

# Genetics of Microcephaly in Man<sup>1</sup>

Gerhard Koch, M. D.

Owing to the initiative of Professor von Verschuier, an extensive registration of pathologic traits and syndromes in man (that are considered to be caused by mutant genes) was started in 1957 at the Institute for Human Genetics, University of Münster, Westfalia. This research project is thought to supply data for a considerable number of studies in population genetics. The program in population genetics had been organized in accordance with the recommendations given at the meeting of a study group of the World Health Organization in 1956, dealing with the effect of radiation on human hereditary traits.

The material has been collected within the District of Münster which includes somewhat more than two million people (fig. 1). In this area a number of investigations on normal anthropological traits, on blood-groups and on the frequency of intermarriage have been carried out in the last few years. Two pathological conditions were also investigated in this way: amyotrophic lateral sclerosis including progressive bulbar paralysis studied by W. F. Haberlandt and microcephaly by myself.

In looking over the literature of the last years, microcephaly (more correctly speaking micrencephaly) has become an important scientific subject through studies in phenocopies as well as in population genetics carried out in various countries. In the field of human genetics the investigations of Böök, Schut and Neel, Grebe, Komai, Penrose and of Van den Bosch have been of particular interest. Hanhart called my attention to his own unpublished investigation of microcephaly in Switzerland. For some of the clinical and genetic data I intend to compare my results with those of the authors named above.

My own series of microcephaly consists of 106 index cases being collected during the last year. Among 145,000 individuals who were treated in the University Hospitals of Münster since January 1950, 34 microcephalics were discovered. Two cases became known through marriage counseling at our Institute. 70 more cases were found through systematic search in mental hospitals of Westfalia, where about 16,000 mentally defectives are hospitalized at the present time. Although most cases of microcephaly are concentrated in the Hospital for Mentally Defective Children (St. Johannes Stift Niedermarsberg), there is one case of microcephaly out of 600 to 800 adult pa-

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<sup>1</sup> Presented at the X<sup>th</sup> International Congress of Genetics, Montreal (Canada), August 20 to 27, 1958.

tients found in the general mental hospitals of Westfalia. This fact can be explained by the semi-lethal effect of the microcephaly gene. Therefore, a good number of microcephalics die during the first period of life, i.e., within the first days up to a few months or years.

Among 23,000 children born at the Department of Gynecology and Obstetrics at the University Hospital of Münster only three were found to be microcephalic. Of

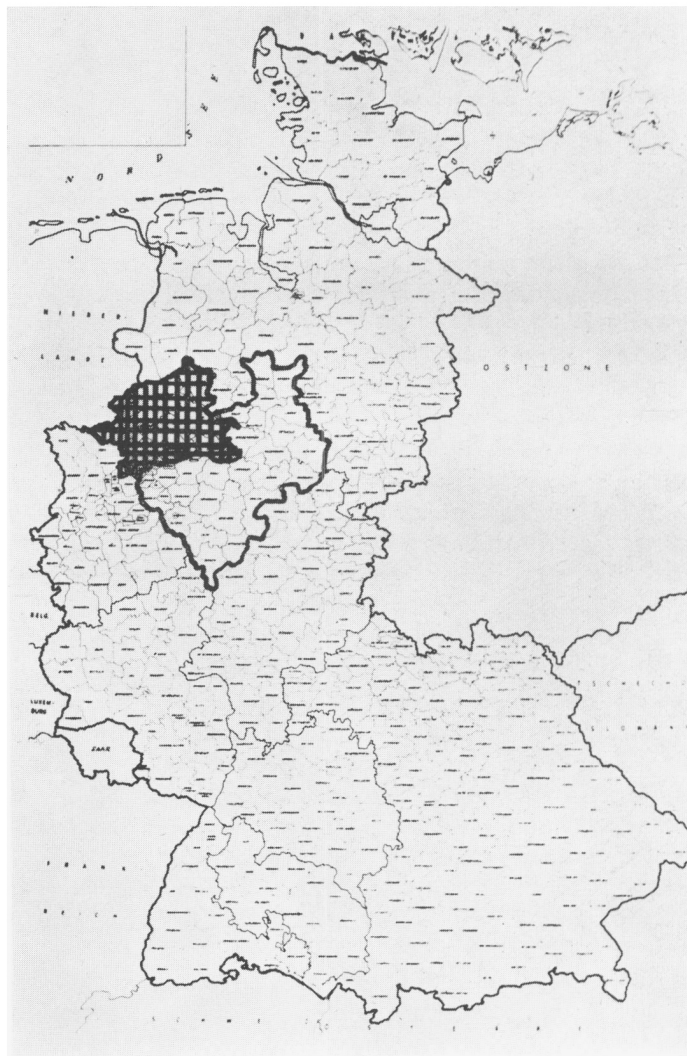


Fig. 1

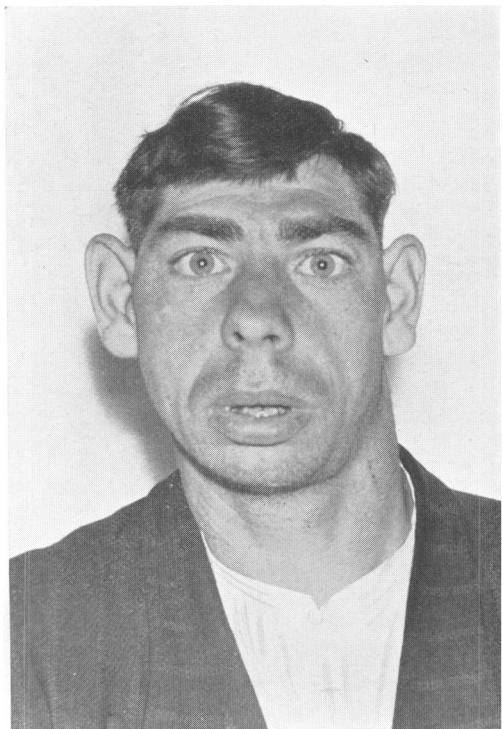


Fig. 2



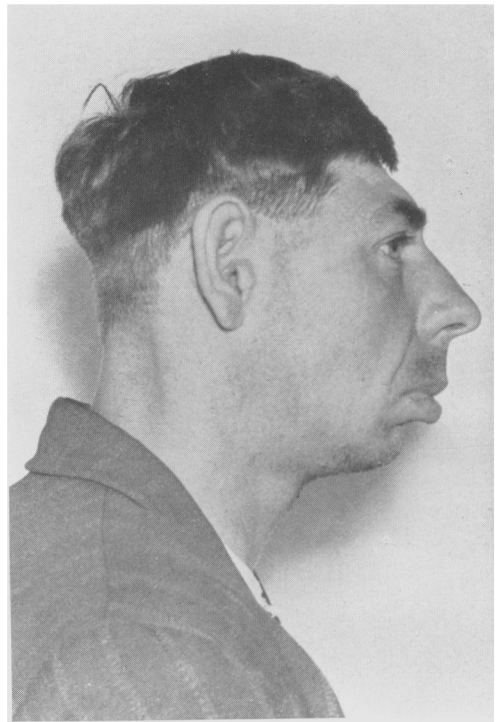


Fig. 3



these three cases two were caused by exogenous factors during the fetal period. The rate of genetic cases of microcephaly in this material, i.e., 1 per 23.000, is lower than that reported by Bööck. In this earlier registration of 44.109 unselected births carried out in one district of Sweden, Bööck found 1,6 microcephalic individuals per 10.000 births. We must say that our material of the new-born is not yet large enough to clearly indicate the frequency of genetically determined microcephaly.

In order to limit the scope of our investigation, only those cases showing a distinct disproportion between facial and cranial skull were taken into consideration. Patients whose small heads were merely a manifestation of reduced or dwarfed stature were not accepted as microcephalics. Cases presenting a combination of mongolism and microcephaly were also excluded from our study. Our illustrations (fig. 2 and 3) show typical cases with small cranial skull, bird-like face, slanting brow, recessed chin and flattened occiput. The head circumference of adult male microcephalics averages 46,3 cm, that of females 45,8 cm. The head length of males is 15,9 cm, that of females 15,1 cm. The head breadth is 12,4 cm for males and 12,2 cm for females. The cephalic index, i.e., the proportion between head breadth and head length is 78,0 for males and 80,1 for females.

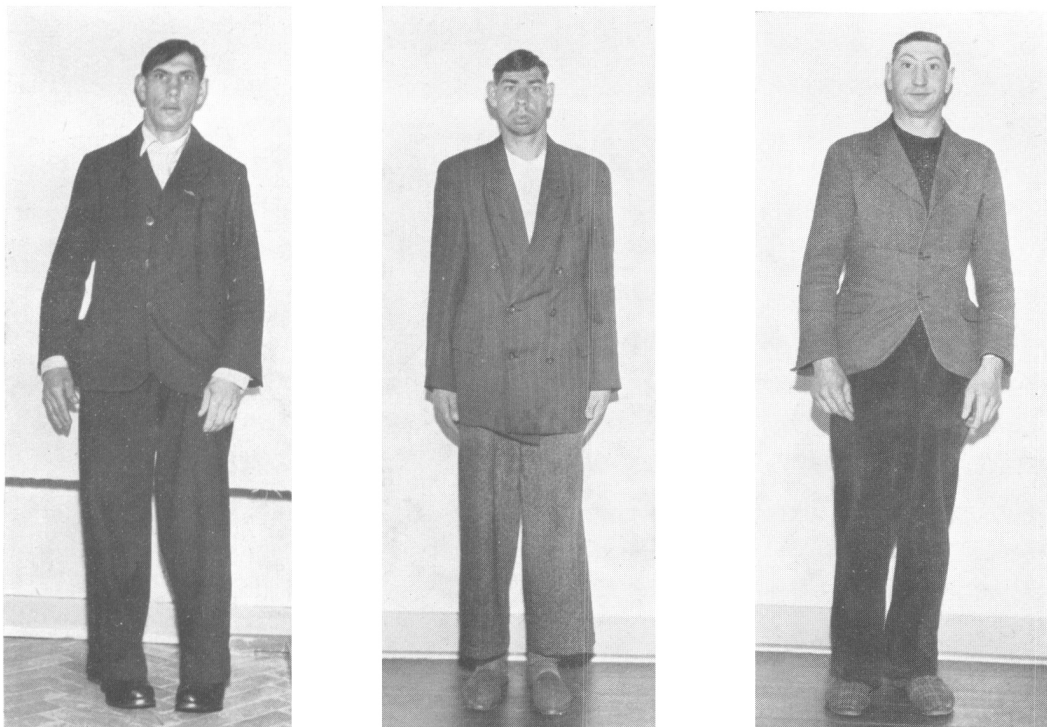
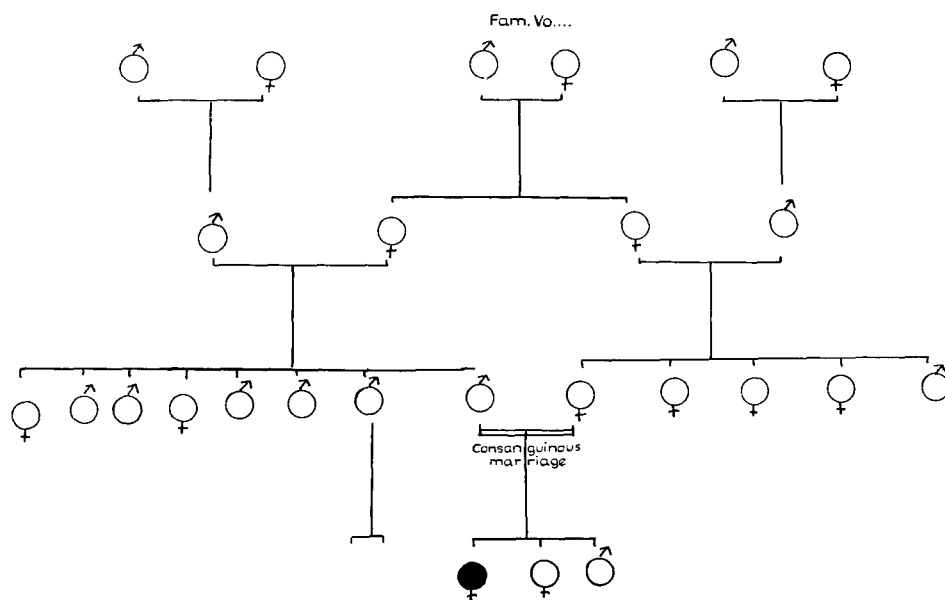


Fig. 4

The stature of patients without cerebral hemiplegia is somewhat reduced but in general not disproportionate (fig. 4 and 5). The average height of males is 161,3 cm (against 171,0 of the normale male), that of females 147,7 cm (against 160,0 cm as an average). The degree of mental deficiency is that of imbecillity or idiocy. Epileptic seizures as an expression of cerebral dysrhythmia are often observed in our material and can be interpreted as a hereditary manifestation of this convulsionary condition (« Krampfbereitschaft », according to the terminology suggested in my own monography (Koch)).

Our sample of 106 microcephalics must be divided into two groups: hereditary and non-hereditary cases. Among the peristatic factors determining this condition there are various exogenous influences during the pregnancy of the mother, such as virus infections, primarily German measles (Gregg's syndrome), toxoplasmosis, hypoglycemia and anoxia, vitamin deficiency and X-ray exposure. Microcephaly due to incompatibility of ABO blood-groups or of the Rhesus factor between mother and child has not been detected, in contradistinction to some observations of cases of feeble-mindedness, of epileptic convulsions, of spastic paraplegia and of athetosis. The general clinical picture of the non-genetic cases of microcephaly often includes hemiplegia, diplegia and tetraplegia combined with spastic and athetoid movements. The encephalogram of some cases shows such changes as porencephaly and calcifications.

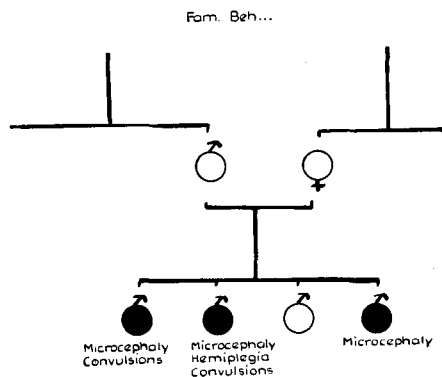
Until now only 36 of the 106 microcephalic probands appear to be hereditary cases. In our study there are 13 families with secondary cases of microcephaly in



Graph. 1

addition to the index cases. 18 more cases were found in these proband families; most of these 18 secondary cases were sibs. Consanguinous marriage of the parents of our probands was found in four families only. In two instances the parents were first cousins (pedigree Vo...), in the other families they were second cousins.

Among most hereditary cases spastic symptoms were absent. I would agree with Hanhart and other authors who say that there are several genetically different forms of microcephaly. That means, microcephalies have a heterogenic basis. In these family groups there are sibs exhibiting microcephaly with or without cerebral symptoms. In such cases we may think that the clinical picture composed of microcephaly and cerebral palsy is the result of both, hereditary and environmental factors. A further hypothesis supported by the results of investigations in phenocopies might be the assumption of cryptogenes activated by exogenous agents (pedigree Beh...).



Graph. 2

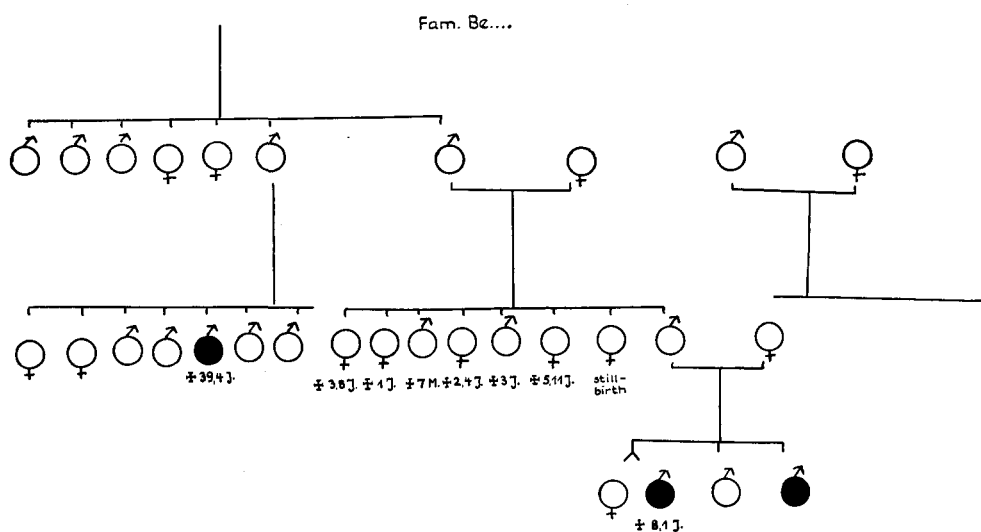
The present data of my own investigation suggest that hereditary microcephaly is due to an autosomal recessive gene. The heterozygous carriers, at least a part of them, exhibit a somewhat reduced stature, a smaller head circumference and a lesser degree of mental deficiency, i.e., debility. Only with parents of microcephalics we can be certain that we are dealing with heterozygous carriers of the disease. The sex ratio as determined for our 54 hereditary cases (proband and additional cases) is 28 males to 26 females, i.e., about 1 : 1. This ratio is in good agreement with the result of the study carried out by Hanhart in Switzerland who found a proportion of 17 males to 18 females for his group of microcephalics. These values are opposed to those given by Komai in Japan and by Van den Bosch in the Netherlands. Komai calculated for his material of 93 males and 57 females a sex ratio of about 2 : 1, whereas Van den Bosch found a proportion of 3,5 : 1 in his sample of 28 males and 8 females.

As of yet, our material of microcephalics comprises a series of three twin pairs that are found to be discordant as to microcephaly (Tab. I). In the monozygotic pairs





Fig. 5



and in one of the dizygotic pairs microcephaly was caused by exogenous factors. The etiology of the third twin pair (fig. 6) was hereditary, as we found several other cases of microcephaly among the relatives of this pair (Pedigree Be...).

Tab. 1 - Microcephaly in twins

No.	Twin pair	Age and sexe	Clinical findings
1.	Nie...	<p>A. Monozygotic twins</p> <p>I ■ +      II □ +</p>	<p>I idiocy, died at 5 years</p> <p>II cerebral tumor of the left hemisphere; died at 6 years</p>
2.	Ha...	<p>B. Dizygotic twins</p> <p>I ■      II □</p>	<p>I idiocy, hospitalized</p> <p>II healthy, 29 years of age</p>
3.	Be...	<p>I ○      II ■ +</p>	<p>I healthy, 28 years of age</p> <p>II idiocy, died at 8 years of difteria (several more cases of microcephaly in the kindred)</p>



Fig. 6

As to our present data on ABO and MN blood-group systems as well as on Rhesus-factors, we have not yet found correlations between these hereditary traits and the clinical picture of microcephaly.

We want to emphasize that the findings of our family study on microcephaly in man are preliminary results that must be corroborated by completing our sample collected within the District of Münster or eventually within the entire Province of Westfalia. By evaluating the data of such a large and representative sample we might be able to reach conclusions that will be both of clinical and of genetic interest. It would be of great importance to know the mutation rate of microcephaly as it holds true for many other conditions.

### Summary

According to recommendations in radiation and mutation genetics, made in 1956 at the Copenhagen Meeting of a study group of the World Health Organization, a registration of hereditary traits and clinical syndromes is being carried out within the District of Münster, Province of Westfalia (Germany) since 1957. One of the pathological conditions included in this research program is microcephaly investigated from a clinical as well as from a genetic stand-point. The preliminary results of our study on microcephaly in man are given in this report.

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## RIASSUNTO

Interessati alle raccomandazioni formulate a Copenhagen nel 1956 dal Gruppo Internazionale di Studi della Organizzazione Mondiale della Sanità, tendenti a raccogliere elementi di studio sugli effetti causati dalla energia ionizzante nel campo della genetica, abbiamo rivolto le nostre indagini alle malattie e sindrome ereditarie registrate nel distretto di Münster in Westfalia, a far tempo dal 1° aprile 1957. Nel presente articolo sono esposti i primi risultati ottenuti, riguardanti le caratteristiche cliniche ed ereditarie della microcefalia.

## RÉSUMÉ

Le groupe international des études de l'Organisation Mondiale de la Santé (Copenhague, août 1956) recommanda les investigations sur les dommages génétiques causés par l'énergie ionisante. D'accord avec ces recommandations nous avons commencé le 1<sup>er</sup> avril 1957 dans

l'arrondissement de Münster/Westphalie, Allemagne, l'enregistrement des maladies et syndromes héréditaires. Les premiers résultats, obtenus pendant l'enregistrement, sur les caractéristiques cliniques et l'hérédité de la microcéphalie sont déjà publiés.

## ZUSAMMENFASSUNG

Am 1 April 1957 wurde entsprechend den im Interesse der Forschung in der Strahlen- und Mutationsgenetik von der « Internationalen Studiengruppe der Weltgesundheitsorganisation (Kopenhagen, August 1956) empfohlenen Richtlinien eine Registrierung pathologischer Erbmerkmale und klinischer Syndrome im

Regierungsbezirk Münster/Westfalen (Deutschland) begonnen. Eines der Krankheitsbilder, welches im Rahmen dieses Forschungsprogrammes vom klinischen wie vom genetischen Standpunkt untersucht wird, ist die Mikrocephalie. Ergebnisse dieser Untersuchung auf dem Gebiete der Mikrocephalie werden mitgeteilt.