Physiology. — *"A Contribution to the pathological histology of striated muscle-tissue"*. By P. NIEUWENHUIJSE. (Communicated by Prof. C. A. PEKELHARING).

(Communicated in the meeting of December 29, 1917).

During my stay on the isle of *Urk* as medical officer I found in the dorsal muscles of a plaice a rather big hard white knob, which consisted of striated muscle tissue and looked like a tumour.

At the microscopical examination I was struck with the peculiar changes of the muscle fibres which were quite unknown to me, and which in the beginning I considered as belonging perhaps specifically to muscles of a fish.

When however later on I found that similar changes also occur in human muscles, it became evident that we had to do in this case with a process of more universal significance, which can appear in striated muscles in general.

Macroscopical examination: A plaice (Pleuronectus platessa), caught in the North-sea, long 31 c.m. showed at the right upper side of its body an irregular hard knob nearly as big as a child's fist which was prominent under the undamaged skin.

In sections it appeared that this knob consisted of muscle tissue, rather hard of consistence, pale coloured with yellow spots here and there and sharply marked against the surrounding tissue.

The knob could in some places easily be detached from the surrounding muscle tissue, so that it reminded us in many respects of a fibromyoma in the musculature of the uterus and consequently looked quite like a tumour.

The knob consisted principally of two parts, separated by connective tissue, which diverged in the proximal direction and so in some sections they made the impression of two single knobs (Fig. 1).

The plaice was for the rest normal and well nourished; neither in the other muscles nor in the internal organs any abnormities could be stated.

Microscopical: The pieces were fixed in formalin (10 %) imbedded in paraffin or celloidin and stained in different ways. Some pieces were before imbedding hardened in Müller's solution; after that a number of frozen sections were made and finally by means of teased preparations I tried to isolate some fibres.

In the preparations we could see that the knob consisted only of striated muscle tissue, the fibres of which, showing many signs of degeneration, were of different size.

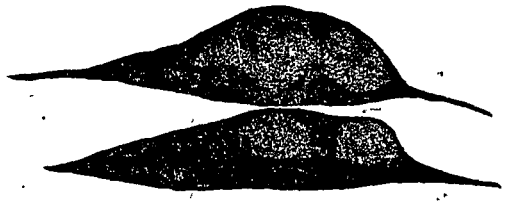

Fig. 1. Section of the fish, in which the muscle-knob is to be seen. The knob is divided into two parts, which diverge in the proximal direction and make by doing so the impression in the lower section as if there were two single knobs.

The fibrous tissue between the muscle fibres had increased; the arrangement of the great septa of connective tissue pretty well agrees with normal proportions, but the thinner bundles surrounding the separate muscle fibres are often irregularly and considerably thickened.

In some places in the connective tissue an accumulation of small cells with round irregularly coloured nuclei and a small quantity of protoplasm is to be found; other sections show much fatty tissue with rests of degenerated muscle fibres.

Neither haemorrhage nor bloodpigment could be stated.

Studying the structure of the muscle fibres, the question arose how the normal dorsal muscles of Pleuronectus were built. It is well known that fishes normally show peculiar grouping of the bundles of fibrils and this in such a way that the fibres of a given muscle group in a given fish species ordinarily have in this respect a characteristic structure.

Lansimaki [1], who studied this question carefully, found in the dorsal muscles of Pleuronectus that each fibre showed in its exterior part a thin layer of ribbon-shaped bundles of fibrils, whilst the inner part was filled up with cylindric bundles.

In self-made preparations of a normal plaice I could confirm these statements (Fig. 2).

In the preparations of the muscle-knob the fibrils are generally coarser than normal; the transverse striation, however, shows the usual dimensions, and is in all non-degenerated fibres distinctly visible. The typical normal form and grouping of the bundles of fibrils is in the various smaller fibres clearly to be seen, the big fibres however do not often show the peripheral ribbon-shaped fibrils. Some very small fibres possess only ribbon-shaped bundles which form a starlike figure in transverse sections.

In longitudinal sections one can see that the fibres here and there give off greater and smaller branches. The myoplasm has in some places a little increased in volume.

The muscle-nuclei are in the smaller as well as in the bigger fibres not more numerous than normal generally they are situated at the periphery, but sometimes also between the fibrils; the nuclei are somewhat swollen; nuclear divisions could not be detected.

Among the big non-degenerated fibres many show a curious and striking structure. In transverse sections they seem to consist of two concentric parts: the inner

[1]) T. A. Lansimaki (Helsinfors) Ueber die Anordnung der Fibrillenbundel in den quergestreiften Muskeln einiger Fische. Anat. Hefte. Heft. 126, S. 254.

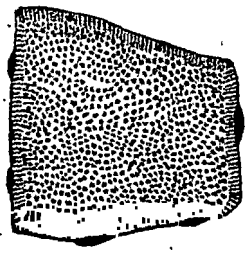

Fig. 2. Cross-section of a normal muscle-fibre of a plaice; one sees the transversely cut cylindric bundles of fibrils in the centre and a small layer of ribbon shaped bundles on the edge (Zenker's liquid, iron-haematoxylin, enlargement 600).

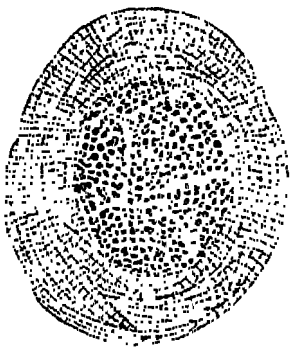

Fig. 3. Cross-section of a fibre of the muscle-knob. One sees two concentric parts: an interior part with fibrils which are transversely cut and an exterior part with circular fibrils. (formalin, ironhaematoxylin, enlargement 500).

part shows the cross-cut longitudinal fibrils, while in the exterior part only circular fibrils are visible. Between the two parts a narrow fissure is generally to be seen (Fig. 3 and 4).

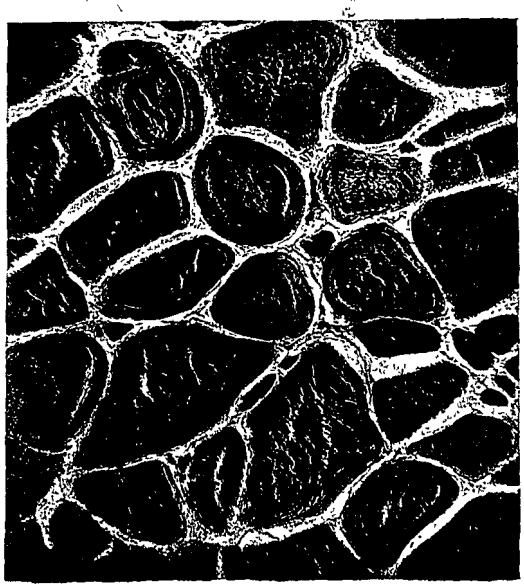

Fig. 4. Fotograph in which a great number of fibres as mentioned in fig. 3, are visible.

In longitudinal sections we see, that the circular fibrils do not appear along the whole length of the fibre but are localized to one or more places, while the muscle fibre has become here more voluminous (Fig. 5). The fissure between the central and peripheral fibrils is not always present: here and there longitudinal fibrils bend aside and join the circular-ones (Fig. 6).

In teased preparations it was further to be seen that many peripheral fibrils do not surround the fibres in rings, but go around them in a spiral fashion.

The fibres in question are generally bigger than normal; they branch sometimes just like the other fibres; in their neighbourhoud one often sees very thin muscle-elements, which are a single time in connection with the peripheral fibrils. The fibres often undergo degeneration, about which more later on.

The nuclei are greatly swollen; they have become oval vesicules with a darkly stained point in the centre and remind us sometimes of protozoa. Their number has not or only a little augmented; they are situated either in the circumference of the fibre or in the centre and frequently between the peripheral and central fibrils. Nuclear divisions were not to be found.

Fig. 5. Longitudinal section of a fibre as mentioned in fig. 3. One sees that the circular fibrils only appear in some places of the fibre. (enlargement 60).

As mentioned above, most muscle fibres show considerable signs of degeneration: first an extensive fatty degeneration, further a change, which strikingly resembles the well known "Zenker"-degeneration.

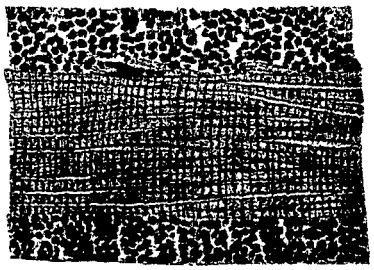

Fig. 6. Longitudinal section of a fibre as mentioned in fig. 3 more enlarged than the preceding one. One sees that some longitudinal striped fibrils join the circular ones (formalin, ironheamatoxylin, enlargement 500).

This change appears locally, and does not occupy the whole fibre; both the longitudinal and the transverse striation get invisible so that a homogeneous mass results, which afterwards is reduced to pieces and coarse corns.

Between the homogeneous pieces in more advanced stages many round nuclei appear. The contents of some fibres become liquid and get resorbed and consequently the walls of the fibre fall together.

The above mentioned muscle fibres with the mantle of circular fibrils seem very seldom to undergo the "Zenker" degeneration. They very often show however another kind of degeneration: their fibrils become thinner, lose their transverse striation and are reduced to very fine threads and grains; these grains get resorbed, so that in the end a rather homogeneous mass remains, which can hardly be

stained and which is easily distinguished from the homogeneous masses in the "Zenker" degeneration.

This degeneration principally occupies the circular fibrils, which are often already quite changed into very small threads and grains while the central fibrils are still normal.

In many fibres the figure becomes still more intricate, because bundles of longitudinal fibrils are visible between the circular ones. This phenomenon sometimes appears to such an extent, that we can call it a real twisted-work. This twisted-work is generally only to be seen in the peripheral fibrils, but may also occur in the central part of the fibre.

The twisted fibrils always show signs of degeneration and it is a general rule that: the more the figure is intricate, the more the degeneration is advanced.

These pathological changes are nearly always accompanied by thickening of the muscle fibre, which may become so extensive that a diameter of $250 \times 250\ \mu$ in transverse sections is not uncommon.

With this kind of degeneration there is not much activity of the nuclei; in some spots they have become more numerous, but accumulations of nuclei as in the fibres with "Zenker" degeneration were not to be seen.

Although the muscle knob seemed to be distinctly contrasted with the surrounding tissue, microscopical investigation showed us the presence of divers degenerated fibres and also fibres with a mantle of circular fibrils in the immediate vicinity.

With the exception of the above described groups of cells in the connective tissue no signs of inflammation were apparent; these cells have probably something to do with the evacuation of rests of degenerated muscle fibres; we may therefore not deduce from this that it is a process of inflammation.

We looked carefully for the presence of bacteria, protozoa and of other parasites, but without result. [1])

The microscopical examination of the brain, the spinal cord and some peripheral nerves showed nothing interesting.

Some viscera were examined, but these neither showed any abnormities.

Among the different pathological changes which were present, we must pay special attention to the numerous peculiar muscle fibres, which in transverse sections seem to exist of two concentric parts, the exterior part containing circular fibrils, the interior part containing longitudinal-ones.

How can this figure be explained?

As in the beginning I could not find in the literature any description of these changes, nor any connecting statement which made it possible to explain them, I was inclined to think that these changes could possibly be connected with the peculiar structure of the muscle fibres of fishes, which normally already show a difference between the centre and the periphery and to consider this stucture as the cause of these curious changes.

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[1]) I wish to express my gratitude to Mr. J. H. SCHUURMANS STEKHOVEN JR., interem-zoologist of the Institute for Tropical Hygiene at Amsterdam, for his kind help with this part of my investigations.

This interpretation, however, was not quite satisfactory because the difference between the centre and the periphery of a muscle fibre of Pleuronectus is really not a difference in structure, but a difference in grouping of the fibrils, while all the fibrils are, as far as it is known, identic in form and function. Fortunately I perceived at last that similar changes were already described in human muscles viz. in a case of acromegaly that was communicated by C. MARTINOTTI in 1902. [1])

As I could not get possession of his original publication, I am obliged to cite the following sentences of an epitome of the "Ergebnisse der allgemeinen Pathologie und pathologische Anatomie", 12 Jahrg. p. 317. Muscle fibres of the musculus biceps show the following pathological changés: "Es bestand Hypertrophie der Muskelfasern mit betrachtlicher Vermehrung der Muskelkerne. An einigen Muskelfasern sah man Bundel von querverlaufenden Fibrillen, die die längsverlaufenden umfassten oder durchkreuzten. Die querverlaufenden Fibrillen waren nicht überall, sondern nur an einzelnen Stellen der Muskelfasern zu sehen und konnten nicht auf weite Strecken verfolgt werden. Verf. glaubt dass die Fibrillen mit abnormen Verlaufe neugebildet seien und dass sie einer Form von pathol. Muskelhypertrophie entsprechen, die vielleicht mit den akromegal. Prozesse in Zusammenhang steht".

Although the muscle nuclei in this case are more active than in our preparations, the resemblance of the two pathological changes is so striking, that we may surely identify them.

In the human pathology a few cases more are mentioned in which the alterations resembled our process in some ways.

ERB [2]) described in 1891 in a case of dystrophia muscularis progressiva "ineinandergeschachelte Muskelfasern", of which he says p. 184 "Stellenweise sieht man auch sehr sonderbare Spaltungs- und Theilungsfiguren, wie wenn sich im Centrum der Faser eine neue Faser entwickelt oder abgespalten hatte".

DURANTE [3]) described in 1900 in a case of hypertrophy of the muscles of the arm similar figures which he interprets as being

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[1]) C. MARTINOTTI: Su alcune particalarità di struttura della fibra muscolare striata in rapporto con la diagnosi di acromegalia Annali di freniatria e scienze affini del R. Manicomio di Torino Vol. XII, p 76.

[2]) W. ERB: Dystrophia muscularis progressiva. Deutsche Zeitschr. f. Nervenheilk. Bd. I S. 173.

[3]) G. DURANTE: Hypertrophie musculaire volumétrique vraie du membre superieur par augmentation de volume des fibres musculaires. Comptes Rendus de la Soc. Anat. Paris Mars 1900.

the result of concentric divisions; he says p. 275: "C'est ainsi que cette division peut être concentrique et au lieu de donner naissance à deux fibres acollées, peut séparer deux éléments, l'un entourant l'autre comme les parois d'un tube entourent le mandrin qu'on y introduit".

It is a pity that neither in the text nor in the figures these authors give any indication about the course of the fibrils, so that it is impossible to compare their changes with those in our case. Their interpretations appear to me to be not very plausible; it is difficult to understand how it can be possible, that a new fibre develops within the centre of an old one, and it is still more difficult to imagine how a muscle fibre by means of division could give rise to two concentric parts; both ideas are so little analogical with other better known processes.

ERB described in the dystrophia muscularis progressiva a second peculiarity, which may be important in this respect; he saw in transverse sections that many muscle fibres were encircled by very small and larger muscle elements, which he could follow a good way in the surrounding connective tissue; they seemed to bifurcate there and resembled in their behaviour the capillaries. ERB considers them fine bifurcations of muscle fibres and was reminded by them of the so called "Muskelknospen" of NEUMANN.

Although these figures, superficially considered, have nothing to do with ours, this statement of ERB seems to me of great interest.

However important we must consider the above mentioned data of the literature, still they do not explain to us the nature of the changes in question.

If we now try with the aid of the preparations to analyze the peculiar figures, we must begin to look for the origin of the circular fibrils.

In transverse sections we see that they are nearly always separated from the central fibrils by a small fissure, but in longitudinal sections we could demonstrate a distinct connection between them: in some places we saw many central fibrils bend aside and join the peripheral ones. Teased preparations taught us that the peripheral fibrils do not follow exactly the circular direction, but often go around the fibre in a spiral fashion.

I should like to say thus, that the muscle-fibres give off here and there thin lateral branches which do not enter into the surrounding tissue, but remain within the sarcolemma and go around the fibre in circles and spirals.

The fibre is enveloped in this manner over a certain length by a thick mantle of these branches, so that in cross sections we see

two concentric parts, which however is not the result of a concentric division, but of abnormal branching.

If moreover we consider that we have to do with fibres which are strongly proliferating, take as evidences the hypertrophy, the longitudinal divisions and the presence of a great number of young fibres, it may be clear that this process is nearly related to the well known lateral buddings of muscle-fibres the so called "Muskelknospen" of NEUMANN, especially because the before mentioned second observation of ERB already informed us of the encircling of muscle fibres by elements which have grown out of these "Muskelknospen."

Therefore I should wish to conceive the peripheral mantle of the fibres as a complex of defectively developed and abnormally grown lateral branches.

With this conception it is easily understood that the circular fibrils often appear only on one or more spots of the fibre, and leave sometimes a great deal of the fibre free; it is just as well comprehensible that on transverse sections we generally see a narrow fissure between the central and peripheral fibrils, moreover it will be clear that sometimes out of these fibres originate very thin muscle-elements, which can be followed into the surrounding fibrous tissue, whilst finally it becomes explainable that the peripheral fibrils, abnormal of origin as they are, sooner undergo degeneration than the central fibrils which form the real fibre.

This conception leaves of course many facts unexplained: first of all is it not clear why these fibres should give off so many abnormal branches, and why their nuclei have swollen so peculiarly and taken the form of vesicules, while the nuclei in the surrounding fibres are much smaller and more solid; finally the curious behaviour of the fibres with regard to degenerations is still unexplained: while the surrounding fibres undergo "ZENKER" degeneration, we see here rather constantly the above described peculiar reducing of the fibrils to very fine threads and grains.

All this cannot be quite accidental, because these alterations appear too regularly; I could not find however a satisfactory explanation for these facts.

We now come to the question how this abnormally proliferated tissue must be considered: is it allowed to classify it among the tumours or not?

Macroscopically it looks quite like a tumour, but we shall see that after microscopical examination this diagnosis cannot be sustained; firstly we find in rhabdomyoma always very small muscle-fibres.

(in cross sections generally smaller than 20 μ, only RIBBERT found some bigger fibres up to 80 μ); here however the fibres are generally enlarged, some of them even reach a diameter of 300 μ.

Secondly one sees in rhabdomyoma that the small muscle-fibres have a very defective structure; frequently they can hardly be recognised; a rhabdomyoma of a fish published by FIEBIGER [1]) showed just as well very small elements which could scarcely be identified with muscle-fibres.

In our case however the small fibres have generally a normal structure, whilst the abnormities appear in the big fibres. Further we see that the arrangement of the septa of fibrous-tissue resembles for the greater part the normal conditions; we do not see here a capricious grouping of the muscle-fibres, as can be expected in tumours, and finally we see that hypertrophic fibres also occur in the normal muscle-tissue that surrounds the knob. From these observations I conclude that in this case we have not to do with a new grown tissue which to a certain extent carries on an independent existence, but with a tissue that has grown by hypertrophy and abnormal proliferation of muscle-fibres which were already locally present.

Such a local proliferation of striped muscle-fibres looking like a tumour is very uncommon.

In the literature I could only find one similar case: LORENZ [2]) described a "geschwulstartige Hypertrophie" in the musculus glutaeus maximus of a man 52 years old, which has grown after "Ueberanstrengung".

Here he found very big muscle-fibres even 100 μ and 200 μ in transverse section. The fibrils were coarser than normal, the transverse striation was less distinct, in longitudinal sections he saw many divisions of muscle-fibres; divers fibres showed degeneration. ("ZENKER" degeneration and "fibrillaire Zerklüftung").

The nuclei of the sarcolemma had not augmented, signs of inflammation were not present.

The case of LORENZ rather resembles ours; as for the etiology it does not teach us anything.

Neither in our case could I find the cause of this abnormal proliferation: bacteria, protozoa and other parasites were not to be found, evident signs of inflammation could not be discerned, the peri-

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[1]) J. FIEBIGER: Ein Rhabdomyom bei einem Kabljau. Zeitschr. f. Krebsforschung Bd. 7. S. 382.

[2]) Handb. der spec. Pathol. u. Therapie (NOTHNAGEL) Bd. XI. S. 415. 1904.

pheral nerves, the spinal cord and the brain did not show us any changes and with regard to the communication of MARTINOTTI I took moreover special notice of the hypophysis, which however was quite normal.

Still it could be possible that we had to do with an excessive regeneration of the muscle-tissue, after a trauma, but for this we have no positive data.

Though in this case we have to do with a local tumourlike proliferation of muscle-tissue, of which no cause can be discerned, and which is of no use for the body, still I should not like to speak of a tumour for just in strange proliferations of the tissues of lower animals, it is in my opinion far better not to be too liberal with the word tumour.