THE IMMOTILE-CILIA SYNDROME: A MICROTUBULE-ASSOCIATED DEFECT

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I. INTRODUCTION

In the latest edition of McKusick's monograph[1] the number of different inherited diseases in man is given as 3,368. New disorders have been added in successive editions and this at a rate of about one disease every 3rd day. Within a foreseeable future the number might approach that given by the eccentric Italian physician Santorio (1561—1631), who claimed that there is a total of 80,000 possible diseases. Although Santorio's figure is for all kinds of diseases in man, it is of interest that his conjecture comes close to the present estimate of the number of human structural genes (between 30,000 and 100,000)[2] and hence presumably close to the maximum figure of genetic diseases in man.

The relation between inherited disease and its genetic background is particularly well illustrated by the immotile-cilia syndrome as will be shown in this paper. The immotile-cilia syndrome is an inborn human (or animal) disorder characterized by an inability of the cilia to beat normally. As a consequence, the patient will suffer from respiratory disease and will probably have a decreased fertility. The disease is a homogeneous one when studied clinically, but actually is a heterogeneous one in that any one of many different structural genes may be involved. In the clinic it will be regarded as one disease, however, the geneticist will see it as a bag of perhaps 200 different diseases. It is also a disease in which the clinical picture can be readily understood from ultrastructural or biochemical data.

II. HYPOTHESES

Much of the text in this review is based on the following assumptions:

1. The immotile-cilia syndrome is caused by a genetic disorder.
2. The primary defect may reside in any one of the perhaps 200 genes that code for the ciliary polypeptides.
3. A mutation in any one of these ciliary genes will result in defective cilia or in an inability to grow cilia.
4. Lack of normal ciliary motility will have multiple effects; symptoms will be registered from loci where ciliated epithelia are located.
5. If a mutated gene codes for a polypeptide that functions only in cilia, defects will be restricted to these; if the gene codes for a protein that also is present and active in the cell body, the defects may be registered also from these parts of the cell.
6. A syndrome, that was previously described by Kartagener and Siewert and named after them, is included in the immotile-cilia syndrome.

If these assumptions are correct, patients with the immotile-cilia syndrome have a mutation affecting their cilia and the resulting disorder will have cytologic similarities to the so-called paralyzed-flagella mutants (pf-mutants) of the unicellular alga *Chlamydomonas*. In order to present an intelligible account of the immotile-cilia syndrome it is necessary to begin with a brief description of the cilium. This description will also be valid for the human sperm tail as this organelle can be regarded as a slightly modified, long cilium or a flagellum.

III. CILIARY ULTRASTRUCTURE

A. Cilia and Flagella

Mucus-propelling cilia in the human body have a length of about 6 μm and fluid-propelling cilia in the brain have twice that length.[3,4] Cilia are found in large numbers at the free surface of the ciliated cells. In some epithelia the cells carry only one or a few cilia. One single cell type of the mammalian body, namely the spermatozoon, has a long flagellum. The core structure of the cilium or the flagellum is called the axoneme and has a characteristic structure of nine microtubular doublets and two central single microtubules. About 70% of the axonemal protein mass is comprised of α- or β-tubulins that have a molecular weight of 54 kdaltons. There are nearly 200 additional polypeptide species in the axoneme.[5]

The tubulins together with the various microtubule-associated proteins assemble into the nine doublets and two singlets to which various other protein species become bound. Some of these proteins form the many links that keep the 9 + 2 tubules together. These are

1. Dynein and other proteins, which constitute the outer and inner dynein arms. The dynein arms extend from one side of the microtubular doublets to the neighboring doublet. It is the sliding force produced by the nine double rows of dynein arms that is responsible for the bending movement of cilia and flagella. This sliding theory for ciliary and flagellar undulations was proposed by Afzelius[6] and experimentally supported by Satir,[7] Gibbons,[8] and, on mammalian cilia, by Dirksen and Zeira.[9] A dynein is defined by Gibbons[10] as a member of a group of high molecular weight proteins having ATPase activity and occurring in motile, intracellular systems that are based on microtubules. The dyneins play a major role in the transduction of chemical energy provided by ATP hydrolysis into mechanical work. They are Mg^{2+} or Ca^{2+} activated and undergo conformational changes during ATP hydrolysis.[11,12] It is likely that dyneins occur on cytoplasmic microtubules as well as on ciliary microtubules[13,14] and conceivable that some dyneins are common to both types of microtubules. The ciliary dyneins have a molecular weight of 300 to 350 kdaltons and hence belong to the largest proteins that are formed as a single polypeptide. The outer dynein arms have two types of dynein and the inner one a third type. A dynein arm contains 15 to 20 further protein species, which is why it has a complexity in the chemical and enzymatic sense that is considerably greater than its functional analogue in the muscle, namely the myosin cross-bridge.[10] The outer dynein arm is larger and more complex than the inner one. The appearance of the dynein arms is shown with Figure 1 and even more clearly in Figure 2 that have been obtained by a new, quick-freeze and deep-etch technique.[15]

2. Nexin forms the nexin links, also called the interdoublet linkages, that bridge the gap from one microtubular doublet to its neighboring doublet. Nexin is an unusual protein in that it evidently can be stretched during microtubular sliding to about tenfold resting length.[16,17] The nexin links seem to be capable of maintaining the structural integrity of the axoneme against the sliding forces generated by the dynein arms. As a result the sliding of the doublets is converted into a bending of the cilium; bending hence

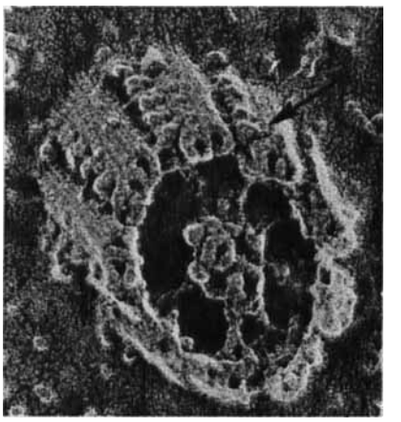

FIGURE 1. Cross-fracture of a *Chlamydomonas* flagellar axoneme quick-frozen in the presence of ATP. Arrow points out a row of outer dynein arms attached to one doublet; other rows are seen on contiguous doublets. (Magnification × 200,000.) (Courtesy of Goodenough, U. W. and Heuser, J. E., *J. Cell Biol.*, 95, 798, 1982. With permission.)

is a consequence of the restricted elasticity of the nexin links. During sliding the nexin links may pull the doublets closer together allowing the dynein arms to interact with the adjacent doublet.[18] In this manner the dynein activity will be controlled by the degree of flagellar bending.

3. Various "spoke proteins" form the spokes that project from the doublets toward the central singlets or, more specifically, to the so-called central sheath that surrounds the two central microtubules. The inner portion of a spoke can, in suitable preparations, be induced to terminate in a bulbous enlargement that has been called "spoke head". Spokes are often called radial spokes, but as there is no protein termed "radial" and as a spoke by definition has a radial orientation, there is no need for the qualification. It appears that one of the main roles of the spokes is to maintain rigidity of the cilium (or flagellum) when it bends. It is also possible that the spokes have a more active role during ciliary beatings as they have been shown to interact with the central tubule-central sheath complex in an intricate fashion that has been interpreted as part of the conversion of sliding into bending.[19]
4. One set of proteins form peripheral linkages that, similar to the nexin links, connect neighboring microtubular doublets. They are limited to the proximal end of the cilium and resist such elastase treatment as will digest the nexin links.[20] Their function in the intact axoneme probably is one of tying the doublets together at their proximal end and hence to prevent sliding at this region.

There are other connections in cilia and flagella and some of these have been described from the human sperm tail:[21] (1) links between outer dynein arms and the so-called coarse fibers (which only exist in sperm flagella); (2) links between outer and inner dynein arms within a doublet; (3) links between spoke head and central sheath; (4) links between spoke head and dynein arm; (5) links between spoke head and inner dynein arm; and (6) double bridges between the two central microtubular singlets. Nothing is known about the functions of these links, but it may be conjectured that at least some of them are structural bonds.

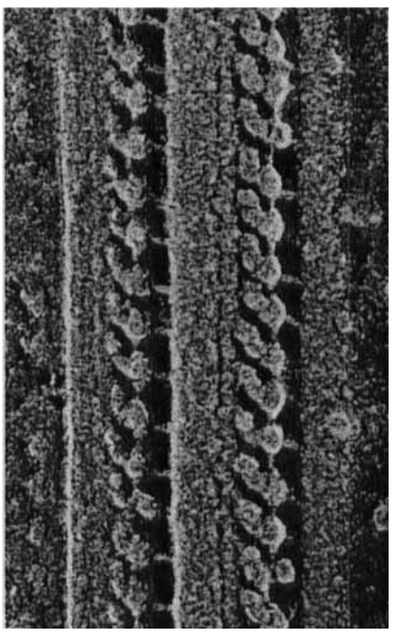

FIGURE 2. Longitudinal view of a *Tetrahymena* ciliary axoneme quick-frozen in the presence of ATP. Periodic dynein arms are anchored on the A microtubule of one doublet and attach to the B microtubule of adjacent doublets via slender stalks. (Magnification × 270,000.) (Courtesy of Goodenough, U. W. and Heuser, J. E., *J. Cell Biol.*, 95, 798, 1982. With permission.)

Even from this simplified account it is obvious that the axoneme has a considerable complexity. No wonder that many genes are involved and that the cilium is a delicate and sensitive machinery that, due to many types of external agents or inborn errors, may be faulty.

The cilium is more than an axoneme. It has a limiting membrane, which is an extension of the cell membrane, but which has its own specialized proteins and functions. Among others there are some species of tubulin in the membrane.[22] The membrane of *Paramecium* cilia thus contains about 70 protein species,[23] and for all we know the membrane of the mammalian cilia may be similar in complexity. Some morphologically prominent proteins are located in the membrane of the ciliary neck region. They form what has been called the ciliary necklace,[24] a structure suspected to exert a regulatory role in ciliary beatings by controlling the influx of calcium ions. The ciliary necklace was first seen by investigators using the freeze-fracture technique. It was later demonstrated also by other techniques, e.g., by the application of electron-dense markers for negative surface charges; hereby both the ciliary necklace and some other specialized domains of the ciliary membrane are visualized.[25-27] The tip of the cilium is also labeled by this technique at what has been called the ciliary crown;[28] this is a set of claw-like filaments that project from the membrane and which may be anchored at a capping plate inside the cell membrane.[29,30]

The proteins of the ciliary matrix have not been characterized. It has been shown, however, that one of these proteins is calmodulin,[31] which may be associated with the nexin links.[32] Calmodulin inhibitors influence the direction of the wave propagation at least in protistan flagella.[33]

B. Basal Bodies

Cilia emerge from basal bodies which are formed in the cytoplasm from certain precursors called fibrogranular masses.[34] The basal bodies then move to the cell surface, where they give rise to the cilia. A basal body is a short tube consisting of nine interconnected microtubular triplets and possessing a basal foot and often a short striated root or rootlet.[35]

The basal foot projects parallel to the cell surface and in the same direction as that of the effective stroke of the cilium.[36] The basal foot hence can be regarded as a pointer that shows the direction of the ciliary transport.[37] The majority of the basal feet point in the same direction (in normal cases). Similarly, the orientation of the axonemes, as seen in ciliary cross-section, is uniform. The direction of the effective stroke has been determined to be the direction perpendicular to the two central singlets and toward the two doublets called no. 5 and 6, that lie at an equal distance from the perpendicular line through the central pair.[36]

The three-dimensional organization of microtubules and microfilaments of the basal body apparatus of ciliated epithelia has been described by Gordon.[38]

IV. CILIARY FUNCTIONS

Human cilia have a beat frequency of 10 to 15 Hz.[39-41] Most act by propelling a mucus blanket, others are fluid-propelling cilia. According to Sanderson and Sleigh,[42] less than half the cilia within a ciliated epithelium (from rabbit trachea) beat at any particular moment; the others rest in the downstroke position that is reached at the end of the effective stroke. A beat will hence begin with a recovery stroke, which may be better called a preparatory stroke; the cilium rotates backwards with a clockwise sweep as seen from above. In the effective stroke the cilium moves forward again in an almost planar beat and will bend almost by 110° before coming back to the downstroke position. As the cilium is nearly straight in this effective downstroke, its tip will attain a maximal height above the cell surface. It also has its maximal speed at this stage. In the effective stroke the cilium will push the mucus blanket forward, whereas at the recovery stroke the cilia will crawl under the mucus blanket and will not drag it back again. The group of cilia will continue to oscillate for a time — seconds or minutes — maybe as long as the mucus blanket rests on their tips; then they stop in the rest position.

By their work cilia push the mucus blanket forward with a speed of 2 to 20 mm/min.[43,44] The bronchial mucus is then driven along the airways toward the trachea and further to the pharynx, where it is swallowed. Mucus from the nasal cavity and middle ear is similarly driven toward the pharynx, except for the outer part of the nose where mucociliary clearance is directed anteriorly.[43] The total amount of mucus transported this way by the cilia has been estimated to be 0.5 mℓ/kg body weight and day in man.[45]

V. DISTRIBUTION OF CILIA

Ciliated epithelia line the *nasal passages* (except for the outermost portion, which is keratinized), *paranasal sinuses, eustachian tubes, pharynx* down to the orifice of the esophagus, *trachea, bronchi, bronchioles,* and *middle ear mucosa.*[37] The *inner ear* may also have a ciliated lining.[46] The *lacrymal sac* contains ciliated cells[47] and such cells also may be discovered elsewhere in the human body. All these epithelia contain mucus-producing goblet cells as well as ciliated cells. Particularly the bronchial mucosa contains a number of other cell types apart from these cells.[28,45,48]

The *ependymal lining* of the brain and spinal cord is ciliated,[49-51] but the 13-μm-long cilia probably are fluid-propelling rather than mucus-propelling cilia. The *ductuli efferentes* on the border between the testes and the epididymides have a ciliated epithelium as has the

endometrial lining of the deeper parts of the cervix and the *oviducts*. The oviduct cilia are claimed to play a critical role in ovum transport at least in the rabbit ampulla.[52]

The epithelia listed above consist of cells that are "multiciliated," which is to say that each ciliated cell carries a great number of cilia — usually in the order of 200 for mucus-propelling cells and 20 for fluid-propelling cells. Other epithelia have cells that have been called "monociliated" in which each cell carries just one cilium. The single cilium has been called a monocilium or a primary, solitary, isolated, immature, residual, or vestigial cilium. Rarely the cells are pauci-ciliated, that is when they have two or three cilia. The inner surfaces of the corneal epithelium[53] or the ciliary epithelium of the eye[54] are examples of mono- or pauci-ciliated epithelia. Most embryonic epithelia also are monociliated,[55,56] and so are many nonepithelial cells like the cartilage cells[57] or the neurons.[58]

The length of a monocilium is variable (from 1 to 15 μm); typically it is shorter than mucus-propelling cilia. It emerges from a basal body (centriole) at the cell surface with another centriole located close to it. Monocilia tend to have a simplified ultrastructure and are presumed to be immotile. Usually there are no central microtubules and no dynein arms. There are exceptions to this statement, e.g., cases of monocilia with dynein arms, a 9 + 2 ultrastructure,[59,60] and an assumed or proven motility.[61]

The role of the single cilium remains obscure.[62] Possibly it has no function at all. Alternatively, by binding the diplosome (i.e., the two centrioles of a cell) to the cell surface, the monocilium may prevent it from acting as the poles of the mitotic spindle. It has long been known that single cilia are found in nonmitotic, but not in mitotic cells.[63]

In the monociliated cell line called PtK, the cell resorbs its cilium during an early stage of spindle formation, suggesting that its tubulin may become part of the cytoplasmic microtubule complex.[64,65] The blockage of mitosis hence is temporary. It is possible that the single cilium may have a sensory function or by its ciliary necklace can exert a calcium-regulatory role.[66]

Some of the sensory cells carry a single cilium that is modified for its function and is called a sensory hair. This is true of the rods and cones of our eyes and of the hair cells in the labyrinth of our inner ears. Each mammalian olfactory cell carries several cilia (17 on the average), which, however, lack dynein arms and are immotile.[67] It has been shown that the sense of smell is dependent on the presence of cilia on the olfactory cells; presumably the receptor sites are located on the ciliary membrane.[68] The motility motor of the axoneme may play an active role in sensory transduction.[69,70]

One single cell type in the human body — the spermatozoon — has a flagellum, that is to say a 9 + 2 organelle that is long and that moves with undulating waves that propagate from the basal body to the tip. The length of the flagellum is 60 μm in man.[71] Its axonemal structure has been described in great detail.[21] Of interest in this connection is the fact that the 9 + 2 axoneme is surrounded by an additional set of nine coarse fibers and also by what has been called the fibrous sheath. The axoneme itself is indistinguishable from that of a cilium, although it often appears with more contrast in the electron microscope.

The above description may have given the impression that every cell in the human body either has one or more cilia or at least has had some at an earlier stage. This is not far from the truth. It has been claimed that all definite vertebrate cells have cilia or have had one just before the final stage of differentiation.[58,63] The white blood cells may be nearly unique in always being nonciliated. They have, however, a pair of centrioles,[72] and the migration of the white cells, like that of certain tissue culture cells, may somehow be controlled by the orientation of the centrioles.[73] This proposed role of the centrioles is of interest in the present connection, as even the white cells may have altered functions in the immotile-cilia syndrome, as will be detailed below (Section IX.H.).

VI. CILIARY MUTANTS IN UNICELLULAR ORGANISMS

Ciliary mutants have been investigated for at least 30 years. In 1954, Lewin[74] isolated several strains of the unicellular alga *Chlamydomonas* that were paralyzed due to an absence, immotility, or altered function of the cilia. Since then a great number of different paralyzed flagella (*pf*) strains have been isolated and investigated, i.e., mutants with no flagella (called "bald" or "flagella-less"), short (or "stumpy") flagella,[75] oversized flagella,[76] slow flagella, or paralyzed flagella. The immotility may be due to deficiency of the outer dynein arms, the inner dynein arms, central sheath-spoke complex, the two central microtubules, etc. One slow mutant lacks spokes.[77] Many of these mutants have been characterized biochemically.[5]

Mutants from another protist, *Paramecium*, may have a normal axonemal ultrastructure, but be swimming backwards, presumably because of a defect in what has been called the ciliary plaques (aggregates of intramembranous particles close to the ciliary necklace with no equivalent in the mammalian cilia).[78] In a backward-swimming mutant of *Chlamydomonas* the defect was localized to the axoneme rather than to the membrane.[79]

It has been noted that there are genes for ciliary motility (or ciliary immotility in the *pf* mutants) in every chromosome of the *Chlamydomonas* nucleus.[76]

VII. CILIARY MUTANTS IN ANIMALS

Ciliary mutants will probably be found in any animal or plant that has cilia and is studied in sufficient detail. This means that ciliary mutants are most likely to be recognized in the fruitfly, *Drosophila*, the mouse, *Mus*, and in dogs, bulls, and other valuable domestic animals.

There are no ciliated cells in the fruitfly, but the sperm tail has a conventional 9 + 2 axoneme. Some male-sterile mutants either lack the sperm tail[80] or else have an immotile sperm tail.[81] In a temperature-sensitive mutant the dynein arms are lacking in a certain temperature interval causing the sperm to be immotile at these temperatures.[82]

Mouse mutants with defective cilia have been described among others by Bryan.[83] He showed that a mutant, which he called *hpy/hpy*, was male-sterile because it lacked the sperm tail and that it further had axonemal abnormalities in 24% of the cilia in the tracheal epithelium. This mutant had postnatal hydrocephalus and polydactyly and the females had a decreased fertility. Contrary to the immotile-cilia syndrome in man, there are no cases having *situs inversus* in this mutant nor any significant increase in the incidence of respiratory problems.

Layton has studied a mouse strain that does have *situs inversus* in half the number of cases, but the ciliated epithelia seem to be normal.[84] This strain is derived from a mutant that apart from having *situs inversus* also had respiratory tract disease and a certain risk of hydrocephalus.[85]

Dogs with the typical signs of immotile-cilia syndrome have been described.[86,87] In one litter of a springer spaniel there were five sibs, three of which had respiratory tract disease and *situs inversus;* their cilia were randomly oriented.[86] In a young golden retriever with chronic bronchitis and *situs inversus*, the cilia were found to have specific abnormalities to a high percentage.[87]

VIII. IMMOTILE-CILIA SYNDROME IN MAN

The immotile-cilia syndrome was detected in 1975 when four men with the following clinical and laboratory symptoms were examined:

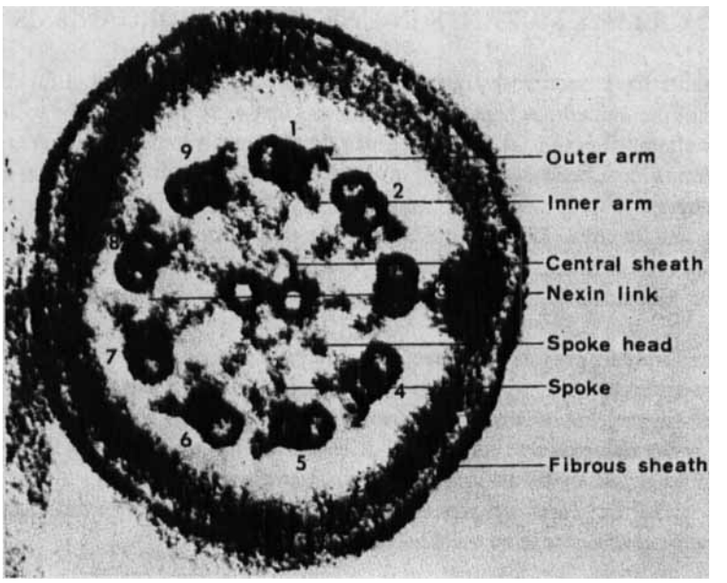

FIGURE 3. Cross-section of a human sperm tail. The axoneme within the fibrous sheath can be seen to consist of nine microtubular doublets surrounding two central single microtubules. Three types of bonds maintain the structure and make it into a functional unit: the dynein arms, the nexin links, and the spokes.

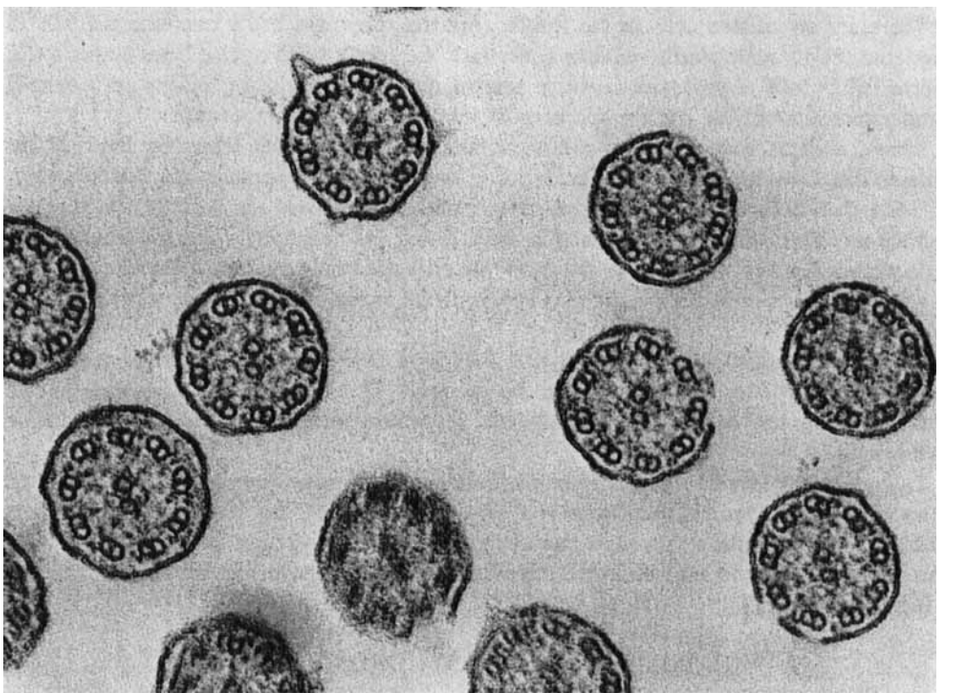

FIGURE 4. Cross-section of cilia from a healthy control person.

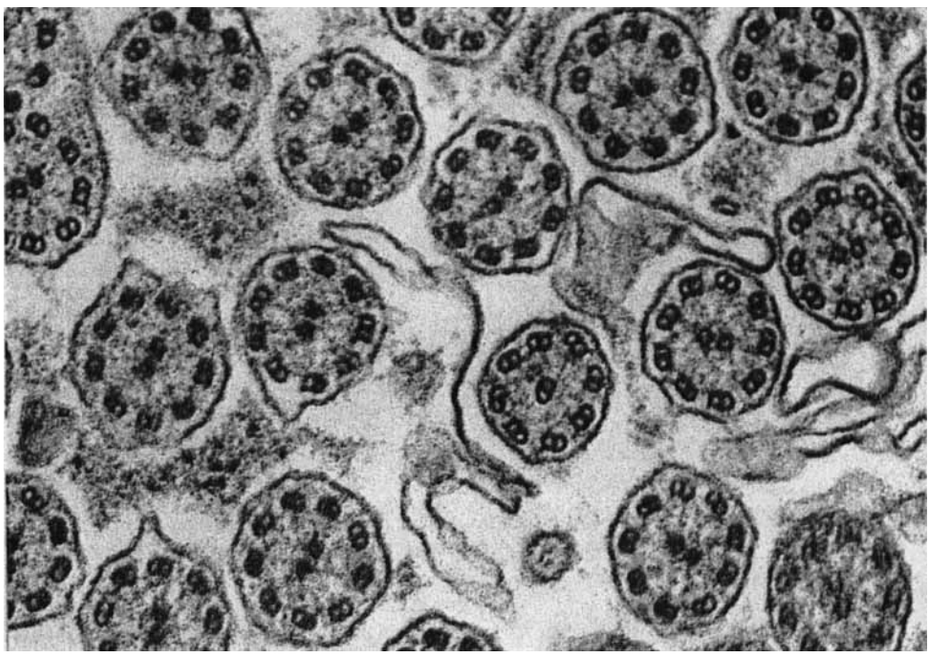

FIGURE 5. Cross-section through the cilia of a person suffering from the immotile-cilia syndrome. The dynein arms are missing.

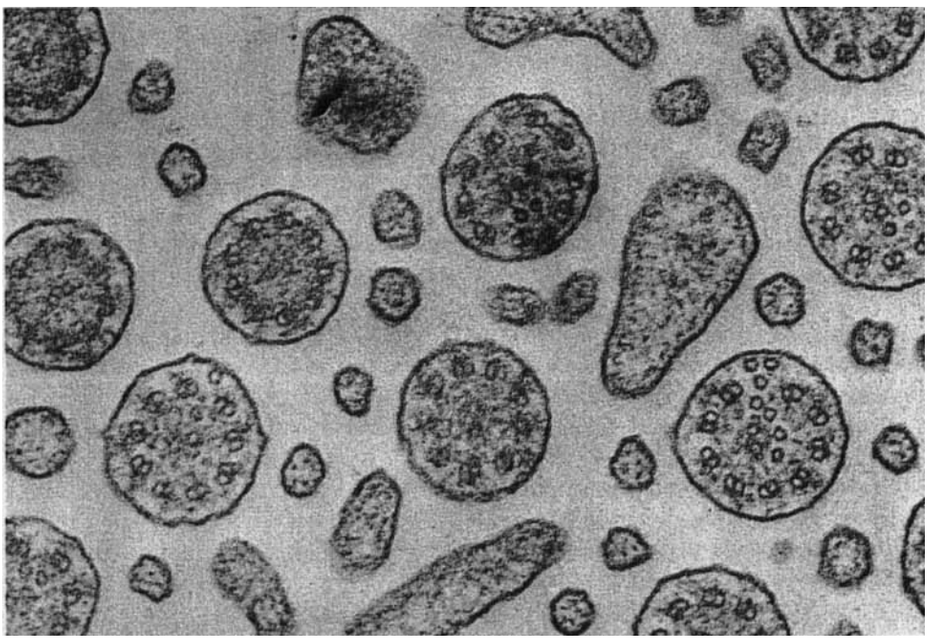

FIGURE 6. Cross-section of cilia from another person suffering from the immotile-cilia syndrome. In this case there is a high percentage of cilia that have extra microtubules and the dynein arms are largely lacking.

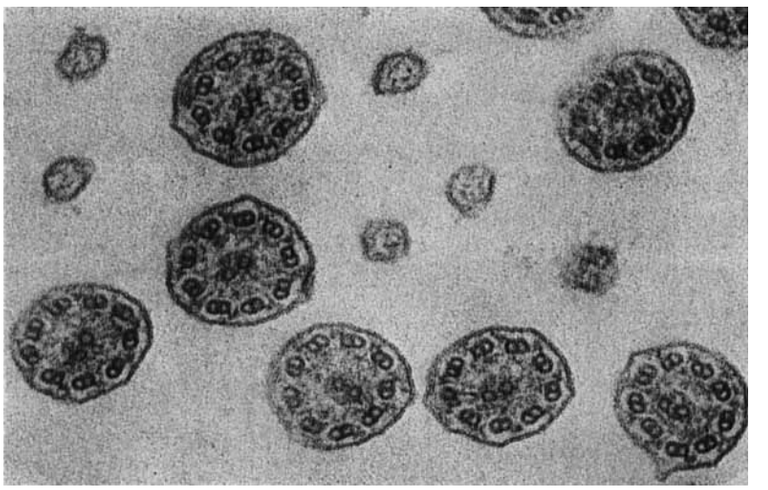

FIGURE 7. Cross-section of cilia from a patient with the immotile-cilia syndrome. In the cilia of this patient the central microtubules take an eccentric position, presumably because the spokes are absent or defective. (Magnification × 60,000.)

1. Spermatozoa that were living but immotile; the sperm tail was shown to lack dynein arms.[88,89] (Because of their infertility the men attended fertility clinics.)
2. A mucociliary transport in the tracheobronchial tract that was extremely slow or probably absent.[90]
3. Chronic respiratory tract disease since early childhood.
4. *Situs inversus* totalis.

It was proposed that all components of the syndrome were caused by a genetic defect of the gene(s) for dynein causing an inability of the dynein arms to be synthesized or assembled on their proper locations.

Since 1975 many more patients have been examined with respect to ciliary structure, nasal or tracheobronchial clearance, sperm motility, and clinical data. Many hundreds of cases have presently been described. It has become evident that the syndrome is a heterogeneous one when examined at electron-microscopical magnifications, whereas clinically it is fairly uniform. Many subgroups can be distinguished and their classification will differ according to the investigator and his or her prejudices. The following list is nearly exhaustive:

1. Absence of outer and inner dynein arms.[91-97] In most surveys this subgroup has been the most common one.
2. Absence of most of the dynein arms.[96-98]
3. Absence of outer and inner dynein arms and usually, also, of the central microtubules.[93,95,98]
4. Absence of outer dynein arms only.[91,93,95,96,99]
5. Outer dynein arms are abnormally short.[100-105]
6. Absence of inner dynein arms.[92,93,95,96,99,103,104,106,107]
7. Absence of inner dynein arms and spokes.[95]
8. Absence of inner dynein arms and central microtubules.[95]
9. Absence of inner dynein arms and nexin links. Usually one of the outer microtubular doublets is transposed to a central position. The outer arms are prominent.[91,92,101,108-110]

10. Absence of spokes; the two central microtubules take an eccentric position.[96,102,111-113]
11. Absence of spoke head and central sheath.[91]
12. Absence of central sheath and one or both central microtubules.[91,95,104]
13. A high percentage (>10%) of the cilia have supernumerary doublets.[114]
14. Absence of the entire axoneme within an intact ciliary membrane.[115] This peculiar defect might be due to a defect in one of the microtubule-associated proteins that stabilize the microtubules; the axoneme would then exist in the living state but would not be preserved by standard methods of fixation. It is *a priori* unlikely that a cilium may grow out without an axoneme.
15. Absence of cilia on cells that by other criteria (long microvilli, many centrioles) can be presumed to be ciliated cells.[100,116-118]
16. Cilia having twice the normal length.[119]
17. Cilia having a normal ultrastructure, but a random orientation.[120]
18. Cilia with a normal ultrastructure and normal orientation as seen in the electron-microscopical sections.[120,121] It is possible that a structurally visible defect is present, at least in some of the described cases, but has gone unrecognized. If the error resides in, e.g. the ciliary necklace, the defect would be visible only by the freeze-fracturing procedure.

Patients from all of these subgroups are claimed to have had chronic respiratory problems from early infancy, often with difficulties in the neonatal period and also having other clinical signs of the immotile-cilia syndrome. In some subgroups the cilia show motility and even hypermotility, but evidently they are incapable of normal tracheobronchial clearance. Several types of abnormal motility patterns have been described and claimed to be characteristic for the different subtypes. Thus cilia in the spoke-deficient subgroup (group 10 above) may show a corkscrew type of motility,[122] those in the microtubule-transposition subgroup (group 9) have grabbing movements,[122,123] oversized cilia (group 16) may show flagellum-type undulating movements.[124] Still other types of defective cilia show movements that have been described as similar to a stiff metronome arm,[125] or an egg-beater-like rotation with fixed upper and lower ends of the cilium.[122]

It is legitimate to ask whether ciliary abnormalities, such as those presented above as 18 subgroups, are the primary cause of the respiratory-tract disease or are secondary to some other defect which might be caused by an infection or a medication. This problem will be treated further under Section X. It will suffice here to mention that such abnormalities, as seen in subgroups 12 to 15 and 17, can be and usually are secondary effects.

It should also be noted that two or more defects often are found in the same person; it is thus common to see that dynein arm-deficient cilia are randomly oriented and that cilia lacking inner arms and spokes also may have eccentric inner microtubules.

In order to ascertain that the ciliary abnormalities are generalized rather than a local phenomenon, it is preferable to examine cilia from more than one site. When this has been done it has usually been found that cilia have the same appearance regardless of whether they are taken from the nose, bronchi, middle ear, or cervix and also whether true cilia or sperm tails have been examined. There are exceptions to this statement. Fox et al.[126] have investigated two samples from the same person and found a strongly different percentage of ciliary abnormalities. Similarly Jonsson et al.[127] have described a man with Kartagener's syndrome whose cilia, as expected, were devoid of the dynein arms, but whose spermatozoa had normal dynein arms and a normal motility. The reverse situation has also been found, i.e., a man with dynein arm-less and immotile spermatozoa, but with cilia of a normal ultrastructure and with healthy respiratory functions.[128] It is evident from these two cases that errors may reside in cilia-specific and sperm tail-specific proteins; the two types of

organelles are similar, but not identical. It has often been claimed that cilia from two or more sibs that have the immotile-cilia syndrome have the same type of ciliary abnormality.[99]

The discovery that the cilia in some subgroups of the immotile-cilia syndrome have a motility — although an abnormal one — has prompted many investigators to invent new names for the disease. The following names are among those that have been suggested:

1. Abnormal cilia syndrome[129]
2. Sick cilia syndrome[130]
3. Slow cilia syndrome[131]
4. Dyskinetic cilia syndrome[132]
5. Ciliary dysfunction syndrome[125]
6. Syndrome of the ciliar dyskinesia[133]
7. Sick cilia with *situs inversus*[134]
8. Primary ciliary dysfunction[135]
9. Primary ciliary dyskinesia[136]
10. Ciliary dyskinesia[137]

To this list of names may be added some minor variations of the original name such as immotile cilia syndrome (thus spelled without a hyphen), immotile cilia syndromes (to stress the heterogeneity), immobile cilia syndrome, immotile syndrome, ciliary immotility syndrome, and ciliary motility syndrome.

IX. CLINICAL DATA

The characteristic symptoms of the immotile-cilia syndrome will be described and discussed in this section.

A. Situs inversus

Situs inversus totalis (or sometimes partialis) is common within most subgroups of the immotile-cilia syndrome. Actually about half of the cases in subgroups 1 to 9 and isolated cases in subgroup 15 have *situs inversus*. It is interesting to speculate about the reason for a connection between *situs inversus* and ciliary immotility or dysmotility. In one hypothesis monocilia on the normal embryonic epithelia have a certain position and a fixed beat direction and the beating is instrumental in determining the correct visceral *situs* (heart to the left whereupon viscera rotate to a dextral spiral).[138] If the monocilia show no motility or are absent it can be assumed that chance alone will decide whether heart and viscera will take up the normal or the reversed position during embryogenesis. The weakness of this hypothesis is that most monocilia seem to be immotile or poorly motile even in normal mammals. In an attempt to demonstrate a difference between normal murine embryos and embryos from the *iv/iv* mice (with 50% chance of *situs inversus*) no difference in ciliary fine structure was found in embryonic epithelia of an age where the first asymmetry appears.[203]

In a refined version of this hypothesis it is assumed that the *iv* gene causes a "loss of developmental control of the cytoskeleton and cytomusculature."[139] If the centriolar apparatus, with or without a ciliary shaft, acts as a compass to make a distinction between right and left, this capacity is lost in embryos of *iv/iv* mice or of humans with the immotile-cilia syndrome.

In a third hypothesis it is assumed that the gene for the dynein arms is located close to that portion of the genetic material that is associated with the normal position of internal organs.[140] This hypothesis has the weakness that there is not one but are several genes for the various dyneins and that at least perhaps ten subgroups of the immotile-cilia syndrome convey a 50% risk of *situs inversus*.

B. Nose and Respiratory Tract

Respiratory distress may be common in babies with immotile-cilia syndrome.[92,97,141-143] Mucopurulent nasal secretions and coughs with abundant mucoid secretions may also be common.

There is a mixed flora of pathogenic bacteria, but *Haemophilus influenza* seems to be the most common one. During childhood the nasal problems may aggravate so that it becomes necessary to perform tonsillectomy, adenoidectomy, and sometimes endonasal trepanation.[97,144,145] Nasal polyps may develop and sometimes will cause a broadening of the nasal bridge.[145] Daily nose blowings since birth is a characteristic of the immotile-cilia syndrome.[146]

Respiratory infections tend to already start in the first weeks after birth and in most cases the patients will develop chronic or recurrent infections also in the paranasal sinuses and in the bronchi.[143,147] Atelectasis may be diagnosed in the first week[97] and bronchiectasis can develop early in childhood.[148-150] When bronchiectasis has developed there may be a marked worsening of the lower respiratory tract disease with increased expectoration, fever, and hemoptysis. Clubbing of the fingers is sometimes noted.

It is remarkable, however, that lung functions, although impaired, may remain fairly stable in the adult stage,[92,144,147,151] unless the patient is a smoker.

C. Paranasal sinuses

Chronic or recurrent maxillary sinusitis is almost always present and the frontal sinuses often fail to develop. By radiography the other paranasal sinuses can be seen to be normal or to have mucosal thickenings. As a consequence of the reduced size of the sinuses, the voice often will be more flat or nasal than in healthy persons.

D. Ears

The otological manifestations of the immotile-cilia syndrome have recently been reviewed.[97,152]

In childhood there are almost interminably recurrent bouts of acute otitis media against a background state of secretory otitis media.[97] The eustachian tubes may become obstructed. The adults show only the sequelae and usually they have aerated middle ears. The prognosis in the long-term hence is favorable. As a consequence of the chronic otitis a certain degree of conductive hearing impairment is common. Many patients have a grommet; a few have conductive deafness due to fluid in the middle ear.

E. Brain

Seven persons with the immotile-cilia syndrome have been examined by Dr. T. Hindmarsh, Karolinska Hospital, Stockholm, by the use of computer tomography of the brain. In two or three of these cases the ventricular system was found to be slightly enlarged,[153] although the changes had no consequences to the mental capacity. In another study hydrocephalus was found together with the immotile-cilia syndrome in a boy.[154] The head of the boy was seen to grow excessively at 2 weeks of age, at what time the lateral ventricles started to become dilated. The boy was treated with a ventriculo atrial followed by a ventriculo peritoneal shunt and is now, at 12 years of age, of normal intelligence. His immotile-cilia syndrome is of the subgroup characterized by the outer dynein arms being absent and the cilia completely immotile.

The concurrence of hydrocephalus and immotile-cilia syndrome (and also of *situs inversus* and Kartagener's syndrome) has further been registered by Dr. Anne Child[204] and by Olsen.[155] It thus seems probable that ciliary immotility in the ventricular ependyma may bring about a certain risk of hydrocephalus in man as well as in the mouse (see Section VII). The risk in man probably is less than 1%, however, only a few cases with both defects have been recorded. It is of interest in this connection that a rat strain selected for hereditary hydro-

cephalus was seen to have shorter and clumped cilia in the ventricles[156] and that reo-virus infections[157] or treatment with antitubulin compounds[158] will induce hydrocephalus in rats and also will cause the cilia to become matted or lost. These forms of hydrocephalus, hence are caused by ciliary dysfunction or damage.

What other effects ciliary immotility or dysmotility may have on the brain functions is unknown. It has commonly been noted that persons with the immotile-cilia syndrome suffer from severe headaches,[153] which may be due to inadequate circulation of the cerebro-spinal fluid or, perhaps more likely, to the sinusitis and other infections.

Pedersen and Stafanger[159] have noted that nearly all patients with the immotile-cilia syndrome examined by them showed an abnormal tiredness and an increased need for sleep. This feature, however, may be a consequence of chronic respiratory disease.

F. Male and Female Fertility

Most men with the immotile-cilia syndrome have immotile or at least poorly motile spermatozoa.[89,104,153,160] Hence they are infertile. In a few cases the spermatozoa are normally motile, whereas the cilia are immotile or dysmotile and there is no infertility. This has been noted by Jonsson et al.[127] as mentioned above (Section VIII). One unusual case has been reported by Van der Baan et al.[121] A man with the clinical signs of Kartagener's syndrome claimed to have regular, motile cilia and, evidently, also normal, motile spermatozoa; the patient is the father of a boy who also has the complete Kartagener's syndrome. A close examination of the mucociliary clearance and the ciliary ultrastructure of these cases and of cases of a similar kind would be of interest.

In the beginning of the exploration of the immotile-cilia syndrome it was believed that female fertility was unaffected by the ciliary immotility.[153]

When a larger patient material had been examined it became clear that, also for women, a ciliary immotility or dysmotility involves a risk of infertility.[160] Twelve women in the Swedish patient material are married or else have wanted to become pregnant. Nine of them have been unable to become mothers, whereas three had children (one, one, and two children). It is apparent that fertility is at risk, but not definitely excluded in women with this syndrome. Whether the risks are due to the particular subtype of the immotile-cilia syndrome is unknown.

It would *a priori* appear likely that the disease will also carry a certain risk of ectopic pregnancy, but no evidence hereof has been found, nor does the prevalence of salpingitis appear increased. Evidently peristaltic mechanisms and other mechanisms may compensate for a loss of the normal ciliary defense mechanism of the oviducts.

G. Sensory Organs

It has been remarked above (Section IX.D.) that most patients suffering from immotile-cilia syndrome have a hearing impairment. This has developed as a result of the frequent middle-ear infections, to scarred ear drums, or to nonaerated middle ears, rather than to a defect in the sensory cells themselves, the so-called hair cells of the inner ear. Whether there also exist cases that have a primary defect in the sensory hairs of the hair cells is unknown. Most patients, but not necessarily all, have a normal sense of balance.[153] This is a feature that should be further tested.

A similar situation prevails with the sense of smell. Most patients with this syndrome have a poor sense of smell, which is a consequence of a stuffed nose or an inadequate mucus flow over the olfactory epithelium rather than of defective olfactory cilia on the sensory cells in the nose. In 1975 Douek et al.[161] described a.o. a case with congenital anosmia, who lacked the olfactory cilia and hence had no sites for the olfactory receptors. The authors do not give any data on the functions of the respiratory tract of that patient.

The immotile-cilia syndrome is also of interest to the ophthalmologists. The corneal

epithelium is a mono- or pauci-ciliated epithelium (Section V) and many kinds of abnormalities have been detected in the corneal epithelium.[53] These abnormalities are of no practical consequences to the patients. There is no evidence for the rods and cones in the retina to be changed in this syndrome. It was also hypothesized that the orientation of the rods and cones may be more random in patients with the immotile-cilia syndrome whereas it is ordered in normal persons, just as the respiratory cilia usually are randomly oriented. One way to check this hypothesis was to test for the possibility to detect the polarization of light. Five patients did not differ in this ability from five normal controls of similar age.[53]

H. Leukocytes

Shortly after the initial publication of the immotile-cilia syndrome,[138] a brief report appeared which contained data on the defective chemotactic response of the polymorphonuclear neutrophils of a boy with the immotile-cilia syndrome.[162] This was an unexpected finding, as neutrophils as well as the other leukocytes are cells without cilia.

Since that report neutrophil functions have been investigated in many persons with this syndrome. In one paper the neutrophil functions are reported not to differ from those in healthy control persons,[163] whereas, in others, abnormally short migration distances[164-166] and a less good orientation capacity[164-168] have been recorded. The findings have given rise to the speculation that not only the ciliated cells, but also other cells may have inadequate functions due to a lowered amount of dynein[166] or alternatively, that there is an underlying defect regulating both the motility of the cilia and the motility of migrating cells.[166] It has also been speculated that the increased frequency of respiratory tract infections in this syndrome might be due to defects in the locomotor system of the neutrophils, as well as to the defective mucociliary clearance. An alternative explanation to the abnormalities of the neutrophils is that these cells may have become secondarily damaged because of the frequent infections and that their defective migratory capacity hence is an acquired property.[163]

X. ACQUIRED CILIARY ABNORMALITIES

The ciliated epithelium in our airways forms the primary line of defense against inhaled particles and in this property it will be exposed to many kinds of insults. In some cases the injured cilia will have an altered ultrastructure and this may either be distinct from the specific inborn errors treated above or else resemble these.

The membrane surrounding the cilium thus may be visibly damaged by externally applied agents. In one experiment Fonzi and Lungarelli[169] exposed the tracheal epithelium to elastase and noted that this enzyme could digest the membrane and leave the axoneme naked. This experiment is of interest in that elastase can be liberated from neutrophils upon their disintegration. Swelling of the ciliary membrane is another frequently registered damage inflicted upon the ciliated cells and so is the formation of so called "compound cilia" (also called megacilia or multicilia), i.e., multiple axonemes within a common membrane. Treatment with the mucolytic agent *N*-acetyl-L-cystein (trade name Mucomyst®) results in an excessive formation of compound cilia.[170]

Another kind of compound cilia is that formed by a cytoplasmic hernia in which the cytoplasm has flown out along several axonemes. In this kind of compound cilium ribosomes and other cytoplasmic constituents fill the space between the axonemes.

Cilia which are missing one or both of the central microtubules while at least remnants of the central sheath are seen and which have outer doublets that appear moth-eaten, presumably represent cilia that have been partly digested by autolysis or that have been poorly preserved during fixation. Such cilia have been seen in some patients suffering from asthma[171,172] and cystic fibrosis and may represent an unspecific defect. Their incidence is increased in the post-mortem period.

Asthma patients or patients with recurrent bronchitis and rhinitis may also have axonemes that are completely disorganized and have extra or missing microtubules.[171] Other rather unspecific reactions by the cilia are the internalization of the axoneme into the cell body or their shedding. The entire ciliated cell could also be shed and the ciliated epithelium in nose or at other places where irritation is the greatest might be transformed into a squamous or a keratinized epithelium. This may occur after irritation by sulfuric acid aerosol of after rhinovirus infection.[173] For further references of induced changes vs. inborn errors of cilia see Afzelius[174] and Rutland et al.[175]

Some of the ciliary abnormalities listed in Section VIII might be acquired rather than inborn and the primary cause of the respiratory problems. This is particularly the case for subgroups 13, 15, and 17 and perhaps also subgroup 9, the microtubule transposition defect.[176]

The various subgroups that are characterized by a dynein arm-deficiency are generally believed to be hereditary rather than acquired. There is no complete consensus, however. Corbeel et al.[103] have reported on two patients with unilateral bronchiectasis and with cilia that lacked the inner dynein arms, and who, after a gradual regression, had normal cilia. Lee et al.[177] have examined a prematurely born boy who developed a classic hyaline membrane disease and required assisted ventilation. Biopsies from his nasal mucosa showed very few cilia at 4.5 months of age and those that were seen had a spoke defect and, possibly, short dynein arms. At the age of 10 months the cilia had a normal motility and ultrastructure. Further studies of this kind are clearly needed.

Another and somewhat simpler way to test for the immotile-cilia syndrome is that by Boat et al.[178] They introduced a cotton-tipped nasopharyngeal swab verically into the nasal passage beyond the middle turbinate, rotated the swab 360°, withdrew, and gently agitated it in 0.5 mℓ of a warm balanced salt solution and examined the aliquot microscopically on an uncovered slide for ciliary motility. Most initial samples showed a brisk ciliary activity. Some cases with chronic airways disease had no ciliary motility and upon a subsequent electron-microscopical analysis were shown to lack the dynein arms. Other subjects with acute nasopharyngitis also had no ciliary motility, although subsequent samples from the same persons showed full activity. The ultrastructure of these samples were not examined. A similar technique has been used by Rutland et al.[175]

XI. RELATION TO OTHER DISEASES

A. Kartagener's Syndrome

Kartagener's syndrome was described in 1904 by Siewert[179] and in 1933 by Manes Kartagener.[180] It is the combination of the following three symptoms: *situs inversus*, bronchiectasis, and chronic sinusitis. *Situs inversus* is found in half the cases with a proven immotile-cilia syndrome of those subgroups where the dynein arms are missing or are short and in some other subgroups.[153,181] If the persons also have developed bronchiectasis, as many of them have at an adult age, then these persons have developed a true Kartagener's syndrome. Kartagener's syndrome can hence be regarded as a subgroup of the immotile-cilia syndrome.

The inheritance of the immotile-cilia syndrome seems to be that of an autosomal recessive disease, whereas *situs inversus* occurs only in half the cases with immotile-cilia syndrome. In a similar way, not all persons with *situs inversus* have the immotile-cilia syndrome. It has been estimated that about 20 to 40% of all persons having *situs inversus* also have chronic sinusitis and bronchiectasis;[149,153] the others have normal respiratory epithelia. A more extensive discussion of the genetics of these two syndromes is found in a recent review.[182]

B. Polysplenia and Asplenia Syndromes

Persons with *situs inversus* have a normal body asymmetry: the number of lung lobes that

differ on the two sides, the position of the tip of the heart, and the location of the liver, appendix, or the spleen. They differ from ordinary persons only by the asymmetry being the reversed one. The appendix thus is on the left side and the heart tips points to the right side.

A different situation prevails with the polysplenia and the asplenia syndromes. Here the body is unusually symmetrical also with respect to such features as lung lobes, liver lobes, and location of the heart. The body has an appearance as if it consists of two left-sided or two right-sided halves, respectively, in polysplenia and asplenia, and with one of the sides being the mirror-side of the other.[183] In the polysplenia syndrome there are thus spleens on both sides, whereas in the asplenia syndrome there is no spleen (and the life expectancy is quite short).

It is of interest that three sibships have been recognized in which one sib has polysplenia or asplenia and another sib (or a parent) has Kartagener's syndrome.[184-186] Both types of sibs have productive cough and have cilia that have been shown to be defective in dynein arms.[184,186] It is hence apparent that the polysplenia and asplenia syndromes somehow are related to the immotile-cilia syndrome and that some of their problems are due to defective cilia.

C. Cystic Fibrosis

The respiratory tract disease in cystic fibrosis resembles that in the immotile-cilia syndrome, except that the airways problems are more severe. As cystic fibrosis is the better known disease, it is probable that many children with the immotile-cilia syndrome will be diagnosed as having some kind of atypical cystic fibrosis and will be treated accordingly. This is of no disadvantage as the physiotherapeutic treatment given to children with cystic fibrosis is the best therapy a child with the immotile-cilia syndrome can get.

In cystic fibrosis the primary cause is unknown; possibly there is some error in one of the ion pumps of the cell membrane.[187] As a consequence hereof the ion composition of secretions as well as of the cytoplasm is abnormal and the mucus of the respiratory tract will have too much calcium ions and will be too viscous. The cilia themselves have a normal ultrastructure[188] and are capable of a normal motility[189] although the mucus apparently is too viscous for them. Another name of cystic fibrosis reflects this hypothesis: mucoviscoidosis.

It is essential to both cystic fibrosis patients and to cases with the immotile-cilia syndrome that they are coughing; this is the only remaining method of clearing the main ducts of the respiratory tract. Two reports give information on patients that are diagnosed as having cystic fibrosis as well as immotile-cilia syndrome, a hard fate in the genetic lottery.[190,191]

Males suffering from cystic fibrosis are sterile because their semen contains no spermatozoa; the male ducts have become obstructed by sticky mucus and secretions.

D. Young's Syndrome

The syndrome named after Young[192] is similar to immotile-cilia syndrome and to cystic fibrosis in that it is a respiratory tract disease in combination with male infertility. It differs from cystic fibrosis in that the ion composition of secretions is normal and in that the pancreatic secretion performs its functions normally. The patients tend to be above ideal weight rather than emaciated.[193] The respiratory tract disease consists of a chronic cough, which will often lead to bronchiectasis. Most patients also have chronic sinusitis. Unlike cystic fibrosis, but similar to immotile-cilia syndrome, there is a symptomatic improvement after adolescence.[193] Electron microscopy has shown the cilia in most patients to be normal; in a few cases the cilia had a random orientation.[120,194] The tracheobronchial clearance has been shown to be reduced.[194,195]

Young's syndrome is known only from men. Their sterility is due to an idiopathic obstruction of the vasa efferentia which makes the semen devoid of spermatozoa (azoospermia).

Spermiogenesis is normal in testis biopsies,[193,196] and some men have previously been fertile and have become fathers before the male ducts have become obstructed. It has been noted that the intraluminal obstruction may not be complete until years after puberty.[123]

A genetic origin of Young's syndrome has been suggested,[193] but the primary cause has remained unknown. Hendry et al.[120] have expressed their belief that it is due to malfunctioning microtubules, but the data available rather indicates that the primary defect resides in the mucus-producing component of the mucociliary system.

E. Mounier-Kuhn's Syndrome

This syndrome is the combination of a dilation of the trachea with ethmoid sinusitis and bronchiectasis.[197] It has also been termed tracheobronchiomegaly or tracheobronchiectasis. It is believed to be due to an insufficient rigidity of the connective tissue of the airways. No study of the mucociliary activity or of the ciliary ultrastructure seems to have been performed. It is possible that some cases previously diagnosed as having Mounier-Kuhn's syndrome in reality had defective cilia, rather than defective connective tissue, and hence should have been diagnosed as cases of the immotile-cilia syndrome.

F. Immunoglobulin Deficiency

This disease has also been called agammaglobulinemia or hypogammaglobulinemia. It is a disorder in which the patients are liable to bacterial infections in the airways and have a cough with purulent or mucopurulent expectorations, frequent pneumonia, and in most cases rhinitis, sinusitis, and otitis. Many symptoms hence are similar to those of the immotile-cilia syndrome and if the mucociliary clearance rate is measured, it is also often found to be very slow.[198] The mucociliary transport system hence may be damaged, but not necessarily irreversibly so. After a six-month-long treatment with antibiotics and with gammaglobulins the mucociliary clearance rate in one of the examined patients had returned to normal values.[198] It was also shown that the cilia of patients with immunoglobulin deficiency have a normal ultrastructure.[198] The cause of the frequent infections obviously has to be sought in the immunological system rather than in the ciliary apparatus.

G. Retinitis Pigmentosa

In a report from 1980, Fox et al.[199] made the claim that patients suffering from retinitis pigmentosa (a hereditary and slowly progressive retinal degeneration) have a slightly increased percentage of abnormal cilia. This finding was later confirmed by Finkelstein et al.[200] and has led to the speculation that the cause of retinitis pigmentosa is due to abnormalities in the modified cilia of the rods and cones in the retina or else in some factor which will influence both the multiciliated cells and the monociliated sensory cells. The abnormalities of the respiratory cells are relatively minor and will not noticeably affect the respiratory tract-functions, but the assumed abnormalities of the modified cilia of the sensory cells could be more severe. The fertility of men and women is reduced to 0.14 of that to be expected in the general population.[201]

One subgroup of retinitis pigmentosa, amounting to about 10% of the total number, is further characterized by an early deafness and can hence be assumed to have defective sensory hairs on the hair cells of the inner ear.[201] It is called Usher's syndrome. If the hypothesis is correct, then retinitis pigmentosa is related to the immotile-cilia syndrome and differs from it mainly by the types of ciliated cells that are involved.

XII. CONCLUSIONS

The immotile-cilia syndrome is a disorder that is of interest to specialists in many fields. The molecular biologists will have the task to determine what proteins are missing in any

particular subgroup and why; they will be challenged to figure out methods to cure the disease or to alleviate its consequences. The cell biologists have been given a unique opportunity to get an answer to the question on what roles the cilia play in our body; they have also been provided with a possibility to dissect the cilium genetically. The reproduction biologists have obtained a material by which they can study such questions as the transport mechanisms of the egg and the importance of motility for the spermatozoon. Aitken et al.[202] have already shown that an immotile, but otherwise normal spermatozoon from a man with the immotile-cilia syndrome will be taken up by the hamster egg and fertilize it, whereas presumably a human egg will be impenetrable to these spermatozoa because of the presence of a zona pellucida. The embryologists can get an insight in the old problem of right and left; the mechanism that determines the normal asymmetry of the viscera. To the medical profession the immotile-cilia syndrome has given new and unexpected insights into such problems as the pathogenesis of obstructed lung disease and of hydrocephalus, and has had further consequences for pediatrics, otologists, ophthalmologists, hematologists, and cardiologists.

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