TWIN STUDIES IN MEDICAL GENETICS

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It is the aim of twin studies to obtain results which are not only valid for twins, but apply to the whole population. Therefore the following questions have to be answered first: do twins differ from nontwins in the trait under study? Do different nongenetic factors act upon MZ and DZ twins which alter the probability of manifestation of a trait, even before birth? There are important differences in embryogenesis and placental blood flow in mono- and dichorionic twins; this can influence the normal fetal development. Therefore the value of twin studies alone in analysing the genetic component in the etiology of congenital malformations is rather ambiguous. Twin studies beyond the newborn period can be classified into four approaches: (1) Case reports; (2) Accumulated case reports; (3) Limited representative sample; (4) Unlimited representative sample. The most frequent systematic method in medical genetics is the establishment of all twins in a defined population of probands (3). Another successful application in the last few years has been in pharmacogenetics. Although no simple mode of inheritance could be discovered, it was possible to estimate the genetic component within the interindividual variability of the metabolism of certain drugs (nortriptyline, antipyrine, phenylbutazone, ethanol). Now, additional nontwin research is needed to work out single factors within the observed polygenic systems.

We will limit our considerations on " Twins in Medical Genetics " to the following aspects:
1. Limitations of the twin method due to peculiarities in prenatal development;
2. Methodical possibilities of systematic twin research in traits which are alternatively distributed, e.g., diseases;
3. Examination of normal twins as a tool in pharmacogenetics.

The aim of twin studies is to obtain results which do not only apply to twins but to the whole population. Therefore, the following question has to be answered first: *Do twins differ from nontwins in the trait under study?*

In spite of the peculiarities of the development of multiple zygotes during early embryogenesis, there is no doubt that, from the genetic point of view, twins are comparable to nontwins. Nevertheless, the comparison of a number of physiological parameters shows that there are differences between twins and nontwins: twins suffer from a higher frequency of abnormalities during pregnancy and at birth than single babies; they weigh less at birth, which can only partly be attributed to the shorter duration of gestation; the stillbirth rate and infant mortality in early life are considerably higher in multiple births than in single ones; in later years twins are more frequent among mentally defective patients than would be expected. The reasons for mental retardation may at least in part be traced back to the peculiarities during pregnancy and birth.

If there are differences between twins and nontwins owing to various prenatal developments, the second question has to be: *Do different nongenetic factors act upon MZ and DZ twins which alter the probability of manifestation of a certain trait, even before birth?*

It is important to know this, because the twin method assumes that the two different types of twins are exposed to the same environmental factors. Again, weight at birth can serve as a simple analysable parameter. In a recent extensive survey, Corney et al. (1972) compared the average birth weights

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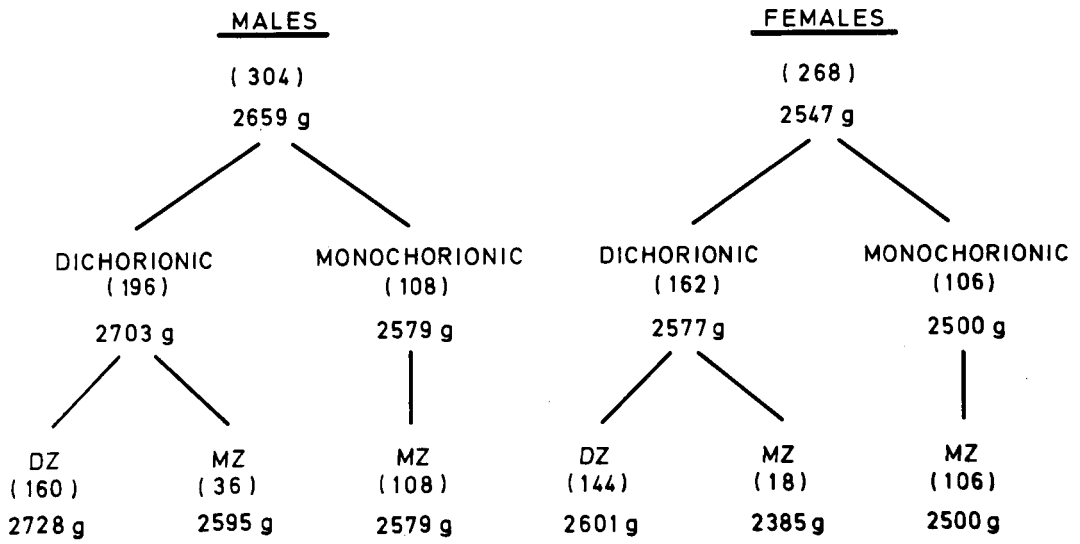

Fig. 1. Mean birth weight of like-sexed twin subjects (survivors only), classified by sex, placentation, and zygosity. Numbers in parentheses. (From Corney et al. 1972).

of 572 individuals from twin pairs of the same sex, classified by sex, placentation and zygosity. Fig. 1 not only shows that MZ twins of both sexes weigh less than DZ twins, but also that the type of the placenta has no effect on the mean birth weight of the surviving individuals. Therefore, it appears likely that zygosity, rather than placentation, is responsible for the differences in birth weight (Corney et al. 1972). But, when individuals within the (always MZ) monochorionic pairs are compared, greater differences come to light. In its extreme manifestation, these MZ twins differ in size by more than 1000 g (Benirschke and Kim 1973). Such differences may be the result of arteriovenous anastomoses which are assumed to be the basis of the chronic «transfusion syndrome». These very common anastomoses can lead to chronic malnutrition with a reduction of cytoplasmic mass of parenchymal organs, as well as markedly reduced hemoglobin and serum protein values in the donor twin (Benirschke and Kim 1973). Since more than 20% of the MZ twins have only one chorion (Potter 1963), the transfusion syndrome can account for the greater intrapair differences at birth which do not arise in DZ twins. Therefore, the twin method cannot be applied to those traits in which the two types of twins are influenced in different ways by the intrauterine environment.

In medical genetics, the twin method is preferentially used in cases where a multifactorial system of inheritance is supposed to exist. Are there congenital diseases to which the peculiarities of the twin pregnancy contribute? The following data show that this has to be assumed, at least for some types of congenital malformation.

Table 1 shows congenital malformation frequencies in twins and in single births compiled from different series. Although frequencies of congenital malformations vary greatly in the five series, presumably due to different definitions, on the whole these anomalies appear to be more frequent in twins than in singletons in every analysis published. This is already a sign of differences present during the gestation period. This tendency is more obvious when particular types of malformation are taken into consideration. At least, as far as the diseases are concerned such as congenital heart disease, anencephalus, hydrocephalus, cleft lip or palate, the risk in twins is higher than in single births.

Table 2 shows frequencies of malformation in singletons compared with like-sexed and unlike-sexed twins. In all four cases, the individual risk is higher in same-sexed than in opposite-sexed twins.

Table 1. *Incidence of congenital malformations in twins and singletons per 1000 births*

Source	Approximate sample size	Incidence in singletons	Incidence in twins
Hendricks 1966	~ 35,000	33	106
Stevenson et al. 1966	421,000	12.7	14.4
Hay and Wehrung 1970	10,200,000	5.8	6.2
Onyskowová et al. 1971	240,000	13.2	26.4
Emanuel et al. 1972	25,000	13.2	23.2

Table 2. *Incidence of selected congenital malformations in twins and singletons per 1000 births*

Type of malformation	Source*	Incidence in singletons	Incidence in twins		
			Total	Like sexed	Unlike sexed
Congenital heart disease	a	0.74	1.65	1.82	1.27
	b	2.8	6.3	—	—
	c	0.59	0.71	0.81	0.49
Anencephalus	a	0.92	1.24	1.52	0.64
	b	1.3	1.2	—	—
	c	0.23	0.37	0.45	0.22
Hydrocephalus	a	0.61	0.72	0.91	0.32
	b	1.0	3.1	—	—
	c	0.30	0.40	0.45	0.31
Cleft lip and/or cleft palate	a	1.21	0.34	1.68	0.64
	b	0.8	0.4	—	—
	c	1.11	1.07	1.10	1.01

* a = Stevenson et al. 1966; b = Edwards 1968; c = Hay and Wehrung 1970.

This points to the fact that MZ twins are more frequently encountered than DZ ones. The actual figure concerning risk, however, must be higher, because only about 50% of the like-sexed twins are MZ. The reason for the greater portion of MZ among malformed twin individuals could be the consequence of the " transfusion syndrome ". This conclusion is supported by the fact that, in the majority of cases, malformation arises in only one of the twins. Unfortunately, there are no series on congenital malformation in twins available in which the type of placentation is taken into account. Twin studies on congenital malformation using unselected cases show relatively low concordance rates in MZ twins. Table 3 summarizes the available twin data on congenital cleft lip and/or cleft palate (Jörgensen and Gabka 1971). Table 4 shows the concordance rates of 5 twin studies on congenital cardiac malformation. The higher concordance rates in MZ twins in both examples indicate a genetic component. It has to be supposed, however, that the concordance rate in the monochorionic twins within the MZ group is lowered due to differential developmental conditions of the twin individuals. A thorough analysis of discordant MZ twins, which can be so valuable in other diseases, is not possible in cases of congenital malformation unless we know the placental type. Therefore, the twin method can only produce rather ambiguous results in these anomalies.

Table 3. *Summarized twin studies on congenital cleft lip and/or cleft palate.* (From Jörgensen and Gabka 1971)

MZ twins		DZ twins	
No. of pairs	Concordant	No. of pairs	Concordant
125	37 = 29.60% ± 4.1%	236	11 = 4.66% ± 1.16%

Table 4. *Congenital cardiac malformations in unselected twin series.* (From Fuhrmann 1972)

Source	Sample size	MZ twins		DZ twins	
		Concordant	Discordant	Concordant	Discordant
Uchida and Rowe 1957	?		13		13
Lamy et al. 1957	1188		7	1 = 3%	8
Campbell 1961	942		12		4
Nora et al. 1967	?	6 = 46%	7	1 = 4.2%	23
Jörgensen 1970	2427	4 = 19%	17	1 = 4.2%	23
Total		10 = 15.2% ± 4.4%	56	3 = 4.1% ± 2.3%	71

In the following, we will briefly discuss how to proceed in medical genetics when there are no objections to the application of the twin method, and when a clear distinction between affected and unaffected individuals is possible. According to Luxenburger (1940, cf. Vogel 1961), four approaches have to be differentiated (Table 5).

1. The most simple application of twin research is the *case report:* descriptions of single cases of concordant or discordant twins, especially MZ, are continuously being published, mostly in non-genetic journals. These cases are preferentially published for the sake of curiosity and have, therefore, no representative character. The only scientific value using this approach results from the possibility of a thorough analysis of discordant MZ twins. Furthermore, in very rare conditions, case reports may contain the only available information on a genetic basis of the trait.

2. *Accumulated case reports.* Even when a number of case reports are accumulated, the same limitations apply as for single case reports. Twin pairs compiled in this way are not representative, but the systematic analysis of MZ twins discordant for a certain trait can give valuable information on the conditions favouring manifestation. Relatively small series of discordant twins could produce much better information on risk factors in manifestation of e.g., diabetes, dermatologic or psychiatric diseases, than the survey of a large population in which the control problem is overwhelming.

Table 5. *Possibilities of data collection in twin studies*

1. Case reports	
2. Accumulated case reports	
3. « Limited representative » Ascertainment (« Beschränkt repräsentative Stichprobe »: Luxenburger 1940)	Ascertainment according to special rules to avoid biases
4. « Unlimited representative » ascertainment (« Unbeschränkt repräsentative Stichprobe »: Luxenburger 1940)	

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3. The "*limited representative ascertainment*" is the most frequent approach in medical genetics to obtain large unbiased series: all twin individuals are extracted out of a sample of trait carriers. It then has to be established whether or not the twin's sib is also affected. It is important, however, that all twins within the initial population are discovered; otherwise concordant twins have a higher chance to be ascertained than discordant ones, because two individuals are at risk. Successful ascertainment of all twins is proved when the frequency of detected twins in the series is as high as in the general population; such factors as age, maternal age, and race, however, have to be considered. Correspondingly, the proportion of like-sexed and unlike-sexed twins should agree with that of the general population. The practical procedure would be much easier if the routine questionnaire for hospital patients were supplemented by the question: is the patient a twin? Luxenburger described this approach as "limited representative", because the sample does not originate from a defined region and time period, but from hospital patients selected on the basis of probandship.
4. In an "*unlimited representative ascertainment*" every twin is ascertained and checked as to whether he is a carrier of the trait in question. This is done for a definite period and local area. The number of individuals, however, who have to be examined is enormous in comparison to the "limited representative approach". Table 6 shows the number of individuals required at the beginning, when 200 carriers of the trait shall be discovered and the incidence of the disease is 0.5%.

Table 6. *Necessary population size when 200 trait-carrying twin individuals shall be discovered*

« Limited representative sample » (starting from probands): 10.000
« Unlimited representative sample » (starting from all twins within a defined population): 2.000.000
Supposed conditions: incidence of twin individuals, 1:50; Incidence of the trait, 0.5%

For economic reasons, the establishment of all twins in a defined population of probands is the most frequently applied method. The twin study on leprosy in India (Chakravartti and Vogel 1973) can serve as a recent example.
The first prerequisite for the application of the twin method has to be that there are certain hints for the implication of genetic factors in the origin of the trait under study. In the case of leprosy, the following observations indicated the importance of genetic factors: not necessarily everybody exposed to the leprosy bacillus actually becomes infected, and not everybody who becomes infected develops clinical symptoms. Furthermore, this infection may produce different types of the disease, depending on the immunity of the organism. One patient may only show depigmented and anaesthetic macules (tuberculoid leprosy) whereas another patient may be full of diffuse infiltrations, the nose perhaps being destroyed (lepromatous leprosy). The apparent differences in liability, however, may have many causes, but additional information obtained makes a genetic influence probable: clustering of the same type of leprosy among near relatives; racial differences in relative frequencies of different leprosy types; investigations carried out in twins suffering from tuberculosis had shown the importance of genetic factors in this comparable disease; some smaller studies already made, although not satisfying due to methodical insufficiency, suggested genetic influences also in the case of leprosy.
The twin study was carried out in endemic leprosy areas of West Bengal, India, where at least 2-4% of the total population is known to be affected, and in some further Indian districts. A total of 102 twins pairs were selected, of which at least one twin suffered from leprosy. Table 7 shows that the concordance rate of the MZ twins is higher than that of the DZ. In addition, in many of the afflicted MZ twin pairs, the course of the disease, as well as the extent of the lesions, show striking similarity. The intrapair differences in the ages of onset of the concordant twin pairs tended to be smaller in MZ than in DZ twins (Table 8). The number of DZ pairs concordant for leprosy, however, was relatively small.

Table 7. *Concordance and discordance in 102 twin pairs with leprosy.* (From Chakravartti and Vogel 1973)

Sex	MZ pairs		DZ pairs	
	Concordant	Discordant	Concordant	Discordant
Male	24 = 60.0%	16 = 40%	5 = 22.7%	17 = 77.3%
Female	13 = 59.1%	9 = 40.9%	1 = 16.7%	5 = 83.3%
Male-Female	—	—	2 = 16.7%	10 = 83.3%
Total	37 = 59.7%	25 = 40.3%	8 = 20.0%	32 = 80.0%

$\chi^2 = 15.53$; $p \sim 0.003$

Table 8. *Difference in the age of onset of leprosy between the members of concordant twin pairs.* (From Chakravartti and Vogel 1973)

	Same age	0-1 years	2 years	3 years	4 years	5 years	Total
MZ	15	15	5	0	1	1	37
DZ	2	3	1	1	0	1	8

The twin method not only permits an estimate of the contribution of genetic factors to the liability for a certain condition, but also affords the opportunity to evaluate exogenous factors favouring the manifestation by a thorough analysis of the discordant MZ pairs. The risk factors found are classified in Table 9. The most important seems to be a closer contact between the afflicted sibs with infectious cases.

As leprosy can show rather different clinical manifestations, this disease offers the possibility to analyse the concordance as to the particular type of leprosy present. In DZ twins, the number of concordant pairs is so low that it is pointless to draw comparisons of leprosy types, either with the MZ pairs or with the discordant DZ pairs. But it is possible to compare the leprosy types of the twin probands with those of the afflicted family members. Table 10 shows that parents and sibs of

Table 9. *Differences of risk factors in 25 MZ twin pairs, discordant for leprosy.* (From Chakravartti and Vogel 1973)

	Affected twin	Healthy twin
Poor constitution in childhood	3	1
Infectious diseases in childhood (diarrhea, dysentery)	6	6
Strenous and harder living conditions	1	2
Close contact with open cases	15	—

Table 10. *Comparison between leprosy types of twins and their parents and siblings.* (From Chakravartti and Vogel 1973)

Twins	Parents and siblings		
	Lepromatous	Tuberculoid	Total
Lepromatous	18	6	24
Tuberculoid	27	50	77
Total	45	56	101
$\chi^2 = 11.81$	$p = 0.0007$		

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lepromatous twins, if afflicted, have a higher probability of suffering from the lepromatous type than parents and sibs of twins with tuberculoid leprosy. Furthermore, the relative number of patients among siblings is about the same in families of concordant and discordant MZ pairs.

At least four, but probably five, of the MZ pairs concordant for leprosy but discordant for its type afford the opportunity for an additional conclusion. It had been hypothesized in the past that a certain factor with a simple Mendelian mode of inheritance would be responsible for the development of lepromatous leprosy. Such a possible candidate could be an impaired function of the T-cell system of lepromatous leprosy patients. This defect could provide a clue that the genetic basis for susceptibility to lepromatous leprosy could be found in a special immune defect of the T-cell system. However, the observation of at least four MZ twins concordant for leprosy but discordant for the type renders this possibility at least very unlikely.

The most important results of this twin study will be discussed briefly: there are definite genetic differences in susceptibility to the clinical manifest infection with the leprosy bacterium in the population examined. Among leprosy patients, genetic differences are responsible for a major part of the variability observed regarding type and severity of the disease. However, even when ample opportunity to infection is present, not all genetically susceptible individuals are clinically afflicted.

Are there any objections to generalizing the results obtained from twins to nontwins? Unfortunately, no study has been carried out as yet as to whether leprosy occurs more frequently among twins than among the population in general.

Although it is also possible that MZ twins have a higher risk of infection due to closer mutual skin contact than DZ twins, the authors were under the impression that both types of twins lived together comparably and were exposed in the same way to external contacts. Therefore, it is assumed that the results are not biased too much by any of the particular pregnancy and living conditions of twins.

But another bias has to be taken into account: as the relative frequencies show, ascertainment of MZ was much more complete than that of DZ. The reason for this bias might well be certain living conditions in this part of India: most of the inhabitants examined live in rural areas where there is a high percentage of illiteracy; most patients do not even know their exact age; therefore, a twin pair is mainly known as such when the similarity cannot be overlooked; on the other hand, DZ will not be noticed and they themselves sometimes do not even realize that they are twins. How could the incomplete ascertainment of DZ have influenced the results? As ascertainment of concordant pairs will, in most cases, be favoured, the differences between MZ and DZ pairs may be underestimated.

More important is the next question: were the MZ pairs completely ascertained? It is likely that, for the following reasons, not all MZ pairs could be ascertained. Some pairs might have successfully hidden their affliction; many of the pairs live in beggars' colonies and receive no treatment; twins from higher classes might have escaped due to treatment by private doctors; some patients may have even given wrong answers in order to avoid social stigma. As most of these factors apply to both MZ and DZ twins, regardless of concordance or discordance, proband selection is improbable, at least for the major sources of bias. Nevertheless, the concordance figure may still be a little too high.

Concerning the environmental risk factors, analysis of discordant MZ pairs has confirmed that continuous and intensive contact with infectious cases is most important. Therefore, only in those areas where leprosy is highly endemic, concordance figures of the same order of magnitude are to be expected, because the liability to infection is genetic in origin although, however, requiring close contact with sick people.

The twin study on leprosy shows that — as in the case of tuberculosis — it is possible to draw a rather differentiated picture about the influence of genetic factors on the frequency, course and conditions of manifestation of the disease. Now, further studies are necessary to work out more specific factors, e.g., the effect of the immune system.

Now we will turn to quite another application of the twin method in medical genetics, namely pharmacogenetics. Pharmacogenetics (Vogel 1959) is the interdisciplinary field that deals with the influence of heredity on the response to drugs. After an enthusiastic start in the late fifties, only a few well-

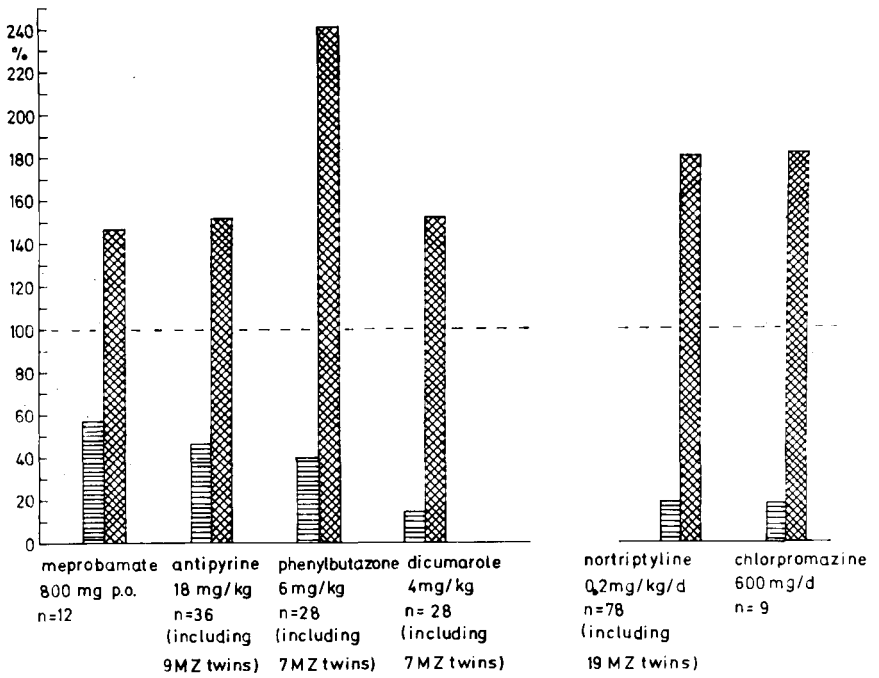

Fig. 2. Left: Extremes of biological half life of some drugs after one application (% of the mean). Right: Extremes of serum concentrations during chronic intake (% of the mean).

defined pharmacogenetic polymorphisms have been discovered. The uptake of a drug is — from the evolutionary point of view — a highly artificial process for man. Each of the pharmacokinetic parameters — absorption, distribution, metabolism, receptor binding, excretion — can theoretically be subject to genetic variability. In fact, for many drugs there is a pronounced variability in serum levels between different individuals to which genetic mechanisms may essentially contribute. Fig. 2 shows some examples of biological half lives or of serum concentrations under steady-state conditions of drugs. In contrast, the deviation from the mean value in the concentrations of normal serum constituents is small (Fig. 3).

One of the first pharmacogenetic phenomena which came to light was the acetylation polymorphism of the antituberculosis drug isoniazid. Interestingly enough, the most important hints arose from a twin study (Bönicke and Lisboa 1957). The authors, however, who described a tenfold intrapair difference in the DZ twins compared to the MZ twins, failed to recognize the Mendelian mode of inheritance of the isoniazid excretion rate. This only became possible by family studies.

During the past five years, several investigators used the twin method to estimate the genetic component within the metabolism of certain drugs. It had been established that patients treated with the same doses of various tricyclic antidepressants, such as imipramine, desmethylimipramine or nortriptyline, showed large differences in their steady-state plasma levels. Table 11 shows the order of magnitude of the steady-state plasma levels of four tricyclic antidepressants (Propping and Kopun 1973). Starting from such observations, a Swedish group of clinical pharmacologists performed a twin study with nortriptyline. The twins received three oral doses for a period of eight days (Alexanderson et al. 1969). The identical twins achieved similar steady-state plasma concentrations of nortriptyline whereas the intrapair differences in fraternal twins were far greater. This twin study demonstrates that most of the variability in nortriptyline steady-plasma concentrations between different

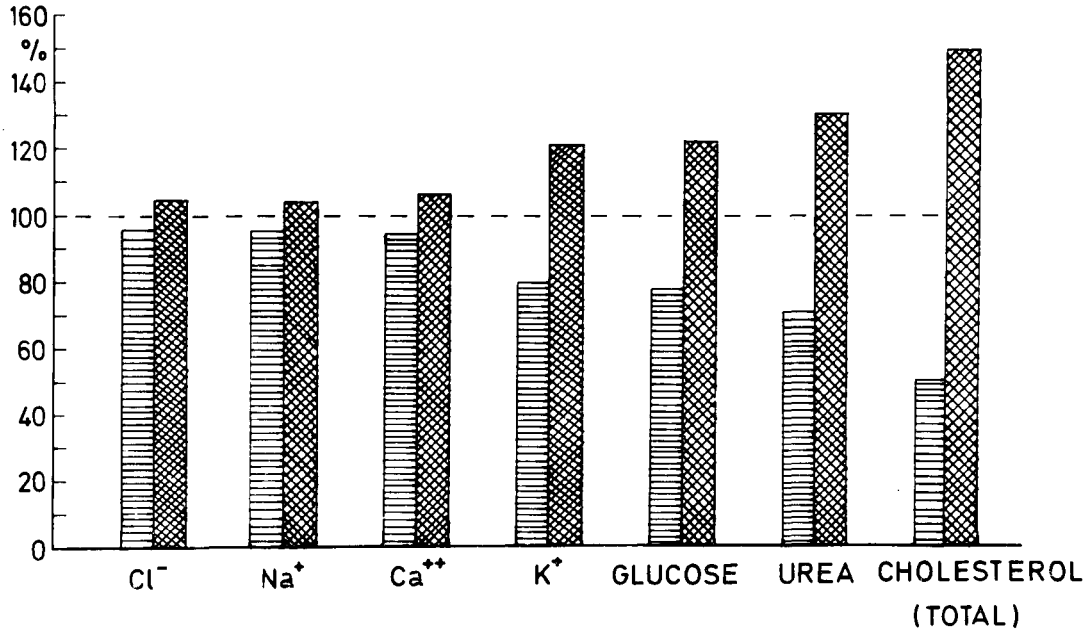

Fig. 3. Variability (95% range) of some serum concentrations (% of the mean).

Table 11. *Variability of steady-state plasma levels of four commonly used tricyclic antidepressants*

	n	Daily dose (mg)	Range of the serum concentration (ng/ml)
Nortriptyline			
Sjöqvist et al. (1968)	25	75	10 — 275
Kragh-Sorensen et al. (1973)	30	150	48 — 238
Amitriptyline			
Braithwaite et al. (1972)	15	150	20 — 228
Imipramine			
Walter (1971)	16	150 — 225	2.5 — 71.0
Zeidenberg et al. (1971)	7	450	170 — 750
Desmethylimipramine			
Sjöqvist et al. (1968)	16	75	8 — 290

individuals is genetically determined. But plasma concentrations are affected by the above mentioned factors as absorption, protein binding, rate of metabolism and excretion. According to the authors' opinion, the pronounced interindividual differences in the plasma levels of nortriptyline can be explained by metabolic differences. A simple mode of inheritance, however, could not be established.

Vesell and coworkers quantified the genetic and environmental components of large individual variations in rates of drug elimination from plasma after an acute ingestion of the drug (for review see Vesell 1973). In a cross-over study, a sample of healthy, untreated twins received single doses of the following drugs: phenylbutazone, bishydroxycoumarine, antipyrine, ethanol. The mean intrapair difference in MZ is essentially smaller than in DZ. The contribution of heredity to variations in the half-lives was calculated to be greater than 0.97 for the drugs examined. Again, the authors assumed that the differences in the speed of drug metabolism are the basis for the variability observed. However,

it has not been possible to draw any conclusions about the nature of the underlying genetic factors, and no simple mode of inheritance could be established. Obviously, too many factors are involved in the elimination rate of most drugs.

It was for similar reasons that the twin method has often been criticized in the past, because it would be a rather poor result to conclude that MZ are more similar than DZ in the trait under study. These objections and successful sophistication of laboratory methods have now pushed aside the twin method from the first position of scientific progress.

What will the prospects of the twin method in the future be?

1. There will always remain traits or conditions in which the extent of inherent or environmental factors is unclear. Only the twin method can provide reliable evidence for the implication of genetic factors without knowing these factors individually.
2. A thorough analysis of discordant identical twin pairs is a valuable tool for the disclosure of single exogenous factors. An analysis of first-degree relatives of these twin pairs can give additional information.
3. The twin method can provide the best basis for testing reasonable hypotheses, as has been done in pharmacogenetics. Here, the method has been a starting point for the development of a new field of human genetics.

The limitations of the twin method, however, have to be kept in mind, as there are many problems in human genetics which cannot be solved by twins. The method is only applicable when twins do not essentially differ from nontwins. Furthermore, the twin method is not suitable, e.g., for the analysis of modes of inheritance which have to be elucidated in family studies. Nevertheless, for a number of questions in medical genetics, the study of twins will remain a valuable tool within the methodical equipment of human genetics.

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