

# THE CHANGES OF HYPOTHALAMIC NUCLEI IN SCHIZOPHRENIA.

WALDEMAR WAHREN

(Neustadt i/Schwarzwald, Deutschland)

## *Introduction.*

It is one of the fundamental problems of the researches on schizophrenia to find out those elements of the brain, which by deterioration cause the symptoms of schizophrenia. Some clinical experts, who, by studying vegetative phenomena have got their concept of the nature of schizophrenia, think, that the central vegetative regions play a special and important part in causing schizophrenia. In the following investigation it shall be examined how far this supposition can be verified in the field of anatomy.

In the early thirties HECHST has investigated the hypothalamus of persons suffering from schizophrenia without a positive result.

## *Material.*

The brains examined were those of 8 people suffering from catatonic schizophrenia and of 2 people suffering from paranoic schizophrenia. They have died in the years between 1930 and 1933, before the shock-therapy came into use (Table I). To compare the brains of the persons mentioned above with those of persons not suffering from schizophrenia, I examined 30 brains of nonpsychotics aged from 7 to 99. Besides, I had still 33 brains of choreatic persons, whose hypothalamus I had worked on before. All the brains are frontally cut, fixed in formol, embedded in paraffin, and stained according to Nissl and Feulgen.

## *Method of Architectonic Examination.*

In studying the hypothalamus I used BROCKHAUS' architectonic division as a fundamental basis. On reviewing the sections I made use of comparison microscope of Zeiss and of survey photographs. On these photographs the limiting outlines of the several architectonic fields have been entered and their nerve- and glia-cells counted (Fig. 1 and 2). Considering the high variability of the extension and density

---

From the Brain Research Institute, Neustadt/Schwzw. Germany. Director: Prof. Dr. O. Vogt.

The author is grateful to Prof. O. Vogt, for giving the problem, providing space and material, and for helpful suggestions and criticisms.

Brain :	Age at the beginning of the disease :	Age on the day of death :	Sex :	Diagnose :	Cause of death :	Hereditary taint .
Bu 3	18	22	♀	catatonic schizophrenia	delirium acutum	+
Bu 20	18	26	♀	catatonic schizophrenia	pneumonia	∅
Bu 46	19	19	♂	catatonic schizophrenia	myodegeneratio cordis	+
Bu 52	21	23	♂	catatonic schizophrenia	sepsis	+
Bu 24	23	28	♀	catatonic schizophrenia, pellagra?	insufficiencia cordis, bronchopneumonia	+
Bu 53	24	27	♂	catatonic schizophrenia, pellagra?	myodegeneratio cordis	+
Bu 19	29	44	♀	catatonic schizophrenia	insufficiencia cordis	+
Bu 21	36	42	♀	catatonic schizophrenia	bronchopneumonia	∅
Bu 62	40	64	♀	paranoic schizophrenia	suicide	+
Bu 7	49	73	♀	paranoic schizophrenia	infarctus cordis	+

Wahren : Changes of Hypothalamic Nuclei in Schizophrenia.

Table I

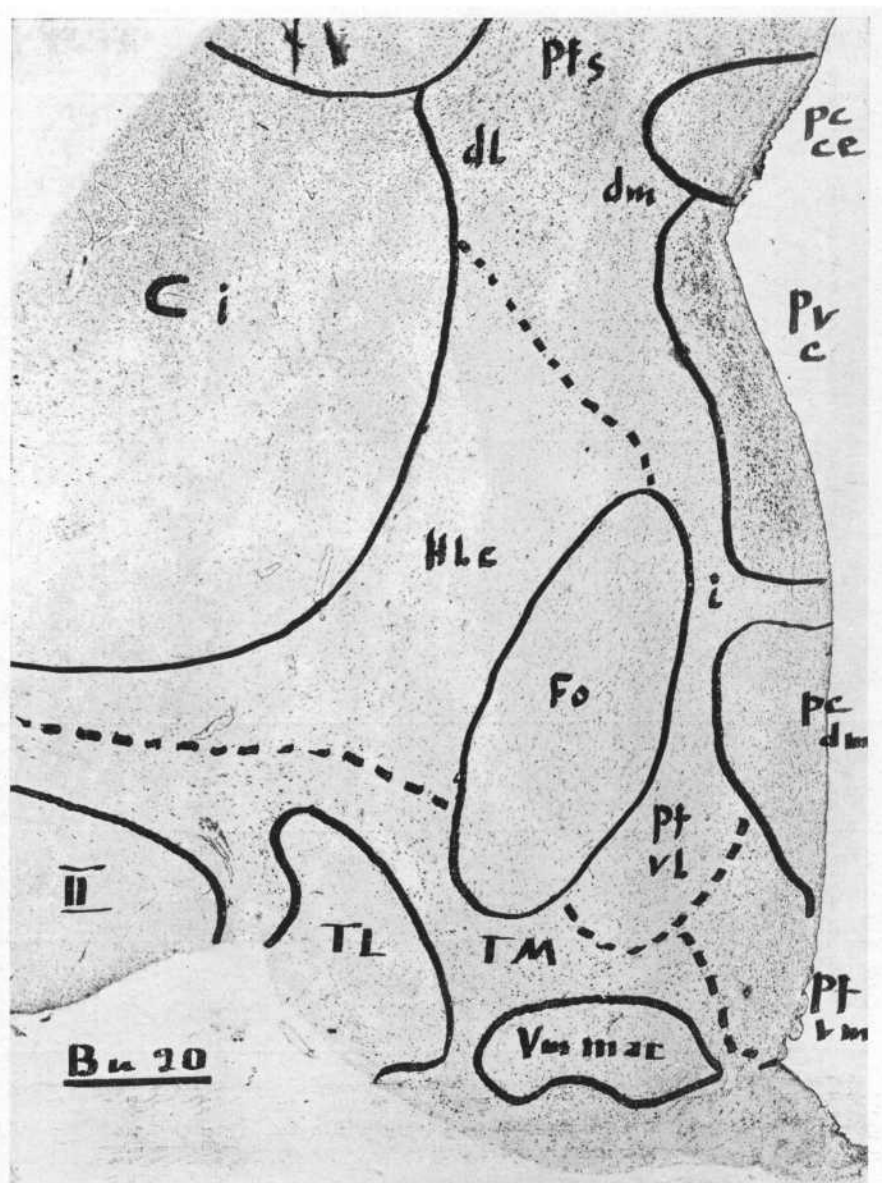


FIG. 1. Survey photograph of the tuber cinereum of the schizophrenic Bu 20.

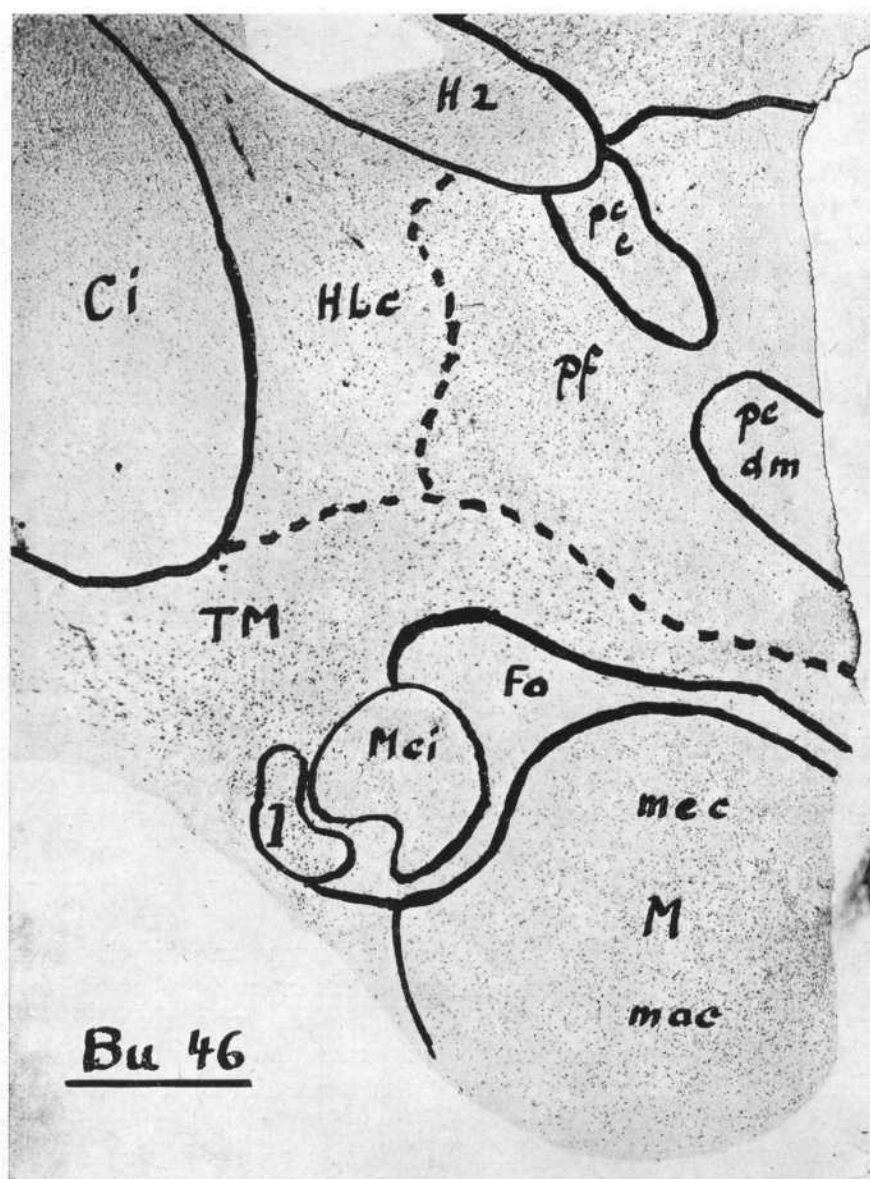


FIG. 2. Survey photograph of the corpus mammillare of the schizophrenic Bu 46

of cell in the hypothalamic regions a change there must be evident, before we can look upon it as morbid. Even if there are many more nerve- and glia-cells than those counted in the cases compared, this can only be interpreted as a symptom of stunted growth if this increase in cells is not ubiquitous.

*Result of the architectonic investigation.*

In examining the 10 cases of schizophrenia, I could not observe any extraordinary architectonic changes. There could be found neither any important losses of nerve cells nor any spectacular stunted growth in isolated grisea. Considerable changes could also not be observed on glia and vessels.

*Method of the analytical investigation of the nerve-cell structure.*

In reviewing the sections there could be seen not very rarely a special paleness of the nerve cells, a paleness not to be explained in all cases by the old age of the colored sections. I found similar phenomena in the hypothalami of nonpsychotics, but they were, as I believe not so numerous. Since there is only a short way from the finding of pale cells short of chromatin to the statement, that the cells in question are «wasting-cells» («Schwundzellen») and since I don't want to allow myself to be deceived by the impression made upon me by the physiognomy of the cell, I analysed all the special structures of the nerve cells as they can be seen in the Nissl-stain. I try to get hold of those special structures as far as possible in detailed examinations of their quality and quantity. If there are constant and demonstrable changes of certain organs of the cell at the bottom of these pale cells short of chromatin, those changes should be defined as to their nature. This method could lead to the solid construction of the notion of «wasting-cell» (Schwundzelle). Further motives for employing an analysis of the structure of the nerve cells which must be as intensive as possible, are the experience, that the usual divisions of the changes of the nerve cells fail occasionally in relation to the special condition of the hypothalamic cells, and the supposition, that the optical perceptibility of a change in the Nissl stain does not yet represent a standard for judging the degree of the functional injury of the cell. A simple change in the structure or a special manner of behavior of the organs of the cell could show the general denominator of the hypothalamic cells of schizophrenics. The cell analysis comprises the following detailed examinations:

1°) Measuring out the size of the plasma, nucleus and nucleolus with the help of the Okularmikrometer of Leitz.

2°) Critical examination and interpretation of the form as to plasma, nucleus, and nucleolus.

3°) Definition of the degree of the tinction as to plasma, nucleus and nucleolus. The absolute values of the tinction being in the vast majority caused technically the differences of tinction amongst the single organs of the cell is the only thing that matters.

4°) Definition of the quality of the margin as to plasma, nucleus, and nucleolus.

5°) Critical examination and interpretation of the structure of plasma, nucleus, and nucleolus.

As to the nucleolus the question is above all to count and to measure the existent vacuoles. As to the nucleus it is important to see how far the normal transparency is injured by the rise of structured and structurless-diffuse substances. As to the plasma, it is important to get hold of numerous differences concerning the structure and the tincture. Within the cell there is still a central field, a field around the periphery and one around the nucleus, that behave in a different way. All together I could distinguish 15 different qualities of the plasma, which, with its great variability is the most sensitive indicator of cell injuries.

6°) Localisation of nucleus and nucleolus.

7°) The counting out of the thymochromatic which is located:

a) around the nucleolus,

b) immediately around and in close connection with the membrane and the folds of the nucleus,

c) in some other place with no connection either with the nucleolus, not to any structured part of the nucleus.

8°) The determining of the quantity, position, and structure of the tigroid chromatin.

9°) Occurrence of « Lagerungen », that is, of the accumulation of the Feulgen-negative chromatin, which, by its position has any relation to the membrane of the nucleus.

10°) Interpretation of the number, form, and structure of the visible dendrides and axons of the cells.

All together 25 detailed observations of every cell are recorded. Therefore the total number of the cells, which can be examined in this way, is limited. For the critical examination and interpretation of such a complex region as that of the hypothalamus, it would be necessary to study some thousands of cells. This high number results from:

a) the amount of the cases to be studied,

b) the amount of the single hypothalamic grisea to be studied.

c) the amount of the single griseum cells to be studied, an amount which is necessary to study for the interpretation of the average state of the cells.

To reduce this number to a measure, which is possible to work on, I have undertaken, the following steps:

The cytoarchitectonic particularities of 25 hypothalamic grisea, have been reduced to modifications in outward form, number, position and mixture of 6 basic types of cells. Of every brain I investigated only the 6 basic types of cells taken from characteristic places. I found out - by testing at random - that the members of the same basic type of cells behave generally in the same way at different places.

Furthermore, I made a selection from the cells, which had typically changed within a griseum, so that the examination of 10 to 20 exemplary cells was sufficient to set off the characteristic symptoms of the cell structure of every brain.

All together I examined 1000 cells of the 10 schizophrenic and of 3 nonschizophrenic cases. The 3 nonschizophrenic cases are:

A 58, a 24 years old nonpsychotic man, shot dead in a street-fighting.

A 61, a 38 years old nonpsychotic man, who died of kidney-shrinking after 2 days of coma uraemicum.

A 76, a 99 years old nonpsychotic woman, who, until the end of her life, was very active.

#### *Result of the analytical investigation of the nerve-cell-structure.*

All the recorded detailed results made on the cells of a basic type in one case have been reduced to an average value. The average value of one category of symptoms of all investigated brains had been confronted in a diagram. From these I have taken out 4 typical examples in the figures 3 - 5. Fig. 3 represents the size of the plasma, nucleus and nucleolus in the tuberis-lateralis-cells. The schizophrenic cases together with the case A 61 hold there medium values, which are surpassed upwards and downwards by the 2 nonpsychotic cases A 58 and A 76. The greater variation in the value of the plasma compared with those of the nucleus and nucleolus are in keeping with its greater structural instability and is not only caused by the more differentiated measuring values which this greater object had yielded. A similar relation between the results of the examination of schizophrenic and nonpsychotic cases can be seen in the following figures. Fig. 4 shows the thymochromatin values of the mammillaris cells. In Fig. 5, below, the nucleolus vacuols of the tuberomammillaris cells are represented, and



above the degrees of intensity of the nucleus membrane and the nucleus folds and their 2 different structural states. So I had to make use of an other 2 cases in order to compare the changes of the schizophrenics Bu 52 and Bu 53 with similar findings made on nonpsychotics. These 2 cases are:

N 1, a 42 years old nonpsychotic man, who died of paralysis of Landry.

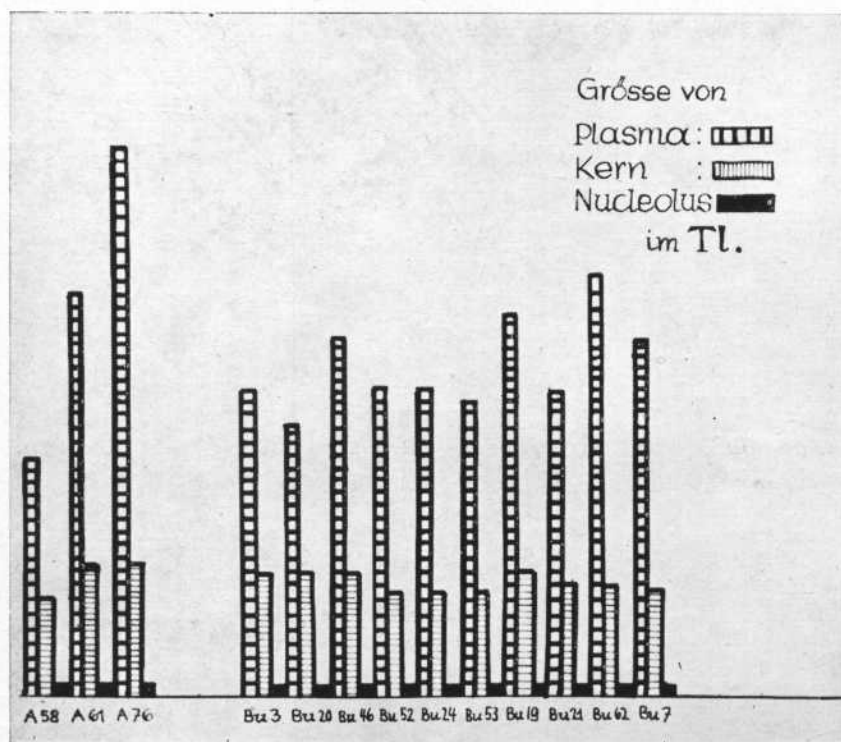


FIG. 3. Size of plasma, nucleus and nucleolus of the tuberislatialis cells of 3 nonpsychotic and 10 schizophrenic cases.

Md 2, a 26 years old man, executed as a murderer.

These 3 cases, which were regularly studied together with the schizophrenic cases, did not suffice for the examination, whether there are equivalences for single extreme values of the schizophrenics amongst the nonpsychotics. Generally it was not difficult to find out those equivalences amongst the nonpsychotic cases. There are but the qualities of the plasma, which, in the single cases, behave so differently, that I



could not find for every schizophrenic case a corresponding nonpsychotic one. But even amongst the schizophrenic cases there are hardly 2, which are in accord with each other concerning their structure of the plasma. Here, then, the individuality of each single case manifests itself already, so that there is the slightest chance of finding out common and specific symptoms of schizophrenia. The plasma of the single basic types of cells do not behave in the same way in regard to the

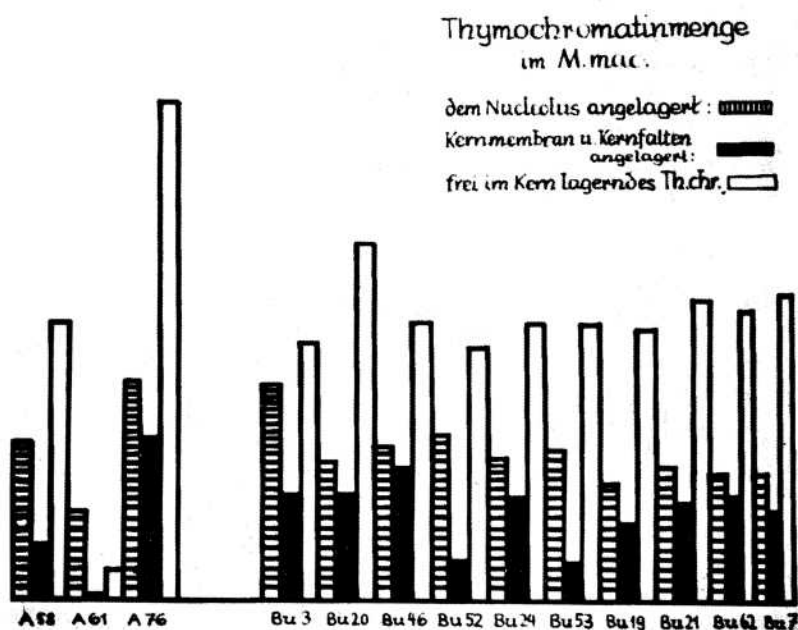


FIG. 4. The thymochromatin values of the mammillaris cells of 3 nonpsychotic and 10 schizophrenic cases.

variability of their structure. Some of them, e.g. the mammillaris cells always change their structure. The others, e.g. the supraoptic cells are so stable, that any differences there are hardly amongst the 13 investigated cases. The same behavior could be observed amongst the 63 nonpsychotic cases, which I used for the purpose of comparison.

When, finally, the detailed results of a case are summed up and the 10 schizophrenic cases are compared with one another, then we have still a greater variability of the combination of symptoms than that manifested itself in the behavior of the plasma. Only in a few single

symptoms 2 cases occasionally resemble each other, the differences are always in the majority. Not one case is like the other.

As a counter example in order to find out, whether, by using this analytical method a uniform behavior of 2 cases on a long distance will be possible, I investigated 2 cases of amaurotic idiotism and 2 cases with a extensive ischaemic cell disease. In doing so, I found far

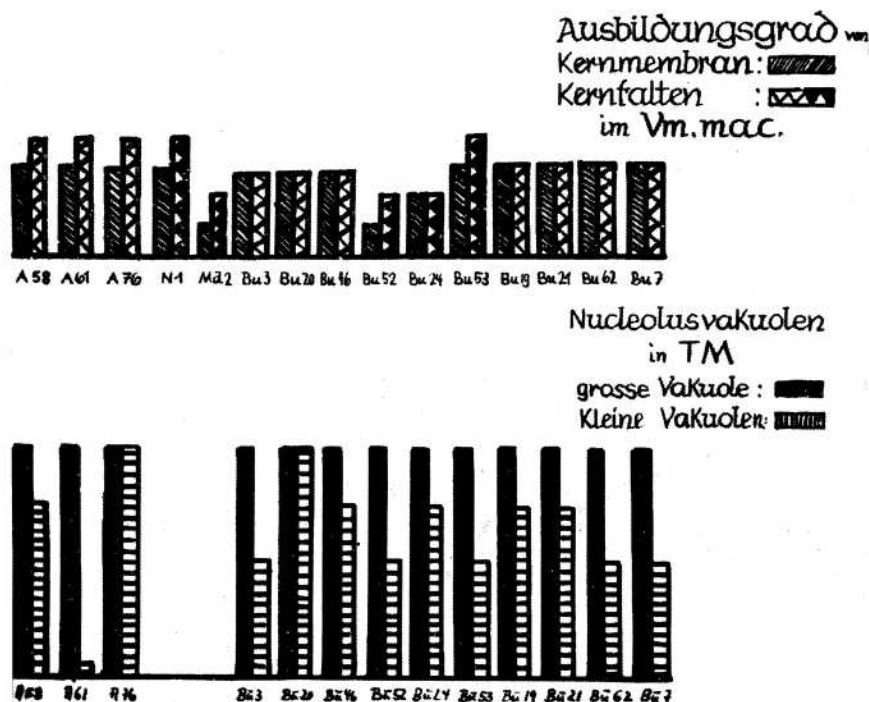


FIG. 5. Below, the nucleolus vacuols of the tuberomammillaris cells of 3 nonpsychotic and 10 schizophrenic cases, above, the degrees of intensity of the nucleus membrane and the nucleus folds and their 2 different structural states of 3 non-psychotic and 10 schizophrenic cases.

reaching accords between the members of the same cases. Even the plasma of the unstable basic types of the cells behave in the same way.

The result of a special comparison of the cases with pale cells is the following:

The impression of pale cells short of chromatin is not supported by a uniform finding of the analytical investigation of the structure of the cell. Apart from the symptom of shortage of tigroid chromatin,

which, because of its general frequency, is not suitable for our special purposes the cell paleness does not depend on a demonstrable deviation of certain cell organs. We did not succeed in placing the notion «wasting cell» («Schwundzelle») upon a real basis, by reducing it to well defined and demonstrable structural changes.

Heres is the summary up of the analytical investigation of the structure of the cell:

1°) All the detailed changes observed on the hypothalamic cells of schizophrenics can also be found in the hypothalami of nonschizophrenics.

2°) If all detailed results of a case are brought together and the 10 schizophrenic cases are then compared with one another, not one single case is like the other concerning its actual combination of structural symptoms.

3°) We did not succeed in placing the notion «wasting cell» («Schwundzelle») upon a real basis, by reducing it to well defined and demonstrable structural changes.

## DISCUSSION

We have to face the following questions with the help of the results made in this study:

1°) With regard to the anatomical changes have we a right to speak of a special participation of the hypothalamus in producing schizophrenia?

2°) Is there a direct relation between the changes of nerve cells found in the hypothalamic nuclei of schizophrenics and the aetiologic main factors of schizophrenia?

Ad 1°).

I am inclined to answer this question in the negative relying on the following facts:

a) There are evident anatomical changes missing in the hypothalamic nuclei, changes, which I could clearly found in other diseases.

b) Amongst the changes of nerve cells in the hypothalami of schizophrenics no specific signs can be found, which offer an anatomical basis for the supposition, that they behave differently from those of nonpsychotics.

Finally, for a complete answer of the above question, an investigation of the cells belonging to those grisea, which, from the anatomical view point, are believed to be particularly affected, would be necessary, (Nucleus medialis thalami, nucleus basalis compactus; O.

Vogt and co-workers). These investigations shall be carried out in the following weeks.

Ad 2°).

As some known aetiologic factors, which lead to anatomically visible changes of the brain, damage different structural elements not in the same way, so one could look upon the subtle changes of the nerve cells as part of the effect of the aetiologic factors leading to schizophrenia. Then, one could try to draw conclusion from these changes to the nature of the actual aetiologic main factors. Now it must be proved, how far the results can give us any informations of one possible, direct relation of the observed changes to the aetiologic main factors of schizophrenia. At first one would be inclined to deny the existence of such a direct relation in regard to the disseminating and non specific morphological symptoms of the cells. The chorea, however, has shown us, that not even amongst the cases of hereditary taint, we are allowed to suppose as a matter of course, that the same aetiologic main factor is their cause. Not even, if every aetiologic main factor caused a specific change in the cell, could we expect to get always the same finding. It is to be added, that specific changes in the cell are very rare, as experience shows. Even the few insides in the molecular and organismic ways of the cell activity we have shown how far originally, that is, in their first molecular impetus *specific* attacking aetiological factors can fall into general and *non-* specific curses, according to their progressive efficiency and to the reactions caused by them.

In all this, not even the changes caused by secondary, intercurrent, final, agonal, and technical factors are taken into consideration.

Therefore, it is not possible to give a definite answer to the question concerning the relation of the found cell changes to the aetiologic main factors of schizophrenia and, with that to the aetiology of this disease at all.

## SUMMARY

One of the fundamental problems of the researches on schizophrenia is to discover those elements of the brain which by changing cause the symptoms of schizophrenia. Clinical experts have taken in consideration the central vegetative regions. Therefore the hypothalamic regions of 8 cases of catatonic schizophrenia and of 2 cases of paranoic schizophrenia were examined with Nissl's and Feulgen's stain. By this examination it was not found that a greater number of nerve cells were destroyed or that the glia and the vessels were considerably changed.

Of the elementary 6 types of nerve cells which make up 25 architectonic fields of the tuber cinereum and the corpus mammillare 1000 single cells were analysed. The analysis comprises 25 observations on each cell which characterize

the state of the different organs of the cells, particularly that of the nucleolar apparatus.

The cases of schizophrenia examined do not show identical changes. In addition to that, these changes occur with a certain number of normal old people or of patients suffering from nerve diseases other than schizophrenia.

Therefore they have not any specific importance. The question whether the changes are in direct relation to the chief aetiologic factors of schizophrenia must be left open. To sum up, our method has not led us to discover any changes entitling us to think that the hypothalamic regions play an important part in producing the symptoms of schizophrenia.

### RÉSUMÉ

Un des problèmes élémentaires de la recherche de la schizophrénie est de trouver les parties, qui étant atteintes, causent l'image symptomatique de cette maladie. Des cliniciens ont pensé aux régions végétatives centrales. Pour cette raison on a examiné l'hypothalamus de 8 cas de schizophrénie avec catatonie et de 2 cas avec paranoïa, avec la coloration de Nissl et en plus la coloration nucléaire de Feulgen. On n'a pas pu constater des disparitions cellulaires, ni des modifications gliales ou vasculaires.

Des 6 espèces principales de cellules nerveuses, qui constituent 25 régions architectoniques du tuber cinereum et du corps mammillaire, 1000 cellules ont été analysées. L'étude cytologique envisage 25 points dans chaque cellule, qui correspond aux divers éléments ou « organelles » du neurone, et en particulier à son appareil nucléolaire.

L'apparition des altérations cellulaires dans ces cas de schizophrénie n'est pas uniforme. Elles se retrouvent chez des sujets âgés et des malades nerveux sans schizophrénie. Donc elles n'ont pas une relation avec les causes de la schizophrénie. Avec nos méthodes nous n'avons pas pu constater jusqu'à présent des altérations, qui permettent d'admettre une participation essentielle de l'hypothalamus à la schizophrénie.

### RIASSUNTO

Uno dei problemi fondamentali della schizofrenia è la ricerca degli elementi patologici cerebrali che causano la sintomatologia schizofrenica. Alcuni clinici hanno preso in considerazione i centri vegetativi centrali. Per tali ragioni è stato studiato l'ipotalamo di 8 casi di schizofrenia con catatonìa e di 2 casi di paranoia mediante il metodo di Nissl e il metodo nucleare di Feulgen.

Non è stato possibile rintracciare nè perdite cellulari nè alterazioni gliali o vascolari. Dei sei tipi principali di cellule nervose che costituiscono le 25 regioni architettiche del tuber cinereum e del corpo mammillare, sono state esaminate 1000 cellule. Lo studio citologico prende in esame 25 punti in ogni cellula, corrispondenti ai diversi elementi del neurone in particolare al suo apparato nucleolare.

L'apparizione delle alterazioni cellulari in tali casi di schizofrenia non è uniforme. Esse si riscontrano in soggetti in età avanzata e in malati neurologici e pertanto non hanno alcuna importanza specifica. Non può essere affermato pertanto che tali alterazioni siano direttamente in rapporto con le cause della schizo-

frènia. Con i nostri metodi non abbiamo potuto constatare fino ad oggi delle alterazioni che permettono di ammettere una partecipazione essenziale dell'ipotalamo alla schizofrenia.

#### CITED LITERATURE

- Brockhaus: Journ. Psych. u. Neur. 51; 96-196 (1942).  
Hechst: Z. ges. Neur. u. Psychiatr. 134; 164-267 (1931).  
—, Mschr. Psychiatr. u. Neur., 87; 32-47 (1933).  
Reichardt: Journ. Psych. u. Neur. 34; 168-184, (1919).  
C. u. O. Vogt: Kli. Wo. 25; 608-625 (1947).