second pregnancy ended with the birth of a healthy son. The third child died on the first day of life with respiratory distress. Like her sister, she was mildly growth retarded with a birth weight (2820 g) and head circumference (32.3 cm) between the 10th and 25th centiles. Body length (50.5 cm) and foot length (8.1 cm) were normal. The radiological and histological pathological findings were exactly the same as in case 1. The combined lung weight was 18.9 g, with a lung weight/body weight ratio of 0.0067. The karyotype was normal.

Acinar hypoplasia is a common cause of intractable neonatal respiratory distress. As a rule, pulmonary hypoplasia is not a primary malformation but a secondary deformation. Thus, the lung anlagen and initial organogenesis are normal, until a mechanical factor intervenes during development, which thereafter proceeds abnormally. Secondary pulmonary hypoplasia is usually caused by one of the following conditions: prolonged oligohydramnios, diaphragmatic anomalies, skeletal dysplasia, massive chronic pleural effusions, or maternal respiratory disease. Primary pulmonary hypoplasia, that is, an intrinsic abnormality of the lungs with poor development from the beginning, does exist but is exceedingly rare. It is a diagnosis of exclusion that can only be made after the known aetiologies of secondary pulmonary hypoplasia have been ruled out. This needs thorough pathological examination, including examination of the central and peripheral nervous system and skeletal muscle tissue.

To date, only a limited number of cases of primary pulmonary hypoplasia have been reported, with both sporadic and familial occurrences. There is a striking lack of uniformity in the histology of these cases. Swischuk et al and Langer and Kaufmann described reduced alveolar counts without other architectural abnormalities of the alveoli. Surprisingly, Frey et al and Hamel found severely hypoplastic but histologically normal lungs with normal alveolar cell counts. In our two sibs, the lungs were normal but weighed less than 30% of the expected value for the gestational age. Histological examination showed an almost complete lack of alveolar development, increased amounts of interstitial connective tissue, and abnormal (dysplastic) bronchial cartilage. While, admittedly, primary pulmonary hypoplasia is a heterogeneous condition, the two cases reported here represent a specific entity. Similar histological findings have been described in only two previous cases, also without alveolar counts. We agree with Ruthledge and Jensen and Chambers that this lesion represents a severe form of peripheral pulmonary maldevelopment or “acinar dysplasia”, rather than pure hypoplasia. Apparently, the lung development was arrested in the early canalicular stage and development of the alveolar tissue did not take place. Stocker suggested that this form of pulmonary hypoplasia might be included in an expanded classification of cystic adenomatoid malformation of the lung (“type 0”).

The aetiology and pathogenesis of pulmonary acinar dysplasia are unknown. The epithelium of the respiratory tract up to the alveolar ducts and the acini are of endodermal origin. Experimental embryological studies have shown that the sequential branching of the tracheobronchial tree is induced by the splanchnopleural mesoderm. This leads to the conclusion that acinar dysplasia may be an intrinsic defect of the lung mesoderm. The observation of increased interstitial connective tissue in dysplastic bronchial canalisation in two cases appears to corroborate this. However, pulmonary development is an extremely complicated process, depending upon reciprocal epithelial-mesenchymal interactions. For instance, the developing pulmonary epithelium is the site of growth factors such as epidermal growth factor and transforming growth factor-α, which influence differentiation of the mesenchymal compartment and overall organogenesis. More specifically, defects in lung specific transcription factors, such as thyroid specific enhancer binding protein-1, normally expressed in the developing pulmonary epithelium, have been shown to inhibit normal lung development, resulting in rudimentary cystic lungs. Thus, we cannot rule out a defect in the epithelial cell compartment as the initial cause of this malformation.

This is the first familial report of pulmonary acinar dysplasia, suggesting an autosomal recessive mode of inheritance for a gene critical for normal lung parenchymal development.

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Coexistence of Gaucher disease type 1 and Joubert syndrome

Joubert syndrome (JS) is an autosomal recessive disorder in which cytogenetic, biochemical, and molecular markers are unknown. It is a distinct clinicopathological entity, characterised by cerebellar vermis dysgenesis, episodic tachypnoea and apnoea in the neonatal period, jerky eye movements, developmental delay, and hypotonia. Associated features may include agenesis of the corpus callosum, chorioretinal colobomas, renal cysts, congenital hepatic fibrosis, and polydactyly. The molecular basis of JS has recently been investigated by analysing the WNT1 gene, the human homologue of murine wnt-1, for mutations in patients with JS. It was concluded that WNT1 is not a critical gene for JS.

In contrast to JS, the enzymatic and molecular basis in Gaucher disease (GD), an autosomal recessively transmitted lysosomal storage disorder has been elucidated. GD is caused by a deficiency of glucocerebrosidase activity and the gene is located in chromosome 1q21. Clinically, there are three major variants of GD classified by the age of onset, severity of the visceral symptoms, and by the presence or absence of neurological involvement: type 1, the most common variant has a non-neuronopathic course; type 2 presents in infancy with severe neurological involvement; type 3 usually presents as a severe, slowly progressive neurodegenerative disease. Recently, new infantile and fetal subtypes with a severe course have been described. In this human subtype and in murine models a total disruption of the glucocerebrosidase gene caused the fulminating disease. More than 50 different mutations in the glucocerebrosidase gene have been identified in patients with GD, producing an enzyme which is catalytically abnormal, rapidly degraded, or truncated. Although there is an extensive variation in the penetrance in GD which cannot generally be explained by the genotype alone, the four most frequently identified mutations are to some degree predictive of the course of the disease. For example, patients having at least one N370S mutation, whether as homozygotes or compound heterozygotes, are at a very low risk for primary neurological involvement, while those who are homozygotes for the L444P mutation usually present with neurological abnormalities. In one hydrops fetus a...
complete absence of glucocerebrosidase was caused by homozygosity for a null mutation. This report describes an unusual association of GD type 1 and JS in a non-consanguineous family of Indonesian and white Dutch ancestry (fig 1). The proband, patient II.1, was a 16 year old Asian male with a height of 155 cm and a weight of 355 g, a length of 54.5 cm, and a head circumference of 38.5 cm (98th centile). The diagnosis of JS was made by the presence of features including episodic hyperpnoea/apnoea, agenesis of the cerebellar vermis and corpora collosum, hydrocephalus, and chorioretinal colobomas. Severely delayed psychomotor development and generalised seizures were the major clinical features until death at the age of 4 years. Unexpectedly, lysosomal enzyme investigations showed a severe deficiency of glucocerebrosidase activity in cultured skin fibroblasts. Molecular studies showed compound heterozygosity N370S/L444P, the most common genotype in patients with GD type 1 in The Netherlands. Patient II.3 was born after an uneventful pregnancy and delivery to a consanguineous couple of normal weight, length, and head circumference. At the age of 2 years, she had retarded mental development and autistic behaviour. Magnetic resonance imaging of the brain was normal at 7 years. At this age, she had no clinical features of GD type 1, except for a normal head circumference. At age 26, she showed mild hepatosplenomegaly. Like her older brother, she appeared to have deficient glucocerebrosidase activity associated with compound heterozygosity for GD type 1. In the third patient (II.4) at 16 weeks of gestation, hydrocephalus was detected by ultrasound. Birth weight was 3220 g and head circumference 39.3 cm (98th centile). The patient fulfilled the diagnostic criteria for JS and he died at the age of 8 month; no material can be found.

This non-consanguineous family with two boys affected by JS and a girl with autistic behaviour was identified to have the most frequent genotype of GD type 1 in the Dutch population. The presence of a severe neurological disorder such as JS and autistic behaviour cannot be explained by the N370S/L444P GD genotype alone. To address the possibility that the features of GD type 1 have been masked by the early onset of severe manifestations of JS, we investigated eight additional patients with JS. In these patients, we found a normal glucocerebrosidase activity in fibroblasts. These results suggest that the JS and GD loci do not (simply) coincide. The most likely explanation for the coexistence of the two disorders in one person is the independent occurrence of GD and JS. In this case, our observation may be unique, since the statistical probability of this event is extremely small in a non-consanguineous and interracial relationship. The incidence of GD type 1 is estimated at 1/10,000 and over 100 cases of JS have been reported. Therefore, it may be worth considering other explanations. In this respect it is of interest to note the large clinical variability among GD patients. The severity of the condition is different even within families. All patients with GD type 1, 2, and 3 have significant levels of residual glucocerebrosidase activity (3-8% of those in controls; Kleijer and Aerts, unpublished data), with the exception of a neonatal variant of GD type 1, with a prenatal onset of fetal hydrops. Although our patients have a residual activity of 3-8% in fibroblasts, it remains possible that a complete knock-out of glucocerebrosidase activity is present in some tissues, for example, the central nervous system in patient II.1 (but not in patient II.3) by an as yet unknown factor, interacting with the transcription or translation of the gene or with the enzyme activity.

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BOOK REVIEW

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Lancelot Hobgen Scientific Humanist.

Unauthorised Autobiography.


Unauthorised autobiographies are rare, but the title is arresting rather than accurate. After Hobgen's death Professor G F Wells, who wrote an extensive obituary in the "Biological Memoir of the Royal Society", attempted to get a mass of papers, which was clearly an unfinished autobiography, published. Ten years ago I met Hobgen's eldest son, Adrian, who had retired to Barbados, and made an equally unsuccessful attempt to interest Oxford University Press. This unfinished and extensively annotated manuscript had limited value for publication unless extensively edited, when it feared it would lose more than could be gained. However, it has been edited without losing the forceful elegance of his prose and the occasional explosion of his vocabulary, which has been welded into a seamless narrative. Additionally, many photographs taken by Adrian, although only a small representation of his extensive collection after, when a child, he had been given a camera by Frank Bodmer, are included, an essential, but all too brief, appendix of the cast.

Hobgen, like Newton, started life as a very precocious and precocious baby. His parents, who devoted all their lives to missionary work in Portsmouth, had raised him as a product of fundamental Methodism, provided an unusual physical and intellectual environment which changed abruptly after he went to Cambridge with a scholarship to Trinity. While there the war started, providing additional work, including being picked up by a Quaker and given a camera by Frank Bodmer, and becoming a Quaker under the influence of the distinguished trio of Doncaster, Barcroft, and Edington—a geneticist, a physiologist, and an astrophysicist. His attempts to study medicine were interrupted by voluntary work, mainly building huts, among those displaced by the war, and making an unmentioned and unacknowledged journey to Paris and the fate of many others, to war. While there he was deprived of books, paper, or pencil. Although his medical career was interrupted his further education allowed him to acquire an extensive knowledge and understanding of every living thing he could observe, animal or plant, large or small. His persistence overcome numerous obstacles, initially including poverty, and later episodes of typhoid fever, eventually moderated by a five-hour operation to remove a retrosternal gland.

His first major discovery was made after studying over a thousand sections of the cockpit: at last he caught chromosomes in the act of side to side synapsis, solving the conflict between Morgan and his experiments. Interpretation of recombinant and previous observations showing end to end synapsis, Morgan visited him. Batey was later converted to crossing over as an explanation of the cistron cogenes using the human lobe, and made an incision 8 years after Morgenstern's death. His book, he feared, was a disaster.

Later his career took him to Edinburgh, then Montreal, Cape Town, the London School of Economics, and Aberdeen, from where he eventually retired. He and his Siberian railway after lecturing in Oslo when the Germans invaded. As an active opponent of their eugenic activities and supporter of Jewish scientists, he was on the blackest of blacklists. With his wife Lilian he escaped to Sweden, eventually returning via Russia and the USA to become Professor of Zoology in Birmingham, only to be invited to head the Medical Statistics division of the American army. In London during the blitz. He finally returned to Birmingham, where