Neurobiology. — *"A hypothesis concerning the mutual relation between some hereditary abnormalities that occurr combined".* By Dr. N. VOORHOEVE. (Communicated by Prof. Dr. I. K. A. WERTHEIM SALOMONSON).

(Communicated in the meeting of May 26, 1917).

In the following lines I intend:

1. to explain the grounds on which my hypothesis rests *that a hereditary inferiority of the mesenchyme occurs,*
2. to elucidate the significance and the scope of this hypothesis.

I. I was induced *to state this hypothesis* in consequence of considerations concerning the results of an examination of three patients, whilst an examination of the family relations afforded *strong proofs for the validity* of this hypothesis.

It appeared, that a father and his two daughters were troubled with *blue sclerotics* and *brittle bones*, a combination which, though very rare, has already several times been described, and the heredity of which has been proved.

The father was moreover suffering from *haemophily*, an abnormality, which is likewise exceedingly hereditary.

If we account for the *anatomical substratum* of these abnormalities, then it appears:

a. that the blue colour of the sclerotics is caused by their congenital excessive thinness;

b. that the brittle bones which in my cases proved to be the consequence of osteopsathyrosis infantilis, is a consequence of an *inferiority of the ossificating elements*;

c. that so much may be stated with certainty concerning haemophily, though its pathogenesis may not yet be perfectly clear, that it is a consequence of an *inferiority of blood resp. bloodvessels.*

Consequently there existed in these individuals a hereditary inferiority of 3 systems of organs: sclerotics, skeleton and blood resp. bloodvessels. Their hereditary transmission pointed to an endogenous cause, or in other words, to a defect in design.

The abnormalities found here belong in fact to the rarities, and it was obvious that the combined occurrence of these abnormalities, which in themselves are already rare, could not be regarded as merely accidental. Consequently not 3 abnormalities existing beside and independently of each other, but 3 consequences of one and the same germinal defect. If this were indeed the case, there should be one point in the embryonal development from which these three systems of organs differentiate. And now embryology teaches us that this is indeed the case, and that they are all three products of the mesenchyme. We have now therefore put forward the hypothesis, *that we have here to do with an hereditary inferiority of the mesenchyme.*

The foregoing hypothesis is now supported:

A. By the results of a closer examination of the 3 *patients.*

It appeared namely that in these patients still other products of the mesenchyme showed abnormalities, which were either congenital, or consequences of an inferiority revealing itself in abnormally early wastage of the respective organs.

So we find in the father (at the age of 54 years):

on both sides *a very strong arcus senilis corneae*;

a *rather strong sclerosis of the bloodvessels*, though there were no propitiating causes at work as lues, intoxications (lead, alcohol, tobacco) or nephritis;

a *rectangular position of the two auricles* with regard to the skull.

In the elder girl *the two little fingers were in radial adduction in the metacarpophalangeal joint.*

B. By the examination of the other members of the family.

I could obtain information about 244 members of the family extending over 5 generations (children that died very young, are not included). Only the branch of my patient's father has been included in the scheme. Of these 59 children I myself could interrogate and examine superficially 40. It appeared now that already from my patient's grand-parents haemophily occurred in this family, and that there were several cases of blue sclerotics and also of haemophily among the 59 individuals whom I included in the scheme. Moreover there was one case of *congenital defect of the heart*, one of *split palate with harelip*, one of *rachischisis.*

This is of course the minimum of the existing abnormalities for I could only make a thorough examination of a few of the 40 individuals whom I saw myself. Two cases of *very severe rickets*

are likewise indicated in the scheme, in the first place, because it is possible that someother, perhaps hereditary, abnormality of the skeleton was present, and in the second place, because perhaps the occurrence of severe rachitis point to an heriditary inferiority of the skeleton

Now it appears that all the congenital defects in this family relate to products of the mesenchyme. There are however some mesenchyme-derivations, where about we did not yet speak. These are the spleen, the lymph-glands and -vessels, the conjunctive cellular tissue and the involuntary muscles. Were these groups of organs perhaps not defect in design? In order to find an answer to this question we must consider the following:

We still know so little about the physiology of the spleen that we cannot be astonished, if an inferiority of this organ, which we can miss entirely even without any disturbance worth mentioning, does not come to expression in a clinical respect. But moreover and especially, it is very doubtful whether the spleen originates in the mesenchyme.

As to the *lymph-glands* and *-vessels* we are struck by the fact that so much lymph-gland-tuberculosis occurs in this family, whereas the relation of frequency between tuberculosis of the lymph-glands on the one hand and that of other organs on the other hand is very large. Perhaps we may see in this fact a proof of inferiority expressing itself in a diminished resistance of the lymph-apparatus against infection with the bacilli of tuberculosis.

With regard to the three latter groups: *conjunctive cellular tissue, ligaments and involuntary muscles* it must be born in mind, that the physiological signification of this tissues, hidden in the body, is only of a secondary vital interest. And if we consider now, that the blue sclerotics are only recognised as such, thanks to their superficial situation, we need not be astonished that a less strong design and a decreased power of resistance of these tissues needs not come to expression in a clinical respect. We still remark moreover that many women of this family and even men showed the type of the *"habitus atonicus sive asthenicus"*; I leave undecided however, whether this should be considered as a proof of a congenital inferiority of the ligaments.

Taking all in all it is not doubtful, but the results of the *scrutinous examination* of these three patients and of the other members of the family form a *strong support* for the *hypothesis* stated above.

There is however more. Whilst the three patients showed us an

entirely developed inferiority of the mesenchyme, the examination of the other members of the family enables us *to follow the development of all the phases of our disease and to observe the precursors of the outbreak.*

Indeed the inferiority of the bloodvessels is not seen exclusively in the presence of haemophily, a congenital defect of the heart shows in what a labile equilibrium the constitution of this organic system is found. Osteopsathyrosis does not yet occur, but the skeleton already shows signs here and there of abnormal design, the rachischisis and the split palate are there to prove it. Blue sclerotics, although less intensive than in my patients are already found in several individuals, and one of them shows moreover a congenital cornea-abnormality (embryotoxon).

The catastrophe first take place in the person of my patient and his daughters; what had been threatening for some generations is realised: the mesenchyme shows its insufficient design in an unmistakable inferiority.

II. The *significance of this hypothesis* is of for greater general scope than to explain the origin of these abnormalities in my patients.

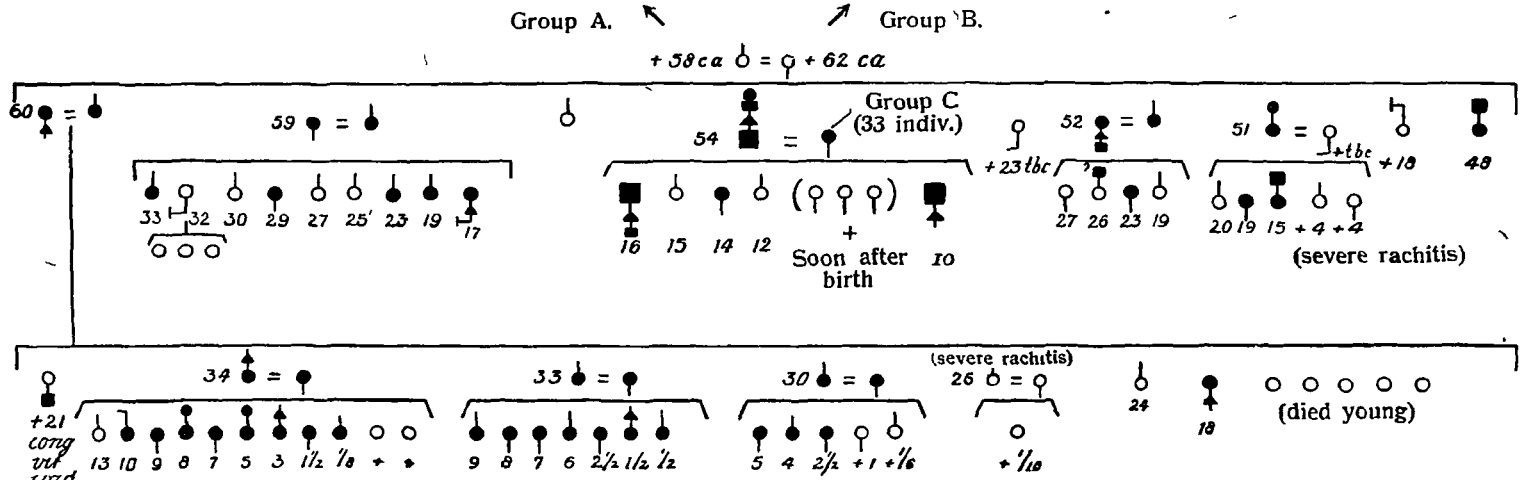
In this family we had to do with a hereditary inferiority in design of one of the 4 great groups into which the embryonal cells are differentiated in the very first phase of the development of the germ. It seems to me that it is of great interest for the doctrine of hereditary abnormalities that it is possible that germinal defects exist affecting the individual already at so early a stage, and set their stamp upon him.

Do such inferiorities of the whole mesenchyme or of the greater part of it occur more? Can they likewise be restricted to the exclusion of the mesenchyme and of the two other germinal layers to one germinal layer? Do they likewise occur hereditarily? Numerous facts indeed seem to point that way. Innumerable are the questions rising with regard to this hypothesis. It is really *a working hypothesis.* And it seems to me that it is a very important undertaking to examine, guided by this hypothesis, the combinations of hereditary abnormalities in connection with other degenerations in one and the same family. For what is known of these combinations or correlations is, almost without any exception, limited to the mere statement of the facts as such, and a dominant idea, if there was one, in the explanation of these correlations, has not been succesful.

GENEALOGICAL TREE.

Group A. 83 indiv.
- 1 + *haemophily* (Son of daughter of ancestors)
- 1 + epilepsy
- 7 cases of tuberculosis

Group B. 69 indiv.
- 1 + *morbid coerul.* (Grandchildren of ancestors)
- 1 + born lame } Great-grandchildren
- 1 + dwarf } of ancestors
- 1 hunch-back
- 6 + tuberculosis



Explanation of the signs:

- individual examined by me
- » not seen » »
- man
- woman
- osteopsathyrosis infantilis
- blue sclerotics.
- haemophily
- congenital abnormality.
- tuberculosis.
- tuberc. of lymphgland.
- = married with

The figures placed under or beside the indiv. indicate the age in years.

Remark. In order not to make the survey too difficult, the details of Group C have not been indicated; they are indeed of no interest for the critical examination.

One question be still mentioned here, because I had to put it already when studying this family:

How far can the degeneration of the mesenchyme proceed in a family before one or more of the other germinal layers also begin to degenerate? It is obvious, that precisely families with a defective mesenchyme are the most suited to give an answer to this question, in view of the comparatively less important functions of most of the mesenchyme-organs.

I was able to have two members of this family and two of my patients examined otologically (Prof. BURGER). All four of them, though they had no complaints worth mentioning, proved to be suffering from a *labyrinth deafness,* an hereditary disease par excellence. But an affection of an ectodermal organ.

On the contrary VAN DER HOEVE and DE KLEYN found in their patients who suffered from blue sclerotics and brittle bones, otosclerosis (mesenchyme), although they could state with one patient a combination of otosclerosis and labyrinth deafness. I doubted however immediately, whether the affection of the organ of CORTI in my patients was a primary or a secondary one. For according to the investigations of QUIX and VAN LENNEP the atrophy of the organ of CORTI, is most probably caused in some cases of hereditary labyrinth-deafness (in casu the dancing-mouse) by a primary affection of the stria vascularis. Now the latter is a product of the mesenchyme.

And so at any rate the possibility is present that the affection of the labyrinth in this family is a further proof of an inferior mesenchyme, and the occurrence of this abnormality need not lead to the conclusion that the inferiority in this family is not restricted to the mesenchyme.