Situs inversus, Asymmetry, and Twinning

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INTRODUCTION

THE relation of situs inversus to twinning has attracted much attention from experimental embryologists. Thus, Spemann and Ruud (1922) produced situs inversus by division of the amphibian egg, the twin derived from the right half frequently showing situs inversus. Komai (1938) observed situs inversus in the salmon, particularly in one partner of conjoined twins and relatively frequently in the smaller twin.

Naturally students of human twins have been interested in situs inversus in connection with the general problem of mirror-image asymmetry in twins. The relatively great dissimilarity observed in some human twins discordant for situs inversus has been considered as evidence of a mirror-image mechanism, the dissimilarity being supposed to be an indicator of the bilateral differentiation at the time when the division took place (Dubreuil-Chambardel, 1927; Cockayne, 1939; Helweg-Larsen, 1947). However, it can hardly be excluded that both the dissimilarity and the inversion in these cases are due to causes having no relation to the division or a mirror-image mechanism. In this connection, it is noteworthy that Mattison (1933) found only 1.3 per cent twin births among a total of 615 births occurring in the families of 4 individuals with situs inversus, compared with a frequency of 1.5 per cent twin births in Sweden generally.

As this problem is a fundamental one in twin research, the following data which have been collected in a rather extensive study of situs inversus in Norway may be of interest.

THE MATERIAL

The material includes 270 cases of situs inversus observed during a 7 year period, 1944–1950. During this time the interest of the author has focused on various aspects of the problem. In the earlier years, attention was directed to the relation between situs inversus and other anomalies, particularly to abnormalities of the lungs, nose, lower jaw, spine, and heart. These problems have been dealt with in a series of papers (Torgersen, 1946–1950).

Most of the cases of situs inversus have been discovered in mass x-ray photography of the Norwegian population. In some regions of the country, having

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a total population of about 1,000,000 approximately 90 per cent of the inhabitants over 15 years of age have been examined. Up to the present time, 200 cases of situs inversus have been discovered among 1,800,000 individuals above 15 years of age. The frequency is thus 0.011 per cent, or slightly over 1 per 10,000.

The 70 additional cases have been discovered through hospitals and municipal health departments. These cases are most probably derived from regions of the country not thoroughly covered by the populational surveys or represent children younger than 15 years. Assuming the same frequency within these less extensively sampled portions of the population, one would estimate that the total Norwegian population of 3,100,000 persons contains about 340 cases of situs inversus.

In the miniature radiogram the position of the heart, the liver and the gas bubble in the stomach indicate the situs of the viscera. In a very few cases, the picture is taken with the back instead of with the front towards the screen. The technicians make a note in such cases. Besides such pictures are easily recognized. The diagnosis has been confirmed by fluoroscopy in most of the cases in which the individual did not know about the anomaly from previous examinations. It can be excluded that any case of normal situs has been taken for a case of situs inversus. However, it can not be excluded that a very few cases have been discarded due to lack of confirmation by fluoroscopy.

In the mass x-ray series were found 2 cases of dextrocardia alone, without other visceral inversions. The frequency of this type of inversion is thus about 0.0001 per cent. Inversion of the abdominal organs alone was observed twice in the 70 additional cases and once in a secondary case, in the twin the brother of whom had situs inversus totalis. Inversion of the abdominal organs alone is probably as rare as inversion of the heart alone.

The occurrence of situs inversus totalis and of inversion of the abdominal organs or metameres of the heart alone in the same family (Torgersen, 1950) indicates that all types of inversion are manifestations of the same factors, the rareness of the partial inversions being partly due to prenatal selection.

Family data. For obvious reasons, a direct examination of all members of the families of such a large series of cases would not have been feasible. In the beginning of the study, I succeeded in examining 60 sibs and parents of a number of cases without encountering additional cases of the anomaly. Earlier studies had, in fact, shown this procedure to be unpromising. Mattison (1933) examined 448 relatives of individuals showing the anomaly, and Gutzeit and Lehmann (1940) performed an extensive examination of the families of 3 cases; in both instances the results were negative.

The best, and in fact the only practicable, way of ascertaining or excluding cases among the sibs and of avoiding selection of data is to examine all of the inhabitants of a limited area having a fairly stationary population. The present

material approaches this goal rather closely. Considering the large numbers of individuals examined, it is highly improbable that cases of situs inversus have been overlooked among the sibs, especially those over 15 years of age. The families have shown much interest in the investigations and have cooperated well in supplying information, probably because situs inversus, unlike other anomalies, is regarded merely as a curiosity rather than a malformation.

It of course cannot be excluded that situs inversus may have passed undetected in some of the parents and sibs. However, the chance of finding additional cases in families has been high. Among the 200 cases found by mass x-ray photography 65 per cent knew of their anomaly from previous examinations, a percentage indicating the relatively high value of hearsay evidence in this condition in Norway at the present time. Internal migration, emigration, prenatal and infant mortality—which is not increased in these families—cannot be considered as sources of serious error.

Through the mass x-ray surveys I found 8 familial cases, among them two cases previously reported (Frøhlich, 1920; Natvig, 1939). Only 25 such families are on record in the world's literature. Affected cases in parent and child have been recorded only twice, in a mother and daughter (Mattison, 1933) and in a father and child of unspecified sex (Pernkopf, 1937). Considering the extensive sampling employed in the present study, which revealed no cases in 2 consecutive generations, such occurrences must be exceedingly rare, even rarer than the cases in sibs.

More emphasis has been placed upon the relation of the data to the population as a whole than to genealogical studies, the results of which are of limited value if the size of the population and conditions of sampling are unknown.

RESULTS

Situs inversus and twinning. The frequencies of situs inversus and twinning in different regions of Norway are shown in table 1. The frequency of situs inversus is lowest in urbanized counties in the East, and highest in the West. The difference between these two groups is 0.013 ± 0.0045 per cent. In a previous report (Torgersen, 1949*a*) the author suggested a possible relation between the geographical distribution of situs inversus and twinning. This preliminary hypothesis, based upon relatively few observations, has since proved to be no doubt erroneous. There is no apparent parallelism between the frequencies of twinning and of situs inversus. As far as the geographical distribution is concerned, the two phenomena seem to behave as manifestations of independent factors.

One reason why a parallelism had been anticipated, both in the geographical distribution and in the familial occurrence, is the fact that both situs inversus and twinning tend to occur in the offspring of older mothers. The average age of the mothers at the time of birth of children with situs inversus is 31.73 years for 227 cases in the present study. On the basis of official Norwegian statistics, E. Sverdrup, of the University Institute of Economics, has calculated that the average maternal age for all births in the interval 1920–30, which is the middle of the period in which the births of the individuals with situs in-

versus in this material took place, is 30.5 years, with a standard deviation of 6 years. The difference, 1.23 ± 0.4 years, shows that maternal age is of importance in situs inversus. However, the influence of this factor is not of such importance as to conceal the independence of the factors in twinning and situs inversus. Unlike twinning, situs inversus is relatively frequent in regions with a high degree of inbreeding.

The data on twinning in the propositi themselves also fail to reveal any significant correlation between situs inversus and twinning. Among 240 unselected cases of the anomaly, 4 were members of twin pairs—about the number to be expected on the basis of chance association. Two of these constituted a pair of dizygotic twins, concordant for situs inversus (Torgersen, 1948*b*). The remaining two cases belong to two different pairs of same-sexed twins; in one case a twin sister had died at one month of age, in the other, a twin sister

TABLE 1. FREQUENCY OF SITUS INVERSUS COMPARED WITH THE TOTAL TWIN FREQUENCY IN VARIOUS PARTS OF NORWAY

REGION	SITUS INVERSUS CASES/TOTAL	SITUS INVERSUS PER CENT	TWINS (§) PER CENT
Districts nearby Oslo Fjord	19/246,602	0.0077	2.76
Eastern and central Norway	22/156,906	0.0140	2.76
Southern Norway	22/161,153	0.0137	2.82
Western Norway	25/120,354	0.0208	2.58
Troendelag (near Trondheim)	20/201,922	0.0099	2.83
Northern Norway	14/111,925	0.0125	2.32
Totals	122/998,862	0.0122	

§ Percentage incidence of twins represents twin-born individuals (counting both partners) relative to total births, according to official Norwegian statistics.

died at age 6 years; there is no conclusive evidence regarding the zygosity of these pairs or about the situs of the viscera in the twins that died.

Data concerning the familial occurrence of twins were secured in 100 unselected families of the index cases. The information regarding twins in the parents and sibs, and possibly also in the grandparents, is probably more reliable than information about twinning in more remote relatives. For this reason, the frequencies of twins in the parents, grandparents and sibs are compared with the frequency in the population. Six of the 200 parents were members of twin pairs, as were 4 of the 400 grandparents. Among the 500 sibs in these families there were 7 pairs of twins. The total of 24 twins among 1,100 individuals is about what is to be expected in a country in which the frequency of twin births is about 1.5 per cent.

How frequently have twins occurred in the families of those cases of situs inversus who were themselves members of twin pairs? In answering this question, the family in which both members of a pair of dizygotic twins showed

situs inversus has to be reckoned twice. Of 16 grandparents, 3 were twins; of 8 parents, none. Two twin pairs were found among 23 sibs. In all, 15 per cent of these 47 relatives were twins. The difference between this frequency and the population incidence is about 13 ± 5 per cent. Thus, the frequency of twinning is probably increased in the very few families in which the individual with situs inversus is a twin.

The number of sibs is known in 229 unselected families, the ratio of affected (situs inversus) sibs to normal sibs being 11:1,221, the 229 index cases being, of course, excluded. In 221 families the index case was the only individual found to be affected. Three sibs were affected in 3 sibships, 2 in 5 sibships; in all, 36 normal sibs were present in these 8 sibships. These data do not agree with the supposition of a single recessive gene. In fact, they can hardly be considered as proof of an influence of the genes at all, environmental factors not being excluded.

On the other hand, evidence for the hereditary nature of situs inversus is available from other observations. There is first the genetical relationship with other anomalies, as demonstrated by the author in connection with developmental anomalies of the lungs and heart (Torgersen, 1946, 1949*a*, *b* and 1950). Situs inversus behaves in these families as a manifestation of genes which, in the previous generation or in the sibs, show quite different manifestations. Additional evidence of heredity is furnished by the frequency of consanguineous marriages among the parents of situs inversus cases, and particularly of first cousin marriages, which, in 189 unselected cases, was found to be 3.7 per cent.

A more detailed analysis shows that the parents were second cousins twice in the 8 familial cases, first cousins in none of them. It is remarkable that no secondary case occurs among 48 sibs of 7 sibships in which the parents were first cousins. But in 44 families having symptoms of a defective development of the bronchi and the paranasal sinuses, the patient with situs inversus had parents who were first cousins in 3 cases (7 per cent) and second cousins in 7 cases (16 per cent), in contrast to 2.2 per cent first cousin marriages and 3.8 per cent second cousin marriages in the other families. This varying frequency of parental consanguinity for different groups of cases of situs inversus is in accord with the assumption of several genes, the number of factors and their relative importance varying from group to group. The genes causing bronchiectasis and nasal polyps show incomplete dominance. The probability of their manifestation increases with the probability of visceral inversion, which in turn is increased by homozygosity for certain genes influencing the asymmetry of the viscera.

The parents were not related in any of the cases in which the individual with situs inversus was a twin. One of the twin cases was a woman who had severe symptoms of bronchiectasis and nasal polyps, her father also had shown the same symptoms. In one case of situs inversus, the mother was a twin and was a first cousin of the father. In another case, the father was a twin and two of his children (including the propositus) showed situs inversus, one of them (the propositus) having bronchiectasis as well. In another family, the male propositus, an only child, showed situs inversus and congenital heart disease; twin births occurred as a probable hereditary trait in his father's family, and congenital heart disease occurred in the family of his mother.

Situs inversus and left-handedness. As the question of left-handedness looms prominently in the literature both on twinning and on situs inversus, a summary of the data concerning handedness in the present material may also be of interest. My observations confirm the statement of Cockayne (1938) that the incidence of left-handedness is not increased in situs inversus. Among 160 unselected individuals with the anomaly 11, or 6.9 per cent, were left-handed; among 715 of their sibs 25, or 3.5 per cent, were left-handed; and among 320 parents 17, or 5.3 per cent, were left-handed. The differences can be explained by the fact that information about handedness was obtained from the individual with situs inversus. The data do not, of course, indicate the absolute frequency of left-handedness in the material; they serve merely as an indicator of the relative frequencies of left-handedness in the groups compared. They cannot be fairly compared with material from other countries nor with surveys conducted in other ways. However, in passing, we may note that Mattison (1933) found left-handedness in 3.4 per cent of 448 relatives of his situs inversus cases.

The present observations on single-born subjects with situs inversus agree in general with the findings of Verschuer (1933), who stressed the independent nature of particular asymmetries observed by him in twins. Verschuer considered this as evidence that a mirror-image mechanism is of little importance in producing symmetry reversals in twins.

Both parents were left-handed in two of the cases contained in the present series of situs inversus cases; in these sibships 2 out of 16 sibs were left-handed. In one family, 3 children and the mother were left-handed; the child with situs inversus suffered from bronchiectasis, and a sib from nasal polyps. The father, who was right-handed, had 7 sibs all of whom were said to be left-handed. These observations offer no proof of a genetic relationship between situs inversus and left-handedness, however, since coincidental occurrence of hereditary factors for the two conditions would be expected in a few families in survey that comprises a large fraction of the total population.

Left-handedness was found among 13 $\pm$ 3 per cent of 131 children in families having one or both parents left-handed, and in 3 $\pm$ 0.6 per cent of 980 children of right-handed parents. Previously, Rife (1940) found, among children resulting from these same two mating categories, 40 out of 145 and 151 out of 1842 left-handers, respectively. The data so far indicate that genes showing incomplete dominance are of importance both in left-handedness and in situs inversus.

DISCUSSION

In the case-history literature, situs inversus has been observed in 12 pairs of probable MZ twins, 6 times concordantly and 6 times discordantly (Reinhardt, 1912; Cockayne, 1938; Gänslen *et al.*, 1940; Werner, 1940; Kean, 1942;

Helweg-Larsen, 1947). In Reinhardt's case of concordant MZ twins, the parents were first cousins and the mother was one of twins. In the discordant pair of male twins described by Helweg-Larsen, the unaffected twin produced one single-born child and a pair of twins that miscarried in the third month of pregnancy.

Only three cases of DZ twins with situs inversus are recorded. One of these is a concordant pair described by the author (Torgersen, 1948*b*). Doolittle (1907) observed dextrocardia in a man who had a twin sister; both of his parents were members of twin pairs, and he himself produced opposite-sexed twins, the boy again showing dextrocardia.

As already emphasized, such case-history observations are of limited value because the sizes of the populations from which they have been drawn are unknown. They no doubt merely parallel the coincidental cases observed in the present population study. At any rate, they can hardly be considered as providing crucial evidence either for the existence of genetic factors in situs inversus or for a relationship between visceral inversion and twinning. The concordant MZ cases might be due to prenatal environmental factors acting similarly on both twins. On the other hand, the discordant MZ cases do not prove the operation of a difference-producing mirror-image mechanism; the responsible prenatal environmental factors may be supposed to act only on one of the twins, or the hereditary factors may be expressed in only one of them. The occurrence of concordant DZ twins suggest an influence of hereditary or environmental factors acting on both twins. As to the relative scarcity of reported cases of situs inversus in DZ twins, this might be attributable merely to a preferential recording of MZ pairs, or it might conceivably indicate a high prenatal mortality in such pregnancies.

The simplest interpretation of the relatively high frequency of twins in the families in which the propositus with situs inversus is one of twins is to assume a coincidental occurrence of genetical factors for twinning and for visceral inversion in these families.

The hereditary mechanism in situs inversus is still far from being cleared up. The importance of the genes is evident, however. The genetic behavior shows some striking similarities to the interpretations of Landauer concerning the inheritance of asymmetrical expression of genes in the domestic fowl (Landauer, 1948; Torgersen, 1949*a*).

Rife (1940) observed a high frequency of left-handedness among relatives of twins showing intrapair difference in handedness, as contrasted with a low frequency of left-handed relatives of twins where both were right-handed. The comparison with the present findings on situs inversus and associated anomalies is striking. The evidence so far suggests similar but independent hereditary mechanisms in situs inversus and left-handedness, and a parallelism in the relations of both kinds of asymmetry to twinning.

The frequency of left-handedness in twins is controversial. Dahlberg (1926) and Newman (1937) are of the opinion that left-handedness is relatively frequent in one of a pair of MZ twins. Siemens (1924) and Newman also found an increased frequency in dizygotic twins; whereas Schiller (1937) concludes that left-handedness is not particularly frequent in either type.

If left-handedness and twinning, in the same way as situs inversus and twinning, depend upon independent genetic factors, one would expect these genes to occur with the same frequency in zygotes giving rise to MZ twins or to single-born individuals. However, the factors may be supposed to have a greater chance of manifestation in two individuals with this genotype than in one individual. For this reason, one has to expect a relatively high frequency of left-handedness in MZ twins. Dahlberg found among 124 pairs: 6 pairs both left-handed, 29 pairs with one left-handed, and 89 pairs both right-handed. Here again, as in situs inversus, it is not necessary to suppose a mirror-image mechanism to account for these asymmetry reversals, nor is there reason to suppose any particular relation to twinning.

Similarly, one would expect to find concordancy for left-handedness or situs inversus relatively frequently in DZ twins, since both are genetically determined. Schiller found among 125 pairs: 1 pair both left-handed, 32 pairs with one left-handed, and 92 pairs both right-handed. The single concordant left-handed pair parallels the single DZ pair concordant for situs inversus in the present material. On non-genetic chance concurrence, the probability of situs inversus in both members of a DZ twin pair would be exceedingly small. However, the probability of finding situs inversus in a full sib of an index case is about 1 in 100, judging from the present study, so concordance in DZ twins would occasionally be expected (Torgersen, 1949*a*).

It is hardly possible at present to estimate the relative influence of hereditary and prenatal environmental factors in the causation of situs inversus and handedness, either as manifested in single-born individuals or in MZ twins. The observations so far indicate that modifiers influencing bilateral differentiation play an important part in these asymmetries. They confirm the suggestion of Dahlberg (1926) that there are genotypically controlled asymmetries not only in the single-born, but also in MZ twins. Probably the fundamental effect of these modifying genes concerns the reactive potency of the embryonic field in which particular genes take effect, as proposed by Laundauer in connection with certain asymmetrically expressed abnormalities in the domestic fowl. The reactive potency of the human egg is apparently relatively strongly determined by these modifying genes, so that the mirror-image mechanism, known from experimental work on amphibian twins, is of relatively little importance in human MZ twins. This greater regulatory power of the human egg tends to allow regeneration of the two halves of the embryo to equipotential systems from the point of view of experimental embryology. Thus, the developmental potentialities are apparently determined mainly by the genes and by genetically determined bilateral differentiation at the time of division. The data of the present study do not, of course, exclude the existence of asymmetries in twins due to incomplete regulation. They do, however, suggest that

the mirror-image mechanism is of relatively little importance compared with the genes influencing visceral asymmetry and handedness.

SUMMARY

The present report is based upon 270 cases of situs inversus, most of which were discovered in mass roentgenographic surveys of the Norwegian population. It is estimated that the entire country contains about 340 cases of the anomaly, or an incidence of 0.011 per cent. Geographically, the varying frequencies of situs inversus do not parallel the total twin birth frequencies in different regions of Norway.

Among 100 unselected cases of situs inversus and their sibs and parents neither twinning or left-handedness was observed with frequencies greater than those expected on the basis of chance association. The evidence thus far indicates that visceral inversion and left-handedness are fundamental asymmetries due to similar-acting but independent hereditary factors having no particular relation to the factors in twinning. The data further suggest that the developmental potentialities for bilateral differentiation of the human egg are so strongly determined genetically that the mirror-image mechanism, as revealed in experimentally produced amphibian twins, is of relatively little importance in human polyembryony.

REFERENCES

COCKAYNE, E. A. 1938. The genetics of transposition of viscera. *Q. J. Med.* 31: 479–493.

COCKAYNE, E. A. 1939. Transposition of viscera and other reversals of symmetry in monozygotic twins. *Biometrika*, Cambr. 31: 287–294.

DAHLBERG, G. 1926. *Twin Births and Twins from a Hereditary Point of View.* Stockholm: Bokförlags A. B. Pp. 296.

DOOLITTLE, W. F. 1907. Cited by Gänslen *et al.*, 1940.

DUBREUIL-CHAMBARDEL, L. 1927. Cited by Cockayne, 1938.

FRØLICH, T. 1920. Situs inversus hos 3 søskend. *Norsk mag. laegevid.* 81: 119–120.

GÄNSLEN, M., LAMPRECHT, K., & WERNER, M. 1940. Die kongenitalen Missbildungen des Herzens. *Handbuch der Erbbiologie des Menschen*, Bd. 4. Berlin: J. Springer. Pp. 198–217.

GUTZEIT, K., & LEHMANN, W. 1940. *Handbuch der Erbbiologie des Menschen*, Bd. 4. Berlin: J. Springer. Pp. 581–673. Erbpathologie des Verdauungsapparates.

HELWEG-LARSEN, H. F. 1947. Situs inversus in one monozygotic twin. *Ann. Eugen.*, Cambr. 14: 1–8.

KEAN, B. H. 1942. Complete transposition of the viscera in both of one-egg twins. *J. Hered.* 33: 217–221.

KOMAI, T. 1938. Problem of situs inversus viscerum, as studied on single and duplicate salmon embryos. *Mem. College Sc. Kyoto Imp. Univ.*, series B, vol. 14, no. 2.

LANDAUER, W. 1948. The phenotypic modification of hereditary polydactylism of fowl by selection and by insulin. *Genetics*, 33: 133–157.

MATTISON, K. 1933. Zur Frage der Heredität bei Situs inversus viscerum totalis. *Zschr. Konstitutionsl.* 17: 325–344.

NATVIG, H. 1939. Familiær situs inversus totalis. *Nord. med.* 1: 681–684.

NEWMAN, H. H., FREEMAN, F. N., & HOLZINGER, K. J. 1937. *Twins: A Study of Heredity and Environment.* Chicago: Univ. Chicago Press. Pp. 369.

PERNKOPF, E. 1937. Asymmetrie, Inversion und Vererbung. *Zschr. menschl. Vererb.* 20: 606–656.

REINHARDT, C. 1912. Cited by Gänslen *et al.*, 1940.

RIFE, D. C. 1940. Handedness, with special reference to twins. *Genetics*, 25: 178–186.

SPEMANN, H., & RUUD, G. 1922. Die Entwicklung isolierter dorsaler und lateraler Gastrulahälften von *Triton taeniatus* und *alpestris*, ihre Regulation und Postgeneration. *Arch. Entwmech.* 52: 97–166.

SCHILLER, M. 1937. Zwillingsprobleme, dargestellt auf Grund von Untersuchungen an Stuttgarter Zwillingen. *Zschr. menschl. Vererb.* 20: 284–337.

SIEMENS, H. W. 1924. Ueber Linkshändigkeit; eine Beitrag zur Kenntnis des Wertes und der Methodik familienanamnestischer und korrelationsstatistischer Erhebungen. *Virchows Arch.* 252: 1–24.

TORGERSEN, J. 1946. Familial transposition of viscera. *Acta med. scand.* 126: 319–322.

TORGERSEN, J. 1947. Transposition of viscera, bronchiectasis and nasal polyps. *Acta radiol.*, Stockh. 28: 17–24.

TORGERSEN, J. 1948*a*. Anomalies of the spine in anomalies of the viscera and constitution. *Acta radiol.*, Stockh. 29: 311–320.

TORGERSEN, J. 1948*b*. Concordant situs inversus in dizygotic twins. *J. Hered.* 39: 293–294.

TORGERSEN, J. 1949*a*. Genic factors in visceral asymmetry and in the development and pathologic changes of the lungs, heart and abdominal organs. *Arch. Path.*, Chic. 47: 566–593.

TORGERSEN, J. 1950. The developmental anatomy of the heart and the etiology of congenital heart disease. *Acta radiol.*, Stockh. 33: 131–146.

VERSCHUER, O., VON. in DIEHL, K., & VERSCHUER, O., VON. 1933. Zwillingstuberkulose. Jena: G. Fischer.