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Endogenous factors in poliomyelitis acuta anterior

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The poliomyelitis acuta anterior or infantile paralysis, which is a scourge of childhood in some regions, is of ancient origin. The earliest indication of the disease has been found on a stela in Egypt of the nineteenth dynasty abt 1300-1200 B.C.

It is now known to be a virus disease, with at least three varieties of this virus causing the disease. Although it has been proved beyond question that acute anterior poliomyelitis is caused only by the specific virus, invading its host, it is equally clear that only a small proportion of the individuals, exposed to the virus, develop clinical signs of the disease. This fact as well as the sporadic occurrence in Europe leads to the presumption that the virus circulates among many people and as a rule makes an innocent symbiosis with its human host. From this point of view those possible inherent and acquired conditions which from usually commensal relation via the abortive case lead to the typically clinical aspect, demand our attention. Thus many children are higher resistant to the disease.

Two groups of factors should be distinguished here, the exogenous and the endogenous factors. Support for the supposition of an endogenous predisposition has been found in literature.

As early as in 1898 Taylor (1) suggested a familial tendency.

Draper and Dupertuis (1939) (2) found that persons susceptible to the virus of acute anterior poliomyelitis show a special constitutional type of morphology.

Aycock (1937) (3), (1941) (4), 1942 (5) made a study of the recurrence of the disease in the same family and published seven pedigrees. He found a much higher frequency among the relatives of those who have had the disease than in the general population. He states that all observations are consistent with the theory that hereditary susceptibility may determine the occurrence of paralysis in the selected few of many, exposed to the virus.

Borgström (1939) (6) confirms that strong individuals are more susceptible than others and that the disposition is determined by heredity, but he does not agree that there is a poliomyelite type. A similar pedigree demonstrating heavy familial aggregation of paralytic poliomyelitis has been published by Czickeli (1948) (7). Addair and Snyder (1942) (8) collected all cases of paralytic poliomyelitis with residual

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paralysis that occurred in an isolated section of McDowell County (West Virginia) over a period of 50 years. All 29 cases thus found proved to be relatives and are listed in one large pedigree. This pedigree is interpreted as suggesting the existence of an autosomal recessive gene for susceptibility to paralytic poliomyelitis with about 70 percent penetrance. The final evidence that a genetic factor controlling at least in part susceptibility to the paralytic form of poliomyelitis is demonstrated by Herndon and Jennings (1951) (9). They report a study of 46 twin pairs, one at least having paralytic poliomyelitis while living with the twin partner. Herndon and Jennings found, with regard to the paralytic form of poliomyelitis, a twin pair concordance in 35,7% with monozygous pairs and 6,06% with dizygous pairs. The difference between those percentages is statistically significant. Concerning the genetic mechanism no conclusion has been drawn but they found the data at least compatible with the theory that susceptibility may be conditioned by a recessive gene with about 35 percent of penetrance.

Other twin studies concerning this problem have been published by Borgström, Aycock, Masini and others.

A summary of the case reports of twins with poliomyelitis, found in the literature, follows here:

Investigation	Year	MzC	MzD	DzC	DzD	XC	XD
Dubois (10)	1923	3					
Crouch (11)	1927	1					
V. Verschuer (12)	1927		1				
Curtius and Korkhaus (13)			1				
Guttman (14)	1933		1				
Kaiser and Muller (15)	1933					1	
Nitsche + Armknecht (16)	1933				1		
Thelander and Pryor (17)	1933	1			1		
H. and W. Blotevogel (18)	1934		2				
Marmann (19)	1934					3	
Camerer and Schleicher (20)	1935		3		1		
Gebbing (21)	1936		1		1		
Schiller (22)	1937		2				
Huber, Lièvre and Néret (24)	1938	1					
De Toni (25)	1939						1
Borgström (26)	1939	1	3		13		

Investigation	Year	MzC	MzD	DzC	DzD	XC	XD
Aycock (4)	1942	1	1	1	4	1	
Messeri (28)	1946	1					
Haumeder (29)	1951	1					
Herndon and Jennings (8)	1952	5	9	2	31		
Masini (30)	1953	1	11	2	14		
Total		16	35	5	66	5	1

A critical opinion only can be given on those studies on twins in which zygosity definitely was determined and where there has been no question of any selection. We will confine ourselves to the researches of Borgström, Herndon and Jennings and Masini. Their results were as follows:

MzC	MzD	DzC	DzD
1	3	—	13
5	9	2	31
1	11	2	14
7	23	4	58

These numbers show a clear difference in concordance and discordance of the Mz and Dz.

Regarding these marks and using the chi square test we find a significant difference, viz. $\chi^2 = 3{,}988$ and P : $\langle 0{,}05- \rangle$ 0,02.

The conclusion has been drawn, that endogenous factors very likely will influence the appearence of the paralytic form of poliomyelitis acuta anterior.

In the hope that we might be able to give further evidence concerning the possible existance of endogenous factors of acuta anterior poliomyelitis, this family study was started.

This investigation was feasible, since the possibilities of making investigations into these possible endogenous factors are in this country exceptionally favourable, owing to the reliable data about ancestors to be obtained through municipal and public record offices, and if need be, the registries of the courts of justice. The names of patients, suffering from acute anterior poliomyelitis, are written down on infection

disease report cards required by law to be filed with the Health Officer, by the attending physician in each case where poliomyelitis is diagnosed. Through the kind cooperation of the Health Officer it was possible for us to obtain the names of the patients in the provinces of Groningen and Drenthe, who were affected by the disease during the years 1936-1951 included, totalling 868 patients. After having checked the accuracy of the diagnoses of all the notifications we found the number of patients to be 754. Of all these patients pedigrees were composed, going back as far as and including the great-grandparents of the probandi (four generations). The number of the pedigrees, however, did not come up to 754, but to 728, since 20 families numbered more patients.

First of all the extent of consanguinity between the parents of the probandi compared with that of the average population was checked. Cards were prepared giving the name, sex, birth-place and birth-day of all great-grand-parents of the probandi. By arranging those cards according to the names, it was possible to find out if probandi came from consanguineous marriages. In those cases we found more cards carrying the name, birth-place and birth-day of the same person. In 15 of the 728 pedigrees consanguinity could be demonstrated, eleven of them being first cousin-marriages, the remaining 4 can be divided into 3 pedigrees with consanguinity in the 6th degree and 1 with consanguinity in the 8th degree. In addition there are 11 pedigrees in which the father of the probandus is descended from a consanguineous marriage and 3 in which the mother is descended from a consanguineous marriage and 3 in which the mother is descended from a consanguineous marriage. The difference between 11 and 3 appears to be no significant.

So we found in 728 pedigrees 15 consanguineous marriages i. e. 2,06%. This percentage should be compared with the consanguinity-percentage of the average population during the years 1918 till 1937, for this is the period in which most of the parents of the probandi got married.

The ages on which the acuta anterior poliomyelitis occurred, are divided as follows:

0 year = 36			
1 » = 107	11 years = 17	21 years = 6	31 years = 3
2 years = 105	12 » = 13	22 » = 5	32 » = 2
3 » = 95	13 » = 11	23 » = 4	33 » = 1
4 » = 57	14 » = 13	24 » = 5	34 » = 5
5 » = 55	15 » = 11	25 » = 5	35 » = 1
6 » = 34	16 » = 10	26 » = 2	36 » = 0
7 » = 27	17 » = 11	27 » = 7	37 » = 2
8 » = 29	18 » = 10	28 » = 1	38 » = 0
9 » = 17	19 » = 6	29 » = 4	39 » = 0
10 » = 24	20 » = 7	30 » = 3	40 » and older = 3.

The greatest number we find in the group from 0 till 6 years i.e. 455 = 60,3%. Further it is of interest to know the number of the patient in the family. Nothing is known about this subject in the group of 754 patients, but we have at our disposal

these data of part of the 754 patients -namely 137 (This being the group used for the third part of this study).

The number distribution in this group appears to be:

1st child : 47	3rd child : 17	5th child : 13	7th child : 3	9th child : 2
2nd child : 25	4th child : 13	6th child : 11	8th child : 4	10th child : 2

Thus in most of the cases the patient has a low number. We may assume, that if we knew the number of all 754 probandi, we should have come to the same conclusion. The cases of illness investigated into date from 1936. If we assume that most of our patients as 1st or 2nd child were affected in 1936 by acute anterior poliomyelitis at the age of 5 the parents were probably married around 1920, 1930. Unfortunately we have not at our disposal the consanguinity percentages of the average population concerning that period. However, we have at our disposal the percentages of the periods 1906 till 1918 and 1937 till 1948 (1945 exclusive), Polman (1951) (31).

They are for the period 1906-1918 : 0.70% and for the period 1937-1948 : 0.169%. As we want to know the percentage concerning the period in between we had best take the percentages of the preceding and of the following period into account, for we may suppose a gradual fall from 0.70% to 0.169%. The consanguinity percentage of the average population concerns only third and fourth degree marriages, so it is much more desirable to consider the first cousin marriages in our group, which show a consanguineous percentage of 1.51%.

We will calculate now the percentage of consanguineous marriages in the average population of the period 1918-1937, as indicated. During the years 1906 till 1918 the number of marriages in the Netherlands amounted to 572932, 4018 of them being consanguineous. During the years 1937 - 1940 (1945 excluded) 1484 of the 843005 marriages were consanguineous.

We find 5502 consanguineous marriages in a total of 1415937, i.e. 0.38%. The chi square test shows a significant difference between 0.38% and 1.51%, the percentage we found in our material being $\chi^2 = 22.38$ and P : <0.001. One could perhaps object to the comparison of the percentage of consanguineous marriages with the same data of the whole country. For that reason the calculation has been made concerning the data of the provinces of Groningen and Drenthe.

In the period 1906-1937 the number of marriages amounted in
Groningen to 31694, 248 of them being consanguineous
Drenthe to 17791, 193 of them being consanguineous.
In the period 1937-1948 (1945 excluded) the numbers were in:
Groningen: 39937, 72 of them being consanguineous
Drenthe: 23623, 69 of them being consanguineous.
In total: 113045 marriages, 572 of them being consanguineous i.e. 0.506%.

Using the chi square test the difference between 0.506% and 1.51% appears to be significant. $\chi^2 = 13.48$ and P : <0.001.

The group of the acuta anterior poliomyelitis patients, consequently, shows a greater number of consanguineous marriages than chance might leave us to expect.

The next item demanding our attention was the tracing of the number of connections between the different pedigrees.

By means of previously mentioned cards we found, that 53 of the 728 patients had one or more ancestors in common with another patient, while 9 of these 728 had one or more ancestors in common with two other patients, making 62 in all.

One can ask if and in how far these numbers deviate from the normal number of connections in the average population. In every group of persons of a size like our acuta anterior poliomyelitis group, and chosen from a similar area, one can expect a number of persons having in common one or more ancestors.

To give a well grounded judgment we need a control group.

Unfortunately we have not a control group at our disposal next to the group of 728 patients but we can use the control group of 137 patients (part of the big group). From this control group pedigrees were made as well. A comparison was now made between the number of connections of the group of 137 patients with the remainder of the patientsgroup (718-137 = 591) and the number of connections of the control group of 137 persons with the remainder of the patients-group.

The control group, as mentioned later, is of the same age, sex and dwellingplace as the patients-group.

Should we deal with a normal number of connections, we might expect about the same number of connections between the two groups of 137 persons and the remainder of the patients-groups. We found in 26 cases connections between the control group and the group of 591 poliomyelitis patients. This difference appeared to be significant, being $\chi^2 = 7.11$ and P $\langle 0.01 \rangle$ 0.001.

The conclusion is that, since poliomyelitis is the only point-in-common of the two groups of patients and the only point of difference between the patients-group and the control group, we may set value on the significant difference found by us.

The third part of the research concerned the appearance of diseases with patients, relatives and the comparison of those with the diseases of relatives of a control group.

To this end a smaller group has been taken from the large group of 754 patients, viz. those who were between 5 and 15 years of age, when they were suffering from acute anterior poliomyelitis. This age-group has purposely been chosen, because a control group could thus more easily be selected, this being the schoolage.

Without a control group a reliable judgement of the result of a study is often impossible. To chose a right control group often involves a lot of trouble. We set about it as follows: we chose for each patient a classmate of the same age and the same sex, whose place in school during the illness had been before, behind or beside the probandus. Consequently, the conditions of their environment might be considered as being identical to a very great extent. As a consequence of the data in the literature and the results of a pilot study, questionnaires were compiled.

These forms contain questions concerning affections of the various tracti, infectious diseases, congenital malformations.

In this way exactly the same questions could be put to the patients-group and to the control group. The reliability of the data can be tested to a certain extent by the

numbers which the study gave us concerning the stillborns. In both groups put together we found on 1375 births 37 stillborns i.e. 2.7%. In comparison with the percentage stillborns in all Groningen and Drenthe (= 2,8%) (Polman-1954) (32) in nearly the same period we find only a very small difference. This fact may be an indication, that answers to the other questions have about the same degree of reliability.

The families of the 137 patients and of the 137 controls were visited personally in their homes, where the questions appearing on the form were asked.

As it concerns anamnestic data, of course the answers were not always complete. The same incompleteness, however, we find in the control group, and thus the final numbers can be compared.

The investigation included: the patients, their sibs, parents, grandparents, aunts, uncles and cousins both of the patients and the control group. In total data about 5565 persons were obtained. A division is made into three groups:

I the group of patients and controls.
II the group of their parents and sibs.
III the group of the patients' grandparents aunts, uncles and cousins and item of the controls.

In group I we found:

	Patients	Controls			Patients	Controls	
number	137	137		urticaria	25	12	+
♂	68	68		eczema	7	3	+
♀	69	69		enuresis nocturna	28	12	+
diphtheria	11	5	+	nervositas	64	7	+
scarlatina	6	8	—	cheiloschisis	—	1	—
pertussis	65	71	—	congenital vitium cordis	2	1	+
morbilli	132	128	+	palatoschisis	—	1	—
rubeola	32	27	+	pyelitis	2	3	—
varicellae	64	47	+	myopie	20	12	+
parotitis epidemica	67	56	+	strabismus	5	3	+
hepatitis infectiosa	28	18	+	birth trauma	4	—	+
meningitis	3	1	+	pylorospasmus	1	—	+
convulsions	7	6	+	epilepsia	1	—	+
encephalitis	1	—	+	infantilismus	1	—	+
tuberculosis	2	3	—	diabete mellitus	—	—	0
herpes zoster	3	1	+	uxatio coxae congenita	—	—	0
catarrhus aestivus	—	2	—	diseases of the tractus digestivus	1	1	0
asthma bronchiale	6	1	+				

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In group II we found:

	Patients-group	Control-group	
number of parents	274	274	
number of sibs	517	447	
luxatio coxae congenita	3	2	+
ulcus ventriculi	19	8	+
ulcus duodeni	9	5	+
asthma bronchiale	18	7	+
migraine	9	6	+
catarrhus aestivus	4	—	+
nervositas	10	2	+
congenital vitium cordis	7	—	+
encephalitis	0	0	0
pylorospasmus	0	0	0
diabetes mellitus	3	5	—
eczema	13	8	+
hydrocephalus	4	2	+
anencephalus	5	4	+
diseases of the tractus urogenitalis	8	4	+
affections of glandula thyreoidea	5	9	—
tumor cerebri	1	1	0
apoplexia	1	—	+
alcoholism	1	—	+
acuta anterior poliomyelitis	15	1	+
epilepsia	9	3	+
rheuma	12	9	+
ischias	16	13	+
neuritiden	2	1	+
tuberculosis	9	7	+
strabismus	6	5	+
debilitas mentis	8	—	+
meningitis	12	3	+
cheiloschisis	3	4	—
psychoses	12	2	+

In group III we found:

	Patients-group	Control-group	
number of grand parents	548	548	
number of aunts	702	660	
number of uncles	669	652	
luxatio coxae congenita	1	6	—
ulcus ventriculi	21	3	+
ulcus duodeni	34	16	+
asthma bronchiale	39	23	+
migraine	4	2	+
meningitis	13	10	+
catarrhus aestivus	4	—	+
nervositas	6	—	+
congenital vitium cordis	3	—	+
diabetes mellitus	14	24	+
encephalitis	1	1	0
eczema	24	8	+
hydrocephalus	1	2	—
affections of the tractus urogenitalis	9	8	+
affections of the glandula thyreoidea	4	9	—
tumor cerebri	4	6	—
apoplexia	37	27	+
alcoholism	12	15	—
acuta anterior poliomyelitis	21	4	+
epilepsia	19	7	+
pylorospasmus	—	1	—
rheuma	15	6	+
ischias	7	5	+
tuberculosjs	46	40	+
strabismus	5	3	+
debilatas mentis	32	14	+
cheiloschisis	1	4	—
psychoses	33	8	+
neuritis	1	10	

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As only anamnestic data were obtained, measure had to be taken to prove the accuracy of the diagnoses.

In group I we only got information from the parents concerning diphtheria, scarlatina, pertussis, morbilli, rubeola, varicellae, parotitis epidemica, hepatitis infectiosa, convulsions, herpes zoster, catarrhus aestivus, enuresis nocturna, nervositas, cheiloschisis, palatoschisis, pyelitis, tuberculosis, urticaria, strabismus, myopia and birth trauma. The diagnoses meningitis, encephalitis and congenital vitium cordis were checked by reading the pathographics.

All children, who suffered from asthma bronchiale, eczema, epilepsia, pylorospasmus and infantilism were treated by consulting physicians.

Group II: apoplexia, arthritis rheumatica acuta, ischias, catarrhus aestivus, tuberculosis, strabismus, cheiloschisis, alcoholism, nervositas, hydrocephalus, anencephalus and luxatio coxae congenita were diagnosed on the description of more relatives.

Ulcus ventriculi and ulcus duodeni were diagnosed only on account of a six weeks bed rest or an operation. Patients suffering from diabetes mellitus, eczema, migraine, affections of the glandula thyreoidea, epilepsia, tumor cerebri, affections of the tractus urogenitalis, neuritides, meningitis were all trated by a consulting physician. Con genital vitia cordis and acuta anterior poliomyelitis were diagnosed in the same way. We regarded persons as mentally defective when elementary tuition was beyond them. The diagnosis psychosis was made only when the patients had been in a psychiatric home.

Group III.

In this group the same measures have been taken as mentioned above.

On the questionnaires there appear in addition questions concerning exogenous factors, namely injections, vaccinations, tonsillectomies, performed shortly before the acuta anterior poliomyelitis existed, psychical and somatical strain. Most of the parents could not remember very well these things, for too much time lay between this research and the time of outbreak of the acuta anterior poliomyelitis. These data therefore were not worked out. Considering the numbers obtained in this part of the research, we see that most of the affections are found more often in the patients-group than in the control-group in all three groups.

A summary of the frequencies follows here:

	Group I	II	III
number of diseases of which more cases were found in the patients group (marked +)	22	24	20
number of diseases of which more cases were found in the control group (marked —)	7	3	7
number of diseases of which an equal number were found in patients and in control group	3	3	2
Total	32	30	29

The differences between both groups are significant differences concerning group I and II on the 1% point, group III on the 5% point.

Considering the numerical rations of the different diseases separately we found a number of significant differences too.

In group I significant differences were found with varicellae (5% point), urticaria 5% point), enuresis nocturna (1% point) and nervositas (1% point).

In group II significant differences were found with congenital vitia cordis (5% point), acuta anterior poliomyelitis (1% point), debilitas mentis (5% point) and psychoses (1% point).

In group III significant differences were found with ulcus ventriculi (1% point), ulcus duodeni (5% point), eczema (1% point), acuta anterior poliomyelitis (1% point), epilepsia (5% point), debilitas mentis (5% point) and psychoses (1% point).

In group I we found a significant difference both with enuresis nocturna and nervositas. We tried to find a possible correlation between them, but it did not exist.

Though no further significant differences could be demonstrated, considerable higher numbers in the patients-group than in the control group were observed.

Finally attention was paid to the twins who occurred in the group of 754 patients.

At the municipal record offices inquiries were made concerning single or multiple birth of all the 754 patients. By this method 12 cases were reported to us as being members of a set of twins.

The twin birth frequency in the Netherlands has been determined as 1,3%. This number corresponds more or less with the frequency for the total population of the Netherlands. Two pairs of differently sexed twins and three twin-pairs of whom one of each died were excluded, while 1 pair retired from the research.

The zygosity diagnosis of the remaining twin pairs was made by Siemens' poly-symptomatic method. The utility of this method is proved by numerous publications.

There appeared to be 3 monozygotic twin pairs, two pairs of them were discordant, while the third according to Borgström could be called " slightly concordant ". All of the dizigotic twin pairs were discordant. The small amount of material, however, did not allow of any conclusion whatsoever.

Discussion

The intention of this research was to find out if endogenous factors might play a part in the appearance of paralysis with acute anterior paralysis. The investigation was divided into three parts:

1. *the extent consanguinity between the parents of the probandi compared with that of the average population.* If we find a consanguinity percentage which exceeds the one characteristic for the average population, we may conclude that endogenous factors do play a part. An increased percentage of consanguinity in parents of patients suffering from a certain disease is, generally, found with affections that inherite in the recessive way.

Our data show a significantly higher consanguinity percentage between the parents of the probandi than in the average population.

Acute anterior poliomyelitis was found during 1928-1952 in Groningen and Drenthe with 150 of the 100.000 inhabitants.

According to some of Dahlberg's publications we may attach value to an increased consanguinity found with an illness occurring in a similar frequency. Consequently we think of a recessive factor playing a part in the appearance of paralysis with acute anterior poliomyelitis.

The literature did not provide us with data concerning the consanguinity percentage between the parents of probandi.

Herndon and Jennings, Addair and Snyder, however, as mentioned earlier, conclude, that the existance of a genetic factor controlling, at least in part, susceptibility of the paralytic form of poliomyelitis is demonstrated. Their data were at least compatible with the theory that susceptibility could be conditioned by the homozygous state of a recessive gene.

2. *the extent to which common ancestors of the patients were found.*

If somewhere an infection appears e.g. paratyphoid fever, we will trace the source, just as when some people show a distinct hereditable mark. In this case, however, we have to use quite a different method. In some respects easier, because we know the way to follow, in others more difficult, because data concerning previous generations become increasingly incomplete. Sometimes it is possible to find common ancestors of two persons who are characterised by a distinct hereditable mark. The family relation between the two parties involved is caused by the possession of partly common genes descended from the same ancestor. Reasoning along the same line one would expect on starting with a much greater number of persons characterised by a distinct hereditable mark to find more common ancestors than on starting with the same number of persons who do not show that distinct hereditable mark.

Our group showed the following result: of the 728 pedigrees 62 could be connected, which means that 62 probandi had one or more ancestors in common with one or two other partners.

Of course in any given group, part of a population, we shall find a number of common ancestors.

Because we had a controlgroup at our disposal, we could find out if the number of connections between the pedigrees of the poliomyelitis patients differed from the normal number.

It appeared that the group of 137 poliomyelitis patients had significantly more connections with the rest of the poliomyelitis group (728-137 = 591) than the control group. The suffering from acute anterior poliomyelitis is the only disputed point between the two groups; consequently this fact can give this group more connections with the big poliomyelitis group than the control group. The hypothesis is supported by this.

3. *the appearance of other diseaces with patients' relatives and the comparison of those with the diseases with relatives of a control group.*

Considering the results of this part of the research and using the hypothesis that suffering from acute anterior poliomyelitis or the occurrence of this disease in the relatives is not connected with the chance to get one of the mentioned diseases, the control group may not deviate from the poliomyelitisgroup regarding the occurrence of these diseases.

The results obtained, however, differ significantly: in group III 20 affections occurred more often in the patients-group than in the control group, 7 affections occurred more often in the control group than in the patients-group, while with two affections there was no difference; the difference being significant on the 5% point; in group II the ratio was as follows: 24, 3, 3, the difference being significant on the 1% point; in group I the ratio was 22, 7, 3, likewise significant on the 1% point.

We always found a " surplus " of diseases in the poliomyelitisgroup. In addition significant differences were found by considering the affections separately, as mentioned before. Whenever the differences were not significant they were still remarkable.

We herewith took the line, that no direct correlation exists between the diseases i.e. the chance that one person suffers from two diseases, is equal to the product of the chances, that he will be suffering from each disease separately. However we found a negative correlation i. e. the number of combinations of the affections is less than might be expected on occount of chance. We will return to this subject.

Studying the differences obtained a common point of contact seems to show up viz. many of the diseases can in some way be related to the central nervous system. One may suppose that a common hightened disposition to several diseases may be the cause, the hightened susceptibility to the paralytic form of acute anterior poliomyelitis, being a part of it. In the literature, for instance, Neustaedter, Dubois, Draper, Hofmeier, Aycock, Pette, Czickeli and Lepine give support to our supposition.

We may conclude, in our opinion, that endogenous factors exercise influence in the origin of paralysis with acute anterior poliomyelitis. Probably we have not to deal with a specific factor, but with a non-specific one, wiz. a greater vulnerability of the central nervous system. When a specific factor existed, we did not find significant differences concerning other affections but only concerning acute anterior poliomyelitis.

Which mode of transmission should eventually be considered? Let us first regard the possibility of a dominant inheritance.

In our group of 137 patients two cases were found in which one of the parents had suffered from the disease at an other point of time.

This number, of course, is much too small to infer a dominant inheritance There is, however, a possibility that the parents did not come into contact with the virus in the period when they were most susceptible to the acute anterior poliomyelitis. Thus they may be carriers of the trait, but this did not manifest itself.

Against the dominant inheritance the following fact militates: in 12 cases 2 chil-

dren in one family were suffering from acute anterior poliomyelitis on a total of 137 families with 571 children.

It may be supposed that all of the children would have been infected in case of a dominant inheritance; even with a reduced penetrance a bigger number of cases might be expected.

To exclude dominant inheritance entirely is very diffecult, but it is not very probable. We could not find in the literature any data about it. Dominant and recessive sex-linked inheritance may be excluded as a result of the ratios concerning acute anterior pliomyelitis found and mentioned in the literature. Addair and Snyder as well as Herndon and Jennings conclude that an autosomal recessive gene for the susceptibility to paralytic poliomyelitis exists. From the data with which literature has provided us and the results of our own investigations we have arrived at the conclusion that endogenous factors exercise influence in the origin of paralysis with acute anterior poliomyelitis.

The results yielded by the third part of the investigations render it probable that we have not to deal with a specific factor, but with a non-specific one, viz. a greater vulnerability of the central nervous system for diverse diseases of which the increased susceptibility of the paralytic form of acute anterior poliomyelitis forms a part. The other parts of the investigation have shown the probability that this factor is inherited in a recessive way.

We will return now to the negative correlation found with the occurrence of other diseases in the poliomyelitis group.

This negative correlation can perhaps be explained by the existance of a susceptibility of the central nervous system revealing itself in some affection or other: i.c. suffering from one disease should exclude suffering from another disease.

The present study was not intended as an approach to this problem.

A research aiming at this problem may prove this hypothesis.

Summary

The object of this study was to ascertain if endogenous factors might play a part in the appearance of paralysis with acuta anterior poliomyelitis.

The investigation concerned 754 patients in Groningen and Drenthe (provinces of the Netherlands), affected by the disease during the years 1936-1951. First of all it appeared that the consanguinity percentage of the parents of the probandi was much higher than that of the average population the difference being significant ($\chi^2 = 22{,}28$; P: <0.001). Secondly we compared the number of connections of a group of 137 patients with a group of 591 patients and the number of connections of a control group of 137 persons with the group of 591 patients. As ignificant difference appeared to exist between the numbers observed. The third part of the research concerned the appearence of diseases with patients' relatives and the comparison of those with the diseases with relatives of a control group. Between the group of patients and relatives and the group of control cases and relatives a difference appeared

to exist in this sense that in each case the group first-mentioned showed a " surplus " of diseases in comparision with the control group; the burdening of the poliomyelitis-group with these diseases showed a significant difference from that of the control group. Also in this case the comparison of several separate diseases showed significant differences. However this was not the case with all the diseases. Attention was paid to the twins who occurred in the group of 754 patients. The small number of twins, however, did not allow of any conclusion whatsoever.

Finally the conclusion has been drawn, that endogenous factors exercise influence in the origin of paralysis with acute anterior poliomyelitis. The results of this investigation render it probable that we have to deal with a non-specific factor, viz. a greater vulnerability of the central nervous system for diverse diseases of which the increased susceptibility of the paralytic form of acute anterior poliomyelitis forms a part.

This factor is inherited in a recessive way.

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RIASSUNTO

Oggetto delle nostre ricerche era di determinare fino a qual punto i fattori endogeni agiscano sullo sviluppo della forma paralitica della poliomielite. Sono stati presi in esame 754 ammalati in Groningen e Drenthe (due provincie dei Paesi Bassi) colpiti dalla malattia negli anni 1936-1951: la percentuale di consanguineità nel gruppo di parentela dei malati era sensibilmente diversa da quella della popolazione generale (χ^2 = 22,8, P: ⟨0.001). Confrontando il numero delle parentele di 137 probandi con un gruppo di 591 malati e quello di un gruppo di controllo costituito ugualmente da 137 individui con lo stesso numero di malati, è risultato che il numero delle parentele del primo gruppo con i malati era superiore al gruppo di controllo (χ^2 = 7. 11, P: ⟨0,01⟩ 0,001). In seguito si sono messe a confronto le altre malattie delle famiglie dei malati con quelle delle famiglie del gruppo di controllo. Essendosi riscontrato che nel gruppo dei malati esiste un « surplus » di altre malattie, ne deriva che le malattie del sistema nervoso sono più frequenti nel gruppo dei famigliari dei malati rispetto a quello di controllo. Differenze significative si notano esaminando a parte le altre malattie, ma non in tutti i casi. Questo conferma l'opinione che fattori endogeni intervengano nella forma paralitica della poliomielite. Probabilmente si tratta di un fattore non specifico, cioè di una maggiore vulnerabilità del sistema nervoso per le varie malattie, essendo l'aumentata sensibilità una manifestazione peculiare della forma paralitica della poliomielite. Questo fattore si trasmette ereditariamente secondo le leggi di recessività. Il numero di gemelli appartenenti al gruppo di 754 ammalati non ha portato il nostro esame a rilievi più ampi.

RÉSUMÉ

L'objet de cette investigation était de déterminer où les facteurs endogènes jouent un rôle dans le développement de la forme paralytique de la poliomyelite. Nous avons examiné 754 malades en Groningen et Drenthe (deux provinces des Pays Bas), qui pendant les années de 1936-1951 étaient attaqués par la maladie. Il se trouvait que le pourcentage de consanguinité des parents des malades était différent du pourcentage de la population générale, la différence étant significative (χ^2 = 22.8, P: ⟨0.001). Le nombre des liaisons de 137 probandes avec une groupe de 591 malades et le nombre des liaisons d'une groupe de contrôle de 137 personnes avec le groupe de 591 malades était comparé. Il se trouvait que le nombre des liaisons dans la première groupe avec les malades était supérieur à la groupe de contrôle (X^2 = 7.11, P: ⟨0.01⟩ 0.001). Ensuite nous avons comparé les autres maladies chez les familles des malades avec les maladies chez les familles de la groupe de contrôle. Entre les deux groupes il existe une différence, c'est à dire que dans la groupe des malades il se trouve un « surplus » des autres maladies. Il ressort que les maladies du système nerveux arrivaient plus souvent dans la groupe des membres de famille des malades que dans la groupe de contrôle. En comparant les autres maladies à part on trouve aussi des différences significatives, mais cette différence n'existe pas pour toutes les maladies. Le résultat de ces recherches confirme l'opinion qui prétend que dans la forme paralytique de la poliomyelite des facteurs endogènes jouent un rôle. Probablement nous avons ici un facteur nonspécifique, c'est à dire une vulnérabilité plus grande du système nerveux pour les maladies différentes, la susceptibilité augmentée pour la forme paralytique de la poliomyelite étant une manifestation. Ce facteur se transmet héréditairement selon les lois de la récessivité. Le nombre des jumeaux dans notre groupe de 754 malades ne faisait pas possible de conclure quelque chose.

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ZUSAMMENFASSUNG

Die Absicht dieser Forschung war fest zu stellen ob vielleicht endogene Faktoren eine Rolle spielten in der Erscheinung von paralytischen Formen der Poliomyelitis acuta anterior. Die Untersuchung betrifft 754 Patienten in Groningen und Drenthe (zwei Provinzen der Niederlände), die während die Jahre 1936-1951 von der Krankheit befallen wurden. Es stellte sich erstens heraus, dasz der Konsanguinitätsprozentsatz der Eltern der Probandi höher war als im Durchschnitt der Bevölkerung. Die Differenz war signifikant ($\chi^2 = 22.8$, P: $\langle 0.001$). Zweitens wurde die Zahl der Verbindungen von einer Gruppe von 137 Patienten mit einer Gruppe von 591 Patienten und die Zahl der Verbindungen von einer Kontrollgruppe von 137 Personen mit der Gruppe von mit der Gruppe von 591 Patienten verglichen. Die Verhindung der ersten Gruppe mit der Gruppe von 591 Patienten war signifikant gröszer als die der Gruppe der Kontrollpersonen mit der Gruppe von 591 Patienten ($\chi^2 = 7.11$, P: $\langle 0.01 \rangle$ 0.001). Im dritten Teil unserer Arbeit haben wir andere Krankheiten in der Familie der Patienten verglichen mit Krankheiten in der Familie der Kontrollgruppe. Zwischen den beiden Gruppen existierte eine Differenz in dem Sinne dasz in jedem Fall bei der Poliomyelitis-Gruppe ein « Surplus » an Krankheiten festgestellt werden konnte. Es stellte sich heraus, dasz ins besondere die Krankheiten, die am Zentralnervensystem verbunden sind in die Gruppe der Angehörigen der Patienten zahlreicher waren als in der Kontrollgruppe. Auch mit anderen Krankheiten konnten signifikante Differenzen festgestellt werden, aber nicht für jede Krankheit. Die kleine Zahl der Zwillingen in der Gruppe von 754 Patienten erlaubte uns nicht irgendeine Folgerung zu ziehen. Schliesslich wurde der Schluss gezogen, dasz endogene Faktoren Einflusz ausüben in der Entstehung paralytischen Poliomyelitisfällen. Die Ergebnisse dieser Forschung machen es wahrscheinlich, dasz wir mit einem nicht-spezifischen Faktor, mit Nahmen einer grossen Vulnerabilität des Zentralnervensystems für verschiedene Krankheiten zu tun haben, wovon die erhöhte Empfindlichkeit für die paralytische Form der Kinderlähmung ein Teil ist. Diese Faktor wird in rezessivem Sinne vererbt.

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