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Genetical and Ultrastructural Aspects of the Immotile-Cilia Syndrome

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SUMMARY

The immotile-cilia syndrome is a congenital disorder characterized by all cilia in the body being either immotile or showing an ineffective beating pattern. Most symptoms, not unexpectedly, come from the ciliated epithelia, but two further symptoms are: (1) male sterility caused by the spermatozoa being unable to swim progressively (the sperm tail has the same structure as a cilium), and (2) situs inversus in 50% of the cases possibly caused by an inability of embryonic cilia to shift the heart to the left side. By electron microscopy, one can see directly which of the many ciliary components is the missing one. The molecular basis of this congenital defect can then be detected, and it has been found to be a heterogeneous disease. There are many genes that, when mutated, will cause the cilia to be dysfunctional or totally immotile. The fact that many genes may be responsible for the syndrome will also explain why it has a relatively high prevalence and why previous investigators have been unable to locate the (assumed single) gene by linkage analysis. The trait, situs inversus, is of particular interest as it occurs in only 50% of the assumed homozygotes. I conclude that the wild-type genes code for a control of the proper body asymmetry and the mutated ones for a lack of control, and, hence, to a random situs determination.

INTRODUCTION

There is a rare congenital disorder that is called Siewert or Zivert syndrome in the Soviet Union [1] and Kartagener syndrome in most other countries [2]. Since first described, it has puzzled investigators, as it displays a combination of symptoms

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that do not seem to have a common basis: situs inversus viscerum, chronic sinusitis, and bronchiectasis. Some have claimed that other traits also are part of the syndrome, such as an IgA deficiency [3, 4], nasal polyposis, or an underdevelopment of the frontal sinuses. Others have maintained that the two cardinal features, situs inversus and bronchiectasis, may not necessarily be part of the syndrome (which, in that case, would be difficult to define).

Early attempts to explain the syndrome are numerous: a malrotation of the umbilical cord [5] or a malrotated heart causing either a weakness of the bronchial tree [6], a mechanical obstruction of the main bronchi [7], or an altered secreting activity of the respiratory tract epithelium [8, 9], an allergic constitution that affects the whole respiratory tract [10], an immunoallergic factor that causes vascular fragility [11], or an environmental factor acting during the embryonic development [12].

The mode of inheritance of Kartagener syndrome has remained unknown, and the location of the (assumed single) gene could not be determined by blood grouping [13–15]. The failure is partly due to an uncertainty or disagreement on which is the cardinal feature of the syndrome. Whereas most investigators have concluded that the inheritance is autosomal recessive [5, 15, 16], others have maintained that there is a dominant gene [17–19]. In either case, an incomplete penetration and a variability of expression of the syndrome have been assumed [13].

A hypothesis has recently been proposed in which a molecular basis of the syndrome is given [20]. Most laboratory and clinical data seem compatible with this hypothesis and will be outlined in the next section. It does not involve inborn defects in the immunological system, and, in fact, the immunosystem has been shown to be perfectly normal in most examined patients with Kartagener syndrome [3, 21–26].

To simplify the description, the assumed etiology of the syndrome will first be given, evidence for its validity will be provided, and the genetic consequences of the hypothesis will finally be discussed.

Hypothesis

The symptoms of Kartagener syndrome all are directly or indirectly a consequence of the inborn inability of the cilia to move or to perform normal and coordinated movements [20, 27]. This inability causes a lacking of or greatly decreased mucociliary transport in the paranasal sinuses that will lead to chronic or recurrent sinusitis, sometimes to reduction of the size of the sinuses. Inadequate mucociliary clearance of the lungs will lead to chronic bronchitis, and at the age of 2–3 years, often to bronchiectasis [28]. Coughing will substitute for the mucociliary work in the respiratory tract. Inadequate mucociliary clearance of the nose will lead to a stuffed or running nose, and often to anosmia. Inadequate mucociliary clearance of the eustachian tubes and middle ear will give an increased risk of otitis, otosalpingitis, and often to a conductive hearing loss. The cilia on the monociliated epithelia (i.e., one cilium per cell) of young embryos are also assumed to be immotile or poorly motile; whereas in normal embryos, the monocilia are assumed to shift the heart to the left side and cause the archenteron to form a

dextral spiral. Without normally working cilia, chance alone will determine whether the archenteron will twist to a dextral or to a sinistral spiral. According to this hypothesis, there will be equally as many persons with a normal position of the viscera as there are those with the reversed position. Regardless of whether the viscera are transposed or not, the clinical symptoms will be the same, and the name, the immotile-cilia syndrome, has been suggested [20, 27, 29].

It has been shown that cilia contain over 100 different polypeptides [30], and hence, there will be equally that many genes. There is no reason to assume that these genes are located close together in the genome. Possibly every human chromosome carries at least one ciliary gene. Some of the ciliary proteins are enzymes, others are structural proteins. It is reasonable to assume that the immotile-cilia syndrome is a heterogeneous disease.

MATERIALS AND METHODS

Ciliated mucosa from the nasal concha inferior, the bronchi, or the middle ear from 45 persons have been examined in this study. The biopsies have been fixed in buffered glutaraldehyde, post-fixed in buffered osmium tetroxide, dehydrated, epon-embedded, sectioned, and examined by electron microscopy at a primary magnification of 10,000–25,000 times [29]. Washed ejaculates from 55 men have been similarly treated and examined by electron microscopy [31, 32].

ULTRASTRUCTURAL FINDINGS

Thirty-eight persons were diagnosed as having the immotile-cilia syndrome based on the clinical data: they have suffered since early infancy from chronic or recurrent rhinosinusitis and chronic bronchitis, and many also from bronchiectasis. Situs inversus was found in 20 cases. Clinical data of many of these subjects have been given in other publications [27, 33].

In 24 cases, a ciliary biopsy was obtained, usually from the concha inferior of the nasal cavity, but in some cases, from the bronchi, and in two further cases, from the uterine mucosa. In two cases, biopsies were taken from more than one location from the same person, and in three cases, a ciliated biopsy and an ejaculate from the same man were examined. A failure to find cilia in the biopsy from the nasal mucosa was occasionally encountered, and was caused by a metaplastic transformation of the normally ciliated epithelium [23]. It is likely that cilia would be found at other sites of the respiratory tract, although a total lack of cilia cannot a priori be excluded [34].

Biopsies containing ciliated epithelia were also obtained from 10 controls, that is, from healthy relatives of the diseased patients, or from normal, volunteer subjects. The cilia from these controls had two characteristics: (1) they conformed to the common "9 + 2 pattern" of cilia (i.e., nine doublets around two microtubular singlets), and there were two sets of dynein arms on each doublet and spokes extending from the doublets to a so-called central sheath that encircles the two central microtubules (figs. 2 and 6), and (2) the orientation of the cilia was fixed. In one of the controls, the uterine cilia were, however, found to have a random orientation. The orientation of the cilia can be evaluated either by inspecting the

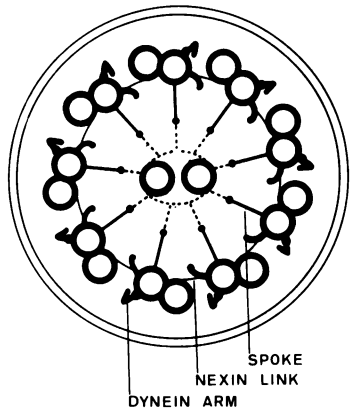


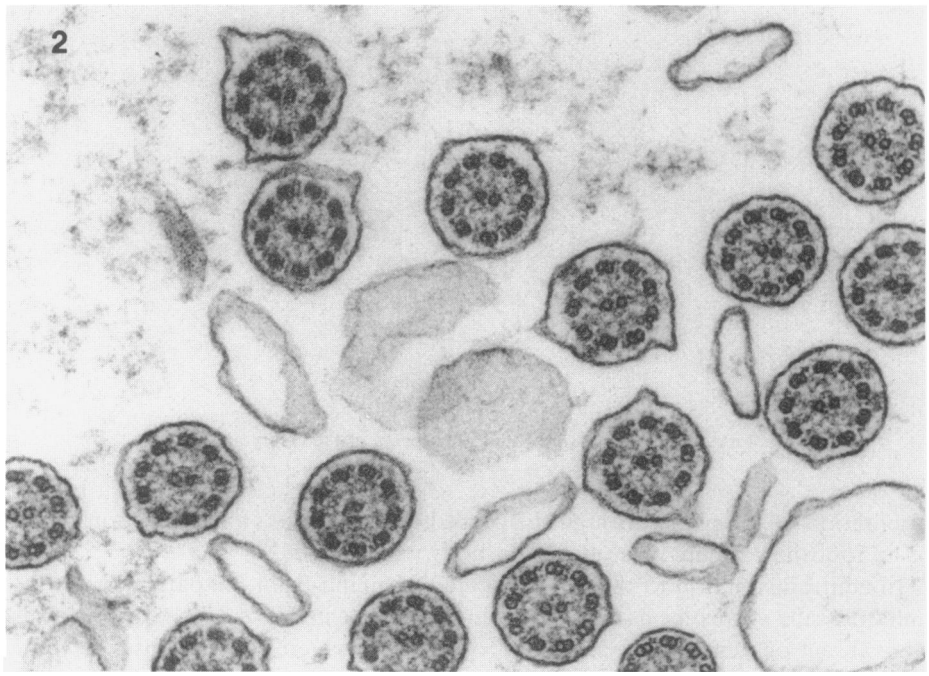
FIG. 1.—Terminology of the components of the ciliary axoneme

orientation of the plane through the central microtubules or the direction of the basal foot that extends from the basal body (figs. 2 and 3).

In contradistinction to these normal cilia, the cilia from the patients with the immotile-cilia syndrome had two or often three characteristics: (1) the dynein arms were absent or were abnormally short, or the spokes were short or absent, (2) the cilia had a random orientation, (3) there was a high proportion of cilia with supernumerary or with lacking microtubules, thus with the patterns 9 + 6, or 3 + 9 + 2, etc., rather than 9 + 2 (figs. 4–8). A reduction in the number of dynein arms and in their length was the most frequently encountered abnormality (14 cases). In two cases, dynein arms were completely absent (fig. 8), and in one case, the spokes were defective (fig. 7) and, as a consequence, the two microtubular singlets took an excentric rather than central position in the cilia. In two cases, no ultrastructural defects of the cilia were detected, but the cilia lacked a fixed orientation.

A third category of patients (nine cases) were those who since adolescence or childhood had frequent airway infections, although not as severe as in those persons diagnosed with some certainty as suffering from the immotile-cilia syndrome. In all but one case, the cilia showed a normal ultrastructure and a good orientation. In the exceptional case, the ultrastructure was normal but the orientation was random. A feature frequently seen in this group was the presence of compound cilia (i.e., of several 9 + 2 axonemes within a single, surrounding membrane). This type of ciliary modification could occasionally be seen also in persons having the immotile-cilia syndrome or in the controls. It is regarded as a rather unspecific lesion.

In 12 male cases with immotile-cilia syndrome, the spermatozoa were examined with respect to their motility and ultrastructure. The sperm tail has a central axoneme of the same type as that of the cilium. As presented in [32], the axoneme was found to be defective either by (1) a partial or complete lack of dynein arms, (2) a lack of outer dynein arms but a presence of the inner ones, (3) a disorganized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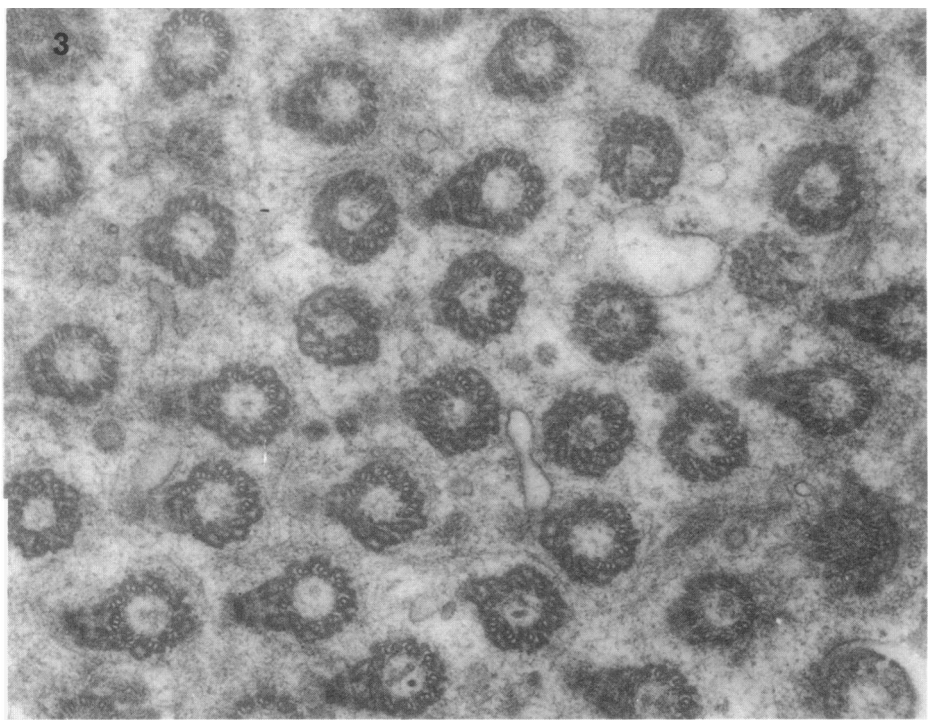
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axoneme with lacking inner arms, or (4) abnormally short spokes and a lack of the central sheath. One man had sperm tails of a completely normal appearance. In instances where a man's cilia *and* spermatozoa were examined, the same type of defect was found in both kinds of axoneme. The sperm tail axoneme often could be seen with greater clarity and a higher contrast, and an examination of the spermatozoon is hence preferred.

It can be concluded from these ultrastructural studies that the immotile-cilia syndrome is a heterogeneous disease. At least five types of ciliary defects can be distinguished on morphological grounds; some of these have first been identified by Sturgess et al. [35, 36] and by Schneeberger et al. [37]. A differentiation between the different subgroups can be made by electron microscopy on thin sections and would presumably also be possible by examining the electrophoretical pattern of polypeptides isolated from either isolated sperm tails or bronchial cilia. The clinical picture, on the other hand, seems identical in patients in different subgroups of this syndrome, at least so far as the respiratory tract is concerned. It is possible that some subgroups can be identified based on the migratory capacity of the leukocytes.

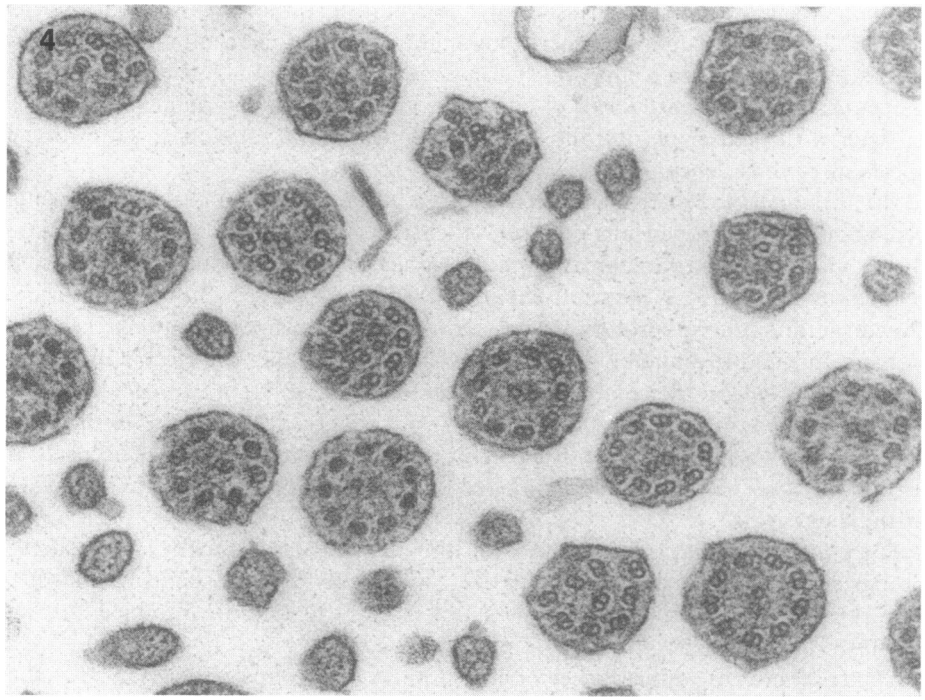
Since the initial characterization of the disease in 1976, a number of studies have been performed on the ciliary ultrastructure in patients with the syndrome [37–55]. In several cases, the motility of either spermatozoa or cilia was examined [26, 41, 47, 50–59] and found to be either absent or abnormal.

The characteristic appearances of cilia in these subgroups of the immotile-cilia syndrome are not to be confused with such changes as are found in pulmonary infections or sinusitis and which are presumably acquired [46, 60, 61]. In those cases, compound cilia are common but their axonemes seem to retain their orientation and usually also their normal ultrastructure. It is also common to find a complete loss of the ciliated cells and stages toward a keratinization of the nasal mucosa [62].

GENETIC ASPECTS

The immotile-cilia syndrome, including its subgroup the Kartagener syndrome, is in all likelihood a genetic disorder. The following facts support this: The syndrome is commonly found among sibs; in the Swedish material of 38 persons, there are two pairs of sibs, both of which are affected. Within a family, there are normally affected and unaffected sibs but no intermediates. The parents of affected persons are relatives (first or second cousins) in a percentage that is higher than average. The syndrome is particularly common in those parts of Sweden that are

FIG. 2. (*top*).—Cross-sectioned nasal cilia from a control, showing the well-known 9 + 2 configuration; most of the outer doublets have two dynein arms. Note the fixed orientation, so that a line through the two central microtubules in all cilia would have a direction parallel to long side of figure. The ciliary beat's effect would be toward lower side of figure. A few cilia are shown at a higher magnification in figure 6. Magnification × 56,000. FIG. 3 (*bottom*).—Deeper level section from nasal epithelium from same person as figure 2. Note ciliary basal bodies with configuration of nine triplets in a circle and wedgeshaped "basal feet" projecting toward left of figure. This is also the direction of the ciliary activity, thus of the mucous flow. Magnification × 32,000.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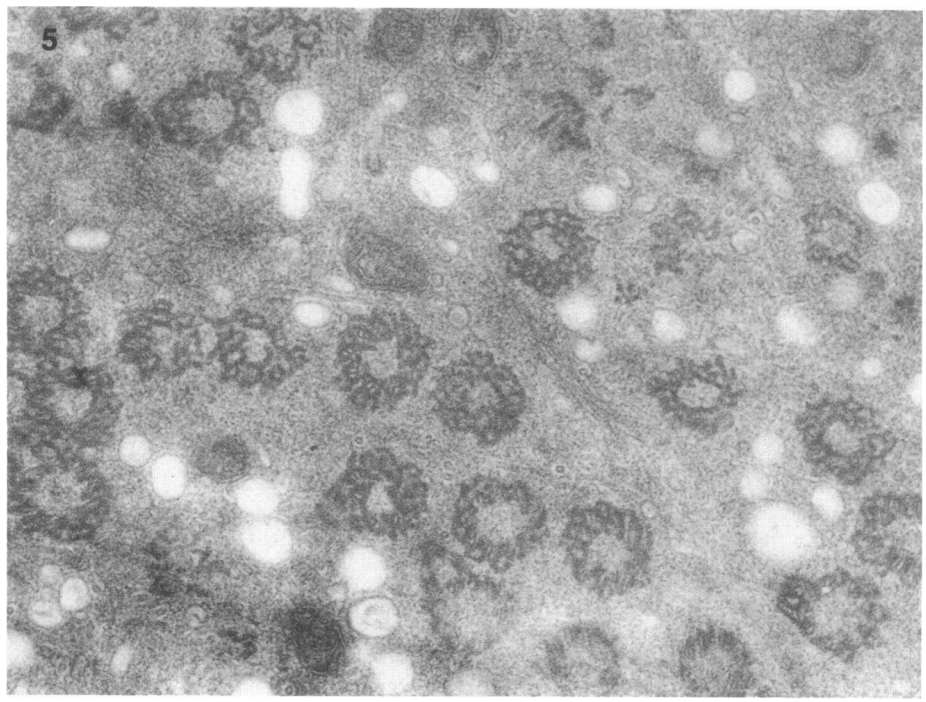
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isolated or sparsely populated, such as the northern part of the country or an island nicknamed by the geneticists "the inbred island." It is possible to produce animal and plant models of this disease; thus strains of mice, algae, or protists have ciliary defects of similar types to those found in man [63].

One of the animal models of this syndrome is the mouse mutant termed *hpy* [64]. It is a male-sterile strain that evidently has been difficult to keep in culture. What is the mechanism by which the incidence of the immotile-cilia syndrome, including its subgroup the Kartagener syndrome, is sustained in man? It is found in all human races [65] and has a prevalence of 1:15,000–1:35,000 [20, 27], which is fairly high considering that nearly all males are sterile and that the females possibly have a decreased fertility. Male sterility in the immotile-cilia syndrome is caused by sperm immotility [20, 31, 32, 36, 39, 50, 55, 66]. Female infertility has been suspected on the ground that oviduct cilia are believed to be critical for pickup and transport of the ovum [67]. However, several women with this syndrome are mothers [43, 68] and an attempt to explain the female fertility in spite of ciliary immotility has been provided by Norwood and Anderson [69]. In a few cases, men with Kartagener syndrome are claimed to be fathers [70, 71], and although the paternity was not investigated, it is feasible that they belong to a subgroup of the syndrome in which motility of cilia is affected more than that of sperm flagella.

A high incidence of a recessive disorder in spite of a reduced fertility may be explained by a "heterozygote advantage" (the heterozygotes having a greater viability or reproductive fitness), by a "gametic advantage" (gametes carrying the particular allele have a higher viability), or by a high mutation rate from the wild-type allele to the mutant one [72]. The high mutation rate would then be caused by the allele being located in an unstable region of the genome, or else the notion of a high rate is false, and in reality, there are many different genes and a mutation in any one of them will give rise to the same disorder. This latter explanation seems to be valid for the immotile-cilia syndrome. There are many genes that when mutated will cause the ciliary machinery to break down but which have no other effects in the cells. The immotile-cilia syndrome hence is to be regarded as due to a genetic heterogeneity, (i.e., a genetic variability). The same or nearly same condition may be caused by an inborn error in the dynein molecules, a dynein-binding factor, one of the spoke-proteins, or the nexin molecule [32].

The number of proteins that have an indispensable function in the ciliary axoneme—and only in the axoneme—is unknown, but is almost certainly higher than 10 (perhaps much higher). This is reflected in the diversity of ultrastructural subtypes of the syndrome seen by electron microscopy. The clinical picture of the syndrome is the same in these varieties. The heterogeneity will also explain why

FIG. 4 (*top*).—Cross-sectioned nasal cilia from person with immotile-cilia syndrome. The 9 + 2 configuration has collapsed, probably because of defects in organization of the structures that would form nexin links between the ring of nine doublets. Magnification × 56,000. FIG. 5 (*bottom*).—Section at deeper level from nasal epithelium from same person as figure 4. Orientation of basal feet (seen best at *upper left* and at *lower middle* and *right*) is random. Magnification × 38,000.

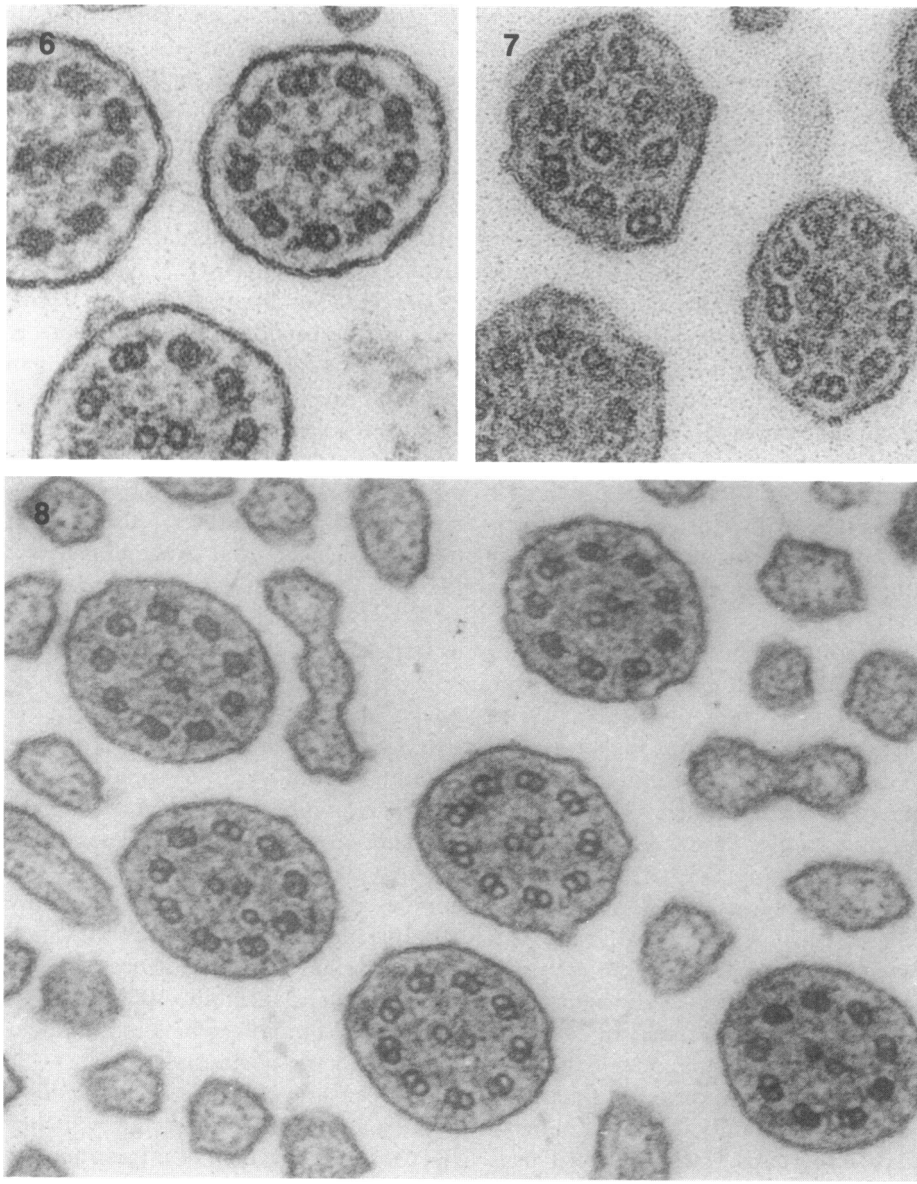

FIG. 6 (*top, left*).—Higher magnification of some cilia from figure 2. Note dynein arms are present, and that the outer ones have hooked appearance. Spokes can be seen between the inner and outer microtubules. Magnification × 110,000. FIG. 7 (*top, right*).—Higher magnification of some cilia from figure 4. Some dynein arms can be seen, but no spokes. Dense matrix material obscures most of fine structure between ciliary microtubules. Magnification × 110,00. FIG. 8 (*bottom*).—Cross section through some nasal cilia from an immotile-cilia syndrome patient. Ciliary defect is a lack of normal dynein arms. A few of the microtubular doublets show a short and straight stub but no normal, hooked dynein arm. Magnification × 90,000.

the location of a gene for Kartagener syndrome has not been determined by linkage analysis.

The genes for the immotile-cilia syndrome have been assumed above to be recessive, because the inheritance of the disorder in most cases seems to be autosomal and recessive as judged from the pedigrees. The mode of inheritance is uncertain, however, and it would a priori appear possible that a mutation of a gene coding for an enzyme would lead to a recessive trait, whereas a mutation in a gene coding for a structural protein would lead to a dominant mode of inheritance [73].

The ratio between affected and healthy sibs to persons with the syndrome is fairly close to 1:3, supporting the hypothesis that the syndrome usually has a recessive inheritance [27]. Whereas the cleavage pattern of the ciliary immotility (or poor motility) probably is 1:3, that of the trait, situs inversus, is 1:7. This is a cleavage pattern that has been found only once in a breeding experiment, namely in the *iv* mouse strain kept by Layton [74] (*iv* stands for *i*nversed *v*iscera, that is, for situs inversus). Layton's conclusion is that there is a normal allele that specifies for the normal position of the viscera, whereas in the absence of this allele, situs is determined in a random fashion. Fifty percent of the *iv/iv* homozygotic mice have situs inversus. The same random determination of the visceral situs is probably found also in the immotile-cilia syndrome. Layton assumed that the action of the *iv* gene is due to a loss of the developmental control of the cytoskeleton [75].

It has been noted that "genes cannot encode directional left-right asymmetries, although factors may determine whether or not underlying asymmetries are expressed" [76]. The immotile-cilia syndrome is a good example of this. A migration occurs to the right or to the left of the heart in individuals lacking a control mechanism, and there will be an equal number of affected persons with situs inversus as with situs solitus. In individuals with a control of the asymmetry, migration is always to the left; the control function is hypothesized to be exerted by the embryonic cilia [20], which in vertebrate embryos have asymmetric directions [77].

A similar situation may prevail in the case of the other major asymmetry in man—that of the brain. If this is so, most persons would be genetically right-handed and also show this feature. Some would lack the gene coding for the right-handedness and in 50% of the cases would be left-handed and in 50%, right-handed. It is evident that genes do not code for right and left, but there may be genes for the correct side and for a random determination of sidedness [78].

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