have, as you know, often been based pretty much upon accidental peculiarities, and not so very unfrequently selected in quite an arbitrary manner. The attempts to establish a regular nomenclature, which were formerly made, were really only based upon the consistence of tumours, reasons for classification having been derived from the circumstance that the substance of new-formations was found to be sometimes hard, at others soft, fluid, pultaceous, gelatinous, etc., and thus meliceris, atheromata, steatomata, scirrhi, etc., were separated from one another. It is self-evident that the ideas which are now attached to several of these things must be done away with, if it be wished to understand the original meaning of these designations. When the presence of an atheromatous process is now-a-days spoken of, something is meant thereby of which the old observers were far from having any idea. When the tumour anatomists of the present day labour hard to revive the name steatoma and would have it designate a firm fatty tumour, you must remember that the manufacture of stearine was not known at the time when the term steatoma first came into use, and that the old observers never entertained the notion, which the tumour teachers of the present day cannot get out of their heads—that a steatoma * was a stearine- or indeed a fatty, tumour at all.

The improved nomenclature which was introduced at the commencement of this century, was based more upon comparisons which were instituted between the new-formations and individual parts or tissues of the body. The term "medullary fungus" (Markschwamm) originally arose out of the idea that medullary cancers originated in the nerves and resembled nervous matter in their composition. These comparisons have, however, until recently been always very arbitrary, because they were founded upon more or less rough resemblances in external appearance, without a due appreciation of the more delicate peculiarities of structure, and particularly of the really histological composition.

Recently attempts have been made, and here and there even with great affectation, to make use of normal structures as aids in terminology. Many attach a certain degree of importance to this, and consider it more scientific to say epithelioma, where others say cancroid or epithelial cancer. Thus in France great stress has, it is well known, been laid upon calling sarcomata fibro-plastic tumours, because Schwann and his followers looked upon caudate corpuscles as directly producing the fibres of connective tissue—which, in my opinion (p. 70), is an error. But in spite of these errors we must consider the histological point of view as the true one, only it is not, I think, advisable, in accordance with this principle, at once to proceed to create new names for everything, and

* The ancients called any firm tumour (*e. g.*, an enchondroma) a steatoma.—*From a MS. Note by the Author.*

by means of these new names to render things which have long been known strange to the minds of people in general. Even new-formations which very evidently follow the type of some definite normal tissue, still for the most part possess peculiarities, whereby they may be more or less distinguished from this tissue, so that in the majority of cases, at least, it is by no means necessary to see the whole of the new-formation in order to know that this is not the normal, regular development of the tissue, but that on the contrary there is something in it, although it does not lose the type, which deviates from the ordinary course of homologous development. Besides there still remain even at the present time a certain number of new-formations, the external appearance or clinical character of which has, in part from the want of known physiological types, been retained as the basis for their names.

We still continue to speak of tubercle, and the name which Fuchs has invented as a substitute, the only new one, as far as I know, which it has been attempted to introduce in its stead, Phyma, is so very indefinite, so readily applicable to every "growth," that it has met with no great favour. Several other names have been recently used to a continually increasing extent, which are also nothing more than stop-gags, as for example that of Colloid. This name was invented at the commencement of the present century by Laennec to designate a form of tumour which he described as analogous in consistence to half-set glue; in its well-developed form it constitutes a half-trembling gelly, colourless or of slightly yellowish hue, which on the whole conveys the impression of a nearly complete absence of all structure. Whilst people formerly declared themselves perfectly content, when tumours of this kind were designated jelly-like, or gelatinous, to many of the more recent observers it has appeared a proof of superior penetration to say, instead of gelatinous tumour or gelatinous mass, colloid tumour or colloid mass. But you must not think that those, who have these denominations the most constantly in their mouths, intend to express anything else by them, than what most others call simply a jelly-like tumour, or only jelly. It is just the same with it, as, in the time of Homer, with the herb Μῶλυ, which was so called in the language of the gods, but by another name by men.* It is, however, very advisable, that these really unmeaning and only high-sounding expressions should not be unnecessarily diffused, and that the habit should be acquired of conveying a precise meaning by every expression, and that therefore from the moment one really aspires to make histological divisions, one should no longer employ, when speaking of every jelly-like tumour, the term colloid which has no histological value whatever, but merely designates an external appearance which tissues of the most different nature may under certain circumstances present. Laennec himself inaugurated the somewhat pernicious practice, by speaking of a colloid transformation of fibrinous exudations of the pleura.

The chief difficulty, which here presents itself, consists in this, that people do not know how to discover any difference between *the mere form and the true nature.* The form ought only to be admitted as a decisive criterion for the diagnosis of new-formations, when it is conjoined with a real difference in the tissue, and does not result from accidental peculiarities of situation or position. If, for example, you wish to make use of the name colloid, you can do so in two ways. You can either employ it to designate nothing more than a kind of appearance, and then you will certainly be able to find

* Odyss. X. 305. Note of the Stenograph.

different tumours which you can distinguish from other tumours of the same genus by means of the addition "colloid." You may therefore say: colloid cancer, colloid sarcoma, colloid fibroma [fibrous (connective-tissue) tumour]. Here colloid means nothing more than jelly-like. Or you must have a distinct notion of the nature, of the chemical or physical peculiarities of the colloid substance, or of the morphological nature of the colloid tissue, and then it will be impossible for you to class together two, chemically and morphologically, entirely different products, such as the colloid of the thyroid body and colloid cancer.

In just the same manner we see that a great number of tumours, when they are seated on the surface, give rise to excretions, which, according to the nature of the surface, appear in the form of villi, papillæ or warts. All these tumours may be comprised under one name and called papillomata, but the tumours which have this form often differ toto cœlo from one another. Whilst in the one case we have a true hyperplastic development, we find in another, at the base of these villi where they rest upon the skin or mucous membrane, some specific form of tumour. In many cases even the villi themselves are filled with a substance analogous to that of the tumour. This is a very important difference. If, for example, you examine a *broad condyloma*, the mucous tubercle or *plaque muqueuse* of Ricord, you will find, under the epidermis which still remains smooth, the papillæ enlarging and ultimately growing out into branched figures so as to represent regular trees. Cancer, however, may give rise to excrescences of the same shape as these condylomata. This we see comparatively less frequently occur on the skin than on the different mucous surfaces. In these cases it may happen that real cancer is seated in the villi. Nor is this in itself indeed at all surprising

The papillæ consists of connective tissue like the skin, or the mucous membrane, upon which they are seated; within the papillæ therefore a cancerous mass may develop itself out of the connective tissue, as out of the connective tissue of the skin or mucous membrane. Moreover, it cannot be denied that this peculiarity of superficial formation very frequently explains certain peculiarities in the course of the disease, whereby a papillary tumour is strikingly distinguished from the same kind of tumour when not papillary. Any one may have a cancer of the bladder—if it be merely seated in the parietes—for a very long time, without any other changes being necessarily displayed in the nature of the secretion, which must be evacuated with the urine, than those exhibited in a simple catarrh. As soon, on the contrary, as a formation of villi takes place upon the surface, nothing is more common than for hematuria to arise as a complication, from the simple reason, that every villus upon the walls of the urinary bladder is not clothed with a firm layer of epidermis, but lies almost bare under a loose epithelial covering. Into the interior of the villi ascend large vascular loops which reach quite up to the surface, and therefore very considerable mechanical irritation supplies a condition for the production of hyperæmia and the rupture of the villi. A spasmodic contraction of the bladder drives the blood up into the apices of the villi, in consequence of the shortening of the surface on which they are seated, and when to this is added the mechanical friction of the surfaces, nothing is more likely to ensue than a sometimes more, sometimes less considerable effusion of blood. But in order that such hæmorrhage should take place it is altogether unnecessary that the papillary tumour should be cancerous. I have seen cases in which, for years, uncontrollable bleedings recurred from time to time, through which at last the patients died anæmic, and yet no trace of any cancerous infiltration of the base of the growth or of the villi existed, but the tumour was quite a simple papillary one, a benignant formation, which on the surface of the skin could easily have been removed by the knife or ligature, but which, owing to its concealed position, was in these cases attended with a series of phenomena, which during life it seemed impossible to refer to anything else than a really malignant new formation.

Just the same is the case with the much-discussed *cauliflower-tumours*, as they are seen on the surface of the genital organs, both in man and woman. In men, these papillary tumours, which proceed from the prepuce and surround the corona glandis, are for the most part covered by a very thick layer of epidermis, so that, when they ulcerate, they yield but a very trifling amount of secretion. In women, on the contrary, the tumour being seated on the neck of the uterus—a very vascular part, provided with a thin stratum of epithelium, and naturally beset with a thick layer of numerous and large papillæ—for the most part very early occasions abundant transudations and occasionally hæmorrhagical exudations of a fluid, like water in which raw meat has been soaked, or really red and bloody. In these cases there frequently exists doubts as to the nature of the disease. I myself was present when a very renowned surgeon came to Dieffenbach's operating room, just as that operator had amputated a penis on account of a "carcinoma" —and when the stranger afterwards declared it to have been a simple condyloma. On the other hand I have examined cases, in which growths of this sort had been doctored about for years as if they had been syphilitic condylomata, because the external appearance is so extremely analogous, and it is so extremely difficult to discover a criterion by which it can be accurately determined whether the formation only involves the surface, or whether it is complicated with disease of the subjacent tissue. There are certainly at the present time very many anatomists and surgeons who entertain the notion that cells may grow on the surface exactly similar to those which are usually only found in the interior of diseased organs—that, for example, a villous tumour must be termed cancerous, if it is covered over with cancer-cells as with an epithelium, without any development of cancerous matter having shown itself in the interior of the villi. In fact, villi, which are very delicate and scarcely contain enough connective-tissue to envelop the vessels that run up in them, are sometimes met with, enclosed in a thick layer of cells which, from the irregularity of their form, the size of their nuclei, and their own large dimensions, present rather the character of cancer than that of epithelium. But I must confess that I have not as yet been able to convince myself that cancer-cells are able to arise upon the free surfaces of membranes, and that they can be produced simply from epithelium; on the contrary, I believe from all that I have seen, that a very strict line of demarcation must be drawn between the cases, where masses of cells, however abundant and curiously shaped they may be, are found seated upon a basis-tissue in itself unaltered, and those, where the cells have been formed in the parenchyma of the parts themselves.

The pathological importance of a papillary tumour is, at least as far as I know, determined by the condition of its basis-substance, or by that of the parenchyma of the villi themselves; and a formation can only be pronounced to be cancroid or carcinoma when, in addition to the growth of the surface, the peculiar degenerations which characterize these two kinds of tumours, take place also in the deeper layers or in the villi themselves. I think, therefore, that all these external differences of form can only serve to distinguish different species of the same genus of tumours, but by no means different tumours, from one another. There are connective-tissue [fibrous] tumours of the surface, which manifest themselves in the form of simple tubera (Knoten *), others which show themselves in the form of warts and papillary tumours. In just the same manner, there are cancerous formations

Fig. 139.

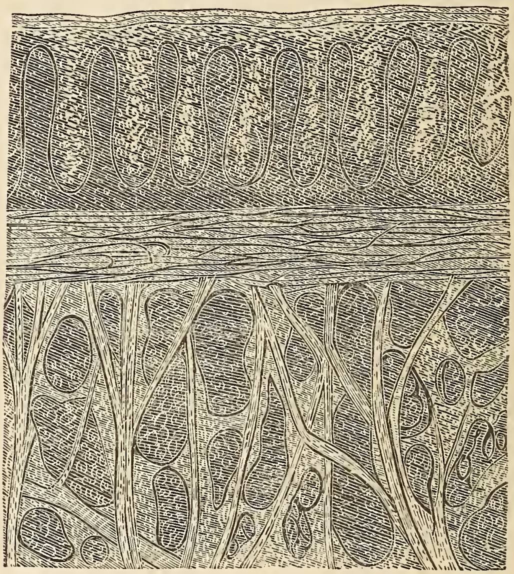


Fig. 139. Vertical section through a commencing cauliflower growth (cancroid) of the neck of the uterus. On the still unchanged surface the tolerably large papillæ of the os uteri are seen invested by a homogeneous, stratified layer of epithelium. The disease begins first on the other side of the mucous membrane in the real parenchyma of the cervix, where large, roundish or irregular, scattered groups of cells (contained in alveoli) are disseminated throughout the tissue. 150 diameters.

* The term Knoten (Eng. *knot*, Lat. *tuber*) having reference rather to the *form* than to the *size* of the tumour, is used in this work as a designation for all sorts of *tuberiform* tumors, even the largest.—*Trans.*

and cancroid formations which may assume this form, and others again, which do not do so.

With reference to the relation of form and nature, there is a question of really cardinal importance, concerning which, in the interest of mankind, a certain degree of unanimity ought soon to be arrived at, namely, what is properly to be understood by the term *tubercle.* The same difficulties which I have just described to you, are again encountered in the case of tubercle in a still higher degree. The old writers introduced the name tubercle merely to express an external form. Everything was called a tubercle which manifested itself in the shape of a small knot. It is, as you are no doubt aware, by no means so very long since this term was employed in the most loose manner. Carcinomatous and scirrhous tubercles were talked about, scrofulous and syphilitic tubercles were distinguished from one another, and these terms are still preserved in France. Cancer too, you know, in old times was not by any means exclusively employed to designate a real tumour, but noma (cancer aquaticus) was considered to have as much right to the appellation as a chancre (cancer syphiliticus).

Now in the course of the present century endeavours have been made gradually to exchange these somewhat superficial views for more accurate conceptions, and here also it is to Laennec especially that credit is due for having sought for precise denominations. Still he himself in his turn has been the cause of this matter's having fallen into a state of nearly irremediable confusion. For, as you no doubt recollect, he asserted that tubercle presented itself in the lungs under two different aspects, the so-called *tubercular infiltration*, and *tubercular granulation.* Now, inasmuch as infiltration signifies something completely at variance with the old notion of tubercle, since it does not at all imply the presence of small knots

(Knötchen), but expresses an equable pervasion of the whole parenchyma, a track was hereby opened, in following which the old idea of tubercle has more and more been departed from. As soon as the infiltration of tubercle had once been created and the form of the neoplasm had thereby been abandoned, the infiltration was generally, as being more extensive and therefore more instructive, taken as the basis of subsequent descriptions, and attempts were made to find out in what respects it really agreed with the other, previously known forms of tubercle. It was in this way, that the cheesy stage of tubercle came to be gradually adopted as the common generic characteristic of all tuberculous products, not merely as the principal aid in diagnosis, but as the starting-point for the interpretation of the process in general. It was in this way, in particular, that the idea came to be entertained, that tubercles could arise simply by any exudation's losing its water constituents, growing thick, turbid, opaque, cheesy, and remaining in this condition.

The term, tubercle-corpuscles (corpuscules tuberculeux), which is, you know, still in very frequent use, has reference to just this cheesy stage, and the accurate description which Lebert has given of them amounts to this—that they are formations which correspond with none of the known organic forms, and are neither cells, nor nuclei, nor anything else of an analogous nature, but appear in the form of little, roundish, solid corpuscles, which frequently have particles of fat scattered through them (Fig. 64). But if the development of these corpuscles be investigated, it is easy to convince oneself that, wherever they occur, they arise out of previous organic morphological elements, and that they are not by any means the first bungling products, unfortunate essays of organization, but that they were once well-grown elements, which by an unhappy chance were early checked in their development and early succumbed to a process of shrivelling. You may with certainty assume that, where you meet with a largish corpuscle of this description, a cell had previously existed, and where you find a small one, there once had been a nucleus, enclosed perhaps within a cell.

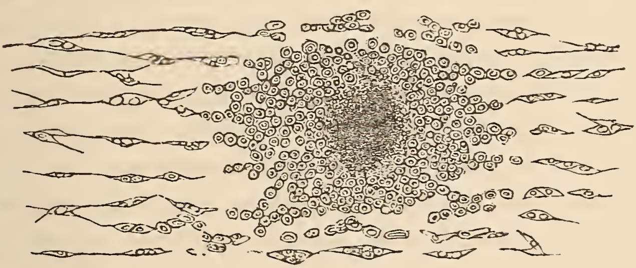
Upon examining the point which has been the leading one in the doctrine of tuberculosis recently advanced, namely tubercular infiltration of the lungs, we readily arrive at the result which Reinhardt has set down as the final one, namely, that tuberculosis is nothing more than one of the forms presented by inflammatory products when undergoing transformation, and especially that all tuberculous matter is really inspissated pus. In fact, what has been termed tubercular infiltration, can with few exceptions be traced to an originally inflammatory, purulent or catarrhal mass which has gradually, in consequence of incomplete reabsorption, fallen into the shrivelled and shrunken state in which it afterwards remains. But Reinhardt was deceived when he thought he was examining tubercle. He was led astray by the false direction which had been given to the whole doctrine of tuberculosis from the time of Laennec until his own, especially through the fault of the Vienna school. If he had confined himself in his investigations to the form of old assigned to tubercle, and knot (granule), if he had examined the constitution of the knot in its different stages and had afterwards compared the different organs in which knotted (granular) tubercle occurs, he would unquestionably have arrived at a different result.

It may, at least according to what I consider to be the correct view of the matter, certainly be said, that the greatest part of whatever in the course of tuberculosis does not appear in the form of granules, is an inspissated inflammatory product, and has at any rate no direct relation to tubercle. But by the side of these inflammatory products, or also independently of them, we find a peculiar structure [the knot, granule] which, if they are to be regarded as real tubercle, would no longer be included in the ordinary classification ; and it is certainly an extremely characteristic circumstance that in France, where the terminology of Lebert has become the prevailing one, and the *corpuscules tuberculeux* are wont to be regarded as the necessary accompaniments of tuberculosis—bodies, concerning the tuberculous nature of which there can be no doubt, have quite recently been set down as something altogether peculiar and which had hitherto remained undescribed. For one of the best, nay perhaps the best, micrographer France possesses, Robin, has, in his examinations of cases of tubercular meningitis, deemed it impossible to regard the little granules in the arachnoid* [pia mater] which every body looks upon as tubercles, as being really tubercles, because the dogma now prevails in France that tubercle consists of solid non-cellular corpuscles, and in the tubercles of the cerebral membrane cells in a state of perfect preservation are met with. To such curious aberrations does this track lead that one ends by being unable to find a name for real tubercle, because so many accidental objects have been confounded with it, that what was sought for, or even what had been found and was already grasped, has,

* The so-called visceral (cerebral) layer of the arachnoid is only the superficial layer of the pia mater which is spread evenly over, and does not dip in between, the convolutions, and being (as the name, arachnoid, implies), of a reticulated texture contains spaces (subarachnoid spaces). The so-called parietal layer of the arachnoid is only the inner superficial layer of the dura mater with the epithelium lining it. The Author employs the term arachnoid in general only for the purpose of making himself more intelligible to others, but as this superficial layer of the dura mater does not possess a reticulated structure and is everywhere inseparably connected with the rest of the membrane, and as epithelial coverings are not wont to be designated by special names, he of course always uses the term of the pia mater. Such expressions, therefore, as the "sac" or "cavity of the arachnoid" are incorrect.—*Based upon MS. Notes by the Author.*

in consequence of the attention of observers being diverted by these objects, been allowed to slip out of one's hand again. I am of opinion that a tubercle is a granule, or a knot, and that this knot constitutes a new-formation, and indeed one, which from the time of its earliest development is necessarily of a cellular nature, and generally, just like all other new-formations, has its origin in connective tissue, and which, when it has reached a certain degree of development, constitutes a minute knot within this tissue, that, when it is at the surface, projects in the form of a little protuberance, and consists throughout its whole mass of small uni- or multinuclear cells. What especially characterizes this formation is the circumstance, that it is extremely rich in nuclei, so that when it is examined as it lies imbedded in

Fig. 140.



the tissue which invests it, at the first glance there seems to be scarcely anything else than nuclei. But upon isolating the constituents of the mass, either very small cells provided with one nucleus are obtained—and these are often so small that the membrane closely invests the nucleus—or larger cells with a manifold division of the nu-

Fig. 140. Development of tubercle from connective tissue in the pleura. The whole succession of transitions is seen from the simple connective-tissue corpuscles, the division of the nuclei and cells up to the production of the tubercle-granule, the cells of which in the middle are disintegrating into fatty granular débris. 300 diameters.

clei, so that from twelve to twenty-four or thirty are contained in one cell, in which case, however, the nuclei are always small and have a homogeneous and somewhat shining appearance.

This structure, which in its development is comparatively most nearly related to pus, inasmuch as it has the smallest nuclei and relatively the smallest cells, is distinguished from all the more highly organized forms of cancer, cancroid and sarcoma, by the circumstance, that these contain large, voluminous, nay often gigantic corpuscles with highly developed nuclei and nucleoli. Tubercle, on the contrary, is always a pitiful production, a new-formation from its very outset miserable. From its very commencement it is, like other new-formations, not unfrequently pervaded by vessels, but when it enlarges, its many little cells throng so closely together, that the vessels gradually become completely impervious and only the larger ones, which merely traverse the tubercle, remain intact. Generally fatty degeneration sets in very early in the centre of the knot (granule), where the oldest cells lie (Fig. 140), but usually does not become complete. Then every trace of fluid disappears, the corpuscles begin to shrivel, the centre becomes yellow and opaque, and a yellowish spot is seen in the middle of the grey translucent granule. This is the commencement of the *cheesy metamorphosis* which subsequently characterizes the tubercle. This change advances from cell to cell farther and farther outwards, and it not unfrequently happens that the whole granule is gradually involved in it.

Now, the reason why I think that the name of tubercle must be specially retained for this formation as being extremely characteristic of it, is this—that the tubercle-granule never attains any considerable size, and that a tuber never arises out of it. Those which are wont to be termed large tubercles, and attain the size of a walnut, or a Borsdorf apple,* as for example in the brain—those are not simple tubercles. You will generally find the tubercles in the brain described as being solitary, but they are not simple bodies; every such mass (tuber) which is as large as an apple, or even not larger than a walnut, contains many thousands of tubercles; it is quite a nest of them which enlarges, not by the growth of the original focus (granule), but rather by the continual formation and adjunction of new foci (granules) at its circumference. If we examine one of these perfectly yellowish white, dry, cheesy tubera, we find immediately surrounding it a soft, vascular layer which marks it off from the adjoining cerebral substance—a closely investing areola of connective tissue and vessels. In this layer lie the small, young granules, now in greater, now in less, number. They establish themselves externally [to the previously existing ones] and the large tuber grows by the continual apposition of new granules (tubercles), of which every one singly becomes cheesy; the whole mass, therefore, cannot in its entirety be regarded as a simple tubercle. The tubercles themselves remain really minute, or as we are wont to say, *miliary*. Even when on the pleura, by the side of quite small granules, large yellow plates, looking as if they were deposited upon the surface, are met with, these too are not simple tubercles, but masses composed of a large aggregate of originally separate granules.

Here, you see, form and nature are in reality inseparably connected. The form is produced by the growth of the tubercle from single cells of connective tissue, by the degenerative proliferation of single groups of connective-tissue corpuscles. Thus, without more ado, it appears

* Borsdolf apples are very constant in their size, and measure from an inch and a half to an inch and three quarters ($1\frac{1}{2}''$—$1\frac{3}{4}''$) in diameter.—*From a MS. Note by the Author.*

at once in the shape of a granule. As soon as it has once attained a certain size, as soon as the generation of new corpuscles which develop themselves out of the old histological elements by a continual succession of divisions, at last lie so close to one another as to cause a mutual arrest of development, gradually to induce the disappearance of the vessels of the tubercle, and thereby to cut off their own supplies, then they begin to break up, they die away and nothing remains behind but débris—shrunken, disintegrated, cheesy material.

The cheesy transformation is the regular termination of tubercle, but, on the one hand, it is not the necessary one, inasmuch as there are rare cases, in which tubercles, in consequence of their undergoing a complete fatty metamorphosis, become capable of reabsorption; and, on the other hand, the same cheesy metamorphosis befalls other kinds of cellular new-formations; for pus may become cheesy, and likewise cancer and sarcoma. This metamorphosis, therefore, being common to more than one formation, cannot well be set down as a criterion for the diagnosis of any particular structure, such as tubercle; on the contrary, there are certain stages in its retrograde metamorphosis, where one cannot help confessing that it is not always possible to come to a decision. If a lung be laid before you with cheesy masses scattered through it, and you are asked if that be tubercle or no, you will frequently be unable to say with certainty what the individual masses originally were. There are periods in the course of development, when that which is inflammatory and that which is tuberculous can with precision be distinguished from one another; but, at last, there comes a time, when both products become confounded, and when, if one does not know how the whole arose, no opinion can any longer be formed as to what its nature is. In the midst of cancerous masses also cheesy spots occur which look exactly like tubercles. I have demonstrated that it is by the gradual transformation of the elements of cancer that this cheesy matter is produced. But if we did not positively know from the history of their development that cancer-cells disintegrate step by step, and that no tubercles form in the middle of cancer, we should in many cases be altogether unable to arrive at any decision from merely examining the specimen.

If those difficulties be surmounted which lie in the external appearance of the formation, and lead the observer astray not only when he considers its grosser features, but also when he investigates its more intimate composition, there remains nothing else to assist us in coming to a right conclusion than the investigation of the type of development displayed by the individual new-formations during the stages of their actual development, not during those of their retrograde metamorphosis. The nature of tubercle cannot be studied after the period when it becomes cheesy, for from that time its history is identical with the history of pus which is becoming cheesy; an earlier period must be chosen when it is really engaged in proliferation. So in the case of other formations, that period must be studied which is comprised between their origin and their culminating point, and we must see with what normal physiological types they agree. Then it is, I think, certainly possible for us to arrive at a just conclusion with the aid of the simple principles of histological classification, which I have already propounded to you (p. 91). *Heterologous tissues also have physiological types.*

A colloid growth, if we really take it to mean what Laennec did—a gelatinous organized new-formation—must necessarily correspond to some type to be met with in the body when in its normal condition. Thus there are a series of tumours, that have been included in the colloid class, which have altogether the structure of the umbilical cord, and which, like this part, essentially contain mucus in their intercellular substance. Now since I had named the tissue of the umbilical cord and analogous parts, mucous tissue, it is a very simple step for me to call these tumours *Mucous tumours* (Schleimgeschwülste), Myxomata. When we demonstrate the occurrence of tumours exhibiting the histological type of the umbilical cord in the midst of the adult body, the striking character of the phenomenon is in no wise lessened, but we have found for them a type among the normal tissues of the body. Another form of colloid, or as Johannes Müller has called it, *Collonema*, turns out to be merely œdematous connective tissue. We find nothing more than a very soft tissue, soaked in an albuminous fluid. Such a tumour cannot be separated from connective-tissue [fibrous] tumours generally, whether they be denominated gelatinous, œdematous, or sclerematous* connective-tissue tumours, and I think there is no occasion to estrange it from the mind by bestowing upon it the name of collonema. So, again, we find certain forms of cancer, in which the stroma, instead of being composed simply of connective tissue, consists of the same mucous tissue which we meet with in a simple mucous tumour. These we may simply name *Mucous Cancer* (Gelatinous or Colloid Cancer). We then know exactly what we have before us. We know it is a cancer, but that its stroma differs in its containing mucus and in its gelatinous nature from the ordinary stroma of cancers.

To revert once more to the consideration of tubercle—it would certainly be something completely abnormal if it were composed of *corpuscles tuberculeux ;* but if you compare the cells which are, as at least I must assume to

* Sclerema=œdema durum.

be the case, the real constituents of the granule, with normal tissues of the body, you will remark the most complete correspondence between them and the corpuscles of the *lymphatic glands*, and this is a correspondence which is neither accidental nor unimportant, for was it not known even of old, that lymphatic glands have an especial tendency to undergo the cheesy degeneration? Even the old writers have stated that a lymphatic constitution disposes to processes of this kind.

With regard to pus, I need only remind you that we have been occupied during several lectures in discussing the question of the possibility of diagnosing between pyæmia and leucocytosis, and that we have recognized in the colourless corpuscles of the blood bodies so perfectly analogous to pus-corpuscles, that some have thought they saw pus when they had colourless blood-corpuscles before them, whilst Addison and Zimmermann, on the contrary, imagined they had found colourless blood-corpuscles when they really were looking upon pus. Both have a like type of formation. It may therefore be said that pus has a *hæmatoid* form, nay, the old doctrine may be revived afresh, namely, that pus is the blood of pathology. But if one would seek a distinction, if one would be able to say in individual cases what is pus and what blood-corpuscles, there is no other criterion than to determine whether the cell arose at a spot where a colourless blood-corpuscle might be expected to arise, or at one where it ought not be produced.

So, moreover, we find amongst pathological new-formation a large category, the natural type of which is epithelium—*Epitheliomata*, if you will. But the term epithelioma, which has recently been introduced by Hannover, is completely inadmissible in the case of the particular kind of tumour which it was intended to designate, because the epithelioma is by no means the only tumour whose elements bear the character of epithelial cells.

Epithelioma cannot be distinguished from other tumours by its elements' having the character of epithelium whilst those of the others have it not. The tumour that [Johannes] Müller called Cholesteatoma, Cruveilhier, *tumeur perlée*—which I have translated *Perlgeschwulst* [pearly tumour]—this tumour has exactly the same epi-

Fig. 141.

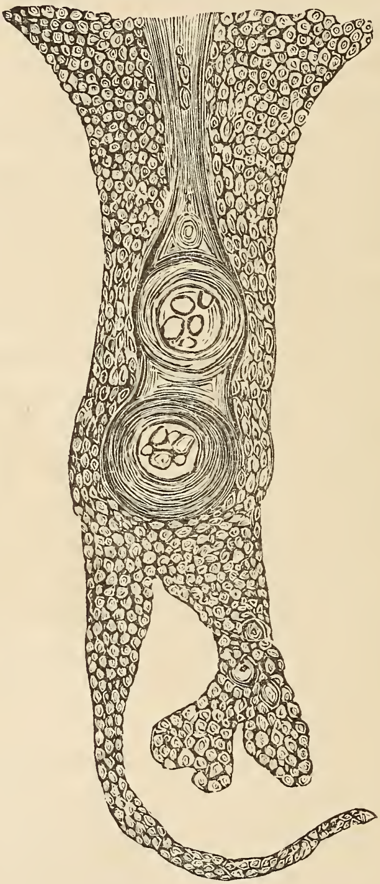


Fig. 141. Solid mass of cancroid from a tumour of the underlip. Closely packed layers of cells at the circumference, presenting all the characters of the rete Malpighii: in one of the processes, globules glistening like fat; in the middle of the body of the growth, a horny, epidermoidal, hair-like structure, with onion-like globules (pearls, globes épidermiques). 300 diameters.

thelial structure as that which Hannover has called epithelioma, nay, ordinary epithelioma very commonly engenders in itself little pearly globules in an often astonishingly great number. Yet both exhibit very essential points of difference. Never as yet have any pearly tumours been seen which, after existing in one place, recurred in remote places, and behaved like malignant tumours ; never did anything else occur than a slight extension—and that at an extremely slow rate—to the immediate neighborhood of the tumour. In the case of epitheliomata on the other hand, or as they are otherwise called, epithelial cancer or cancroid, we see a very marked malignity, for not only are they liable to recur at their original site, but they also reproduce themselves in distant parts. In many cases nearly all the organs of the body are metastatically filled with masses of cancroid.

Again, if you attempt to distinguish cancroid growths from real cancer by the epithelial structure of their elements, you will herein too give yourselves trouble in vain. Cancer proper has also elements of an epithelial character, and you need only turn to those parts of the body, where the epithelial cells are irregularly developed, as for example in the urinary passages (Fig. 15), and you will meet with the same curious bodies, provided with large nuclei and nucleoli, which are described as the specific, polymorphous cells of cancer. Cancer, cancroid or epithelioma, pearly tumours or cholesteatoma, nay

Fig. 142.

Fig. 142. Various, polymorphous cancer-cells, some of them in a state of fatty degeneration, two with multiplication of nuclei. 300 diameters.

perhaps the dermoid growths which produce hairs, teeth, and sebaceous glands, and so frequently occur in the ovary —all these are formations in which there is a pathological production of epithelial cells, but they constitute a graduated series of different kinds, which extend from those which are entirely local, and, in the usual meaning of the word, perfectly benignant, to the extremest malignity. The mere form of the cells which compose a structure, is of no decisive value. Cancer is not malignant because it contains heterologous cells, nor cancroid benignant because its cells are homologous—they are both malignant, and their malignity only differs in degree.

The forms which yield dry, juiceless masses, are relatively benignant. Those which produce succulent tissues have always more or less a malignant character (p. 251). The pearly tumour, for example, yields perfectly dry epithelial masses, almost without a trace of moisture, and it only infects locally. Cancroid remains for a very long

FIG. 143.

Fig. 143. Section through a cancroid of the orbit. Large epidermic globules (pearls), laminated after the manner of an onion, in a closely packed mass of cells, which have partly the character of epidermis, partly that of rete Malpighii. 150 diameters.

time local, so that the nearest lymphatic glands often do not become affected until after the lapse of years, and then again the process is for a long time confined to the disease of the lymphatic glands, so that a general outbreak of the disease in all parts of the body does not take place until late, and only in rare instances. In cancer proper the local progress is often very rapid and the disease early becomes general ; a cure, even for a short, time is so rare, that in France the complete incurability of cancer properly so called has been asserted and maintained with success.

Among the formations also which are analogous to the ordinary connective tissues, and are therefore apparently perfectly homologous and benignant, the succulent ones prove to be much more capable of communicating infection than the dry ones. A myxoma which has always a good deal of juice about it, is at all times a suspicious tumour, and, in proportion to the quantity of juice it contains, is its liability to recur. Cartilaginous tumours (Enchondromata) which were formerly described as unquestionably benignant, sometimes occur in soft and rather gelatinous forms, which may occasion just such internal metastases as cancer properly so-called. Even connective-tissue * [fibrous] tumours become, under certain circumstances, richer in cells and enlarge, whilst their interstitial connective tissue becomes

Fig. 144.

Fig. 144. Diagrammatic representation of the development of sarcoma, as it may very well be seen in sarcoma of the breast. 350 diameters.

* Fibrous tissue is *dense* connective tissue. It is not a special tissue, but only a

more succulent, nay in many cases disappears so completely, that at last scarcely anything but cellular elements remain. This is the kind of tumour which, according to my opinion, ought to be designated by the old name of *Sarcoma.* These sarcomata are frequently, indeed benignant, still they do not unfrequently recur, like epithelial cancer, at their original site, whilst under certain circumstances they appear secondary in the lymphatic glands, and in many cases occur throughout the whole body metastatically to such an extent, that scarcely any organ is spared by them.

In the case of all these formations, every one of which corresponds more or less completely to a normal tissue, investigations ought not to be conducted with a view to determine whether they have a physiological type, or whether they bear a specific stamp impressed upon them ; our final decision depends upon the answer to the question, *whether they arise at a spot to which they belong, or not, and whether they produce a fluid, which, when brought into contact with the neighbouring parts, may there exercise an unfavourable, contagious or irritative influence.*

It is with these formations as with vegetable ones. The nerves and vessels have not the slightest *direct* influence. They are only of importance so far as they determine the greater or less abundance of supply ; they are altogether unable to impel to the development of tumours, to produce them or to modify them in a direct manner. A pathological tumour in man forms in exactly the same way that a swelling on a tree does, whether on the bark, or on the surface of the trunk or a leaf, where any pathological irritation has occurred. The gall-nut which arises

form of connective tissue. Periosteum, perichondrium, tendons &c. all of them consist of connective tissue, in which, however, the cells have in part become converted into elastic fibres and network. In Germany indeed connective (cellular) tissue has ever since the time of Treviranus (1835) been divided into *formed* and *formless*, the former including tendons, fasciæ, ligaments, &c.—*From a MS. Note by the Author.*

in consequence of the puncture of an insect, the tuberous swellings which mark the spots on a tree where a bough has been cut off, and the wall-like elevation which forms around the border of the wounded surface produced by cutting down a tree, and which ultimately covers in the surface—all of them depend upon a proliferation of cells just as abundant and often just as rapid as that which we perceive in a tumour of a proliferating part of the human body. The pathological irritation acts in both cases precisely in the same manner ; the processes in plants conform entirely to the same type, and just as little as the tree produces on its bark or leaves cells of a kind, which it could not bring forth at other times, just as little does the animal body do this.

But if you consider the history of a vegetable tumour, you will see there also that it is above all the diseased spots which become unusually rich in specific constituents, and absorb and store up the peculiar substances which the tree produces, in more than average quantity. The vegetable cells which form on an oak-leaf round the puncture made by an insect contains much more tannic acid than any other part of the tree. The tumour-cells which form with such exuberance in a pine at the spot where an insect has buried itself in the young trunk, are stuffed completely full of resin. The peculiar formative energy which is developed at these spots, occasions also an unusually abundant accumulation of juices. There is no need of any nerves or vessels to instigate the cells to an increased absorption of matter. It is by their own action—by means of the attraction which they exercise upon the neighboring fluids—that they draw in the most serviceable materials. The great importance, which a knowledge of botany possesses for the pathologist also, lies in this—that it enables him to discover in all these processes the existence of an inward correspondence in the whole series of vital phenomena, and to show how the lowest formations may serve to explain the history of the most perfect and complex parts.

I have in the course of these lectures, gentlemen, developed to you as completely as it was possible for me here to do, the principles by means of which alone it is, according to my experience, possible to come to any correct decision in the case of pathological processes. I heartily thank you for the lively interest which you have testified to me up to the last moment. I perfectly know how to appreciate the fact that men like you, whose time is taken up by such manifold labours, still retain a taste for discussions of this kind, and I only wish that many a useful view of recent date may have been rendered more intelligible to you by these lectures, and that the facts I have laid before you may furnish you with recollections which may prove of service in your practice.

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